Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ofatumumab

Proprietary Product Name: Kesimpta

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

June 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

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

Contents

List of abbreviations

Abbreviation	Meaning
3mCDW	3-month confirmed disability worsening
6mCDI	6-month confirmed disability improvement
6mCDW	6-month confirmed disability worsening
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
ADCC	Antibody dependent cell mediated cytotoxicity
ADCP	Antibody dependent cellular phagocytosis
AE	Adverse event
AESI	Adverse event of special interest
AI	Auto-injector (also refers to pre-filled syringe assembled in an auto-injector device)
ACSS	Australia-Canada-Singapore-Switzerland (regulatory consortium)
ARGPM	Australian regulatory guidelines for prescription medicines
ARR	Annualised relapse rate
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific annex
AUC	Area under the plasma concentration time curve
AUC_{0-t}	Area under the plasma concentration time curve from time zero to infinity (time t)
AUC_{tau}	Area under plasma concentration time curve to the end of the dosing period
BVL	Brain volume loss
CDC	Complement-dependent cytotoxicity
CE	Capillary electrophoresis
CHMP	Committee for Medicinal Products for Human Use (European Union)

Abbreviation	Meaning
CLL	Chronic lymphocytic leukaemia
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPMP	Committee for Proprietary Medicinal Products (European Union)
DLP	Data lock point
DMT	Disease-modifying treatment
EC_{50}	Concentration of a drug that gives half-maximal response
EDSS	Expanded Disability Status Scale
EFD	Embryofetal development
EMA	European Medicines Agency (European Union)
EOS	End of study
ePPND	Enhanced pre- and postnatal development
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (United States of America)
GdE	Gadolinium enhancing
GSK	GlaxoSmithKline (public limited company)
GVP	Good Pharmacovigilance Practices
HBV	Hepatitis B virus
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
ISR	Injection site reaction
LLN	Lower limit of normal

Abbreviation	Meaning
mAb	Monoclonal antibody
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NfL	Neurofilament light chain
NOAEL	No observed adverse effect level
NSD	Needle safety device
PASS	Post-authorisation safety study
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic
PDCO	Paediatric Committee
PFS	Pre-filled syringe
PI	Product Information
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
PRIM	Pregnancy outcome intensive monitoring
PSUR	Periodic safety update report
PT	Preferred Term
PV	Pemphigus vulgaris
RA	Rheumatoid arthritis
RMP	Risk management plan
RMS	Relapsing forms of multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
RSABE	Reference scaled average bioequivalence
SAE	Serious adverse event

Abbreviation	Meaning
sBLA	Supplemental Biologics License Application (Food and Drug Administration, United States of America)
SDS	Sodium dodecyl sulfate
SOC	System Organ Class
SPMS	Secondary progressive multiple sclerosis
TGA	Therapeutic Goods Administration
US(A)	United States (of America)
USPI	United States Prescribing Information

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications and major variation (new dosage form)
Product name:	Kesimpta
Active ingredient:	Ofatumumab
Decision:	Approved
Date of decision:	3 March 2021
Date of entry onto ARTG:	4 March 2021
ARTG numbers:	330601 and 330617
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for five years, starting on the date the new indication was approved.
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road Macquarie Park, NSW, 2113
Dose form:	Solution for injection
Strength:	20 mg/0.4 mL
Containers:	Pre-filled pen and pre-filled syringe
Pack size:	One
Approved therapeutic use:	*Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) to delay the progression of physical disability and reduce the frequency of relapse (refer to Section 5.1).*
Route of administration:	Subcutaneous injection
Dosage:	The recommended dose is 20 mg Kesimpta administered by subcutaneous injection with: • initial dosing of 20 mg by subcutaneous injection at Weeks 0, 1 and 2, followed by subsequent monthly dosing of 20 mg by subcutaneous injection, starting at Week 4.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: C

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

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register Kesimpta (ofatumumab) 20 mg/0.4 mL, solution for injection for the following proposed extension of indications:

Treatment of adult patients with relapsing forms of multiple sclerosis (RMS).

Multiple sclerosis is a chronic, progressive immune mediated disease of the central nervous system (CNS) characterised by inflammation, demyelination and axonal/neuronal destruction, ultimately leading to severe disability. Scars occur within the CNS and depending on where they develop, manifest into various symptoms. MS affects over 25,600 patients in Australia and more than two million worldwide. Most people are diagnosed between the ages of 20 to 40 years, but it can affect younger and older people too. Compared to men, approximately three times as many women have MS.

Multiple sclerosis (MS) can be grouped as either relapsing MS or progressive MS. 85% of patients present with a relapsing remitting course of the disease;[2] characterised by relapses of neurological dysfunction followed by a variable state of complete or incomplete recovery. Most people with relapsing remitting multiple sclerosis (RRMS) transition to a more progressive course called secondary progressive multiple sclerosis (SPMS) that is characterised by continuous worsening of disability with or without superimposed relapses.

B-cells play an important role in MS pathogenesis due to production of pro-inflammatory cytokines, release of auto-reactive antibodies and activation of pathogenic T-cells. It has been shown that B-cells are factors contributing to the immune mediated histopathology in MS.[3,4,5,6] B-cells are present in the chronic plaques, areas of demyelination, and in the

[2] Lublin et al. Defining the Clinical Course of Multiple Sclerosis: the 2013 Revisions, *Neurology*, 2014: 15; 83(3): 278-286.
[3] Archelos, J. J. et al. The Role of B Cells and Autoantibodies in Multiple Sclerosis, *Ann Neurol*, 2000; 47: 694-706.
[4] Frohman, E. M. et al. Multiple Sclerosis — the Plaque and Its Pathogenesis, *N Engl J Med*, 2006; 354: 942-955.
[5] McFarland, H. F. The B Cell - Old Player, New Position on the Team, *N Engl J Med*, 2008; 358(7): 664-665.
[6] Claes, N. et al. B Cells are Multifunctional Players in Multiple Sclerosis Pathogenesis: Insights from Therapeutic Interventions, *Front Immunol*, 2015; 6: 642.

cerebrospinal fluid of MS patients.[7] While very few B-cells infiltrate the healthy CNS, their number dramatically increases during inflammation. Increasing evidence suggests that B-cells settling the CNS during inflammation mature outside the CNS, in secondary lymphoid organs, and that T-cell clones attacking brain structures are instructed in the periphery by autoreactive B-cells.[8,9] Consequently, the depletion of B-cells in lymphatic tissues is an efficacious treatment approach in MS.

The current therapeutic approach involves symptomatic treatment, treatment of acute relapses, and disease modifying treatments (DMTs). The standard of care for acute relapses is methylprednisolone, which shortens the duration of a relapse but has no influence on its sequelae. DMTs aim to modify the course of the disease mainly by suppressing or modulating the immune responses involved in MS pathogenesis. These therapies aim to prevent relapses and ultimately intend to decrease the rate of accumulation of disability. Due to the risks of opportunistic infections, malignancies, and other systemic adverse drug reactions, several of the currently available and approved for use in RMS treatment options (DMTs/DMT classes) are considered as second line options.

Monoclonal antibodies (mAbs) directed against proteins expressed by B-cells. For example, anti-CD20 antibodies, such as ocrelizumab and rituximab, are high efficacy therapies offering the same high efficacy as other highly efficacious DMTs, including mAbs like natalizumab and alemtuzumab, but at the same time show a better safety profile. Despite the availability of several DMTs for the treatment of RMS, there remains the medical need for efficacious and safe therapies that are convenient to administer and easy to do safety monitoring in clinical use, to reduce the burden of long term accrual of disability.

The early initiation of treatment with DMTs even after a first event of clinically isolated syndrome (CIS) has shown to improve long term clinical outcomes.[10,11] Guidelines on the management of DMTs recommend that patients begin DMT when first diagnosed.[12,13] The available DMTs vary in their mechanism of action, efficacy, safety, mode of administration and ease of use. When choosing one of the available DMT for the treatment of MS, the use of increasingly effective medication needs to be balanced against the potential safety risk of the treatment. In addition, the convenience of use, route and frequency of administration and the frequency of safety monitoring are individual parameters that vary between patients but are relevant for each patient's quality of life.[14] Despite the availability of several DMTs for the treatment of RMS, there remains a need for therapies that are easy to use and that have a low risk if initiated early during the course of the disease, or later as a switch therapy.

Ofatumumab is a fully human anti-CD20 mAb (immunoglobulin G (IgG)1). It binds to a distinct epitope encompassing both the small and large extracellular loops of the CD20

[7] Lehman-Horn K. et al. Targeting B Cells in the Treatment of Multiple Sclerosis: Recent Advances and Remaining Challenges. *Ther Adv Neurol Disord*, 2013; 6(3): 161–173.
[8] Jelcic, I. et al. Memory B Cells Activate Brain-homing, Autoreactive CD4+ T Cells in Multiple Sclerosis, Cell, 2018: 175: 85-100.
[9] D'Amico, E. et al. Placing CD20-targeted B Cell Depletion in Multiple Sclerosis Therapeutic Scenario: Present and Future Perspectives, *Autoimmun Rev*, 2019; 18: 665–672.
[10] Pardo, G. and Jones, D. E. The sequence of Disease-modifying Therapies in Relapsing Multiple Sclerosis: Safety and Immunologic Considerations, *J Neurol*, 2017; 264: 2351-2374.
[11] Cree, B. A. C. et al. Current Therapeutic Landscape in Multiple Sclerosis: an Evolving Treatment Paradigm, *Curr Opin Neurol*, 2019; 32(3): 365-377.
[12] Montalban, X. et al. ECTRIMS/EAN Guideline on the Pharmacological Treatment of People with Multiple Sclerosis, Mult Scler, 2018; 24(2): 96 –120.
[13] Rae-Grant, A. et al. Comprehensive Systematic Review Summary: Disease-modifying Therapies for Adults with Multiple Sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology, *Neurology*, 2018; 90: 789-800.
[14] Ontaneda, D. et al. Early Highly Effective Versus Escalation Treatment Approaches in Relapsing Multiple Sclerosis, *Lancet Neurol*, 2019; 18: 973–980.

molecule giving rise to a slow off-rate and high binding affinity. The CD20 molecule is a transmembrane phosphoprotein expressed on B-lymphocytes from the precursor B- to mature B -lymphocyte stage. The CD20 molecule is also expressed on a small fraction of activated T-cells. The binding of ofatumumab to CD20 induces lysis of CD20+ B-cells primarily through complement dependent cytotoxicity (CDC) and to a lesser extent, through antibody dependent cell mediated cytotoxicity (ADCC). Due to the broad expression of CD20 on various B-cell subsets, the CD20 dependent mode of action of ofatumumab can induce very pronounced and sustained depletion of B-cells in both, experimental animals and humans. Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells. CD20 expressing T-cells are also depleted by ofatumumab.

