28 January 2021
EMA/160608/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kesimpta

International non-proprietary name: ofatumumab

Procedure No. EMEA/H/C/005410/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

3mCDW	3-month confirmed disability worsening
6mCDI	6-month confirmed disability improvement
6mCDW	6-month confirmed disability worsening
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ARR	Annualized relapse rate
AUC_{tau}	Area under the curve to the end of the dosing period
BVL	Brain Volume Loss
CDC	Complement-dependent cytotoxicity
CHMP	Committee for Medicinal Products for Human Use
CIS	Clinically isolated syndrome
CL	Clearance
C_{max}	Maximum concentration
CNS	Central nervous system
DMT	Disease-modifying treatment
EC_{50}	Concentration of a drug that gives half-maximal response
EDSS	Expanded disability status scale
EOS	End-of-study
FAS	Full analysis set
Gd	Gadolinium
HBV	Hepatitis B virus
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRR	Injection-related reaction
IV	Intravenous/Intravenously
k_{off}	Dissociation rate
LLN	Lower limit of normal
LLQ	Lower limit of quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NfL	Neurofilament light chain
NOAEL	No observed adverse effect level
PASS	Post Authorisation Safety Studies
PD	Pharmacodynamic
PFS	Pre-filled syringe
PFP	Pre-filled pen
PK	Pharmacokinetic

PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
Q4W	Every four weeks
Q12W	Every twelve weeks
RA	Rheumatoid arthritis
RMP	Risk Management Plan
RMS	Relapsing (forms of) multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SAE	Serious adverse event
SAF	Safety set
SC	Subcutaneous/Subcutaneously
SmPC	Summary of Product Characteristics
SOC	System organ class
SPMS	Secondary progressive multiple sclerosis
TEAEs	Treatment-Emergent Adverse Events

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Novartis Ireland Limited submitted on 9 January 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Kesimpta, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on Applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0122/2019 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the P/0122/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The Applicant indicated the active substance ofatumumab contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The Applicant received Scientific Advice on the development of ofatumumab, an IgG1k human monoclonal antibody, for treatment of relapsing multiple sclerosis from the CHMP on 1 April 2016 (EMEA/H/SA/1049/6/FU/1/2016/II).

- The Scientific Advice pertained to the following clinical aspects: the phase III program and the statistical testing procedure (including pooling of key secondary endpoint disability data) are adequate to provide the data in support of the registration of ofatumumab in RMS

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kirstine Moll Harboe Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	9 January 2020
The procedure started on	30 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	16 April 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 April 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 May 2020
The CHMP agreed on the consolidated List of Questions to be sent to the Applicant during the meeting on	28 May 2020
The Applicant submitted the responses to the CHMP consolidated List of Questions on	17 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	21 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 October 2020
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the Applicant on	15 October 2020
The Applicant submitted the responses to the CHMP List of Outstanding Issues on	11 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	25 November 2020
The outstanding issues were addressed by the Applicant during an oral explanation before the CHMP during the meeting on	09 December 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kesimpta on	28 January 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system (CNS) characterised by inflammation, demyelination, and axonal/neuronal destruction, ultimately leading to severe disability. MS is the most common autoimmune demyelinating disorder of the CNS, affecting approximately 2.3 million individuals worldwide. MS typically affects young adults (mean age at onset 30 years), and women are affected more often than men.

Reflecting the current understanding of MS, the disease course of MS can be grouped into 2 corresponding main MS categories:

- relapsing MS: clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), active secondary progressive multiple sclerosis (SPMS).
- progressive MS: secondary progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (PPMS).

At the time of their first MS diagnosis, 80% to 85% of adult patients present with RRMS, characterised by recurrent acute exacerbations (relapses) of neurological dysfunction followed by a variable state of complete or incomplete recovery. Most patients with RRMS may progress to SPMS, which is a stage of the disease characterized by continuous worsening of disability with or without superimposed relapses. Up to 15% of patients clinically present with a disease course referred to as PPMS, which is characterised by accumulation of disability since the beginning of the disease.

The **indication** for Kesimpta (ofatumumab) is:

Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see section 5.1).

The recommended dosing regimen is administered by subcutaneous (SC) injection with initial dosing at weeks 0, 1 and 2, followed by subsequent monthly dosing, starting at week 4.

Despite the availability of several disease modifying therapies (DMT) 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.

2.1.2. Epidemiology

MS is the most common autoimmune demyelinating disorder of the CNS, affecting approximately 2.3 million individuals worldwide.
Globally, the estimated median annual incidence MS in 2013 was 4.0 per 100000 (ranging from 1.5 to 7.5 per 100,000 [interquartile range]) according to estimates from the Multiple Sclerosis International Federation (MSIF, 2013). On a regional level, Europe had the highest estimated median annual incidence in 2013 (5.5 per 100,000), followed by Asia (3.0 per 100,000), Africa (1.0 per 100,000), and the Americas (0.6 per 100,000). Countries reporting the highest estimated median annual incidence of MS included Canada (13.4 per 100,000),

Latvia (11.6 per 100,000), and Czech Republic (11.0 per 100,000). Its prevalence rate varies between regions, ranging from more than 100 per 100,000 in Northern and Central Europe to 50 per 100,000 in Southern Europe.

MS typically affects young adults (mean age at onset 30 years), and women are affected more often than men (median estimated female/male ratio is 2.1). Regionally, the average age of onset is 29.2 years in Europe. The age-standardized (standardized to 2013 European population) prevalence per 100,000 by different ethnicities was 180, 74 and 29 for the White, Black and South Asian populations, respectively.

Globally, there were 18,932 deaths (95% CI 16,577 to 21,033) attributed to MS in 2016. The global age standardized death rates decreased significantly from 1990 to 2016 (change -11.5% (95%CI -35.4% to -4.7%) (GBD 2016 Multiple Sclerosis Collaborators). In 2016, the pooled crude mortality rate was 9.78 per 1000 person-years (95% CI 6.81-14.02). Pooled all-cause standardized mortality rate (SMR) per 1000 person-years was 2.80 (95% CI 2.74-2.87), 2.56 (95% CI 2.47-2.66) in males and 3.06 (95% CI 2.97-3.17) in females. The overall mortality rates in population based French and US MS cohorts were 3.7 and 8.9 per 1000 person-years, respectively. In an administrative database from Manitoba province in Canada, the relative risk (RR) of death in the MS population was 3 times higher at age 39 years and younger (RR 3.65; 95% CI: 3.48–3.83) and ages 40 to 59 years (RR 2.88; 95% CI: 2.81–2.95) and 2 times higher at age 80 and older (RR 1.80; 95% CI: 1.79–1.80). The majority of studies report that 60 to 70% of deaths occurring in MS patients are attributable to the disease itself or its complications.

2.1.3. Aetiology and pathogenesis

The aetiology of MS remains unknown. Generally, it is assumed that MS is mediated by some kind of autoimmune process that is triggered by an infection which, superimposed on a genetic predisposition.

The immune-mediated damage in MS involves both T-cells and B-cells, which play important roles in the pathogenesis of MS. Specifically, it has been shown that B-cells are factors contributing to the immune-mediated histopathology in MS. B-cells are present in the chronic plaques, areas of demyelination, and in the cerebrospinal fluid of MS patients. As B-cells have essential functions in regulating the immune response, they may contribute to disease pathogenesis by

- (Self-)antigen presentation, serving as cellular adjuvants for CD4+ T-cell activation
- Regulating T-cell function and inflammation via cytokine production, i.e. instructing encephalitogenic T-cells
- Producing autoantibodies

While very few B-cells infiltrate the healthy CNS, their number 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. Consequently, the depletion of B-cells in lymphatic tissues is an efficacious treatment approach in MS. Further, anti-CD20 monoclonal antibodies that permit SC administration may offer a more efficient targeting of B-cells residing in the lymphatic circulatory system. The depletion of brain parenchymal and meningeal B-cells may be an additional factor for the mode of action.

2.1.4. Clinical presentation, diagnosis

MS is an acquired idiopathic, inflammatory demyelinating disorder of the CNS in which the myelin sheath is disrupted due to genetic and environmental factors. There are no markers specific for MS diagnosis. Diagnosis mainly depends on the medical history and neurological examination. The attacks are defined as new neurological deficits lasting more than 24 hours, that can be associated with an anatomical localization, in the absence of fever or any infection. Usually the neurological deficit develops subacutely over 2 to 4 weeks, and it usually resolves completely or partially over 6 to 8 weeks, either spontaneously, or after treatment with corticosteroids. Different clinical and pathological subtypes of MS have been identified. In about 80–85% of the patients there are attacks (relapses), and complete or partial remissions following them, whereas in 10–15%, there is a slow progressive course without any relapses. Inflammatory demyelinating magnetic resonance imaging (MRI) findings suggestive of MS in patients who has never experienced a relapse, but had an MRI for other reasons, named as radiological isolated syndrome. Since there are no clinical signs or symptoms associated with MS, this group is not included to the subtypes of MS. On the other hand, patients presenting with isolated optic neuritis, spinal cord involvement, or brainstem syndrome, and/or hemispheric involvement, with findings resembling MS plaques on MRI, are called to have CIS which is considered the first attack of MS. Lublin et al. grouped the clinical patterns in 1996 as RRMS, relapsing progressive MS, SPMS, and PPMS. Moreover, in 2013, active and non-active forms were added:

1. CIS
2. RRMS: Active and non-active RRMS
3. Progressive MS: Active progressive, active non-progressive, non-active progressive, non-active non-progressive (stable) subtypes were described.

Within ten years more than 50% of patients who suffer from a relapsing-remitting form eventually develop sustained disability with or without superimposed relapses; this form is called the SPMS. The term "relapsing MS (RMS)" applies to those affected patients either with a RRMS or SPMS with superimposed relapses. Patients with relapsing MS, in spite of suffering from different MS forms, constitute a common target for current treatment options. There are no clear criteria that mark the transition from RRMS to SPMS.

The diagnostic criteria MS, first developed in the 1950s, have since undergone several revisions, all focused on three main requirements for a diagnosis of MS: 1) Objective clinical evidence of CNS involvement. 2) Evidence of lesions disseminated in time and space. 3) Exclusion of other conditions that could better explain the clinical and paraclinical findings. Before the widespread use of MR imaging, the criteria for dissemination in time and space were fulfilled by two attacks involving different parts of the CNS and clinical evidence of two lesions separated in time, or one attack with additional paraclinical evidence of another lesion. In 2001, McDonald et al fully integrated the use of MRI into the diagnostic schema as an alternative to clinical evidence for dissemination in time and space, allowing an earlier diagnosis of MS. The McDonald criteria were revised in 2005, 2010 and 2017, building on new evidence for the role of MRI.

2.1.5. Management

The current therapeutic approach involves symptomatic treatment, treatment of acute relapses, and DMT. Symptomatic treatment refers to all therapies applied to improve symptoms and complications caused by the disease. More specific treatments are those that intend to interfere with the pathophysiology of MS e.g. facilitate remyelination or axonal conductivity. The standard of care for acute relapses is methylprednisolone intravenous (IV) Methylprednisolone shortens the duration of a relapse but has no influence on its sequelae.

DMT aim to modify the course of the disease mainly by suppressing or modulating the immune responses involved in MS pathogenesis. Biologicals (therapeutic proteins, monoclonal antibodies) and small molecules have been approved for use in this therapeutic context. These therapies aim to prevent relapses and ultimately intend to decrease the rate of accumulation of disability. 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 i.e. treatment is restricted to patients with rapidly evolving MS or those who had a suboptimal response to prior therapies.

It is often recommended that patients should be able to take a DMT as early as they are diagnosed. Two conceptually different treatment approaches have emerged:

- The 'escalation approach' advocates the first line use of moderately effective DMTs (i.e. classical first-line therapies, e.g. interferons and glatiramer acetate) and a later escalation to high-efficacy therapies only if new disease activity breaks through, i.e. relapses or new lesions as shown by MRI.

- The 'highly effective treatment early approach' advocates initiation of high efficacy therapies early on (as first line therapy). Treatment-related risks are weighed against the expected occurrence of brain damage caused by the disease.

Several DMTs/DMT classes are currently available and approved for use in RMS, which vary in their mechanism of action, efficacy, safety, mode of administration and ease of use. Treatments included in these DMT classes, listed in alphabetical order, are: Alemtuzumab; Beta-interferons; Cladribine; Dimethyl fumarate; Fingolimod; Glatiramer acetate; Mitoxantrone; Natalizumab; Ocrelizumab; Ozanimod; Siponimod; Teriflunomide.

Monoclonal antibodies (mAbs) directed against proteins expressed by B-cells, e.g. anti-CD20 antibodies, such as ocrelizumab and rituximab, are high-efficacy therapies offering the same high efficacy as other highly efficacious DMTs, including (but not limited to) mAbs like natalizumab and alemtuzumab, but at the same time show a better safety profile.

Ocrelizumab was the first mAb targeting B-cells approved for the treatment of relapsing (and PP) forms of MS. Ocrelizumab is dosed via the IV route.

About the product

Kesimpta (ofatumumab) is a recombinant fully human type 1 immunoglobulin G1 (IgG1) mAb, which specifically targets a unique composite epitope on the CD20 molecule expressed on B-cells. The binding of ofatumumab to CD20 induces B-cell lysis primarily through complement-dependent cytotoxicity (CDC) and, to a lesser extent, by antibody-dependent cell-mediated cytotoxicity (ADCC). Direct triggering of B-cell death / apoptosis as a third mode of action is less relevant for ofatumumab.

Ofatumumab mode of action

Ofatumumab specifically recognizes a unique conformational epitope encompassing both the large and small extracellular loops on the human CD20 molecule, which allows ofatumumab binding very close to the plasma membrane. This composite epitope is separate from the epitopes on the large loop of CD20 that other anti-CD20 mAbs bind (e.g. rituximab and ocrelizumab).

CD20 is expressed on late pre-B-cells, mature B-cells, and memory B-cells, while not expressed on lymphoid stem or plasma cells. The binding of ofatumumab to CD20 induces B-cell lysis primarily through CDC and, to a

lesser extent, by ADCC. Direct triggering of B-cell death / apoptosis as a third mode of action is less relevant for ofatumumab. 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.

The mode of action of ofatumumab is similar to rituximab and ocrelizumab. No relevant difference in ADCC activity of ofatumumab compared to ocrelizumab was observed, while it was higher than rituximab. In contrast, CDC-dependent B-cell lysis induced by ofatumumab was more active than rituximab and ocrelizumab. CDC occurs when the complement factor C1q binds to the complement binding region of the Fc part of the anti-CD20 antibody and triggers a cascade of events that results in the formation of the membrane attack complex, a pore in the plasma membrane that contains the downstream complement factors C5 to C9. These pores enable the inflow of water into the cell, finally resulting in cell lysis. 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. In addition, B-cell binding studies showed a lower off-rate (i.e. dissociation rate of the antibody from the CD20 receptor) for ofatumumab in comparison to rituximab, which is of functional importance.

In conclusion, nonclinical data indicate that ofatumumab might have higher potency in CDC induction in primary human B-cells when compared with ocrelizumab and rituximab.

Route of administration

It has been shown that biopharmaceuticals with a high molecular weight, such as mAbs, exhibit limited transport into the blood capillaries when administered SC and enter the systemic circulation via an indirect route through the lymphatics. In a human CD20 transgenic mouse model, SC administration of ofatumumab resulted in more direct access to lymph nodes as compared to IV administration of the drug. In addition, the SC administration of an anti-CD20 antibody (in contrast to its IV administration) significantly decreased T-cell infiltration in the brain in a chronic MS mouse model. In summary, these results suggest that the SC administration could be more effective than the IV administration of anti-CD20 antibodies. However, ocrelizumab and rituximab are both administered IV.

The direct access to lymphatic system, a primary location of MS pathology and a target for MS therapies, may contribute to the lower dose selection for ofatumumab to achieve clinical efficacy, with a corresponding better tolerability avoiding some infusion/injection related events observed with higher doses of ofatumumab.

In addition, SC administration of therapeutic proteins, compared to IV administration, might offer more flexibility and convenience for patients depending on lifestyle preferences.

In summary, both the CD20-binding epitope of ofatumumab and its SC route of administration lead to a low required dose, which allows SC administration in a small volume (20 mg in 0.4 ml).

2.2. Quality aspects

2.2.1. Introduction

Ofatumumab, the active substance in Kesimpta, is a fully human anti-CD20 IgG1k monoclonal antibody expressed in a recombinant murine NS0 cell line.

Kesimpta is presented in a solution for SC injection in a single-use pre-filled syringe (PFS) or single-use pre-filled pen (PFP) (Sensoready). Each PFS or PFP contains 20 mg ofatumumab in 0.4 mL solution.

Kesimpta is formulated with L-arginine, sodium acetate trihydrate, sodium chloride, polysorbate 80, disodium edetate dihydrate, hydrochloride acid, and water for injections (WFI).

Kesimpta is available in unit packs containing 1 PFS or 1 PFP and in multipacks containing 3 (3 packs of 1) PFSs or PFPs.

2.2.2. Active Substance

General information

Ofatumumab is a fully human anti-CD20 monoclonal antibody that belongs to the IgG1k isotype subclass, with a standard antibody molecule composition of two heavy and two light chains. Both heavy chains contain oligosaccharide chains linked to the protein backbone at Asn302. The theoretical molecular mass is 146 kDa, calculated from the amino acid composition deduced from the DNA sequence. Ofatumumab recognises an epitope on two extracellular loops of the human CD20 molecule expressed on B cells. CD20 is involved in B cell activation, regulation of B cell growth, and transmembrane flux. Binding of Ofatumumab to CD20 induces B-cell lysis. The B cell depleting activity of Ofatumumab is thought to be primarily mediated by CDC and, to a lesser extent, by ADCC.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

Manufacture and testing of the active substance are performed at Lonza Biologics Inc., 101 International Drive, Portsmouth, NH 03801, United States, except for potency testing, which is performed at Novartis Pharma AG, Basel, Switzerland. Cell banks are stored at two locations. EU GMP compliance was confirmed for all sites.

The manufacturing process is standard for a monoclonal antibody. It consists of a fed-batch upstream cell culture process and a downstream purification process.

The cell culture process involves the propagation of recombinant NS0 cells expressing the ofatumumab protein from a working cell bank (WCB) vial through inoculation of bioreactors of gradually increasing size up to the final fed-batch production bioreactor.

The harvest procedure involves clarification by centrifugation followed by filtration. The clarified supernatant is processed for further clarification and bioburden reduction by continuous filtration.

The downstream purification process consists of several chromatographic steps, ultrafitration, diafiltration, virus inactivation and filtration, followed by filling and freezing steps.

In-process controls (IPCs) and main process parameters have been defined, including their corresponding acceptance limits/acceptable ranges. Hold times are applied for the cell culture process and for the purification process. Critical process parameters (CPPs) have been defined.

In the ofatumumab process, reprocessing is supported.

Control of materials

Raw materials.

The only raw materials of biological or recombinant origin used for the manufacture of the active substance are foetal bovine serum (FBS), used for cryopreservation of the master cell bank (MCB), and recombinant Protein A, used for the affinity chromatography step of the purification process. The FBS is accompanied by a Ph. Eur. CEP for TSE safety. The Protein A is expressed in *E. coli*, fermented in an animal-material free medium.

All components of cell culture media, supplements and feeds are described. All raw materials of non-compendial quality are tested according to in-house specifications, which are provided.

Source, history, and generation of the cell substrate

The parental NS0 cell line was sourced from ECACC (European Collection of Authenticated Cell Cultures) and used to develop the expressing cell line. A parental WCB derived from a parental MCB was used for transfection of the expression vector.

The production cell banks, post-production cell banks (PPCBs) and bulk harvests derived from the parental cell bank have been comprehensively tested for the absence of adventitious and endogenous agents, using both *in vivo* and *in vitro* assays. No adventitious agents were detected, with the exception of A- and C-type endogenous retrovirus-like particles (RVLP). The presence of RVLP in many rodent cell lines is well known and of no concern. No infectious retroviruses were detected in the parental cell banks.

The variable sequences of the heavy chain (VH) and light chain (VL) for ofatumumab were amplified from subcloned hybridoma cells expressing human anti-CD20 IgG. The hybridoma clones were generated by immunisation of a human immunoglobulin transgenic mouse strain with CD20 antigen from transfected NS0 cells, followed by fusion of isolated the splenocytes with a myeloma cell line. The variable gene regions were assembled with the constant heavy and light chain regions into a double-gene expression vector. The DNA sequence of the variable regions was verified by sequencing in both forward and reverse orientation.

The expression vector was used for transfection of cells from the NS0 cell line. Lead clones were selected based on productivity and growth. The final lead cell line was subjected to capillary aided single cell cloning and following adaptation of the clones to chemically defined animal component free medium, a clone was selected as lead cell line.

Cell banking system, characterisation and testing

A MCB and WCBs derived from it have been generated. The MCB can be used to generate additional WCBs, as needed. PPCBs have been generated as well, one was used for determination of limit of *in vitro* cell age (LIVCA).

The cell banks have been tested according to ICH Q5A, Q5B, and Q5E guidelines, including analysis for species identity, adventitious and endogenous agents, cell line homogeneity through determination of productivity, growth characteristics, and product quality, and genetic characterisation at both DNA and mRNA level. The characterisation of the cell banks is in line with current guidelines and considered adequate.

Control of critical steps and intermediates

IPCs have been defined for each step of the manufacturing process. Their corresponding action limits or acceptance criteria are considered appropriate. Critical steps are identified in the manufacturing process.

Process validation

Cell culture process

Commercial scale batches have been included in the process validation studies for the cell culture process. During process validation defined process parameters and IPCs were monitored. Overall, the approach taken for validation of the cell culture process is considered acceptable and in line with current guidelines. The acceptable ranges and control limits were met for all validation runs. All batches met the acceptance criteria for absence of adventitious agents of both viral and non-viral nature (testing performed at pre-harvest). Control limits for ongoing process verification have been established. After purification, all batches met the active substance specifications valid at the time of testing. Overall, the approach taken for validation of the cell culture process is considered acceptable and in line with current guidelines.

Purification process

Commercial scale batches have been included in the process validation studies for the purification process. All batches were also used for validation of the cell culture process. During process validation, defined process parameters and IPCs were monitored. The protein purification process has been validated for consistent manufacturing performance, removal of product- and process related impurities, and sanitary processing. The acceptable ranges and control limits were met for all three validation runs, including in-process acceptance criteria established for microbial control. Yields were observed to be consistent from batch to batch. Product quality was determined in terms of purity, percentage of monomers vs aggregates, and charged variants for the complete purification process. All results complied with the specification valid at the time of testing and indicated consistency of the product quality throughout the purification process.

Efficient and consistent removal of process-related impurities, to levels which are generally below LOQ, have been demonstrated.

Overall, the approach taken for validation of the protein purification process is considered acceptable and in line with current guidelines.

Additional process validation studies

In addition, the following process validation studies were performed:

Re-use of chromatographic resin and ultrafiltration membranes. Resin and membrane lifetimes were determined from concurrent process validation at commercial scale, supported by small scale studies.

Storage conditions were validated and demonstrated to be efficacious in terms of microbial control.

All hold times were validated for potential impact on the biochemical quality and microbial control (bioburden and endotoxin) of the active substance.

Validation of reprocessing at individual steps demonstrate that the claimed reprocessing at these steps does not have any detectable impact on the product quality.

All consumables and equipment used, which could potentially leach chemical substances into the active substance were subjected to a risk assessment for leachables and extractables. Furthermore, the primary active substance packaging material was evaluated for extractables. The results obtained demonstrate that the single-use items and the primary packaging material are safe for their intended use, with respect to leachables.

Manufacturing process development

Process development

During development four different processes have been applied for the manufacture of the active substance, Process A, B, C, and D (commercial process). Only Process C and D material has been used for clinical trials for the indication proposed for this marketing authorisation application, while Process A and B were used for the previous oncological indication only (Arzerra (EMA/H/C/00131, marketing authorisation withdrawn). The changes introduced between Process C and Process D involved a site transfer, a process scale up, introduction of a WCB, introduction of stirred tank bioreactors for expansion of inoculum for the production bioreactor, removal of a step, and a change of the formulation buffer. Post-process validation changes of Process D involved additional sampling points for bioburden and endotoxin, and process optimisations.

Comparability studies

Comparability studies have been performed, involving comparison of release data and extended characterisation. Overall, the results provided support comparability of process C and D material.

Process evaluation.

Prior to the start of the process evaluation studies for Process D, a process risk assessment (based on a gap analysis methodology) was used to assess the process- and product-related risks of the active substance manufacturing process and to identify the process parameters which should be further investigated by process evaluation studies, based on their assessed potential impact on the critical quality attributes (CQA). The approach taken for process evaluation is considered appropriate and sufficient and the conclusions drawn are supported by the results obtained.

The Applicant has applied QbD principles during process development.

Control strategy

The control strategy for the active substance is based on the following control elements: design control, process control, raw material control, in-process testing, process development/process evaluation, process validation, release testing, and stability testing. CQAs have been ranked according to their assessed criticality, and relevant control elements for the individual CQAs have been selected accordingly. Overall, the justifications given for the selection of control elements made and the overall control strategy in place is considered appropriate and capable of ensuring consistent manufacture of the active substance of the intended quality.

Characterisation

Elucidation of structure and other characteristics

Physico-chemical characterisation

The physico-chemical characteristics of ofatumumab has been characterised using a panel of different methods. Biochemical attributes such as primary structure, higher order structures (secondary, tertiary and quaternary structure), carbohydrate structure, heterogeneity (i.e. by size and charge), and other attributes were determined.

It was confirmed that ofatumumab had the expected primary structure with 100% sequence coverage, as well as the expected masses in intact and reduced/alkylated forms. Ofatumumab contains the expected IgG1 disulfide bond linkages.

Structural analyses of ofatumumab active substance show that ofatumumab had the expected higher order structures.

Ofatumumab batches had consistent N-glycan distribution, and the expected N-glycosylation for an antibody produced in NS0 cells. No O-glycosylation sites were detected.

Charge heterogeneity was evaluated and showed similar amounts of charge variants. The isoelectric point (pI) of ofatumumab was determined.

Size variants of ofatumumab were assessed and all tested samples had low and similar amounts of size variants.

In conclusion, the results from all applied analytical techniques showed that ofatumumab has the expected physico-chemical properties consistent with a typical IgG1 molecule.

Biological characterisation

Biological activity/potency of ofatumumab was characterised using several assays. Potency of the samples tested was determined and expressed as relative potency. Relative potency was calculated using a parallel line assay according to Ph. Eur. 5.3.

Ofatumumab binding to cells endogenously expressing human CD20 was analysed based competitive target binding assay. Potency values obtained for batches tested as relative target binding versus the primary reference substance were similar.

The ability of ofatumumab to induce CDC, the primary mode of action, was determined using a functional assay with target cells. Obtained potency values were well within relative potency limits; no difference was observed between the active substance batches tested.

The ability of ofatumumab to induce ADCC was determined using a functional assay with target cells and effector cells. In addition, a surrogate ADCC assay format was applied. With both ADCC assay formats, the obtained relative potency values showed only minor differences between batches tested.

The ability of ofatumumab to induce antibody dependent cellular phagocytosis (ADCP) was assessed qualitatively, using a functional assay with target and effector cells. In addition, a surrogate ADCP assay was applied. With both ADCP assay formats, no differences were observed between the batches tested.

C1q binding of ofatumumab was similar between the batches tested and the primary reference standard.

The binding kinetics and relative affinity of the ofatumumab samples to FcγRIa, FcγRIIaHR, FcγRIIaLR, FcγRIIb, FcgRIIIaF158, FcgRIIIaV158, FcγRIIIb and FcRn were analysed. Binding kinetics and affinity were similar between the tested samples.

In conclusion, the analysed ofatumumab batches showed similar biological activity characteristics with an Fc-effector function profile as expected for the IgG1κ isotype. Overall, the assays used for biological characterisation are considered appropriate and addressing all relevant attributes and effector functions of Ofatumumab.

Impurities

Forced degradation studies

In order to understand the product- and process-related variants and impurities, the impurity profile of ofatumumab active substance was investigated. Forced degradation studies were executed to understand the degradation pathways and to confirm the suitability of the selected stability-indicating methods for detecting

product-related variants or impurities. The degradation products were subjected to characterisation, using a panel of orthogonal methods for detection of product-related impurities. Potential impact on potency was determined.

Potency assays demonstrated sensitivity for thermal, basic, oxidative, and light stress.

Identification and characterisation of product-related substances/impurities:

Identification and characterisation of product-related substances/impurities was performed.

Overall, the stress conditions and methods applied for characterisation of product-related impurities are considered appropriate and the characterisation of the impurities obtained is considered sufficient.

Specification

The release specification for the active substance includes control identity, purity and impurities, potency and other general tests. The test panel is acceptable and in line with the requirements of ICH Q6B.

Overall, the release specifications are considered acceptable and the selected methods are found appropriate and fit for purpose.

Analytical procedures

Reference to Ph. Eur. for compendial methods and brief, but adequate descriptions of non-compendial methods applied for release testing have been provided.

Validation protocols and results have been provided. All non-compendial methods have been validated according to ICH Q2. Bioburden and endotoxin testing are conducted and validated according to Ph. Eur. All acceptance criteria were met. The analytical methods have been adequately validated. The analytical methods chosen to monitor the ofatumumab active substance have been demonstrated to be suitable for their intended purpose.

Batch analysis

Batch release data have been provided for batches manufactured at full scale Process D at Lonza Porthsmouth, US. All batch release results are compliant with the acceptance criteria valid at the time of testing, demonstrating that the proposed commercial Process D is able to consistently deliver ofatumumab active substance of the intended quality.