Other anti-CD20 mAbs available in Australia are ocrelizumab and rituximab, which have similar mode of action as ofatumumab. The sponsors have stated a number of unique properties of ofatumumab:

- Ofatumumab is a fully human mAb, whereas ocrelizumab is a humanised mAb and rituximab is a chimeric mAb.
- No relevant difference in ADCC activity of ofatumumab compared to ocrelizumab was observed, while rituximab was less active.
- Complement dependent cytotoxcitiy dependent B-cell lysis induced by ofatumumab was highly efficacious, while both rituximab and ocrelizumab were less active. In contrast to ocrelizumab or rituximab, the binding epitope of ofatumumab close to the plasma membrane may enable Fc-mediated complement binding to occur in close proximity to the cell surface, contributing to a more efficacious CDC initiated by ofatumumab.
- B-cell binding studies showed a lower off-rate for ofatumumab in comparison to rituximab, which is of functional importance.
- Data indicate that ofatumumab is more potent in CDC induction in primary human B-cells when compared with ocrelizumab and rituximab; ofatumumab may have a greater potential for effector activity, particularly on cells expressing low levels of CD20.
- Unlike ocrelizumab and rituximab which are both administered intravenously, subcutaneous administration of ofatumumab is expected to provide more direct access to the lymphatic system, a primary location of MS pathology and target for MS therapies.[15] This may contribute to a lower dose requirement to achieve clinical efficacy, with a corresponding better tolerability and an expected lower clinical risk when compared to an intravenous route of administration.

This application was evaluated as part of the Australia-Canada-Singapore-Switzerland (ACSS) Regulatory Consortium, with work-sharing between the Therapeutic Goods Administration (TGA), Health Canada, Health Sciences Authority Singapore and Swissmedic. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

Regulatory status

Various presentations of ofatumumab have been registered on the Australian Register of Therapeutic Goods (ARTG) since 2013. Kesimpta (ofatumumab) 20 mg/0.4 mL solution for injection is considered a new strength, new dosage form and new route of

[15] Sabatino Jr, J. J. et al. B Cells in Autoimmune and Neurodegenerative Central Nervoussystem Diseases, *Nat Rev Neurosci,* 2019; 20 (12): 728-745

administration of ofatumumab for Australian regulatory purposes and was evaluated as an extension of indications application.

At the time the TGA considered this application, similar applications had been approved in the United States of America (USA) (approved on 20 August 2020), Switzerland (approved on 1 February 2021), Singapore (approved on 5 February 2021) and Canada (approved on 25 January 2021). Similar applications are under consideration in the European Union (submitted on 9 January 2020) and Japan (submitted on 29 July 2020).

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
USA	20 December 2019	Approved on 20 August 2020	*Kesimpta is a CD20-directed cytolytic antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.*
European Union	9 January 2020	Under consideration	Under consideration
Japan	29 July 2020	Under consideration	Under consideration
Switzerland	28 February 2020	Approved on 1 February 2021	*Kesimpta is indicated for the treatment of adult patients with active, relapsing forms of multiple sclerosis (MS).*
Singapore	28 February 2020	Approved on 5 February 2021	*Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS).*
Canada	20 March 2020	Approved on 25 January 2021	*Kesimpta (ofatumumab injection) is indicated for: the treatment of adult patients with relapsing remitting*

Region	Submission date	Status	Approved indications
			multiple sclerosis (RRMS) with active disease defined by clinical and imaging features.

Product Information

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

II. Registration timeline

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

Table 2: Timeline for Submission PM-2020-00666-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	30 March 2020
First round evaluation completed	4 August 2020
Sponsor provides responses on questions raised in first round evaluation	29 September 2020
Second round evaluation completed	10 November 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	7 January 2021
Sponsor's pre-Advisory Committee response	18 January 2021
Advisory Committee meeting	4 and 5 February 2021
Registration decision (Outcome)	3 March 2021
Completion of administrative activities and registration on the ARTG	4 March 2021
Number of working days from submission dossier acceptance to registration decision*	189

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

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

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

The following guidance documents are of relevance to the submission:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), 26 March 2015. Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis, EMA/CHMP/771815/2011, Rev. 2.
- EMA, CHMP, 25 July 2011. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH): S6 (R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, CPMP/ICH/302/95.
- EMA, Committee for Proprietary Medicinal Products (CPMP), 1 June 1995. ICH Topic E1: Population Exposure: The Extent of Population Exposure to Assess Clinical Safety, CPMP/ICH/375/95.
- Montalban, X. et al. The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)/ European Academy of Neurology (EAN) Guideline on the Pharmacological Treatment of People with Multiple Sclerosis, *Mult Scler*, 2018; 24(2): 96–120.
- Rae-Grant, A. et al. Comprehensive Systematic Review Summary: Disease-modifying Therapies for Adults with Multiple Sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology, *Neurology*, 2018; 90: 789-800.

Quality

Ofatumumab is a high affinity fully human anti-CD20 mAb that belongs to the IgG1/kappa (κ) isotype subclass. The antibody is expressed in a murine NS0 cell line and consists of two identical IgG1 heavy chains of 452 amino acids each and two identical kappa light chains of 214 amino acids each.

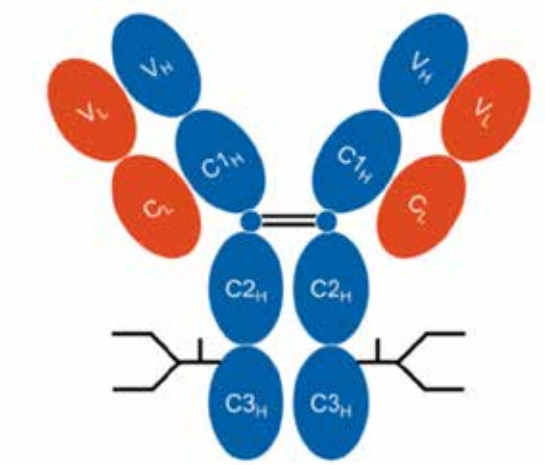
The heavy chain of ofatumumab contains one N-glycosylation site. The C-terminal lysine of the heavy chain is predominantly removed. Ofatumumab has no O-linked glycosylation sites.

The molecular weight of ofatumumab is approximately 146,000 Da which is deduced from its DNA sequence, post-translational modifications are not considered.

There are two interchain disulphide bonds between the heavy chains, one interchain disulphide bond between the light chain and the heavy chain, the light chain has two intrachain disulphide linkages and the heavy chain has four intrachain disulphide linkages.

The characterisation of ofatumumab was done using a panel of different methods.

Figure 1: Structure of ofatumumab immunoglobulin G1



Ofatumumab is expressed in a murine NS0 cell line. The antibody consists of two heavy and two light chains with each individual domain indicated. The heavy chain is N-glycosylated.

Each pre-filled syringe (PFS) and pre-filled pen contains 20 mg ofatumumab solution for injection (0.4 mL of 50 mg/mL solution).

There are no major objections to approval from quality evaluation.

Nonclinical

The sponsor considered the recommendations outlined in the International Conference on Harmonisation (ICH) S6 (R1) Guidance for the nonclinical testing strategy.[16] Pivotal toxicity studies were performed in compliance with Good Laboratory Practice regulations.

Pharmacology

Ofatumumab showed similar *in vitro* binding to normal human and cynomolgus monkey peripheral blood B-cells (peripheral blood mononuclear cells (PBMCs)) with concentration of a drug that gives half-maximal response (EC_{50}) values of 287 and 139 ng/mL, respectively. In *in vitro* cross reactivity studies ofatumumab was shown to bind specifically to CD20+ B-cells in human as well as in cynomolgus monkey PBMCs and lymphoid tissues.

The *in vitro* potential B-cell cytotoxicity of ofatumumab was assessed in normal human primary B-cells and tumour B-cell lines. Ofatumumab was shown to have potent anti-CD20 activity that operates through different mode of actions including CDC, ADCC and antibody dependent cellular phagocytosis (ADCP), with CDC being the most potent and efficacious.

No secondary pharmacodynamics (PDs) and PD drug interactions studies were conducted.

Safety pharmacology endpoints assessing the CNS, cardiovascular, respiratory, and renal functions were integrated in the repeated dose toxicology study in cynomolgus monkeys and were unaffected by treatment.

Pharmacokinetics

The nonclinical pharmacokinetic (PK)/toxicokinetic profiles of ofatumumab were investigated mainly following repeated intravenous administration (infusion over 30 minutes) in cynomolgus monkey although the intended clinical route of administration

[16] ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals

for the applied MS indication is subcutaneous. The PK profiles of ofatumumab following subcutaneous or intravenous administration were similar.

Systemic exposure (area under the plasma concentration-time curve from time zero up to infinity (or time t; AUC_{0-t}) and maximum concentration (C_{max})) at doses of 20 and 100 mg/kg increased dose proportional and in a manner consistent with the long half-life, low clearance and frequency of dosing. However, the elimination half-life of 9.4 days in monkey is shorter than in human (approximate 17 days). No accumulation in systemic exposure occurred and there were no gender differences. Upon subcutaneous administration of ofatumumab, bioavailability was high (70%). Overall, the PKs of ofatumumab in monkey is comparable with that in humans.