Reference standard

The quality of ofatumumab active substance and finished product is monitored by a two-tiered reference standard approach with a PRS and a working reference standard (WRS). Both reference standards were manufactured using commercial Process D. The qualification of reference standards included testing according to the active substance release test specification, in addition to a comprehensive characterisation. All release and stability data met the acceptance criteria in place at the time of testing.

Based on the additional characterisation, comparability was demonstrated.

The system for qualification and retesting of the reference standards for Ofatumumab is considered appropriate and the primary and working reference standards are considered fit for purpose.

In order to ensure continuity of the reference standards over time, a new PRS or WRS is only released on the basis of specific criteria which have been defined. This is acceptable.

Container closure

The ofatumumab bulk active substance is filled into bags.

The contact layer is compliant with Ph.Eur.. Compliance with "*EC regulation no. 10/2011 on plastic materials and articles intended to come into contact with food*" has also been confirmed.

The choice of packaging material for the active substance is considered justified, based on the physical/chemical properties of the active substance, and the fact that the active substance is an aqueous solution. The proposed container is for routine storage and is therefore used in the stability studies, supporting the proposed shelf-life and storage of ofatumumab bulk active substance.

Stability

Active substance batches, manufactured according to Process D at commercial scale, were tested in registration stability studies under the following storage conditions: long-term storage conditions, two different accelerated storage conditions, intermediate storage conditions, and stressed storage conditions. The registration stability studies are all completed and data throughout the entire duration of the studies have been provided.

In addition, a freeze/thaw stability study and a photostability study were performed.

Follow-up stability studies are ongoing, including at least one batch annually from each year, where ofatumumab active substance is manufactured.

The stability studies are conducted in line with current guidelines. The analytical methods applied have been shown to be stability indicating based on forced degradation studies and stability studies performed under stressed storage conditions, including light exposure.

All stability results from studies under long-term, accelerated, and following freeze/thaw cycles, complied with the acceptance criteria in place at the time of testing.

A sufficient number of commercially manufactured active substance batches have been included in the stability studies. The batches tested during stability were stored in the primary packaging material intended for routine storage of ofatumumab active substance.

The proposed shelf life is considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the finished product

The finished product is a sterile single-use, preservative-free, clear to slightly opalescent, colourless to slightly brownish-yellow solution for injection, containing 20 mg ofatumumab in 0.4 mL solution (concentration of 50 mg/mL). Ofatumumab is formulated with the following excipients: arginine, sodium acetate trihydrate, sodium chloride, polysorbate 80, disodium edetate, hydrochloric acid 25% and water for injections. The excipients are all of pharmacopoeial grade and selected for their suitability for SC administration. There are no novel excipients or excipients of human or animal origin.

The primary container closure for ofatumumab finished product is a syringe (type I glass) with two presentations: a PFS assembled with a plunger rod and a needle safety device (NSD) and a PFP (Pen) corresponding to the syringe assembled in an auto-injector (AI).

The syringe assembled with NSD (PFS-NSD) is packaged in a blister, and then placed in a carton box, while the syringe assembled in an AI (PFS-AI) is placed directly in a carton box. The carton boxes are provided with a tamper evident feature.

Pharmaceutical development

A quality target product profile (QTPP) was used in the development of the finished product, outlining the intended product performance. The QTPP covers the active ingredient, mechanism of action, administration, dosage form and strength, packaging material, finished product shelf-life, patient convenience, compendial requirements and impurities. The chosen QTPP is considered adequate to address the clinical needs.

Critical quality attributes and control strategy

The CQAs have been assessed and based on their criticality they were divided into categories, and relevant control elements for each individual CQA have been selected accordingly. CQAs have been assigned for ofatumumab.

The control strategy for the finished product is based on the criticality assessment of the identified quality attributes and applies to the finished product and its manufacturing process, including release and stability testing. The control strategy is based on design control, process control, raw material control, in-process testing, process development/process evaluation, process validation, release testing, and stability testing.

The justifications for the selected control elements and the overall control strategy is considered appropriate and it ensures a consistent manufacture resulting in ofatumumab finished product of the desired quality.

Formulation development

Originally ofatumumab was developed for oncology treatment under the name Arzerra (see above). The initially developed formulation, with a different antibody concentration, and presented in a vial. Clinical development for a MS indication was initiated later. During development the formulation was changed.

Additionally, as ofatumumab is to be delivered SC, a change in primary packaging from vial to PFS was made.

The Applicant has applied QbD principles during the formulation development. Formulation robustness studies were performed to assess the impact of composition variations on the CQAs of the product and the intended commercial presentation of ofatumumab finished product. The proposed commercial formulation is therefore considered robust.

Physicochemical and biological properties

The key physicochemical and biological parameters of the finished product have been identified. The chosen formulation adequately accommodates the physicochemical properties of the active substance. The physicochemical and biological parameters have all been adequately described, and they are adequately controlled during release and shelf-life.

Manufacturing process development

Standard aseptic processing techniques are used for the manufacturing of the finished product. The process involves standard pharmaceutical operations including sterile filtration and aseptic filling which are performed according to pharmacopoeial and current GMP requirements.

Comparability studies were performed during development of the manufacturing process. The studies demonstrate that the changes made during development do not have an impact on the quality attributes of the finished product; the different presentations of ofatumumab finished product, and a change in manufacturing site for ofatumumab finished product resulted in comparable finished products.

The final commercial manufacturing process of the finished product was developed and evaluated by the Applicant. Batches have been manufactured at Novartis in Switzerland with normal operating range (NOR) and proven acceptable range (PAR) of the process parameters were established during process development.

Process development studies have been performed to support the proposed process parameters. Detailed descriptions of the studies have been provided in the dossier, and a summary has been included in this assessment report. The development studies demonstrate that the proposed NORs and PARs are appropriate.

Container closure

The container closure system selected for Kesimpta (see above) is considered suitable. It consists of the following components: a sterile, single-use syringe (glass syringe barrel (type I glass) with staked needle and a plunger rubber stopper) and a rigid needle shield (RNS) as the primary packaging components. It has been demonstrated that there is no sorption to the components of the primary container closure.

The syringe is assembled with two different medical devices (secondary packaging) - a needle safety device (NSD) and an auto-injector (AI). When assembled, the PFS-NSD and PFS-AI are packed in outer secondary packaging. The suitability of the container closure system has been investigated. The components of the primary container closure comply with either pharmacopoeial monographs or ISO standards. None of the components of the medical devices (NSD and AI) are in contact with the finished product.

The PFS was subjected to extractables and leachables studies in order to investigate and determine the level of compounds being extracted from the container closure system components under worst-case and normal conditions. No volatile, semi-volatile or non-volatile compounds, or elements, were detected in the incubation extracts of the selected container closure system in concentrations exceeding the Analytical Evaluation Threshold (AET) corresponding to the safety concern threshold (SCT).

Suitability for storage has been demonstrated during the stability testing performed on the finished product. Suitability for transportation was demonstrated by a shipping verification study. The analysis of results and summary of the shipping study have shown that the finished product with the stated packaging and shipping configurations is considered suitable for transportation when tested according to applicable standards.

For the device parts development activities were performed and demonstrate for the PFS-NSD and PFS-AI that the devices are safe and effective for the intended use by the intended users.

The unassembled PFS as well as the auto-injector are medical devices and comply with the relevant requirements from the Medical Device Directive.

Sufficient information is provided which support the suitability of the container closure system to ensure compatibility with ofatumumab finished product, safety of contained materials, protection of the finished product and dosage delivery.

This data show that the packaging materials and devices are compliant with the test requirements.

In accordance with the sterilisation guideline (EMA/CHMP/CVMP/QWP/850374/2015) information has been provided.

Microbiological attributes

Ofatumumab finished product is a sterile medication that is supplied in a single-dose PFS and is therefore not required to meet the antimicrobial effectiveness testing requirements. A container closure integrity test (CCIT) of containers is performed in order to monitor the integrity and tightness of the primary packaging material.

Compatibility

During development of the product, compatibility with the primary container closure system (i.e. glass syringe and plunger stoppers) was evaluated. Compatibility of ofatumumab finished product with the primary container was evaluated. The results of these studies demonstrated that ofatumumab finished product is compatible with the PFS intended for commercial manufacture.

Compatibility with manufacturing equipment was demonstrated during development studies. The compatibility is also confirmed during the stability studies. A leachables and extractables study was performed on the process contact material. No volatiles, semi-volatiles, or non-volatiles were detected that would lead to parenteral intakes exceeding µg/day threshold. Additionally, it was found that the quality of Ofatumumab was not impacted by the manufacturing process.

Manufacture of the product and process controls

Manufacture

Manufacturing and quality control testing of the finished product are performed by Novartis sites in Switzerland. Besides Novartis in Switzerland, several alternative secondary packaging sites in the EU are used and listed in the dossier. EU release testing is performed by Novartis Pharma GmbH, Nuremberg, Germany and Novartis Farmacéutica SA, Barcelona Spain. EU GMP compliance for all site has been confirmed.

Description of process

Ofatumumab finished product is manufactured under aseptic conditions and is considered standard. The manufacturing process consists of the following steps: manufacturing of the excipient dilution solution (EDS), active substance thawing, manufacture of the bulk finished product solution and manufacture of the primary packaged product. After the filling operation, ofatumumab finished product in PFS is assembled into either an auto-injector (AI), or assembled with a plunger rod, labelled and assembled with a needle safety device (NSD). The PFS in AI is then placed in a cardboard box that serves as secondary (outer) packaging, while the PFS assembled with NSD is first packaged within a blister that holds the syringe in place, and then the blister is inserted into a cardboard box that serves as secondary (outer) packaging. The manufacturing process has been described in sufficient details in the dossier.

Critical process controls

For each operational step during manufacturing of the finished product, the process parameters were tested and validated, and the required performance parameters were defined. The parameters were assessed as either critical, key, or non-key. In-process controls were applied for several of the manufacturing steps during manufacture. Some of these steps were evaluated as critical steps. The proposed critical steps, process parameters and their acceptance criteria have been presented and are considered adequate to control the process leading to a product of consistent quality.

Process validation

The manufacturing process validation covers the entire manufacturing process. The validation studies have been performed to demonstrate the suitability of the manufacturing conditions in order to guarantee consistent and reproducible quality of the final product at the commercial manufacturing site. Validation is performed to demonstrate that the current validated procedures are acceptable.

Production batches were used for validation of manufacturing process of ofatumumab finished product in PFS. All batches fully met the quality control release specifications as defined in the testing monograph. Together with the IPC data and the additional testing it has been demonstrated that the manufacturing process is robust and consistently yields a product capable of meeting the pre-defined quality characteristics.

During process validation the proposed hold times for the manufacture of ofatumumab finished product were also validated. The results show that the obtained hold times during the process validation were well within the limits.

A summary of validation of assembling of the PFS with AI is included in the dossier. The results show that the manufacturing process of ofatumumab finished product is robust and consistently yields PFS in AI which meets the pre-determined quality characteristics.

Product specification

The release specification for the finished product includes control identity, purity and impurities, potency and other general tests. The test panel is acceptable and in line with the requirements of ICH Q6B.

A justification of the specifications, including test parameters, analytical methods and acceptance criteria, has been provided. Ofatumumab analytical specifications for active substance and finished product are aligned in order to follow the basic principles of currently recognised standards of ICH guidelines as well as the Ph. Eur. Monographs, and to ensure the quality of the product within its intended shelf life.

Ofatumumab finished product was analysed regarding the potential elemental impurities of concern in accordance Ph. Eur. 5.20 and ICH Q3D. It can be concluded that the risk and the impact on patient safety associated with the presence of elemental impurities in ofatumumab finished product is negligible.

A risk evaluation concerning the potential presence of nitrosamines in the finished product was performed. The risk evaluation found that there is no risk for the presence and/or introduction of nitrosamines and/or their formation during the active substance manufacturing, in raw materials, in excipients, during the finished product manufacturing process, or in the packaging materials. This is acceptable.

Analytical procedures

The analytical methods chosen to monitor the ofatumumab finished product appearance, description, identity, purity, potency, quantity, microbiology and additional tests to control the finished product and container closure have been demonstrated to be suitable for their intended purpose. The finished product specifications will ensure the product quality and batch-to-batch consistency of ofatumumab finished product throughout shelf life.

The analytical methods chosen to monitor the ofatumumab finished product assembled in an auto-injector have been demonstrated to be suitable for their intended purpose.

Validation of analytical procedures

Validation data has been provided for the methods used for release and stability testing. All acceptance criteria were met. The analytical methods have been adequately validated.

Batch analysis

Batches of ofatumumab finished product in the primary packaging (PFS) have been subjected to batch analysis. Additionally, batches were subjected to additional analysis after assembling with devices (PFS-NSD and PFS-AI). All the batches comply with the finished product release specifications, valid at the time of batch release. The results demonstrate consistency between the batches during development, and uniformity of the product, indicating that the manufacturing process is under control.

Reference standards

The reference standards used for release and stability testing of ofatumumab finished product are the same as those used for the release and stability testing of ofatumumab active substance.

Container closure

The proposed container closure system for Kesimpta is considered adequate (see section on Pharmaceutical development).

Stability of the product

The proposed shelf-life for ofatumumab finished product PFS-NSD and PFS-AI is 24 months when stored at 5°C ± 3°C, protected from light.

The stability studies were designed in accordance with the principles detailed in ICH Q5C and Q1A(R2). The stability testing covered those attributes from the proposed finished product specifications that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The set of stability indicating methods applied provides assurance. The analytical methods used for testing of ofatumumab finished product during stability have been validated in accordance with ICH Q2(R1), and they are stability indicating.

A sufficient number of commercially manufactured finished product batches have been included in the stability studies.

For all the stability studies performed on ofatumumab finished product, it is observed that results for the batches, when stored at long term conditions (5 ± 3°C/ambient RH) are all well within the requirements set for long term storage conditions.

Ofatumumab batches placed on stability have been tested at accelerated conditions (25°C/60% RH) and stressed conditions (40°C/75% RH).

Photostability studies

Photostability studies have been performed in accordance with the requirements of ICH Q1B "Photostability Testing of New Active substances and Products". Ofatumumab is susceptible to the applied light exposure and needs protection from light. For the assembled product in the secondary out packaging, all the results were within specification limits.

Stability program for transport and storage category assignment

The Applicant has presented stability data. All results are within specification limits.

Overall, after review of the data provided, the proposed shelf life of 24 months when stored at 5°C ± 3°C is acceptable. The statement "do not freeze" is acceptable based on the recommendations in Guideline on declaration of storage conditions (CPMP/QWP/609/96/Rev 2), and the claim "protect from light when stored in secondary packaging" is satisfactorily justified by the presented photostability studies.

Adventitious agents

Raw materials – TSE

No raw materials of animal- or human origin are used during the manufacture of ofatumumab. During early steps of the generation of the production cell line, animal-derived raw materials were used. A risk assessment has been conducted evaluating the risk of transmitting TSE from these raw materials, considering the species and/or geographical origin and the manufacturing process of the materials in question. Based on the above considerations, it is concluded that the risk of transmitting infective TSE is negligible.

Cell banks

The MCB and current WCB, and the PPCB were tested for absence of non-viral (mycoplasma, bacteria, fungi) and viral adventitious agents and endogenous retroviruses. The testing was performed in accordance with ICH Q5A and verified the absence of adventitious agents and endogenous viruses, except for type A- and C- RVLP, known to be present in the NS0 cell line.

Bulk harvest

Bulk harvest is tested for the absence of mycoplasma and adventitious viruses. Results have been provided from the testing of active substance batches, verifying the absence of mycoplasma and viral contamination.

Viral clearance studies

The viral clearance capacity of the ofatumumab active substance purification process (of Process D) was evaluated by conducting viral clearance studies in accordance with ICH Q5A.

Conclusion

Overall, the risk of contamination with adventitious agents, including TSE, mycoplasma, bacteria, fungi, and viruses, is considered well contained based on selection of safe raw materials, demonstration of absence of adventitious (and endogenous) agents in cell banks, testing at relevant stages of the process, and finally the substantial virus clearance capacity, demonstrated for the ofatumumab purification process.

Overall, adventitious agents safety is considered acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents safety including TSE have been sufficiently assured.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Kesimpta is considered acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics (SmPC). Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Kesimpta is considered approvable from the quality point of view.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary Pharmacodynamics *in vitro*

Ofatumumab is a fully human monoclonal IgG1 antibody that targets a unique conformational epitope of the human CD20 molecule, which is expressed on B cells and a subset of CD3+ T cells. This epitope is apparently not targeted by other CD20 antibodies such as rituximab and ocrelizumab. Ofatumumab binds to residues in the large loop (distal from residues A170 and P172) and the small extracellular loop of CD20. Ofatumumab is developed to be selective to the CD20 molecule and e.g. epitope mapping studies demonstrate mode of binding and efficacy. Staining in tissue cross reactivity studies was highly consistent and ofatumumab demonstrated tissue reactivity in accordance with its target CD20 antigen specificity.

Initially, ofatumumab was developed for B cell lymphomas. However due to failing to penetrate the market, the product was withdrawn. In this application, ofatumumab is targeting B cells in MS. It should be mentioned that targeting MS require a much lower human dose, namely 20 mg SC at week 0, 1 and 2, followed by subsequent monthly dosing, starting at week 4. In contrast, the dose for the treatment of B cell lymphomas was 300-2000 mg per week by IV infusion.

In *in vitro* primary pharmacology studies, ofatumumab binds to CD20-transfected NS/0 cells but not to their non-transfected counterparts. Binding to human B cells occurred with a concentration of a drug that gives half-maximal response (EC_{50}) of 287 ng/mL and dissociation from CD20 was very slow with a k_{off} for ofatumumab F(ab')2 fragments of 6.4 x 10-5 sec^{-1}.

The mode of action of ofatumumab was characterised by a range of functional assays using cell lines of B cell tumours and normal human cells. Ofatumumab appears to act preferentially through CDC and partly through ADCC. In the ADCC assay (RD-2018-00361), purified NK cells were used as effector cells and human primary B cells as target cells. It was shown that after a 14-h incubation of primary human B cells, the assay resulted in similar B cell death for ofatumumab and ocrelizumab, 22% and 28%, respectively and a moderate depletion for rituximab (13%).

The direct 2-h CDC assay resulted in a potent depletion of primary human B cells when treated with ofatumumab (77.7%) and only a slight depletion when treated with ocrelizumab (7.1%) or rituximab (12.8%).

Ofatumumab-mediated CDC was shown to be less affected by complement inhibitor molecules such as CD55 and CD59 compared to rituximab-mediated CDC.

The delayed CDC demonstrated a long-lasting effect of ofatumumab with 54% of depletion after 6 h of treatment whereas ocrelizumab showed the same lack of activity as an irrelevant antibody, corelating with the slow k_{off} of ofatumumab (RD-2018-00361).

Overall, *in vitro* proof of concept appears to be established.

Primary Pharmacodynamics *in vivo*

Studies in mice bearing human B cell tumours provide evidence that ofatumumab inhibits B cell tumour growth, however these studies do not provide *in vivo* proof of concept in terms of MS as the Applicant also states.

Generally, monoclonal antibodies, administered via SC route, are absorbed via the lymphatic system, although several aspects are still poorly understood (Richter & Jacobsen, 2014).

Nonclinical studies indicate that SC administration targets lymphatic system and brain to a higher degree as compared to IV administration. This was evident in experimental autoimmune encephalomyelitis (EAE) mice (an animal model of MS, Migotto, 2019).

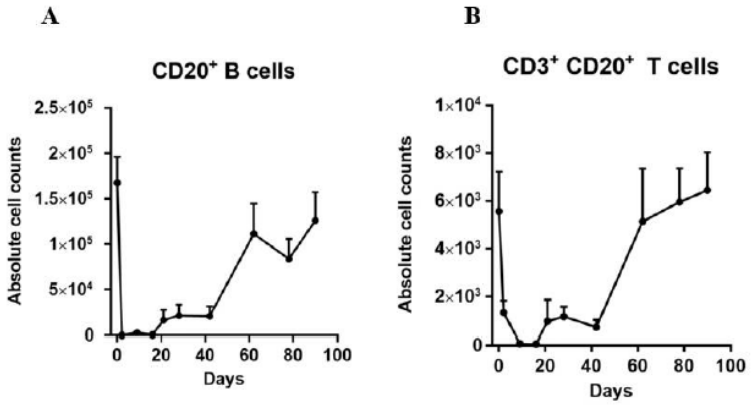
This is of particular relevance since lymph nodes are the site where B cells and T cells interact with each other where B cells present cognate autoantigens to T cell clones. These clones expand, migrate to the brain and inflict damage (Jelcic et al 2018).

Two aspects were described by the Applicant depicting differences in the MoA of ofatumumab and ocrelizumab, and both B cell-killing agents trough different routes of administration (RoAs) and different doses. The data of dead human primary B cells percentage were provided in order to show that ofatumumab, in direct comparison to ocrelizumab and rituximab, not only induces complement-induced B cell death with greater efficacy but also is able to induce strong CDC when complement addition takes place several hours after the exposure to ofatumumab. The Applicant credibly explained the superiority of ofatumumab SC RoA in contrast to the IV RoA. The discussion was furthermore substantiated by evidence collected by Torres et al (2019) and Migotto et al (2019). SC anti-CD20 Ab induces a significantly more effective decrease in T cell accumulation in the brain of delayed-type hypersensitivity (DTH) MS mouse model and accumulation after SC the injection is most prominent in the draining lymph nodes. Moreover, the Applicant provided appropriate data to suggest the potent effect on annualized relapse rate (ARR) of low dose ofatumumab in RMS patients.

A Novartis proprietary study in cynomolgus monkeys was performed to evaluate mechanism of action of ofatumumab at clinically relevant dose of 1 mg/kg SC thrice with 1 week in between doses. This was conducted by several means, e.g. monitoring lymphocyte subsets by FACS and morphological and immune cell changes, IMC or IHC in axillary lymph nodes and blood samples, which were collected at various time points until Day 90. At Day 21, IHC revealed B cell depletion in the perifollicular and interfollicular area of axillary LNs, while only the core of the germinal centre was depleted of CD20+CD21+ cells. By Day 62, the perifollicular and interfollicular areas were abundantly infiltrated by CD21+ B cells and this distribution returned to the baseline cytoarchitecture by Day 90. It was concluded that low dose SC ofatumumab potently depletes both B cells and CD20+ T cells but apparently spares marginal zone (MZ) B cells in the spleen and LN. It was further concluded that the different susceptibility of B cell subtypes may be linked to the bioavailability of the antibody through the lymphatic system after SC injection or may be related to the phenotypic makeup in these specific anatomic regions. However, overall, reversible decrease in B cells in blood and lymphatic tissues was demonstrated as a result of SC administration of ofatumumab, see Figure 2.1.2.1. Apparently, this study was not supported by PK

sampling, which could have provided important quantitative PK/PD relationships to support selection of the human dose.

Figure 1. *Changes in lymphocyte counts in blood samples from cynomolgus monkeys treated acutely with SC ofatumumab. A: CD20+ B cells. B: CD3+CD20+ T cells. Data are expressed as means plus/ minus standard error of the mean (RD-2019-00021)*



Secondary Pharmacodynamics

In order to demonstrate selectivity and species-specific binding, immunohistochemical investigations were performed in human and animal tissues.

Human tissues alone (CD2008-01311, GLP compliant)

Cross reactivity of ofatumumab in human tissues were conducted by immunohistochemical investigations.

Specific, positive, membrane bound staining of fluorescein isothiocyanate conjugated ofatumumab was recorded in tissues belonging to the lymphoid system, e.g. lymphocytes of the lymph node, spleen, thymus and tonsil and also in the mucosa associated lymphoid tissue MALT of the small and large intestines. In addition, there was positive membrane bound staining of lymphocytes scattered in the subepithelial tissues of at least one donor of cervix, endometrium, kidney, prostate, parotid salivary gland, skin, stomach, ureter and urinary bladder. There was no staining in the blood vessels, cerebrum, breast, eye, heart, Fallopian tube, liver, ovary, peripheral nerve, pancreas, parathyroid glands, pituitary gland, placenta, skeletal muscle, spinal cord, testis or thyroid gland. Ofatumumab demonstrates tissue reactivity that is consistent with its target antigen specificity. Staining in reproductive organs is consistent with physiological location of B-lymphocytes and does not point to non-specific binding of ofatumumab to reproductive tissues. B-cells are relatively rare in the male and female reproductive organs (prostate: Hussein 2009, uterus: Agostinis 2019). B cell depletion in reproductive organs is not expected to impact reproductive function, lead to increased risk of malignancies or infections as indicated by available non-clinical and clinical data.

Cross reactivity in rhesus, cynomolgus and human tissues (CD2008-001167, not GLP)

Ofatumumab was shown to bind to tonsils from humans or cynomolgus monkeys and to lymph nodes from rhesus monkey. Binding was found in follicular structures. Human and cynomolgus CD20 were found to differ only by one amino acid in the CD20-second extracellular loop. Binding studies in PBMCs resulted in EC_{50} values of 287, 97 and 139 ng/ml for human, rhesus and cynomolgus PBMCs, respectively. The study supports selecting rhesus and cynomolgus monkeys for safety studies.

Other species (CD2008-01175, not GLP)

Ofatumumab was found not to cross-react with cells in splenic germinal centres from dog, pig, rabbit, mouse and rat. Alignment of human and monkey CD20 sequences with those of mouse, rat and dog showed low homology (72 to 74% homology). Hence, nonclinical studies in these species appear not to be meaningful, when ofatumumab is pharmacologically active in monkeys.

Safety Pharmacology

In alignment with ICH S6, safety pharmacology evaluations were performed as part of repeat-dose toxicity studies. See Table 2.3.1. hERG-testing was not included, since ofatumumab is a monoclonal antibody and not anticipated to elicit any relevant effect on this ion channel.

Cardiovascular parameters were monitored in the 4-week repeat-dose toxicity study. There were no significant differences between baseline or between doses at any occasion. The Lead II trace was evaluated and the interval data (P-R, QRS and Q-T) and heart rate derived. Measurements were taken twice pre-dose and 30 min after completion of dosing and 24 h after commencement of dosing on each day of dosing (i.e. Days 1, 8, 15 and 22). A similar setup was performed in the 7 months study with 5 occasions up to Day 190. Again, no signal on cardiovascular parameters were observed. Blood pressure was not monitored. Since the other parameters did not show any effect of ofatumumab, this is not a concern. There were no changes in any of the urinalysis parameters that were considered to be related to treatment with ofatumumab in the two studies.

CNS, renal and respiratory function was evaluated in the fertility study of 13 weeks duration. Six cynomolgus monkeys/sex/group were administered control item (vehicle), 10 mg/kg weekly and 3 mg/kg bi-weekly, or 100 mg/kg weekly and 20 mg/kg bi-weekly. The first five doses of test item were administered weekly (on study days 1, 8, 15, 22 and 29); then, doses were administered bi-weekly (every other week) until end of the treatment period (four doses, on study days 43, 57, 71 and 85).

Respiratory rate was observed in non-anesthetized, temporarily restrained animals once during the pre-dose phase and during Weeks 1 and 13 of the dosing-phase by counting respiratory phases for 15 seconds for calculation of respiratory frequency (respirations/minute). No change in respiration rate was considered related to treatment with the test item.

Animals were observed pre-dose (-11) and on dosing days 2 and 88 for potential neurobehavioral effects using a standard observation battery, which allowed the assessment of peripheral and central nervous systems activities. Methods were a modified version of a primary observation test described by Irwin for detecting neurological and behavioural changes in mice (Irwin, 1968). All observations indicated normal behaviour.

Differences in urinalysis parameters were present between controls and ofatumumab-treated animals or between pre-dose and dosing phase test results for individual animals. All were consistent with normal variation and considered incidental.

Pharmacodynamic drug interactions

No studies of pharmacodynamic (PD) drug interactions have been performed. This is acceptable considering the nature of the product.

2.3.2. Pharmacokinetics

Methods of Analysis

All bioanalytical methods of ofatumumab and antidrug antibodies (ADA) were based on ligand-binding assays. Different platforms and approaches were used. Apparently, bioanalytical and ADA methods were developed

and adequately validated. The Applicant made an exhaustive list of studies with respective linked validation reports with key validation parameters. Validation reports including analytical methods were submitted.

The bioanalytical program of the repeat-dose toxicity studies was conducted according to guidelines applicable at the time of conduct (2004 and 2009). At this time, incurred sample reproducibility in GLP studies and validation of bioanalytical methods to be conducted under GLP compliance was not a requirement. Quality Assurance statements of the repeat-dose toxicity studies, document inspection of phases in connection with bioanalysis, such as Immunoassay, DMPK QC preparation and Sample receipt. Hence, the lack of incurred sample reproducibility testing (ISR) and formal GLP compliance of the bioanalytical program is considered justified.

It should be mentioned that some studies were reported in ng/mL while other is reported in µg/mL. However, this is solved in toxicokinetic reporting.

Absorption

No systematic effort was undertaken by the Applicant, to quantitatively determine the pharmacokinetic (PK) parameters describing the target mediated drug disposition elimination of ofatumumab after a single dose of SC administration. Studies were using different designs of repeat-dosing. Since monkeys may develop antidrug antibodies against ofatumumab after approximately 2 weeks, these data may be unreliable. The large variability in one study (SC vs IV) and N=1 in the other study (IV low doses) make the data difficult to interpret. The clinical bioequivalence study also reveals that exposure is highly variable after SC administration, see Figure 3.2.3. Despite the suboptimal characterisation of ofatumumab pharmacokinetics in naïve monkeys, it appears that ofatumumab follows the expected PK behaviour of an IgG antibody in the monkey. Ofatumumab was slowly absorbed after SC administration with time for maximal exposure in the range of 48-120 h. Bioavailability was 40% after the second dose (Day 15) of 20 mg/kg SC and 75% after the second dose (Day 15) of 100 mg/kg SC compared to 100 mg/kg IV On Day 1, the bioavailability of 20 mg/kg was 85% (CD2007-01024).