No dedicated studies have been performed to investigate the *in vivo* tissue distribution, metabolism and excretion of ofatumumab in animals, in line with ICH S6.[16]

Ofatumumab as human mAb elicited an anti-drug antibody (ADA) response in monkey. The impact on the animals' respective serum concentration-time profile was minimal and the toxicity profile was not affected in the presence of ADAs. In addition, ofatumumab and ADAs were present in umbilical cord blood and blood samples of cynomolgus monkey foetuses and infants, which indicates that ofatumumab crosses the placental barrier. The recommendations for pregnancy and lactation in the information for healthcare professionals are adequate.

The potential of ofatumumab for systemic drug-drug interactions is considered very low based on the high specificity for CD20 and because it does not bind to any other proteins or macromolecules.

Toxicology

The toxicological evaluation was conducted in cynomolgus monkeys. The species selection is appropriate since ofatumumab showed cross reactivity to cynomolgus monkey CD20. The toxicological profile of ofatumumab was well characterised in repeat dose toxicology studies up to seven months and at doses up to 100 mg/kg administered intravenously (30 minutes injections) although the clinical route of administration is subcutaneous. This is acceptable since the PK profiles of ofatumumab following intravenous or subcutaneous administration were similar. The duration of the toxicity studies supports the chronic use in the clinic. No target organ of toxicity was identified. There were no off-target changes beside the expected pharmacology related effects (marked B-cells depletion) noted in peripheral blood and lymphoid tissues. These findings showed a tendency to recovery or were reversible following the recovery period. The safety margin based on exposure (area under the plasma concentration time curve (AUC)) at 100 mg/kg was > 100 fold higher than the exposure at the clinical dose of 20 mg.

Genotoxicity and carcinogenicity studies with ofatumumab have not been conducted in accordance with ICH S6 (R1) guidance.[16] Based on a weight of evidence approach it was concluded that the risk of carcinogenicity for ofatumumab is low.

In a 13 week study conducted in sexually mature male and female cynomolgus monkeys with doses up to and including 100 mg/kg administered intravenously, treatment with ofatumumab had no effects on the fertility parameters in male (testicular and semen evaluation) and female (menstrual cyclicity monitoring and ovarian or uterine maturation stage). Ofatumumab did not elicit maternal toxicity, developmental toxicity or teratogenicity in the embryo fetal development (EFD) study conducted in cynomolgus monkeys with intravenous doses up to and including 100 mg/kg administered intravenously. In the enhanced pre- and postnatal development (ePPND) study, ofatumumab administered at intravenous doses up to and including 100 mg/kg led to the pharmacologically expected depletion of CD20+ B-cells in maternal animals and their infants, along with a reduced humoral immune response in infants. These changes were

reversible. The maternal exposure at the no observed adverse effect level (NOAEL) for infants was 22 fold higher than exposure at the recommended therapeutic dose. Any risks were adequately reflected in the information for healthcare professionals, and the recommendations are considered appropriate.

The safety margin is multiple times higher than the predicted human therapeutic exposures in MS patients.

The irritant potential and infusion reaction potential of ofatumumab is low. No local effects were noted at the subcutaneous and intravenous injection sites and no ofatumumab related cytokine release syndrome manifestation was seen in monkey after intravenous administration.

There are no safety concerns with regard to impurities or excipients.

Due to the protein nature of ofatumumab, the risk for the environment is considered low.

The nonclinical safety specifications in the risk management plan (RMP) adequately address the nonclinical findings and their relevance for clinical use.

Juvenile toxicity was not warranted given the comprehensive package of nonclinical safety studies with ofatumumab including animal of appropriate age. EMA/the Paediatric Committee (PDCO) granted a waiver for the paediatric population from birth to less than ten years of age and agreed on a paediatric investigation plan (PIP) for the paediatric population from ten years to less than 18 years of age.

In conclusion, the submitted nonclinical documentation supports the approval of Kesimpta with the new active substance ofatumumab in the proposed indication. The pharmacological properties as well as the PKs and toxicity profiles of ofatumumab were adequately characterised. All nonclinical data that are relevant for safety are included in the information for healthcare professionals. There are no major objections to approval from nonclinical evaluation.

Clinical

The clinical dossier consisted of:

- five studies containing clinical pharmacology data were submitted in support of the current application, Phase II, Study OMS115102; Phase II, Study OMS112831; Phase III, Studies COMB157G2301 (the ASCLEPIOS I trial; abbreviated as G2301) and COMB157G2302 (the ASCLEPIOS II trial; abbreviated as G2302); and the Phase II, Study COMB157G2102 (abbreviated as G2102);
- two pivotal Phase III Studies, Study G2301 (the ASCLEPIOS I trial) and Study G2302 (the ASCLEPIOS II trial);
- two supportive Phase II studies, Study OMS112831 (the MIRROR trial) and Study OM115102;
- two ongoing MS studies, Study COMB157G1301 and Study COMB157G2399.

Pharmacology

Pharmacokinetics

The conduct of all of the clinical pharmacology studies submitted in support of the current application was satisfactory, the data analyses undertaken were appropriate and the analytical methods used to measure exposure levels were validated.

The pharmacology programme included three Phase II studies and two Phase III studies. From the Phase II studies PKs and PDs were evaluated and bioequivalence were assessed, and the data from the Phase III studies were included in the population PK analysis.

The absolute bioavailability of subcutaneous ofatumumab in patients with RRMS was estimated to be approximately 17%.

The multiple dose studies showed non-linear PKs. Hence, ofatumumab C_{max} increased ten fold, and AUC increased 14 fold for a seven fold increase in dose (from 100 mg to 700 mg). A lower dose of 20 mg was used in the Phase III studies, where ofatumumab concentrations were measured as trough values at steady state.

Using the reference scaled average bioequivalence (RSABE) method for highly variable drugs, the geometric mean ratios for ofatumumab area under plasma concentration-time curve over a dosing interval (AUC_{tau}) and C_{max} were 1.03 and 1.00, respectively, following subcutaneous administration to the abdomen using either the PFS or PFS assembled in an auto-injector device/auto-injector (AI) devices, indicating that 20 mg doses from both the proposed devices were bioequivalent.

After multiple doses of 20 mg subcutaneous every four weeks following an initial loading regimen, ofatumumab C_{max} increased up until the Day 14 injection of the loading period. The modelling report as well as the Phase III studies indicated that ofatumumab steady state may not be achieved until after two years of dosing with the Phase III dose regimen.

Following subcutaneous dosing of ofatumumab 20 mg every four weeks, the geometric mean AUC_{tau} and mean C_{max} values for ofatumumab were 483 µg h/mL and 1.43 µg/mL, respectively, regardless of administration site or device when measured during the Week 8 to Week 12 dosing interval.

Concentration data from 1451 RMS patients indicated that ofatumumab PKs were well described by a two compartment, quasi-steady state approximation of the target mediated drug disposition model with subcutaneous absorption being described by a first order process.

Although the modelling report identified body weight, gender and administration device (PFS or AI) as statistically significant covariates of ofatumumab PKs, the changes in exposure induced by these factors are unlikely to be clinically relevant. By contrast, age and race had no effect on ofatumumab PKs.

No studies in patients older than 56 years were conducted, and no PK studies were conducted in paediatric subjects.

No drug-drug interaction studies have been conducted. This is considered acceptable as mAbs are degraded to small peptides and amino acids and are not metabolised by the cytochrome p450 system.[17]

The proposed PI accurately reflects the PK data submitted in support of the use of ofatumumab in patients with RMS apart from Review of the Product Information suggested by the Delegate.[18]

[17] **Cytochrome P450 (CYP) enzymes**: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds. Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

[18] Inclusion of these is beyond the scope of the AusPAR.

Pharmacodynamics

PDs were assessed using three Phase II studies and two Phase III studies.

Following 12 weeks of treatment with subcutaneous ofatumumab 3 mg, 30 mg or 60 mg every 12 weeks or 60 mg every four weeks there was a significant reduction (65%) in cumulative new gadolinium enhancing (GdE) T1 lesions compared to placebo for all active dose groups.

In patients with RMS, ofatumumab demonstrated low levels of immunogenicity and in the sporadic cases where ADAs were detected, their presence appeared to have no effect on ofatumumab PKs, safety or B-cell evaluations in these subjects.

60 mg ofatumumab, administered over 12 weeks, provided maximal benefit in regards to GdE T1 lesion suppression, whereas doses higher than 60 mg provided no further benefit.

Depletion of CD20 peripheral B-cells, as measured by CD19+ B-lymphocyte expression, was rapid and dose dependent following subcutaneous ofatumumab administration and the reduction in CD19 cells was highly correlated with the suppression in development of cumulative new GdE T1 lesions.

Regression modelling indicated that the proposed loading and maintenance doses of ofatumumab would attain and maintain the targeted level of B-cell depletion in 98% of patients.

Simulation results from a kinetic pharmacodynamic (K-PD) model estimated median B-cell recovery (defined as values above lower limit of normal (LLN) or baseline) 40 weeks after treatment interruption.

Dose selection

The treatment scheme for ofatumumab in the pivotal Phase III studies was a loading dose regimen of 20 mg at Day 1, Day 7 and Day 14, followed by a maintenance dose regimen of 20 mg administered every four weeks starting at Week 4.

The three times 20 mg subcutaneous loading and maintenance regimen was used in the pivotal studies G2301 and G2302. The selection of the dose regimen for these studies is supported by results from the dose ranging Phase II Study OMS112831 and PK/PD modelling of B-cell data from same study:

- a strong relationship between the ofatumumab dose and the level of B-cell depletion;
- the observed inhibition of brain magnetic resonance imaging (MRI) lesions at the cumulative ofatumumab doses tested, combined with a maintained B-cell depletion;
- the corresponding efficacy of ofatumumab at the tested dose levels, as assessed by the inhibition of brain MRI lesions as a surrogate marker for MS relapses;
- the favourable safety profile observed with proposed doses below the highest tested subcutaneous dose for ofatumumab of 60 mg every four weeks in the Phase II dose finding study in MS.

Overall, the selection of the dose regimen for the Phase III studies was justified.