Toxicokinetics in e.g. the 7-month general toxicity study (IV infusion) suffers from suboptimal design of the study for PK sampling and development of antidrug antibodies, hence PK parameters, as the Applicant also states, are somewhat unreliable. Nevertheless, exposure was calculated, and plasma concentrations are much higher than will ever be achieved in MS patients. Moreover, Day 1 data indicated that ofatumumab PK resembled IgG in the monkey, see Table 3.2.2. Therefore, this is not considered a concern. There were not observed any consistent gender differences in exposure. Exposure was approximately proportional with dose on Day 1 (between 20 and 100 mg/kg) indicating that at 20 mg/kg target mediated clearance (CL) is saturated already after the first dose.

Table 1. Arithmetic Mean (SD) Parameter Estimates Relating to HuMax- CD20 Following Infusion on Day 1 in Male and Female Cynomolgus Monkeys

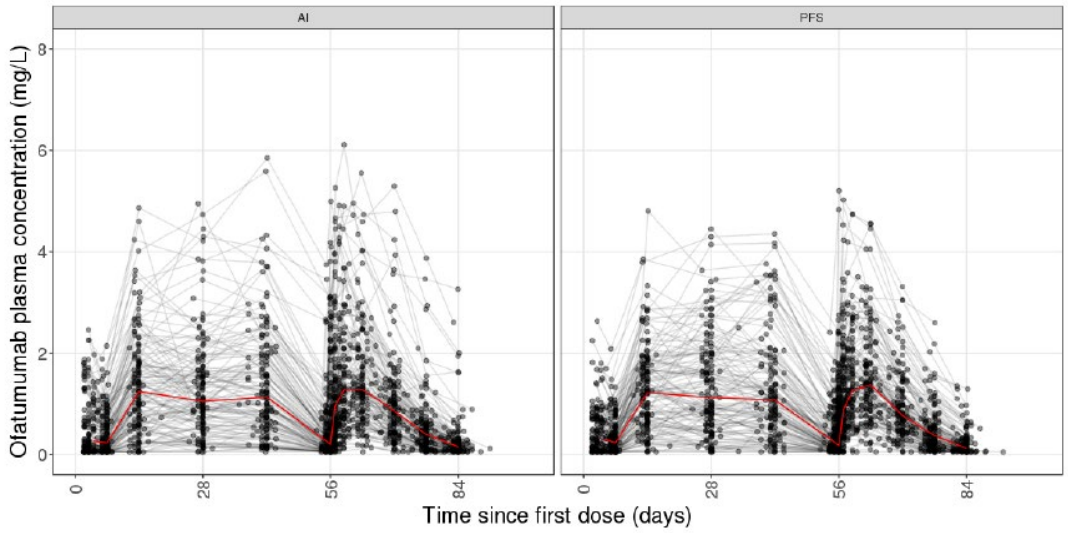
Sex	*Dose (mg/kg)*	*Part*	*Tmax(obs)^ (h) (Range)*	*T½el (h) (SD)*	*Kel (1/h) (SD)*	*CL (mL/h/kg) (SD)*	*Vd (mL/kg) (SD)*	*Vss (mL/kg) (SD)*
Male	20	Main & Recovery	0.50 (0.50, 0.50)	134.81 [n=6] (40.65)	0.005469 [n=6] (0.001403)	0.2819 [n=6] (0.07992)	52.00 [n=6] (11.33)	47.96 [n=6] (12.55)
	100	Main & Recovery	2.00 (0.50, 6.50)	126.68 [n=6] (9.95)	0.005501 [n=6] (0.0004631)	0.2508 [n=6] (0.03572)	45.71 [n=6] (6.623)	42.43 [n=6] (7.019)
Female	20	Main & Recovery	0.50 (0.50, 168.50)	91.92 [n=4] (10.07)	0.007606 [n=4] (0.0008055)	0.3261 [n=4] (0.07815)	42.89 [n=4] (9.313)	39.46 [n=4] (11.83)
	100	Main & Recovery	0.50 (0.50, 6.50)	100.47 [n=3] (9.20)	0.006938 [n=3] (0.0006307)	0.2365 [n=3] (0.01213)	34.27 [n=3] (3.382)	30.95 [n=3] (2.534)

^ Median(range)
n=6 for Day 15 (Main & Recovery) unless otherwise specified [n]

The rationale behind calculation of safety margins is understood, i.e. using AUC_{0-t} at steady state in the maintenance phase. It is a mean to be able to directly compare exposure at a similar place in the dosing regimen between human and monkey exposure. However, the safety margin may not be calculated across the timeframe, where patients are exposed the most, namely just after the loading phase. This is considered acceptable, since the safety margins are high - exemplified by a safety margin on maximum concentration (C_{max}) of >2000 in the 7 month repeat-dose toxicity study, see Table 3.2.3. The recommended dosing regimen in MS patients is 20 mg ofatumumab administered by SC injection with initial dosing at weeks 0, 1 and 2, followed by subsequent monthly dosing, starting at week 4 as used in the bioequivalence study see Figure 3.2.3.

Figure 2

Figure 3.2.3. Dataset used for calculation of safety margins: Observed ofatumumab concentration data and median profile (red line) versus actual time since first dose by device (auto-injector and prefilled syringe) for study COMB157G2102 (human PK/Bioequivalence) – linear scale



Distribution

No conventional distribution studies using radiolabelled ofatumumab was conducted (e.g. protein binding or whole-body autoradiography). This is considered acceptable according to ICHS6(R1). However, ofatumumab potential for placental transfer was evaluated in studies of reproduction toxicity. In study CD2008-01523, it was shown that ofatumumab was transferred to fetus via umbilical cord and that the serum concentrations were similar between fetus and umbilical cord. This is expected for IgG1, which is the most efficiently transported immunoglobulin across placenta (via the neonatal FcRn receptor). Furthermore, in study 1670033, ofatumumab was observed in infants up to 28 days after the low dose regimen and up to PND91 at the high dose regimen despite maternal animals were not dosed after birth of the infant. However, high variability was observed due to antidrug antibodies formed in maternal animals.

Metabolism

No metabolism studies were performed on ofatumumab. Monoclonal antibodies are expected to be metabolised in the same manner as endogenous antibodies. This is acceptable according to ICHS6(R1).

Elimination

Similar to metabolism, modes of excretion are anticipated to be similar to endogenous antibodies (proteolysis protected by Fc-Rn receptor). Studies of excretion is therefore not necessary.

Pharmacokinetic Drug interactions

PK drug interactions are not expected for a selective monoclonal antibody.

2.3.3. Toxicology

Single dose Toxicity

No single dose toxicity studies have been performed. This is considered acceptable, since ofatumumab is indicated for low dose (as compared to the previous cancer indication) chronic treatment.

Repeat-dose Toxicity

Three pivotal repeat-dose toxicity studies were presented. One study using both SC and IV administration serves as a bridging study to the 4-weeks and 7-months repeat-dose studies using IV administration. One study was using cycled dosing imitating dosing schedule in CLL indication. Two other studies were presented. These served as dose-range finding studies and were not performed in compliance with GLP.

2-weeks SC and IV with 8 months recovery (CD2007-01024)

The bridging study was performed GLP compliant with a comprehensive audit program under the responsibility of GlaxoSmithKline.

Ofatumumab was given on Day 1 and Day 15 to female cynomolgus monkeys (6/group at 20 or 100 mg/kg/dose ofatumumab given SC, 6/group at 100 mg/kg/dose ofatumumab given by IV infusion, 4/group at 0 mg/kg/dose given SC). A necropsy was conducted for half the animals in each group on Day 21; the remaining animals were necropsied following an approximate 33-week recovery period.

The main finding in this relatively short study was the depletion of CD20+ B cells, which is the intended pharmacological effect. See Table 4.2.2. This was correlated by a similar decrease in CD40+ B cells. Both subsets increased during recovery, i.e. on Day 250, absolute CD20+ cell numbers were approximately 0.5X of baseline levels at 100 mg/kg given SC or 100 mg/kg given IV. The rate of recovery was dependent on dose and route of administration with 100 mg/kg IV providing the longest time to recovery of B cell counts in peripheral blood illustrating that SC administration does not provide 100% bioavailability in that sense. This could be different if looking for B cells in lymphatic target organ tissues. However, this was not done in this study. Classical end points of clinical observations, body weights, clinical pathology, macro- and microscopic observations did not reveal any significant findings. The highest dose was selected as No observed adverse effect level (NOAEL). This is agreed. Anti-ofatumumab antibodies, detected in 4 ofatumumab-treated monkeys, corresponded with reduced ofatumumab plasma concentrations and accelerated B cell-recovery. On Day 15, mean systemic exposure at 100 mg/kg/dose (based on $AUC_{0\text{-}t}$ and C_{max}, respectively) was 274 mg x h/mL and 1.51 mg/mL (SC) or 392 mg x h/mL and 3.27 mg/mL (IV infusion) providing a safety margin of at least 570 on $AUC_{0\text{-}t}$ (Table 3.2.3).

Table 2. Flow cytometry – Group Means Absolute CD3-/CD20+ Lymphocyte subset Counts (x109/L) in Female Monkeys (CD2007/01024)

			ABS CD20+ (x 10^9/L) – Day of Study											
Group Sex	Treatment		-6	1	15	20	47	76	104	128	163	195	222	250
1F	0 mg/kg sc	Mean	0.53	0.44	0.40	0.44	0.48	0.59	0.60	0.50	0.72	0.77	0.59	0.66
		SEM	0.10	0.09	0.05	0.05	0.04	0.15	0.12	0.10	0.08	0.09	0.08	0.05
		n	4	4	4	4	2	2	2	2	2	2	2	2
2F	20 mg/kg sc	Mean	0.54	0.67	0.00	0.00	0.05	0.12	0.28	0.29	0.37	0.41	0.36	0.38
		SEM	0.12	0.12	0.00	0.00	0.05	0.07	0.14	0.14	0.11	0.18	0.17	0.17
		n	6	6	6	6	3	3	3	3	3	3	3	3
3F	100 mg/kg sc	Mean	0.71	0.84	0.00	0.00	0.00	0.13	0.15	0.16	0.14	0.28	0.43	0.43
		SEM	0.17	0.20	0.00	0.00	0.00	0.13	0.15	0.16	0.14	0.16	0.06	0.08
		n	6	6	6	6	3	3	3	3	3	3	3	3
4F	100 mg/kg iv	Mean	0.53	0.61	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.03	0.17	0.27
		SEM	0.07	0.09	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.07	0.08
		n	6	6	6	6	3	3	3	3	3	3	3	3

Table 3. *Exposure multiples for animal findings based on a 20 mg SC dose in humans*

					Exposure multiples	
Exposure[a] in cynomolgus monkeys in pivotal studies					Human exposure[b] at the therapeutic dose of 20 mg s.c.	
Study Type (Study number)	**NOAEL (mg/kg)**	**Sex**	**AUC0-t[a] (µg·h/mL)**	**Cmax (µg/mL)**	**AUCtau 483.4 µg·h/mL**	**Cmax 1.425 µg/mL**
2-week s.c.+i.v. (CD2007-01024)	100	F	s.c. 274000 / 753000	1510	570 / 1600	1100
			i.v. 392000 / 1005000	3270	810 / 2100	2300
4-week i.v. (CD2008-01520)	100	M	401489 / 1753889	10595	830 / 3600	7400
		F	747248 / 2172502	11535	1500 / 4500	8100
Cycled dosing i.v. (CD2008-01522)	100	M	120585 / 254942	2811	250 / 520	2000
		F	222705 / 267609	4071	460 / 550	2900
7-month i.v. (CD2008-01521)	100	M	54892 / 765564	3110	110 / 1600	2200
		F	59183 / 757219	3460	120 / 1600	2400
Fertility i.v. (1670402)	100/20[c]	M	162000 / 312000[d]	1340	340 / 650	940
		F	124000 / 251000[d]	1090	260 / 520	770
EFD i.v. (CD2008-01523)	100	F[e]	622600 / 1646000[f]	5680	1300 / 3400	4000
ePPND i.v. (1670033)	10/3[c,g]	F[e]	10500 / 16900[i]	90	22 / 35	63
	100/20[c,h]		77900 / 111000[i]	733	160 / 230	510

Footnotes

s.c. = subcutaneous; i.v. = intravenous; M = male, F = female

a: Geometric mean AUC and Cmax in monkeys at the end of the treatment period. Unless otherwise indicated, AUC0-t was calculated from the last administration to the last sample collected at the end of the treatment period (first value) / to the last sample containing quantifiable levels of ofatumumab (second value)

b: Geometric mean AUC and Cmax in subjects of the bioequivalence study [COMB157G2102-Table 14.2-11.1] at approximate steady state, n = 282 subjects. *(Assessors insert: Geomtric Means of AUCtau/Cmax for autoinjector = 487.7 hr*µg/mL/1.409 µg/mL, mean AUCtau/Cmax for prefilled syringe = 474.1 hr*µg/mL/1.409 µg/m determined from week 8 to 12, i.e. tau=4 weeks, see Figure 3.2.3).*

c: The initial dose (10 or 100 mg/kg) was given weekly for 5 weeks followed by the maintenance dose (3 or 20 mg/kg) given once every 2 weeks

d: Fertility study: mean AUC0-168h (first value) / AUC0-t (up to last collected sample, second value)

e: Exposure determined in maternal animals of the EFD and ePPND studies

f: EFD study: mean AUC0-7 days (first value) / AUC0-∞ (second value)

g: NOAEL related to the pharmacological activity in infants

h: NOAEL for maternal animals and pre/post-natal development

i: ePPND study: mean AUC0-168h (first value) / AUC0-336h (second value)

4-weeks IV with 6 months recovery (CD2008/01520)

This study was sponsored by Genmab and appeared fully GLP compliant.

The objective of this study was to assess the toxicity of ofatumumab in Cynomolgus monkeys following 4, weekly IV administrations (i.e. Days 1, 8, 15 and 22) and then during a 6-month recovery period monitor B cell recovery in the blood and lymph nodes of designated animals. The study was including both males and females with 3 in each of the main study groups and 2 in the recovery groups of the control, 20 and 100 mg/kg/week dose groups. Apart from classical core end points, humoral immune function was assessed using immunisation with KLH and lymph node biopsies were also taken for flow cytometry investigations at least once pretrial from all animals and from the recovery animals throughout the dosing and recovery periods. On completion of the 2-week post dose observation period or 6month recovery period, as appropriate, the animals were sacrificed and subjected to a detailed necropsy.

Organs/tissues were subjected to organ weight analysis and histological evaluation. Selected tissues were also stained and evaluated for immunohistochemistry investigations.

For most end-points, there were no difference between dose-groups. However, the following findings (I - III) were observed to be significantly different from control group.

I: Similar to study CD2007-01024, B cell count was reversibly reduced in both peripheral blood and lymph nodes in active dose-groups.

II: For humoral immune function, there was evidence of inhibition of specific KLH antibodies for the high dose of 100 mg/kg/week.

III: Histologically, treatment with ofatumumab at dose levels of 20 and 100 mg/kg/week was associated with minimal to moderate germinal centre or follicular atrophy in the mandibular and mesenteric lymph nodes, Peyer's patch and spleen of the main study animals. Recovery animals showed partial recovery to these findings.

The highest dose was selected as NOAEL. This is agreed. A strong anti-drug antibody (ADA) response with a large degree of variation following administration of ofatumumab was detected in 3/12 animals in Group 2 (20 mg/kg/day) and 2/12 animals in Group 3 (100 mg/kg/day). Exposure was, nevertheless, overall high, and provided safety margins to human exposure of >830, see Table 3.2.3.

7-months IV with 6 months recovery (CD2008/01521)

This study was also sponsored by Genmab and appeared fully GLP compliant.

The objectives of this study were to assess the toxicity of ofatumumab in cynomolgus monkeys following 13 IV administrations over a 7-month period (i.e. Days 1, 8, 15, 22, 29, 36, 43, 50, 78, 106, 134, 162 and 190) and a 6-month recovery period. Male and female cynomolgus monkeys were assigned to 3 dose groups (3 animals in the main study and 4 animals for recovery per group) in which ofatumumab was administered at dose levels of 0, 20 and 100 mg/kg/dose. This study design (e.g. weekly dosing in the initiating phase, and once a month after the first 8 dose administrations) is similar to the treatment schedule of MS, however at much higher exposure/doses. End points to be monitored were similar to study CD2008/01520.

Probably as a consequence of the long duration of this study, mortality was observed. Mortality was not considered directly related to the treatment with ofatumumab, but more likely secondary to i: lethal immune reaction to the human protein leading to anaemia and/or immune-complex related disease or ii: higher susceptibility to common infections (e.g. *C. jejuni)* among cynomolgus monkeys. The observed mortalities are not considered clinically relevant, as they are already known risks of treatment with antibodies against B cells.

Similar to other studies, B cell counts in peripheral blood and lymph nodes was completely depleted during the treatment period and reversed to normal during the recovery period. The duration of cell depletion was dose dependent and produced a rebound effect upon its recovery. Subsets of B cells were monitored and showed that some subsets were more resistant to depletion than others. The apparent differentiated depletion of memory (small fraction – less efficient depletion) and non-memory B cells (more abundant- more efficient depletion) in the non-clinical studies appear not to be clinically relevant, since in patients on continuous treatment of ofatumumab both types of B cells were efficiently depleted and protected from relapse of MS.

The immunisation of animals in the three dose groups with keyhole limpet hemocyanin (KLH) resulted in detectable immune responses generated over the course of the study. A dose dependent inhibitory effect on the IgG humoral immune response was apparent at Day 18 in the 20 mg/kg dose group and 100 mg/kg dose group main study animals. This effect appeared not to be fully reversible in the recovery animals.

As expected from the intended pharmacological effect, lymphoid atrophy in submandibular and mesenteric lymph nodes, Peyer's patch and spleen was observed. Other findings included thymic atrophy, extramedullary hematopoiesis in the liver, inflammation in the kidneys and perivascular inflammatory cell infiltration in the brain and sciatic nerve. For one Group 3 male recovery animal, mild thymic atrophy was noted. The animal also had mild multifocal interstitial nephritis. All these findings were ascribed to a progressive formation of immune complexes leading to organ inflammation and anemia. This conclusion is supported. Mortality was evenly distributed across the two-active dose-groups. NOAEL was set to the highest dose. This appears acceptable, since most of the adverse findings could be attributed to the pharmacology of ofatumumab, species specific infections, or the reaction to treatment with an antibody from a different species (human). For safety margins to clinically relevant exposure, see Table 3.2.3.

Apparently, the incidence of ADA was low in this study except for one animal, which was found dead on Day 44 (probably due to general organ failure). The apparently inconsistent ADA response in monkeys treated with ofatumumab could be due to high amount of ofatumumab in ADA serum samples masking true ADA positive results in the ADA assays. This correlates with the fact that in only one female monkey, ADA was confirmed. This monkey most likely died of immune complex disease and also had lower concentrations of ofatumumab probably due to neutralising antidrug antibodies. More focused assays directed towards red blood cells namely the Direct Coomb's test and stripping of ofatumumab bound to red blood cells was more in correlation with

findings of anaemia and other symptoms of immune complex disease such as vasculitis and inflammation in organs.

Cycled dosing IV with 4 months recovery (CD2008-01522)

This study was sponsored by GlaxoSmithKline and appeared fully GLP compliant.

The objective of this study was to aid the assessment of the systemic toxic potential of ofatumumab in the cynomolgus monkey following two cycles of IV administration, each cycle consisting of two IV administrations (30 min infusion) of ofatumumab given two weeks apart. Three groups of 3 male and 3 female cynomolgus monkeys received ofatumumab at dose levels of 0, 20 or 100 mg/kg on Days 1, 15, 148 and 162.

Anti-drug antibodies were detected in 15 out of 24 treated HuMax-CD20 animals (9 out of 12 at 20 mg/kg and 6 out of 12 at 100 mg/kg). Pharmacokinetics may have been affected by the presence of ADAs.

The main finding in this study, apart from decrease in B cell counts, was low grade anaemia, which was probably the cause of some of the mortalities and adverse findings in the 7 months study. Several clinical chemistry and pathology findings reflected low grade anaemia, namely low haemoglobin concentrations, erythrocyte counts and haematocrits and high reticulocytes, iron and total bilirubin. The increase in reticulocytes in the blood may suggest marrow regeneration due to a loss of peripheral erythrocytes. These findings were not correlated to any histopathological findings.

Moreover, as in the 7 months study, histopathological examinations revealed germinal centre atrophy in the spleen and tonsils as well as in mandibular and mesenteric lymph nodes.

The mean values of B cell depletion showed lower numbers and increased time to repletion in females as compared to males are driven by 3/6 females in the cycled study and 1/6 females in the chronic study. The other females showed B cell data similar to males. This could be interpreted as individual female animals showing longer ofatumumab exposure for the 3 females in the cycled study or being more sensitive to ofatumumab than others for the one female in the chronic study. However, if this is a real effect, it is not clinically relevant, as there are no clinically meaningful imbalances within each of the sub-groups of male and female patients on efficacy endpoints and AE profiles.

The highest dose was considered to be NOAEL. This is supported. See Table 3.2.3. for safety margin on exposure.

Toxicokinetics

Ofatumumab in control and pretrial samples

In study CD2007-01024, no ofatumumab was detected above LOQ. In study CD2008-01520, CD2008-01522 and CD2008-01521, a few samples from control group and pretrial samples in the active dose groups were positive for ofatumumab, however at very low levels, not considered to elicit any pharmacological effect or to impact the conclusions of the studies.

For discussion of toxicokinetics in general, See section 3.2.2. Pharmacokinetics/Absorption.

Genotoxicity

According to guidelines, no studies of the genotoxic potential of ofatumumab were performed. This is justified, since monoclonal antibodies are not expected to interact with DNA and ofatumumab is not modified with unnatural amino acids or linkers etc.

Carcinogenicity

Due to the mechanism of action, i.e. immunosuppression, tumour promoting effects cannot be ruled out. However, since ofatumumab is not pharmacologically active in rodents, conduct of conventional carcinogenicity studies is not feasible. A justification for not conducting such studies were given by a weight of evidence approach. The justification is considered acceptable based on the following statements:

i: At doses up to 100 mg/kg in monkeys for 7 months duration, there was no evidence of increased carcinogenic risk.

ii: There are no identified concerns for genotoxic or carcinogenic potential for ofatumumab.

iii: While certain B cell subsets may play a role in the complex immune surveillance environment, the weight of evidence in the literature does not suggest that B cell depletion plays a driving force in tumour formation and promotion.

iiii: Extensive clinical data for similar CD20 targeting agents already exists, where rituximab appears to not increase risk of malignance, however for ocrelizumab, the risk cannot be ruled out.

Reproductive and developmental toxicity

Fertility and early embryonic development

The fertility study was sponsored by Novartis and conducted according to GLP (1670402).

Groups of 6 animals/sex were given ofatumumab at 10/3 mg/kg, and 100/20 mg/kg. The initial dose (10 or 100 mg/kg) was given weekly for 5 weeks (on Days 1, 8, 15, 22 and 29) followed by a maintenance dose (3 or 20 mg/kg) given once every 2 weeks (four administrations, on Days 43, 57, 71 and 85). A further 6 animals/sex were similarly dosed with the vehicle alone. Four animals/sex/group were necropsied on Day 92. The remaining animals were retained for a further 8-week observation period, prior to necropsy on Day 148. Core end points were evaluated as well as safety pharmacology end points, see section 2.3. Male fertility endpoints were the results of testicular and semen evaluation. Female fertility endpoints were the results of the menstrual cycle monitoring and ovarian/uterine maturation stage. The only noteworthy findings were expected pharmacological effects. Immunophenotyping revealed the expected depletion of CD20+ cells and immune-histochemistry showed depletion of CD20+ and CD3+ cells in lymphoid tissues. Only the low dose showed evidence of recovery. Despite incidence of ADAs in a 5/12 animals in the low dose group leading to lower than expected decrease in B cells and decreased exposure, the conclusions of the study were not impacted as this was not observed in the high dose group. No effects on fertility were noted. Hence the highest does was selected as NOAEL. In terms of exposure, the safety margin to clinically relevant exposure (AUC) is at least 340, see Table 3.2.3.

Embryofoetal development

The embryofoetal development study was sponsored by GlaxoSmithKline and conducted according to GLP (CD2008-01523).

Ofatumumab was administered IV (30 minutes) to cynomolgus monkeys from day 20 to 50 of gestation at 0, 20 or 100 mg/kg. The animals received weekly administrations, i.e. a total of 5 administrations. The fetuses were delivered via caesarean section for necropsy on Day 100±1 of gestation. The study included core end points for dams including lymphocytes subsets and ADAs. Litters were evaluated for implantations, resorptions, live and dead fetuses, fetal weight, sex, splenic lymphocyte subset counts, placental and fetal morphology (external visceral and skeletal), and selected organ weights and histology. Furthermore, fetal cord blood was

collected for ofatumumab concentration measurements, anti-drug antibody analysis and lymphocyte subset counts.

There was no impact on pregnancy outcomes and no findings of malformations or variations in litters. The only finding was a dose-related decrease in spleen weight, however with no microscopic correlates. As expected, depletion of B cells was observed in both dams (blood) and litters (both blood and spleen).

Antibodies against ofatumumab was observed in a few dams and also in their litters as well. Both ofatumumab and ADAs were detected in umbilical cord samples at Day 100. See Table 3.3.1. This is expected, since IgG readily passes the placenta barrier.

Table 4. Serum concentrations of ofatumumab in cord blood samples at GD100 (CD2008-01523)

Dose Group	Concentration of HuMax-CD20 (ng/mL)													
	Animal ID												Mean	SD
1	13380	13634	13336	13419	13585	13699	13722	13646	13326	13525	13445	13791		
	#	LOD	LOD	LOD	LOD	LOD	LOD	LOD	LOD	#	LOQ	LOD	LOD	na
	Animal ID													
2	13600	13183	13683	13234	13513	13328	13732	13725	13160	13294	13186	13636		
	11900	#	8900	LOD	LOD	2380	8320	9350	7230	#	5520	15400	8625	3926
	Animal ID													
3	13415	13635	13686	13161	13625	13398	13703	13348	13484	13478	13603	13383		
	LOD	42600	#	69700	101000	81400	50800	88200	#	55700	31400	77400	66467	22854

- no sample available
na – not applicable
LOD – Limit of Detection (3.125 ng/mL)
LOQ – Limit of Quantification (5 ng/mL)

NOAEL was selected as the high dose of 100 mg/kg/week. This is supported. Safety margin to clinically relevant exposure was 1300, see Table 3.2.3.

Prenatal and postnatal development, including maternal function

The ePPND study was sponsored by Novartis and conducted according to GLP (1670402).

The purpose of this study was to determine the effects of ofatumumab on pregnancy, parturition and lactation, and on pre- and postnatal survival, growth and development of the F1 offspring for six months when given by IV infusion to pregnant monkeys from Gestation Day (GD) 20 until parturition. The control item (vehicle) or ofatumumab was administered IV (30 min infusion) at 0, 10/3 mg/kg, and 100/20 mg/kg from GD 20 until parturition (N=14). The initial dose (0, 10 or 100 mg/kg) was given weekly for 5 weeks (on GD 20, 27, 34, 41, and 48), followed by a maintenance dose (0, 3 or 20 mg/kg) given once every 2 weeks from GD 62 onwards (on GD 62, 76, 90, 104, 118, 132, 146, and 160). After birth of the infants, ofatumumab treatment was stopped and the maternal animals and infants were kept for a 6-month observation period prior to necropsy on LD/PND 180±1.

Maternal animals were evaluated for core end points. Infants were evaluated for core end points and neurobehavioral test battery, testing of grip strength, skeletal and bone mineral assessment as well as T-cell-dependent antibody response (TDAR).

There was no mortality directly attributed to ofatumumab. However, one maternal animal was euthanised in moribund condition probably due to severe immune reaction towards ofatumumab and 3 infants likewise probably due to infections, which could be secondary to impaired immune defence system.

In surviving infants, the only difference from control group on core end points was the expected decrease in CD20+ B cells. ADAs were present in some monkeys especially in the low dose. This correlated with normal levels of CD20+ B cells and low exposure of ofatumumab.

The high dose differentiated from the low dose and control group on immune-toxicological parameters. IgG levels were reduced on PND 70, and reduced IgG and IgM was observed at PND 91 after the first KLH challenge. The low dose was comparable to the control group on these parameters.

Overall, exposure to ofatumumab during gestation caused no maternal toxicity and no adverse effects on pre/post-natal development.

NOAEL was determined as the low dose based on the mortality most likely due to impaired immune response in infants at the high dose. This is supported. Using maternal steady state exposure at the low dose at GD146, the safety margin was 22 to clinically relevant exposure based on AUC0-t. At PND28, the mean plasma concentration was 1.15 µg/mL in infants of the low dose group (NOAEL), comparable to clinical C_{max} of 1.4 µg/mL.

Local Tolerance

Local tolerance was evaluated in the repeat-dose toxicity studies. Apparently, ofatumumab was well tolerated in the nonclinical studies.

Other toxicity studies

The submission of two studies of mechanistic character is appreciated. One study compared ofatumumab with another clone in a single dose *in vivo* study. Both clones were well tolerated and showed the expected pharmacological effect.

The other study was investigating biomarkers of the so-called cytokine release syndrome after single IV dosing of 25-100 mg/kg ofatumumab. Activated complement components (C3b/c, C4b/c), cytokines (interleukin-6), thrombin-anti-thrombin III complex and plasma-anti-plasma complex increased as a sign of cytokine release syndrome, however of limited severity. In general, IV administration to monkeys was associated with a mild and transient increase in circulating inflammatory and coagulation parameters without clinical manifestations. Clinical studies are not reporting any such reactions; hence this phenomenon appear to be of limited clinical relevance for MS patients.