Efficacy

Table 2: Overview of efficacy studies

Source of data	Studies	Details
Pivotal studies (Phase III)	Study G2301 (ASCLEPIOS I) Study G2302 (ASCLEPIOS II)	2 randomized, double-blind, active-controlled studies in patients with RMS in a total of 1882 patients; up to 30 months data
Dose-finding study (Phase II)	Study OMS112831 (MIRROR)	1 randomized, double-blind, placebo-controlled, dose-finding study investigating ofatumumab s.c. in 232 RRMS patients
Supportive study (Phase II)	Study OMS115102	1 randomized, double-blind, placebo-controlled study investigating ofatumumab i.v. in 38 RRMS patients
Studies used for combined efficacy analysis[1]	Study OMS115102	Pool C0: includes Study OMS115102 only, for data up to Week 24
	Study OMS112831	Pool C1: includes Study OMS112831 only, for data up to Week 12
	Studies G2301 and G2302	Pool C2: includes both studies G2301 and G2302: main pool for efficacy and subgroup analyses

s.c. = subcutaneous; RRMS = relapsing remitting multiple sclerosis; i.v. = intravenous.

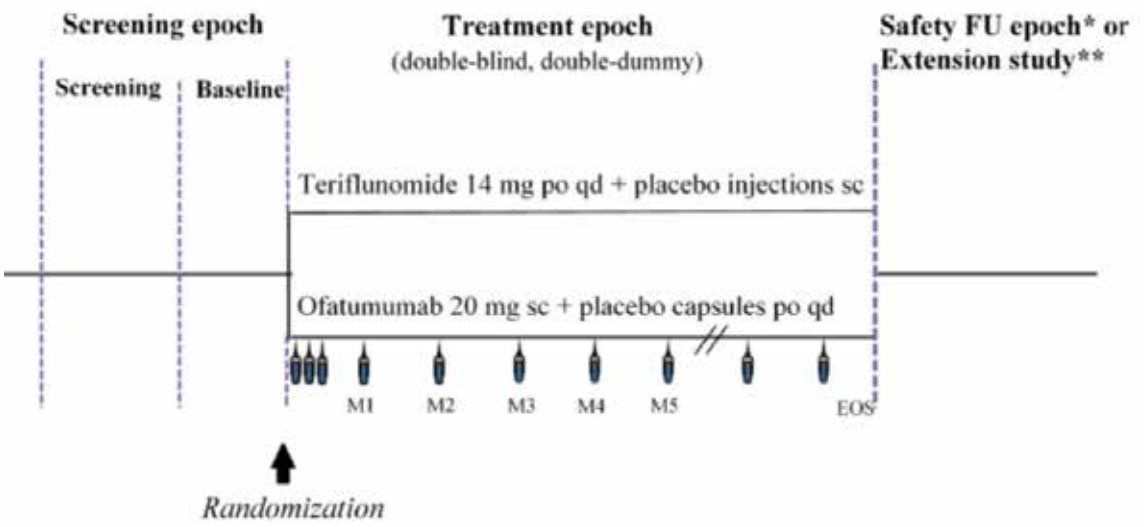
Table 3: Overview of pivotal studies

Study no.	Patients randomized (exposed to ofatumumab)	Study design, objectives, population	Treatment duration	Dosage	Primary efficacy endpoint
G2301	N=927 (465)	Randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab vs. teriflunomide in patients with RMS	Flexible duration in individual patients, but with a maximum of 30 study months	Ofatumumab 20 mg s.c. injections on Days 1, 7, 14 (loading dose regimen) and every 4 weeks thereafter starting at Week 4 (maintenance dose regimen) Comparator: teriflunomide 14 mg capsule orally once daily	ARR, defined as the number of confirmed MS relapses in a year
G2302	N=955 (481)				

N = population size; vs. = versus; RMS = relapsing forms of multiple sclerosis; s.c. = subcutaneous; ARR: annualised relapse rate; MS = multiple sclerosis.

The sponsor submitted data from two pivotal trials, G2301 and G2302, to establish the efficacy of their product in the treatment of adult patients with RMS. The trials were identical multi-centre, prospective, randomised, double blind, double dummy, active controlled, parallel group studies. The trials were designed as superiority studies to demonstrate superiority of ofatumumab 20 mg subcutaneous every four weeks over daily oral administration of teriflunomide 14 mg for primary, secondary and exploratory endpoints. Overall, the choice of comparator is adequately justified. The proposed dosing regimen was a loading dose regimen of 20 mg at Day 1, 7 and 14, followed by a maintenance dose regimen of 20 mg administered subcutaneous every four weeks starting at Week 4 and was used in both the Phase III studies.

Figure 2: Study design for ofatumumab Phase III clinical program in relapsing forms of multiple sclerosis



FU: follow up; sc = subcutaneous; po = by mouth; qd = every day, M: month; EOS: end of study

The treatment duration for an individual patient was variable. End of study (EOS) was declared for both studies simultaneously based on an analysis of blinded data and a projection by when all pre-specified conditions would be met. The maximal treatment duration for an individual patient was 30 study months (approximately 2.5 years).

The trials enrolled 1882 patients aged 18 to 55 years with relapsing MS: RRMS or SPMS course with disease activity. 2010 revised McDonald criteria;[19] was used to diagnose MS. Expanded Disability Status Scale (EDSS) score of 0 to 5.5 was used as inclusion criteria. Documentation of at least: one relapse during the previous one year OR two relapses during the previous two years prior to screening OR a positive GdE MRI scan during the year was needed prior to randomisation.

Patients with primary progressive MS or SPMS without disease activity or neuromyelitis optica or active chronic disease of the immune system other than MS or with immunodeficiency syndrome or neurological findings consistent with progressive multifocal leukoencephalopathy (PML) or risk of developing or having reactivation of hepatitis were excluded.

The primary objective of both studies was to assess the efficacy of ofatumumab 20 mg subcutaneous every four weeks versus daily oral administration of teriflunomide 14 mg as measured by annualised relapse rate (ARR). Key secondary objectives were time to disability worsening as measured by 3-month confirmed worsening (3mCDW) on EDSS, time to disability worsening as measured by 6-month confirmed worsening (6mCDW) on EDSS, time to disability improvement as measured by 6-month confirmed improvement (6mCDI) on EDSS, number of GdE T1 lesions per MRI scan, number of new or enlarging T2 lesions on MRI per year (annualised T2 lesion rate), neurofilament light chain (NfL) concentration in serum, rate of brain volume loss (BVL) based on assessments of percentage brain volume change from Baseline.

The primary endpoint was ARR, which was defined as the number of confirmed MS relapses in a year. Relapse confirmation occurred through the assessment of a clinically relevant change in the EDSS by an independent EDSS rater.

The key secondary endpoints were the following for each study:

[19] Polman et al. Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria, *Ann Neurol*, 2011; 69(2): 292-302.

- Number of GdE T1 lesions per scan,
- Annualised rate of new or enlarging T2 lesions,
- NfL concentration in serum,
- BVL,

and the key secondary endpoints were the following for pooled studies:

- 3mCDW,
- 6mCDW,
- 6mCDI.

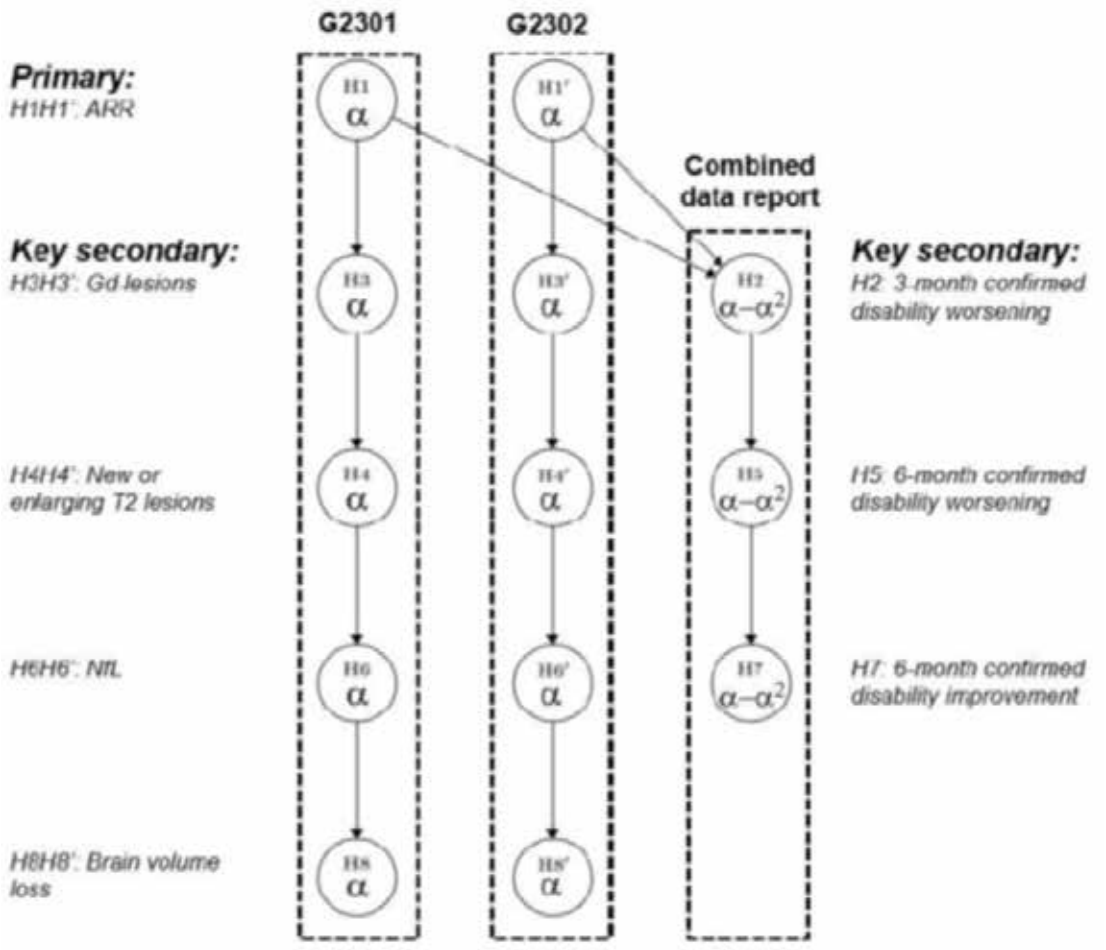
The efficacy analyses were performed using the full analysis set (FAS), which included all randomised patients according to the assigned treatment. The per-protocol set was used in supportive analysis. The ARR was estimated using a negative binomial model with log link. The covariates of the model were treatment and region, number of relapses in previous year, baseline EDSS, baseline number of GdE lesions and the patient's age at Baseline. The response variable was the number of confirmed relapses in the treatment epoch observed and the patient's time in study was used as an offset variable.