Antigenicity

An ADA response against ofatumumab was detected in approx. 40% of all ofatumumab-treated monkeys following IV and SC dosing. At low doses of ofatumumab, the presence of ADAs led to decreased systemic ofatumumab exposure and a subsequent abrogation of the pharmacological activity in some monkeys, along with accelerated circulating B cell recovery. Immunogenicity to ofatumumab occasionally resulted in immune complex-mediated hypersensitivity in a few monkeys causing acute hypersensitivity reactions, a reduced RBC mass, and/or vascular/perivascular inflammation in tissues. Being a human antibody, ofatumumab is considered to be relatively non-immunogenic in humans. It is generally accepted that the immunogenic response in non-human primates is poorly predictive of the response in humans.

In the chronic study, some of the Coomb's test positive animals also showed perivascular inflammatory cell infiltration in the brain, sciatic nerve, and/or kidneys or vasculitis in the brain and liver, further supporting an immunogenic response in these monkeys. Perivascular and/or vascular inflammation was shown to be the most common histologic change attributed to immune complex disease. Some patients treated with ofatumumab in clinical trials showed ADA response. However, the totality of the clinical observations data from the clinical trials and previous clinical experience with ofatumumab in oncology settings at very high doses of 2000 mg/week did not reveal any safety concern for the risk of autoimmune conditions or type III hypersensitivity

reactions in the patients with ADA. The animal findings are generally not adequate to assess hypersensitivity reactions thus it is considered appropriate to review patients' data.

Immunotoxicity

Immunosuppression (B cell depletion) is the pharmacological effect of ofatumumab. Therefore, it is not surprising that adverse findings regarding immunosuppression would be found in the repeat-dose toxicity studies. It appears that adult monkeys were not overly sensitive to the immunosuppressive effect of ofatumumab, although a few incidences of fatal *C. jejuni* infection occurred. Whether these cases were as a result of treatment or incidental remains equivocal, since they occurred only in active dose-groups. In the ePPND study, three infants were deemed lost due to fatal, non-specified, infections as deemed from macro and microscopic pathological evaluation. These deaths drove the selection of NOAEL to the low dose in this study. It is common knowledge that antibodies targeting CD20+ B cell will lead to higher susceptibility to infections. Upper respiratory tract infections were slightly higher (39.4%) in the ofatumumab treated patients as compared to teriflunomide (37.8%) treated patients in the active control group. However, teriflunomide is also an immunomodulatory drug. In the Phase III pivotal clinical studies, 51.6% of ofatumumab-treated patients experienced at least one infection, compared to 52.7% of teriflunomide treated patients (SmPC). The SmPC provides warnings of infections in general, progressive multifocal leukoencephalopathy (PML) and hepatitis B (HBV) reactivation in section 4.4. It should be mentioned that even if the duration of action of ofatumumab is long lasting, the effect is eventually reversible, and the depletion of B cells is transient and will recover if treatment is stopped. Moreover, nonclinical evidence as presented in this report, suggest that only CD20+ B cells are targeted by ofatumumab, hence e.g. the population of NK-cell and T-cells and other immune defence systems should remain intact.

Impurities

No further nonclinical studies should be required for qualification of impurities. It appears that that the immunogenic potential of ofatumumab in monkeys (incidence of ADAs) have been reasonably stable over the years of nonclinical development. This can be seen as a result of a relatively stable purity of the product.

2.3.4. Ecotoxicity/environmental risk assessment

Considering the nature of ofatumumab being a human protein, it is not expected to be stable or remain biologically active in the environment and it is unlikely to pose a risk to the environment. Moreover, the excipients in the product are not expected to be of any risk either. The absence of any ERA studies is therefore acceptable, and in line with the current guidance.

2.3.5. Discussion on non-clinical aspects

Pharmacology

Ofatumumab is a fully human monoclonal IgG1 antibody that targets a unique conformational epitope of the human CD20 molecule, which is expressed on B cells and a subset of CD3+ T cells. Binding to human B cells was potent and the off-rate slow. Functional *in vitro* proof of concept appears well-established.

No dedicated nonclinical *in vivo* studies were presented for the MS indication, however PK/PD and toxicity studies in monkeys showed consistent depletion of B cells and mechanism of action was investigated by e.g. monitoring lymphocyte subsets by FACS.

Furthermore, a published study in humanised mice investigated the distribution and efficacy of ofatumumab after IV and SC administration.

Ofatumumab showed a slightly different in vitro pharmacology profile compared to ocrelizumab. In direct comparison to ocrelizumab and rituximab, ofatumumab not only induces complement-induced B cell death with greater efficacy but also is able to induce strong CDC when complement addition takes place several hours after the exposure to ofatumumab.

Cross reactivity studies showed that ofatumumab binds in the expected lymphoid tissues and organs in humans and monkeys,

Safety pharmacology evaluation of potential effects on cardiovascular, respiratory and CNS systems was conducted in the repeat-dose toxicity studies. No significant changes to control groups were observed.

Pharmacokinetics

Bioanalysis and toxicokinetics was performed for all pivotal toxicity studies.

Pharmacokinetics of ofatumumab appeared to be as expected for a human monoclonal antibody administered to monkeys. All pivotal toxicity studies were conducted using IV administration in support of a previous indication (CLL). SC administration was investigated in one bridging study using similar dose levels. Bioavailability was generally high, although variable as was also observed in a clinical bio-similarity study comparing a prefilled syringe with an autoinjector. Otherwise toxicokinetics appeared sufficient and safety margins very high in support of the low dose of ofatumumab in treatment of MS.

Ofatumumab is transferred from the mother to the foetus via the umbilical cord. This was shown in the ePPND study and is expected for an IgG-type monoclonal antibody. Ofatumumab was detected in infants after birth and the duration of exposure was dose-dependent. Hence, depletion of B cells can be expected in foetuses and infants of mothers in treatment with ofatumumab. This is reflected in the SmPC.

Mechanisms of metabolism and elimination were not investigated. This is acceptable considering the nature of the product.

Toxicology

Ofatumumab was in general well tolerated in repeat-dose toxicity. However, in the study of the longest duration, namely the 7-months study, mortality was observed. Ofatumumab was not considered to a direct cause of mortality and were within the frame of already known risks of B cell depletion in patients. Mortality appeared to be due to lethal immune reaction to a human antibody or increased susceptibility to already known infections among cynomolgus monkeys.

Macroscopic and microscopic findings were typically lymphoid atrophy, which is an expected pharmacological effect. Inflammation in various organs and perivascular spaces appeared to be due to progressive formation of immune complexes. This is also a typical finding in monkeys treated with human antibodies.

In the repeat-dose toxicity studies, immune cell populations were monitored. The apparent differentiated depletion of memory (small fraction – less efficient depletion) and non-memory B cells (more abundant- more efficient depletion) in the non-clinical studies appear not to be clinically relevant, since in patients on continuous treatment of ofatumumab both types of B cells were efficiently depleted and protected from relapse of MS. Abundance of $CD8^+$ T cells were not impacted by ofatumumab treatment.

Moreover, across studies, individual female monkeys appeared to have longer ofatumumab exposure or being more sensitive to ofatumumab effects than others. Clinical data suggest that this is not clinically relevant either.

A full reproductive and developmental toxicity program was presented. Ofatumumab did not show any adverse effects in terms of reproduction as such. However, in the ePPND study 3 infants died of unspecified infections in the high dose group. These deaths were considered secondary to the pharmacological effect of ofatumumab (impaired immune defence). The high dose also showed decreased T-cell-dependent antibody response and reduced response to the first KLH challenge. Therefore, NOAEL was set to the low dose. Maternal exposure provided a safety margin of 22 to human clinical exposure. Infants of the low dose showed exposure at levels similar to clinically relevant exposure.

Ofatumumab was moderately antigenic in the monkeys, which was expected. This is not generally predictive of antigenicity in the clinical setting. However, in the chronic study, some of the animals showed perivascular inflammatory cell infiltration in the brain, sciatic nerve, and/or kidneys or vasculitis in the brain and liver, further supporting an immunogenic response in these monkeys. Nonetheless, the totality of clinical observations has not revealed any safety concern for autoimmune or hypersensitivity reactions in patients with ADA.

Ofatumumab is an immunosuppressant (B cell depletion). The B cell depletion is long lasting but eventually reversible. The SmPC provides warnings of increased risk of progressive leukoencephalopathy and HBV reactivation. These warnings are included as class effects as cases have been observed in patients treated with other monoclonal antibodies targeting B cells.

2.3.6. Conclusion on non-clinical aspects

From a non-clinical point of view, Kesimpta can be recommended for marketing authorisation.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the Applicant.

A routine EMA GCP inspection has been adopted, three sites have been selected for inspection: an investigator site in Poland, one in Russia and the CRO ICON in Ireland.

Following up with the discussion with the inspectors, considering the current COVID-19 situation and the safety and travel restrictions, and the related impact on the deadline for the IIR a cancellation of the routine inspection has been recommended.

2.4.2. Pharmacokinetics

Analytical methods

The methods for the determination of ofatumumab in human plasma have been validated. Methods for determination of anti-ofatumumab antibodies have been described and validated.

- Modelling

The PK of ofatumumab in patients with RMS has been evaluated based on data from studies OMS115102, OMS112831, G2301, G2302 and G2102. Both conventional non-compartmental and model-based analyses were used.

Two PK/PD Modelling Reports are considered as the main studies:

1. Population pharmacokinetics of ofatumumab in relapsing multiple sclerosis patients.

2. Exploratory analyses of the relationship between ofatumumab dose regimen, peripheral blood CD19+ B-cell count and MRI lesions in relapsing-remitting multiple sclerosis patients.

The Applicant has presented PoP-PK (population PK)/PD models in the target populations. The models are overall presented, developed and validated in accordance with the existing the EMA Guideline on reporting the results of population pharmacokinetic analyses (Doc.ref. CHMP/EWP/185990/06, June 2007).

The POP PK analysis (**Population pharmacokinetics of ofatumumab in relapsing multiple sclerosis patients Modelling Report**) suggested a quasi-steady state approximation of the target mediated drug-disposition model with two PK compartments and a first order process for the SC administration. After the loading phase, ofatumumab concentrations decreased to a minimum and then increased to steady state after 2 years (fig. 5-18 below). This was captured in the model by a time-dependent effect on the receptor synthesis rate. The covariates that were selected in the final model (table 5-11 and 5-17 below) included weight effects on the absorption rate, CL, intercompartmental CL, central volume, complex elimination rate constant and the baseline receptor synthesis rate, a sex effect on bioavailability, an AI effect on complex elimination rate constant, and an IV formulation effect on baseline receptor synthesis rate. The covariates anti-drug antibodies, age, race and baseline B-cell count were found not to be related to any of the PK parameters.

Weight is the covariate with the main effect on drug exposure.

Figure 3

Figure 5-18 **Simulated pre-dose OMB157 concentrations versus time over 2 years for the phase 3 dosage regimen administered with the PFS and for the patient population in the 5 studies**

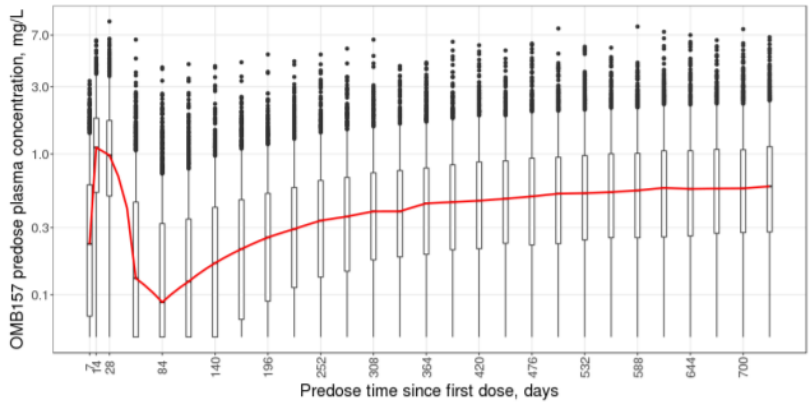


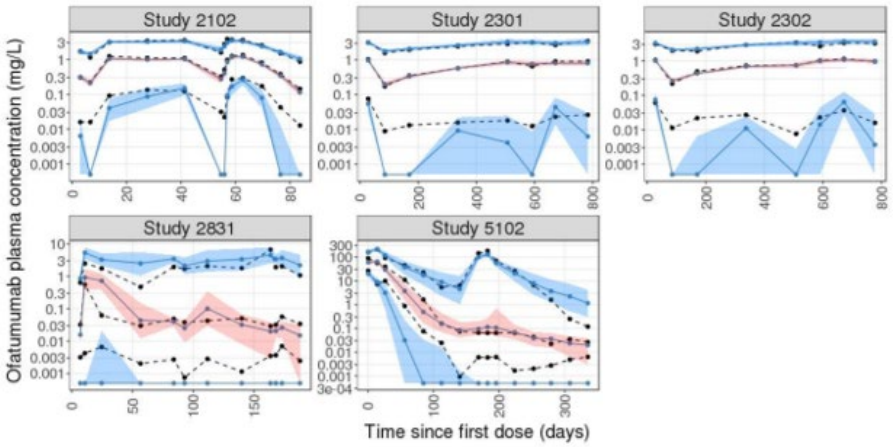
Table 5

Table 5-11 **Population PK parameter estimates for the final mod[illegible]828_9) including covariates using data from all 5 studies**

Parameter (unit)	Estimate	(RSE %)	Inter-subject variability SD (RSE %) [Shrinkage %]
k_a (day^{-1})	0.329	(4.07)	0.829 (4.08) [54.1]
β(k_a,WT_{70})	-0.768	(19.8)	NA
F	0.358	(2.22)	0.252 (6.95) [72.7]
β(F,female)	-0.152	(19.3)b	NA
CL (L/day)	0.156	(2.92)	0.57 (3.53) [36.7]
β(CL,WT_{70})	1.47	(5.02)	NA
Q (L/day)	0.0462	(5.3)	0.425 (10.3) [92.2]
β(Q,WT_{70})	2.33	(8.98)	NA
V_c (L)	2.8	(1.91)	0.2 (7.48) [76.8]
β(V_c,WT_{70})	0.767	(7.03)	NA
V_p (L)	2.8	(fixed)	-
$k_{e(P)}$ (day^{-1})	1.01	(8.41)	1.07 (5.37) [77.0]
β($k_{e(P)}$,WT_{70})	0.936	(32.1)	NA
β($k_{e(P)}$,auto-injector)	0.495	(30.3)	NA
R_0 (nmol/L)	11.2	(3.73)	0.434 (7.8) [78.5]
k_{syn0} (nmol/L/day)	0.49	(2.07)	0.159 (11.6) [88.9]
β(k_{syn0},WT_{70})	-0.387	(19.4)	NA
β(k_{syn0},IV)	1.68	(4.28)	NA
$k_{syn\infty}$ (nmol/L/day)	0.0431	(16.5)	-
k_{des} ($year^{-1}$)	2.65	(6.03)	1.09 (4.18) [42.7]
K_D (nmol/L)	0.167	(fixed)	-
k_{off} (day^{-1})	5.53	(fixed)	-
correlation_k_a_CL	-0.169	(30.4)	NA
correlation_k_{des}_CL	0.802	(3.06)	NA
correlation_k_{des}_k_a	0.239	(24.6)	NA
a [additive] (mg/L)	0.0322	(2.64)	NA
b [proportional]	0.267	(1.49)	NA

Figure 4

Figure 5-17 Visual predictive check of the final population pharmacokinetic model (M828_9) by study – log scale



Black points and dashed lines: 5th, 50th and 95th percentiles of observed OMB157 concentration data
Blue line and points: 5th, 50th and 95th percentiles of simulated OMB157 concentration data
Red shaded area: 90% prediction interval of 50th percentile
Blue shaded area: 90% prediction interval of 5th and 95th percentiles
Study 2102 = COMB157G2102; Study 2301 = COMB157G2301; Study 2301 = COMB157G2302;
Study 2831 = OMS112831; Study 5102 = OMS115102;

The majority of the data came from patients given the phase 3 dosing regimen of 3 weekly loading doses of 20 mg followed by 20 mg given every 4 weeks starting from day 28, corresponding to 1196 patients with 7874 observed concentrations. Dose ranging information came from the IV study OMS115102 and the phase 2 study OMS112831. While OMS112831 provided 650 observations from 219 patients administered doses between 3 and 60 mg, 70.9% of the observations were BLOQ. This meant that most of the rich PK data with dose ranging information came from study OMS115102, although at doses higher than are possibly relevant for RMS patients.