Disability related endpoints were analysed using a Cox proportional hazards model with study as stratum, treatment, and region as factors and baseline EDSS as a continuous covariate. For GdE T1 lesions (which represent acute, transient inflammation on a specific scan), the data was analysed in a negative binomial model with an offset for the number of MRI scans included in the analysis. For the number of new or enlarging T2 lesions (which represent the cumulative increase in the number of lesions between Baseline and the specific post baseline scan), the data was analysed in a negative binomial model with an offset for the time (in years) between the last post baseline scan and the baseline (or screening) scan. The NfL data was analysed in a mixed model for repeated measures (MMRM) with unstructured covariance assumed between assessments within patients. Percent brain volume change from Baseline was analysed in a random coefficient model (with random slope and intercept and unstructured covariance assumed for these random effects).

To control the Type I error rate, a testing strategy containing all primary and key secondary endpoints of Studies G2301 and G2302, as illustrated in Figure 3 (shown below) was implemented.

A meta-analysis for the combined data was pre-planned for key secondary disability related endpoints, as the individual studies were not powered for these analyses. If both studies successfully rejected the null hypothesis of the primary endpoint, disability related endpoints could be tested at one sided significance level of 0.024 (= 0.025 - 0.025^2) using the combined data from both studies, regardless of the outcomes of MRI and NfL related endpoints. The testing procedure was pre-planned and agreed by the Food and Drug Administration (FDA). The testing procedure controls the Type I error rate (one sided) at the study level to ≤ 0.025, and at combined studies level to ≤ 0.000625(= 0.025^2).

Figure 3: Studies G2301 and G2302 Testing procedure and Type I error control



ARR = annualised relapse rate; Gd = gadolinium; NfL = neurofilament light chain.

Testing procedure and Type I error control in the planned ofatumumab submission which consists of studies G2301 and G2302 (both with identical design). Hypotheses can only be tested in sequential order as indicated by the arrows. The number associated with each hypothesis (α, or α - α2) indicates the significance level at which that hypothesis can be tested. Of the null hypothesis for the primary objective (ARR) can be rejected within a study, MRI and NfL related hypotheses will be tested in sequential order within that study as long as all proceeding hypothesis can successfully be rejected. Disability related hypotheses will only be tested in the combined data of the two studies if the primary null hypotheses can be rejected in both studies first. At the study level, the hype I error rate (one-sided) is controlled at ≤ 0.025. In the submission, the Type I error rate is controlled at ≤ 0.000625(= 0.0252) for the primary hypothesis and at ≤ 0.025 when considering all endpoints.

Demographics were generally balanced between the treatment groups for Study G2301 and Study G2302 populations. Most patients were female and White, with a mean age of 38 years (Table 4).

Baseline disease characteristics were generally balanced between the treatment groups for Studies G2301 and G2302. The mean disease duration since MS diagnosis was 5.7 years for Study G2301 and 5.6 years for Study G2302. The mean baseline EDSS was 2.96 for Study G2301 and 2.88 for Study G2302 (Table 5).

Table 4: Studies G2301 and G2302 Patient demographics

	G2301		G2302	
	OMB 20 mg N=465	TER 14 mg N=462	OMB 20 mg N=481	TER 14 mg N=474
Age (yrs)				
Mean (SD)	38.9 (8.77)	37.8 (8.95)	38.0 (9.28)	38.2 (9.47)
Median (min, max)	40.0 (19, 56)	38.0 (18, 55)	38.0 (18, 56)	38.0 (18, 56)
Sex – n (%)				
Male	147 (31.6)	145 (31.4)	162 (33.7)	155 (32.7)
Female	318 (68.4)	317 (68.6)	319 (66.3)	319 (67.3)
Race – n (%)				
Asian	15 (3.2)	16 (3.5)	21 (4.4)	19 (4.0)
Black or African American	15 (3.2)	20 (4.3)	13 (2.7)	18 (3.8)
White	411 (88.4)	412 (89.2)	418 (86.9)	417 (88.0)
Other	22 (4.7)	14 (3.0)	20 (4.2)	14 (3.0)
Unknown	2 (0.4)	0	9 (1.9)	6 (1.3)
Region – n (%)				
Europe	249 (53.5)	246 (53.2)	241 (50.3)	237 (50.0)
North America	103 (22.2)	105 (22.7)	107 (22.2)	106 (22.4)
Rest of world	113 (24.3)	111 (24.0)	132 (27.4)	131 (37.6)

OMB = ofatumumab; TER = teriflunomide; SD = standard deviation.

Table 5: Studies G2301 and G2302 Baseline disease characteristics

	G2301		G2302	
	OMB 20 mg N=465	TER 14 mg N=462	OMB 20 mg N=481	TER 14 mg N=474
Type of MS at study entry, n (%)				
RRMS	438 (94.2)	434 (93.9)	452 (94.0)	450 (94.9)
SPMS	27 (5.8)	28 (6.1)	29 (6.0)	24 (5.1)
Duration of MS since diagnosis (years)				
Mean (SD)	5.8 (6.0)	5.6 (6.2)	5.6 (6.4)	5.5 (6.0)
Median (min, max)	3.9 (0.1, 29.0)	3.5 (0.1, 35.8)	3.2 (0.1, 31.8)	3.1 (0.1, 33.5)
Duration of MS since first symptom (years)				
Mean (SD)	8.36 (6.841)	8.18 (7.207)	8.20 (7.404)	8.19 (7.376)
Median (min, max)	6.41 (0.1, 38.7)	6.69 (0.2, 35.8)	5.70 (0.1, 34.5)	6.30 (0.2, 36.1)
Number of relapses in the last 12 months prior to screening, n (%)				
Mean (SD)	1.2 (0.63)	1.3 (0.69)	1.3 (0.74)	1.3 (0.73)
Median (min, max)	1.0 (0, 4)	1.0 (0, 5)	1.0 (0, 7)	1.0 (0, 6)
EDSS				
Mean (SD)	2.97 (1.357)	2.94 (1.355)	2.90 (1.343)	2.86 (1.374)
Median (min, max)	3.00 (0, 6.0)	3.00 (0, 6.5)	3.00 (0, 6.0)	2.50 (0, 6.0)
Number of Gd-enhancing T1 lesions				
n	454	452	469	470
Mean (SD)	1.7 (4.93)	1.2 (2.58)	1.6 (4.07)	1.5 (4.07)
Median (min, max)	0 (0, 47)	0 (0, 18)	0 (0, 58)	0 (0, 63)
Previously treated patients	274 (58.9)	280 (60.6)	286 (59.5)	293 (61.8)
Treatment-naive patients	191 (41.1)	182 (39.4)	195 (40.5)	181 (38.2)

OMB = ofatumumab; TER = teriflunomide; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; SD = standard deviation; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale.

Results

Annualised relapse rate

Both studies G2301 and G2302 met the primary endpoint with clinically relevant ARR reductions of 50.5% (Study G2301) and 58.5% (Study G2302), respectively (Table 6 and Table 7). Sensitivity and supportive analyses were consistent with the results of the primary analysis.

Table 6: Study G2301 Summary of annualised relapse rate

	OMB 20 mg N=465	TER 14 mg N=462
N: number of patients included in the analysis	454	452
Adjusted ARR	0.11	0.22
(95% CI)	(0.09, 0.14)	(0.18, 0.26)
Rate ratio	0.495	
(95% CI)	(0.374, 0.654)	
Percentage reduction	50.5%	
p-value	<0.001	

OMB = ofatumumab; TER = teriflunomide; ARR = annualised relapse rate; CI = confidence interval.

Table 7: Study G2302 Summary of annualised relapse rate

	OMB 20 mg N=481	TER 14 mg N=474
N: number of patients included in the analysis	469	469
Adjusted ARR	0.10	0.25
(95% CI)	(0.08, 0.13)	(0.21, 0.30)
Rate ratio	0.415	
(95% CI)	(0.308, 0.559)	
Percentage reduction	58.5%	
p-value	<0.001	

OMB = ofatumumab; TER = teriflunomide; ARR = annualised relapse rate; CI = confidence interval.

The endpoint was analysed in a negative binomial model.

Number of gadolinium enhancing T1 lesions

Ofatumumab reduced the number of GdE T1 lesions by 97.5% (Study G2301) and 93.8% (Study G2302), respectively (Table 8 and Table 9).

Table 8: Study G2301 Number of gadolinium enhancing T1 lesions per scan

	OMB 20 mg N=465	TER 14 mg N=462
N: number of patients included in the analysis	432	422
Adjusted mean number of Gd-enhancing lesions per scan	0.01	0.45
(95% CI)	(0.006, 0.022)	(0.356, 0.575)
Rate ratio	0.025	
(95% CI)	(0.013, 0.049)	
Rate reduction	97.5%	
p-value	<0.001	

OMB = ofatumumab; TER = teriflunomide; Gd = gadolinium; CI = confidence interval.

The endpoint was analysed in a negative binomial model.

Table 9: Study G2302 Number of gadolinium enhancing T1 lesions per scan

	OMB 20 mg N=481	TER 14 mg N=474
N: number of patients included in the analysis	439	434
Adjusted mean number of Gd-enhancing lesions per scan	0.03	0.51
(95% CI)	(0.021, 0.048)	(0.402, 0.658)
Rate ratio	0.062	
(95% CI)	(0.037, 0101)	
Rate reduction	93.8%	
p-value	<0.001	

OMB = ofatumumab; TER = teriflunomide; Gd = gadolinium; CI = confidence interval.

The endpoint was analysed in a negative binomial model.

*Annualised rate of new or enlarging T2 lesions**

The number of new or enlarging T2 lesions was reduced with a rate reduction of 82.0% (Study G2301) and 84.5% (Study G2302), respectively (Table 10 and Table 11).

*There was error communicated by the sponsor in the statistical programming of this endpoint analysis (Study G2301) on 24 November 2020. Apart from numerical change from 82.0% reduction to 81.9% reduction, there were no other clinically significant changes.

Table 10: Study G2301 Number of new or enlarging T2 lesions per year

	OMB 20 mg N = 465	TER 14 mg N = 462
N: number of patients included in the analysis	440	431
Adjusted annualized mean rate of new/Enlarging T2 lesions	0.72	4.00
(95% CI)	0.61, 0.85)	(3.47, 4.61)
Rate ratio	0.18	
(95% CI)	(0.15, 0.22)	
Rate reduction	81.9%	
p-value	<0.001	

OMB = ofatumumab; TER = teriflunomide; CI = confidence interval.

The endpoint was analysed in a negative binomial model.

Table 11: Study G2302 Number of new or enlarging T2 lesions per year

	OMB 20 mg N=481	TER 14 mg N=474
N: number of patients included in the analysis	448	443
Adjusted annualized mean rate of new/Enlarging T2 lesions	0.64	4.15
(95% CI)	(0.55, 0.75)	(3.64, 4.74)
Rate ratio	0.15	
(95% CI)	(0.13, 0.19)	
Rate reduction	84.5%	
p-value	<0.001	

OMB = ofatumumab; TER = teriflunomide; CI = confidence interval.

The endpoint was analysed in a negative binomial model.

Neurofilament light chain concentration

In both studies, serum NfL concentrations were reduced at Month 3 and in all subsequent assessments (Table 12 and Table 13). However, although interesting from a scientific point of view, the clinical and prognostic relevance of NfL measurements remains uncertain.

Table 12: Study G2301 Neurofilament light chain concentration at Month 3

	OMB 20 mg N=465	TER 14 mg N=462
Adjusted mean concentration at Month 3	8.80	9.41
(95% CI)	(8.48, 9.12)	(9.06, 9.77)
Ratio (95% CI)	0.93 (0.89, 0.98)	
p-value	0.011	

OMB = ofatumumab; TER = teriflunomide; CI = confidence interval.

This endpoint was analysed using repeated measures mixed effects model.

Table 13: Study G2302 Neurofilament light chain concentrations at Month 3

	OMB 20 mg N=481	TER 14 mg N=474
Adjusted mean concentration at Month 3	8.92	10.02
(95% CI)	(8.62, 9.23)	(9.68, 10.36)
Ratio (95% CI)	0.89 (0.85, 0.93)	
p-value	<0.001	

OMB = ofatumumab; TER = teriflunomide; CI = confidence interval.

This endpoint was analysed using repeated measures mixed effects model.

Percent change in brain volume from Baseline

In both studies, the annual rate of BVL was not statistically different between the ofatumumab and teriflunomide treatment groups based on the random coefficients model (Table 14 and Table 15).

Table 14: Study G2301 Percent change in brain volume from Baseline

	OMB 20 mg N=465	TER 14 mg N=462
N: number of patients included in the analysis	418	409
Annual rate of change from baseline	-0.28	-0.35
(95% CI)	(-0.34, -0.22)	(-0.41, -0.29)
Difference (95% CI)	0.07 (-0.02, 0.15)	
p-value	0.116	

OMB = ofatumumab; TER = teriflunomide; CI = confidence interval.

This endpoint was analysed using a random coefficients model.

Table 15: Study G2302 Percent change in brain volume from Baseline

	OMB 20 mg N=481	TER 14 mg N=462
N: number of patients included in the analysis	437	434
Annual rate of change from baseline	-0.29	-0.35
(95% CI)	(-0.35, -0.23)	(-0.42, -0.29)
Difference (95% CI)	0.07 (-0.02, 0.15)	
p-value	0.129	

OMB = ofatumumab; TER = teriflunomide; CI = confidence interval.

This endpoint was analysed using a random coefficients model.

Pooled Studies G2301 and G2302

As pre-specified, disability-related key secondary efficacy endpoints were analysed using the combined data of Studies G2301 and G2302.

Disability worsening (time to 3-month confirmed disability worsening)

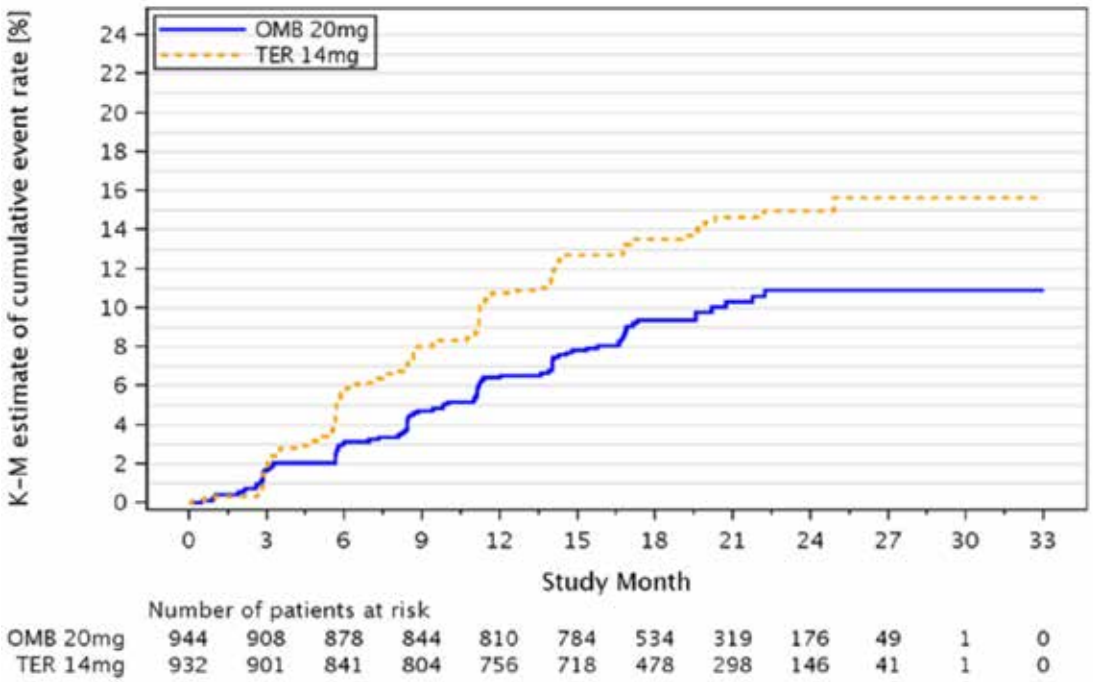
Ofatumumab significantly lowered the risk of 3mCDW by 34.4%, compared to teriflunomide (p = 0.002) in pooled Studies G2301 and G2302 (Table 16). There was a consistent trend in favour of ofatumumab in each individual study. Treatment with ofatumumab delayed the time to first 3mCDW as shown in the corresponding Kaplan-Meier curves (Figure 4). The pre-specified supportive and sensitivity analyses were generally consistent, including the worst case type of analysis in which ofatumumab patients who discontinued from the study due to lack of efficacy and/or died were considered as having 3mCDW (a risk reduction for ofatumumab versus teriflunomide of 32.9%, p = 0.004).

Table 16: Studies G2301 and G2302 Time to first 3-month confirmed disability worsening

Data source	KM estimate at Month 24 % (95% CI)	n/N (%)	Hazard ratio (95% CI)	Risk reduction	P-value
Combined data G2301 + G2302					
OMB 20mg	10.9 (8.8,13.4)	88/944 (9.3)	0.656 (0.499, 0.862)	34.4%	0.002
TER 14mg	15.0 (12.6,17.7)	125/931 (13.4)			
By study					
G2301					
OMB 20mg	19.5 (15.5,24.2)	76/465 (16.3)	0.652 (0.445, 0.957)	34.8%	0.029
TER 14mg	22.9 (18.7,27.8)	88/459 (19.2)			
G2302					
OMB 20mg	10.5 (7.8,14.1)	43/479 (9.0)	0.660 (0.447, 0.974)	34.0%	0.036
TER 14mg	14.6 (11.5,18.6)	62/472 (13.1)			

KM = Kaplan-Meier; CI = confidence interval; OMB = ofatumumab; TER = teriflunomide; CI = confidence interval.

Figure 4: Studies G2301 and G2302 Time to first 3-month confirmed disability worsening



Disability worsening (time to 6-month confirmed disability worsening)

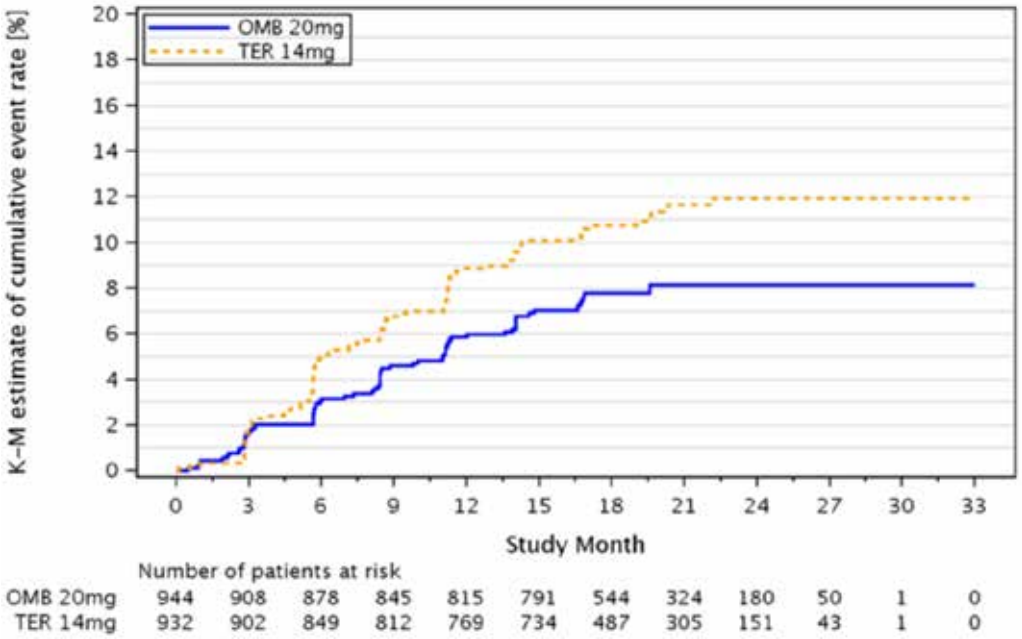
Ofatumumab significantly lowered the risk of 6mCDW by 32.5%, compared to teriflunomide (p = 0.012) in pooled Studies G2301 and G2302 (Table 17). Trends in favour of ofatumumab were observed in each individual study, and the risk reduction was numerically larger in Study G2301 than Study G2302. Treatment with ofatumumab delayed the time to first 6mCDW as shown in the corresponding Kaplan-Meier curves (Figure 5). The pre-specified supportive and sensitivity analyses were generally consistent, including the worst case type of analysis in which ofatumumab patients who discontinued from the study due to lack of efficacy and/or died were considered as having 6mCDW (a risk reduction for ofatumumab versus teriflunomide of 29.6%, p = 0.022)

Table 17: Studies G2301 and G2302 Time to first 6-month confirmed disability worsening

Data source	KM estimate at Month 24 % (95% CI)	n/N (%)	Hazard ratio (95% CI)	Risk reduction	P-value
Combined data G2301 + G2302					
OMB 20mg	8.1 (6.5,10.2)	71/944 (7.5)	0.675 (0.498, 0.916)	32.5%	0.012
TER 14mg	12.0 (9.9,14.5)	99/931 (10.6)			
By study					
G2301					
OMB 20mg	8.2 (6.0,11.3)	35/465 (7.5)	0.607 (0.396, 0.930)	39.3%	0.022
TER 14mg	13.0 (10.0,16.9)	53/459 (11.5)			
G2302					
OMB 20mg	8.0 (5.9,11.0)	36/479 (7.5)	0.756 (0.489, 1.170)	24.4%	0.209
TER 14mg	10.9 (8.2,14.4)	46/472 (9.7)			

KM = Kaplan-Meier; CI = confidence interval; OMB = ofatumumab; TER = teriflunomide; CI = confidence interval.

Figure 5: Studies G2301 and G2302 Time to first 6-month confirmed disability worsening



OMB = ofatumumab; TER = teriflunomide

Additionally, ofatumumab demonstrated a higher efficacy than teriflunomide and the treatment effect appeared consistent across the subgroups except for small subgroups of race.

Safety

Overall, 2499 patients with MS have been treated in blinded or open label studies in the ofatumumab MS clinical program. In Studies G2301, G2302, G2102, OMS112831 and OMS115102, 1497 patients had received at least one dose of ofatumumab, two patients had received only placebo and 936 patients had received an active comparator. The pivotal Phase III studies, Study G2301 and Study G2302 that form Pool C2, are the primary sources of safety data supporting the safety profile of ofatumumab in patients with MS. The total cumulative duration of exposure in the ofatumumab group (N = 946) was 1486.7 patient years with 832 patients (87.9%) exposed for ≥ one study year and 312 patients (33.0%) exposed for > two years. However, long term safety data beyond two years was missing.

Compared with the adverse event (AE) profile of the main patient population (Pool C2), no relevant differences were found in the supportive studies (Study OMS112831 (Pool C1), Study OMS115102 (Pool C0), and Study G2102).

The majority of the patients reported at least one AE and the frequency of AEs was similar between the ofatumumab and teriflunomide treatment groups. Most AEs were of Grade 1 or Grade 2 severity and the proportions of patients reporting Grade 3 or Grade 4 AEs were similar in both the ofatumumab group and the teriflunomide group. The most frequently reported AEs by System Organ Class (SOC) were injection related reactions and 'infections and infestations' in both ofatumumab and teriflunomide groups.

Injection related reaction, which includes both injection systemic and injection site related reactions, was the most frequently reported AE by Preferred Term (PT) in the ofatumumab group, with systemic reactions (ofatumumab versus teriflunomide/placebo: 20.2% versus 15.3%) followed by injection site reactions (10.9% versus 5.6%), both of which were predominantly reported with the first injection and the incidence reduced with subsequent injections in both treatment groups. Most of the injection systemic reactions were mild to moderate (99.8%) in severity. There were no life-threatening injection reactions in RMS clinical studies. Only one patient in the ofatumumab group discontinued study treatment because of injection systemic reactions. There were no study treatment interruptions for an injection reaction in the ofatumumab group. Any potential benefit of premedication intravenous steroid use should be weighed against its risks, especially in light of fact that majority of the injection reactions associated with ofatumumab administration were mild to moderate. Although, ofatumumab is proposed for self-administration, the proposed PI mentions that the first injection of ofatumumab should be administered by an appropriately trained healthcare professional. Use of nonsteroid premedication did not appear to reduce risk of injection reactions.

'Infections and infestations' was the most frequently reported SOC category in both the ofatumumab and teriflunomide groups, with numerically higher incidences in the teriflunomide group compared with the ofatumumab group. Most 'infection' AEs were mild to moderate and non-serious. The incidence of serious infection events was low and balanced between the two groups. The overall incidences of infection AEs and discontinuations due to infection AEs were comparable across the treatment groups. Upper respiratory tract infections and urinary tract infections, as retrieved by predefined search criteria, were the most frequently reported types of infections in patients treated with ofatumumab. No opportunistic infections were identified using broad search for potential opportunistic infection AEs. No cases of hepatitis B virus (HBV) reactivation or PML were reported with ofatumumab in the RMS studies.

Most AEs were not treatment limiting. The proportion of patients who discontinued from treatment with ofatumumab was low (5.7%) and similar to teriflunomide (5.2%). No deaths were reported with ofatumumab. The frequency of serious adverse events (SAEs) was low as compared to the frequency of all AEs and was similar in the ofatumumab and the teriflunomide groups. Infections were the most frequently reported SAEs.

Discontinuation in Kesimpta due to the PT: blood immunoglobulin M decreased is 2%. The incidence of treatment induced ADAs was low (0.2% in Pool C2 and 0.35% in Study G2102). No patients tested positive for neutralising antibodies to ofatumumab. There was no impact of positive ADA titres on PK, B-cell kinetics or safety in any of the patients.

Overall, the proportion of patients with 'malignant and premalignant disorders' related AEs was low in both the ofatumumab and teriflunomide groups. Review of data showed no increased incidence of malignancy with ofatumumab treatment relative to teriflunomide group. Thus, these data do not support any labelling recommendation; however, monitored as part of routine pharmacovigilance and reassessed periodically.

Suicidality ideation and behaviour related AE terms were low, confounded, and reported as not related by the investigator. Based on a review of the Columbia scale, no differences between treatment groups or discernible trends in post baseline changes were observed; the proportion of patients developing suicidal ideation or behaviour post baseline without prior history was low and similar in both groups. Review of the AE terms, Columbia scale, in conjunction with biology of anti-CD20 and background rates in MS patient population did not identify any signal or safety concern.

The patterns of AEs and adverse events of special interest (AESI) in the different subgroups of intrinsic factors (age, sex, race, treatment naive or previously treated) were broadly consistent with that observed for the overall population. There was no pattern of treatment differences between the sub-groups and the pattern was generally comparable to that observed in the overall population. There was no evidence that ofatumumab increased the risk of infections in the any of the sub-groups.

Safety of ofatumumab in MS was not evaluated beyond 30 months although results from ongoing studies could help provide long term safety data.

Ofatumumab was first developed and approved for the treatment of chronic lymphocytic leukaemia (CLL) refractory to prior therapies (that is alemtuzumab and fludarabine) under the trade name Arzerra.[20] In addition, it has been investigated in other oncology indications (follicular lymphoma, diffuse large B-cell lymphoma), chronic obstructive pulmonary disease (COPD), and autoimmune indications (rheumatoid arthritis (RA) and Pemphigus vulgaris (PV)). Due to the different doses and dosing regimens, route of administration, and treatment durations, the contribution of the safety data from studies in other indications to the overall safety evaluation of ofatumumab 20 mg in patients with RMS is very limited.

Risk management plan

The most recently evaluated RMP was an updated RMP for ofatumumab (Arzerra;[20]) and included EU-RMP version 15.0 (28 May 2019; data lock point (DLP) 25 October 2015) and Australian specific annex (ASA) version 8.0 (11 July 2019). In support of the extended indications, the sponsor submitted EU-RMP version 1.0 (17 December 2019; DLP 10 July 2019) and ASA version 1.0 (7 February 2020) for Kesimpta.

ASA version 1.1 (21 August 2020) and EU-RMP version 1.1 (30 July 2020; DLP 10 July 2019) were provided with the response to questions raised by TGA.

[20] Arzerra was first registered on the ARTG on 11 February 2013 (ARTG numbers: 196945)

The sponsor provided ASA version 1.2 (11 November 2020) and EU-RMP version 1.2 (2 November 2020; DLP 10 July 2019) with the response to the second round RMP evaluation report.

No further updated ASA or EU-RMP have been provided in response to the third round RMP evaluation report.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 18.[21]

Table 18: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Serious infections including opportunistic infections (for example, progressive multifocal leukoencephalopathy (PML), hepatitis B virus (HBV) reactivation)	ü[1]	ü[2,3]	ü	–
	Malignancy	ü	ü[2,3]	–	–
	Impaired Immunisation response, including vaccination of newborns after exposure in utero	ü	ü[4]	ü	–
Missing information	Safety in pregnancy and lactation	ü	ü[5]	ü	–

[21] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Use in paediatric population	ü	–	ü	–
	Long term safety of ofatumumab treatment	ü	ü [2,3]	–	–
	Use in patients > 55 years and Elderly population	ü	ü [2,3]	ü	–

1 Follow-up form for suspected PML and AE report form

2 Clinical study (the ALITHIOS trial)

3 Post-authorisation safety study (PASS) (planned study in MS patients)

4 Clinical study (Substudy COMB157G2399)

5 Pregnancy outcome intensive monitoring (PRIM)

The summary of safety concerns was considered acceptable from an RMP perspective in the first round RMP evaluation report. In the response to questions raised by TGA, missing information: Use in patients > 55 years and elderly population was added. The safety specification was acceptable from an RMP perspective. The safety specification has been updated at the third round to reword two of the safety concerns and continues to be acceptable from an RMP perspective.

The sponsor proposed routine and additional pharmacovigilance activities and this approach was considered acceptable in the first round RMP evaluation report. The sponsor updated the pharmacovigilance plan to include a follow-up form for suspected PML, change pregnancy outcome intensive monitoring (PRIM) to an additional pharmacovigilance activity and add a new planned post-authorisation safety study (PASS). The sponsor was requested to amend the follow-up form as recommended below. At the third round, the sponsor has provided an AE follow-up form that is to be provided together with the follow-up form for PML and this form contain the recommended fields. The pharmacovigilance plan is considered acceptable.

The sponsor proposed routine risk minimisation activities only for this submission, which includes an Instructions for Use. This approach was acceptable; however, the sponsor was requested to amend the Consumer Medicines Information (CMI) as recommended. Most of the changes recommended were made but further updates were recommended. At the third round, the sponsor made the recommended changes to the draft CMI but further amendment were requested. At the fourth round, the sponsor has amended the CMI to align with the PI as requested and this is acceptable. The risk minimisation plan is acceptable.

Risk-benefit analysis

Delegate's considerations

Ofatumumab (OMB157) is a human Type I immunoglobulin G1 kappa (IgG1κ) mAb, which specifically targets a unique composite epitope on the CD20 molecule expressed on B-cells. Ocrelizumab was the first mAb targeting B-cells approved for the treatment of relapsing (and primary progressive) forms of MS. Ocrelizumab is dosed via the intravenous route.

Overall PK of ofatumumab is well characterised in the clinical program without posing any substantial issues and the proposed dosing regimen: 20 mg weekly loading dose for three weeks followed by 20 mg every four weeks maintenance dose is acceptable.

Bioequivalence was demonstrated between the PFS assembled with a needle safety device (NSD) used in the Phase III studies and AI device for commercial use. Even though AUC and C_{max} were not compared between injection site, the depletion of B-cells irrespective of injection site supports that ofatumumab can be administered in the upper arm as well in the thigh and abdomen. subcutaneous administration also allows ofatumumab to access lymph nodes directly, which leads to a lower dose requirement to achieve clinical efficacy, with a corresponding better tolerability and an expected lower clinical risk (that is, fewer adverse drug reactions) when compared to an intravenous route of administration.

The study design, endpoints and patients evaluated in the pivotal studies complied with TGA adopted guideline;[22] although the study duration of 2.5 years was slightly less than the three years recommended in the guidelines.

The patients evaluated in the pivotal study were representative of the target patient population with RMS (RRMS or SPMS with disease activity as defined by with EDSS scores of 0 to 5.5, mean of one relapse in past 12 months or one or more GdE lesions on MRI). However, specific disease activity criteria defined a population with active inflammatory disease based on recent relapse in the one or two years before enrolment in the year prior to randomization. The clinical evaluator suggested it to incorporate into the wording of proposed indication but was satisfied with the current proposed indication after the response from the sponsor to questions raised by the TGA.

Ofatumumab was superior to teriflunomide in lowering ARR, delaying disability worsening, reducing brain lesion formation, and reducing NfL levels across the range of demographic characteristics, disability status, and prior disease history. However, although interesting from a scientific point of view, the clinical and prognostic relevance of NfL measurements remains uncertain. Ofatumumab demonstrated a higher efficacy than teriflunomide and the treatment effect appeared consistent across the subgroups except for small subgroups of race. No studies in patients > 55 years were conducted.

The safety data in Phase III studies and amount of exposure to ofatumumab 20 mg subcutaneous dose is considered adequate for characterisation of the short term safety of ofatumumab 20 mg subcutaneously in RMS patients. Long term safety data have been collected in accordance with requirements of TGA adopted guidance.[23] In main safety set, 832 patients were exposed to ofatumumab 20 mg subcutaneously over 48 weeks, 312 patients were exposed over 96 weeks and the number of patients exposed for more than one year were sufficient.

The most common AEs associated with ofatumumab were injection reactions and infections and majority were mild to moderate severity. Injection reactions were

[22] EMA, CHMP, 26 March 2015. Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis, EMA/CHMP/771815/2011, Rev. 2.
[23] EMA, CPMP, 1 June 1995. ICH Topic E1: Population Exposure: The Extent of Population Exposure to Assess Clinical Safety, CPMP/ICH/375/95.

predominantly reported with the first injection and the incidence reduced with subsequent injections in both treatment groups. Upper respiratory tract infections and urinary tract infections were the most frequently reported types of infections in patients treated with ofatumumab. No opportunistic infections were identified using broad search for potential opportunistic infection AEs. No cases of HBV reactivation or PML were reported with ofatumumab in the RMS studies. Most AEs were not treatment limiting. The proportion of patients who discontinued from treatment with ofatumumab and the frequency of SAEs was low and similar to teriflunomide. No deaths were reported with ofatumumab.

A limitation of the submitted data was lack of evidence for efficacy and safety of ofatumumab in relapsing MS beyond 30 months. However, the ongoing long-term extension Study G2399 could help address this. There is also no comparison of efficacy of ofatumumab with other parenteral treatments approved for RMS.

Overall, the benefit risk balance of ofatumumab in the proposed indication is favourable.

Deficiencies of the data

- Patient aged > 55
- Paediatric patient population.
- Pregnancy
- Long term safety beyond 30 months

Proposed action

Overall, ofatumumab is approvable as the quality, nonclinical and clinical evaluators (subjected to product information changes) have all recommended approval. The Delegate considers that sufficient data and justification have been provided to support the registration of ofatumumab on quality, safety and efficacy grounds for the treatment of adult patients with RMS.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***The US FDA label does not refer anything on NfL data. Please provide the rationale.***

NfL data was part of the supplemental Biologics License Application (sBLA) submission, as a key secondary objective, with an outcome consistent with other clinical measures, demonstrating superiority of ofatumumab compared with teriflunomide in the reduction of NfL levels.

In discussion on the US sBLA submission, the sponsor was informed that the FDA considered it premature to include NfL data in the label given uncertainty of utility to a typical US prescriber. During the United States Prescribing Information (USPI) negotiations, NfL data was removed from the label on request of FDA.

However, the sponsor is not seeking to include this information in the Australian PI to be used by prescribers in clinical decision making. The sponsor accepts that a NfL measurement would be insufficient for informing treatment decisions and prognosis and the sponsor does not propose any instructions or guidance for prescribers on the possible clinical utility of NfL data. Given that MS is an unpredictable disease and varies so much from one patient to the next, the sponsor believed it is important to raise awareness amongst prescribers of the emerging evidence in a promising new technology. A suitable

qualifying statement alongside the proposed NfL data in the PI to ensure prescribers remain fully aware of this can also be proposed.

Based on the accumulating evidence for NfL as biomarker that correlates with treatment response and is prognostic of future disease activity, as well as the NfL results in the ASCLEPIOS Phase III studies, the sponsor nevertheless considers the NfL data as valuable additional information for the treating physician and that it should therefore be included under Section 5.1 of the PI.

Advisory Committee considerations[24]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***What are ACM's view's on the patient population studied, dose and indication sought by the sponsor for ofatumumab?***

The ACM agreed that the patient population studied in the trials was acceptable. In addition, the dose and indication presented to the ACM were suitable. They noted that the inclusion of *'to delay the progression of physical disability and reduce the frequency of relapse*' within the indication was consistent with other recent MS drug approvals.

2. ***Does the ACM consider that the safety of ofatumumab in the proposed indication is sufficiently well characterised and communicated in the PI?***

The ACM considered the safety information provided in the PI to be limited. The ACM advised that more comprehensive safety information would be of benefit within the PI including the adverse event rates of the placebo and the comparator product.

3. ***Does the ACM think NfL and brain volume change data in Section 5.1 provide clinically meaningful information and should be included in the PI?***

The ACM advised that both NfL and brain volume change data are useful secondary markers. However, the ACM noted that the sponsor did not provide pre-treatment levels of NfL in the studies. The ACM also noted that while changes in NfL is a good measure of disease activity, it is not widely used in clinical settings.

4. ***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 ACM recommended the wording of the dose instructions in the indication and PI to be changed to 'subsequent 4-weekly dosing' instead of 'subsequent monthly dosing'. The ACM also recommended that a visual guide for injection is provided in the CMI for the consumer.

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

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) to delay the progression of physical disability and reduce the frequency of relapse (refer to Section 5.1).*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Kesimpta (ofatumumab) 20 mg/0.4mL, solution for injection, pre-filled pen and PFS, for the following extension of indications:

> *Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) to delay the progression of physical disability and reduce the frequency of relapse (refer to Section 5.1).*

As such, the full indications at this time were:

> *Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) to delay the progression of physical disability and reduce the frequency of relapse (refer to Section 5.1).*

Specific conditions of registration applying to these goods

- Kesimpta (ofatumumab) is to be included in the Black Triangle Scheme. The PI and CMI for Kesimpta must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.
- The Kesimpta EU-RMP (version 1.2, dated 2 November 2020, DLP 10 July 2019), with ASA (version 1.2, dated 11 November 2020), included with submission PM-2020-00666-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of RMPs is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the EMA's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-PSUR (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar day of the DLP for that report.

- Laboratory testing and compliance with Certified Product Details

  All batches of

  – Kesimpta ofatumumab 20 mg/0.4 mL solution for injection in a PFS

  – Kesimpta ofatumumab 20 mg/0.4 mL solution for injection in a pre-filled pen

  supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the product. Outcomes of laboratory testing are published biannually in the TGA database of laboratory testing results http://www.tga.gov.au/wslabs-index and periodically in testing reports on the TGA website.

  Certified Product Details

  The CPD, as described in Guidance 7: Certified product details of the Australian regulatory guidelines for prescription medicines (ARGPM) (http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Kesimpta 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>.

Therapeutic Goods Administration

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