Modelling Report: "Exploratory analyses of the relationship between ofatumumab dose regimen, peripheral blood CD19+ B-cell count and MRI lesions in relapsing-remitting multiple sclerosis patients": From the OMS112831 study data, the Applicant prospectively explored the performance of a novel phase 3 regimen in attaining B-cell depletion (i.e., 20 mg loading on weeks 0, 1, and 2 followed by 20mg every four weeks [Q4W]). The Applicant states that the majority of PK measurements were below LLQ, so a K-PD modelling approach with a virtual PK compartment was used to perform a population analysis of B-cell count dynamics. The Applicant should further clarify and also justify the use of a virtual PK compartment in regards of the validity of the presented PD model.

Presence of lesion activity at screening was associated with increased new GdE cumulative lesion volumes by week 24 and related to the mean CD19+ B-cells count (from weeks 4 to 20). The largest reduction in the new GdE cumulative lesion volumes was observed when the B-cell count was $\leq$8 cells/μL. Based on these results, a B-cell count of 8cells/μL was proposed as a target level in order to achieve low new GdE lesion counts and new GdE cumulative lesion volumes, which is accepted.

Absorption

Bioavailability

Study OMS112831 (phase 2 study)

This study provided seminal data to inform on the optimal dosage regimen in RRMS that was utilized in the Phase III studies (see dose response study in section 3.2).

Patients were randomized to one of the following 8 treatment arms:

Table 6

Table 2-11 Treatment arms in OMS112831

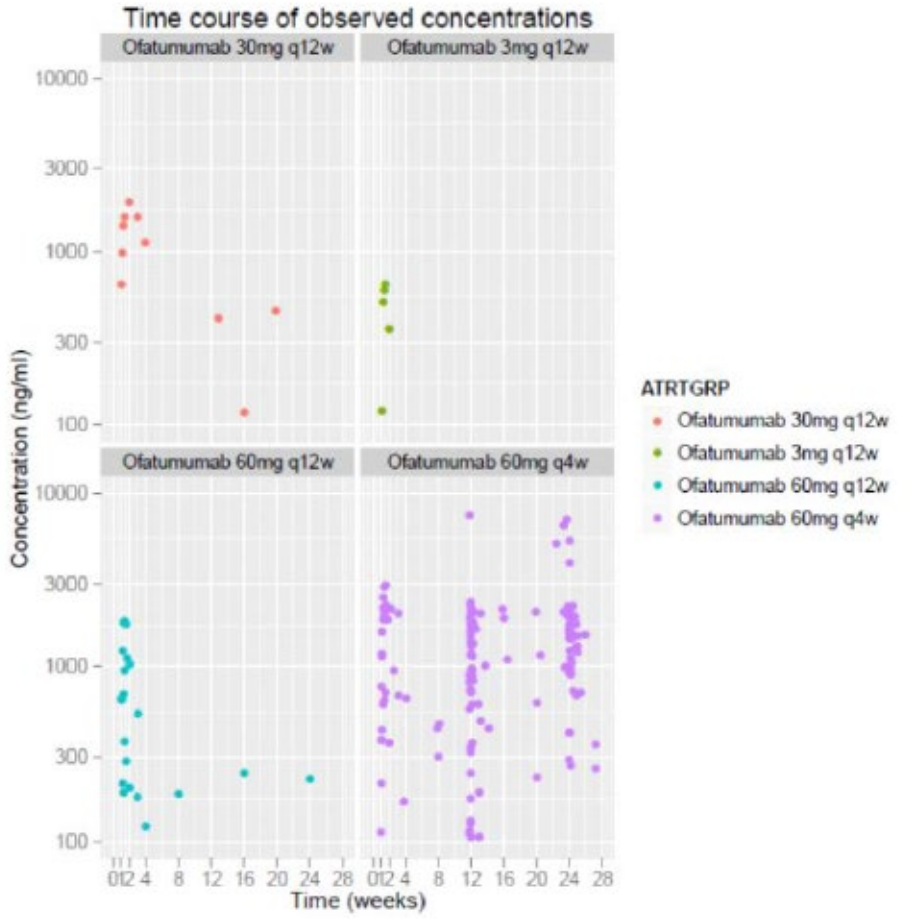
	Week 0	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20
Placebo	Placebo	Placebo	Placebo	Placebo	3 mg	Placebo	Placebo
Ofa 3mg q12w	Placebo	3 mg	Placebo	Placebo	3 mg	Placebo	Placebo
Ofa 30mg q12w	Placebo	30 mg	Placebo	Placebo	30 mg	Placebo	Placebo
Ofa 30mg q12w + conditioning dose	3 mg	30 mg	Placebo	Placebo	30 mg	Placebo	Placebo
Ofa 60mg q12w	Placebo	60 mg	Placebo	Placebo	60 mg	Placebo	Placebo
Ofa 60mg q12w + conditioning dose	3 mg	60 mg	Placebo	Placebo	60 mg	Placebo	Placebo
Ofa 60mg q4w	Placebo	60 mg	60 mg	60 mg	60 mg	60 mg	60 mg
Ofa 60mg q4w + conditioning dose	3 mg	60 mg	60 mg	60 mg	60 mg	60 mg	60 mg

Trough PK samples were collected at every SC infusion as well as at Week 24. PK parameters estimated for each of the above dosage regimen were: C_{max}, AUC0-t and Tmax. PD endpoints included B-cell depletion and repletion, measured by CD19+ and CD20+ cell counts. PK/PD evaluations, although planned, were not performed due to sparse PK samples.

Due to relatively high limit of quantification (100 ng/mL), the majority of PK samples were available from the 60 mg every 4-week dosing group, which included 58 patients. Therefore, the PK analysis included data from this group in majority. Available PK data across the dosing groups indicate increasing plasma concentrations with increasing doses (Figure 2-11, below).

Figure 5

Figure 2-11 Observed ofatumumab plasma concentrations by treatment group (Pharmacokinetic Population)



Considering the lack of PK data concerning other than 60 mg Q4 doses and the scanty PK parameters after administration of ofatumumab presented data do not allow for their direct reference to lower doses**.** However, PK data after administration of 3, 30 and 60 mg allowed the characterisation of the PK across different dose levels and the result from the study was included in the popPK analysis.

Study 2301 and 2302 (phase 3 studies)

Pivotal PK parameters like C_{max} and AUC are not available for the chosen dosing regimen, as only trough values were measured. The bioequivalence study (COMB157G2102), provided rich PK information from the 284 participating patients and combined results from these studies and from two phase II studies were used to develop a PKPD model.

Ofatumumab concentrations were observed to increase during the loading regimen, and exposure was subsequently maintained at a concentration level sufficient to suppress B-cells (Table 2-1 and Table 2-2, below). In study OMS112831, patients were randomised to 8 treatment arms. The highest dose was 60 mg ofatumumab every 4th week. Due to relatively high lower limit of quantification (LLQ) of 100 ng/ml, the majority of pk samples were available for this dose, and not for the lower doses, and this dose was therefore used for pk analysis. An accumulation ratio of 1.75 was demonstrated (12 week compared 24 week).

Data from the phase 3 studies shows a median ofatumumab concentration of 300-1100 ng/ml from month 1 to month 24 with an accumulation factor of ~3 fold from month 3 (after the loading phase) to month 24. The accumulation of ofatumumab is considered caused by a reduced degradation of ofatumumab due to the depletion of B-cells. The plasma concentration of ofatumumab in the phase 3 studies does not exceed the concentration, when ofatumumab is administered as 700 mg iv. There is no evidence of a higher frequency of adverse events in patients of low bodyweight (higher plasma concentration), and there is no temporal trend in adverse events (AE).

Table 7

Table 2-1 Summary statistics of pharmacokinetic (PK) concentrations (ug/mL) (Full analysis set) (N=465)

Timepoint	n (log)	Geo-mean	Geo-CV (%)
Baseline	4	0.13	141.47
Month 1	428	0.90	122.01
Month 3	333	0.29	146.18
Month 6	361	0.42	135.57
Month 12	355	0.63	125.17
Month 24	82	0.79	121.90
End of treatment	12	0.28	164.21
End of Study	351	0.85	136.40

N: number of patients in the analysis set.

n: number of patients with non-missing values in the respective visit.

CV: Coefficient of Variation (=SD/Mean).

Geo: Geometric.

n (log): number of patients included in calculating geo-mean concentration and geo-mean CV.

Table 8

Table 2-2 Summary statistics of pharmacokinetic (PK) concentrations (ug/mL) (Full analysis set) (N=481)

Timepoint	n (log)	Geo-mean Concentration (ug/mL)	Geo-mean CV (%)
Baseline	6	0.16	72.32
Month 1	423	0.92	121.27
Month 3	343	0.36	160.33
Month 6	382	0.50	147.63
Month 12	370	0.74	132.04
Month 24	81	1.10	103.51
End of treatment	13	0.46	106.35
End of Study	357	0.94	118.28

N: number of patients in the analysis set.

n: number of patients with non-missing values in the respective visit for calculation of geo-mean.

CV: Coefficient of Variation (=SD/Mean).

Geo: Geometric.

n (log): number of patients included in calculating geo-mean and geo-CV.

As a secondary objective, the Applicant evaluated whether administration of ofatumumab in the thigh differed from administration in the abdomen. No formal tests were performed. Based on figure 2-6 and table 2-5, high inter-subject variability was demonstrated for both administration routes and administration methods. There was no clear tendency of differences in AUC or C_{max} between administration routes and administration methods.

Figure 6

Figure 2-6 PK concentrations by nominal visit (PK analysis set)

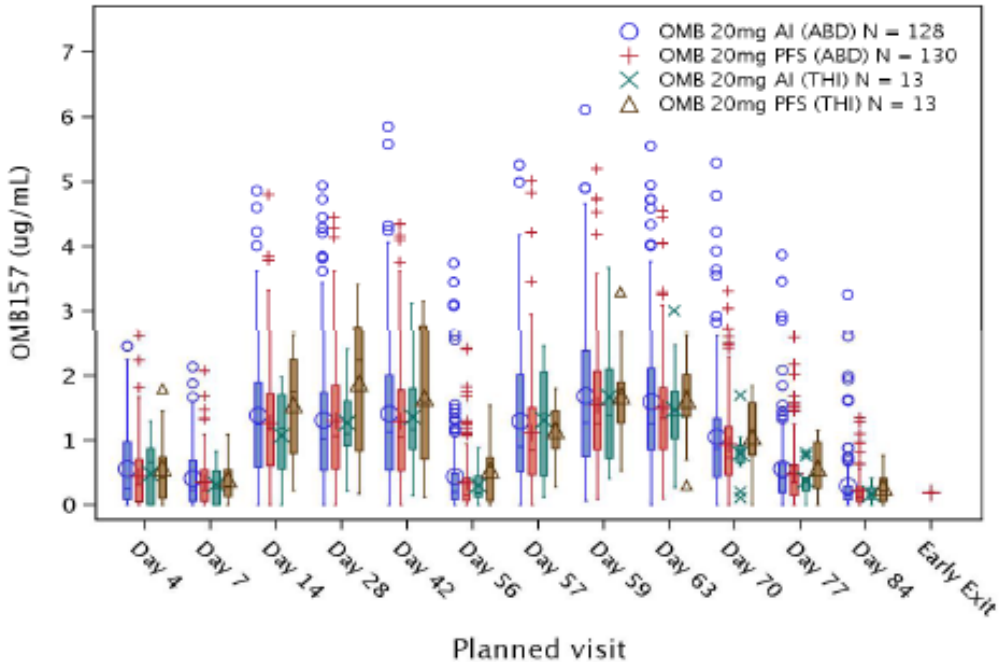


Table 9

Table 2-5 Summary statistics of AUCtau and Cmax at Week 8 dosing interval (PK analysis set)

Parameter	Statistics	OMB 20mg AI (ABD) N=128	OMB 20mg PFS (ABD) N=130	OMB 20mg AI (THI) N=13	OMB 20mg PFS (THI) N=13
AUCtau	n	128	128	13	13
	Geo-mean	487.7	474.1	476	544.1
	Geo-CV (%)	103.5	79.7	73.1	93.8
Cmax	n	128	128	13	13
	Geo-mean	1.409	1.409	1.563	1.635
	Geo-CV (%)	89.2	67.9	71.3	50.7

AI: autoinjector
PFS: Pre-filled syringe
N: number of patients in the analysis set.
n: number of patients with non-missing values in the respective visit.
CV: Coefficient of Variation (=SD/Mean).
Geo: Geometric mean.

In the SmPC, the abdomen, thigh and upper outer arm have been mentioned as administration sites. In the PK studies, the upper outer arm was not used as administration site. However, in the phase 3 studies upper arm, thigh and abdomen were used as injection sites. 552 patients (58.4 % of the study population) had at least one injection in the upper arm.

Bioequivalence

The Applicant evaluated bioequivalence between the PFS assembled with a needle safety device (NSD) used in the Phase III studies and PFS assembled in an autoinjector (AI) device for commercial use.

The Applicant used a parallel design and the PK parameters were measured at steady state. This alternative approach is acceptable due to long half-life of the drug. PK parameters (C_{max} and AUC_{tau}) were measured between week 8 and week 12.

Due to high inter-subject variability and a parallel design, the Applicant used a mixed scaling approach, which was discussed with the FDA. Based on this method, the Applicant demonstrated bioequivalence between NSD and AI. The bioequivalence guideline from EMA recommends a similar approach as FDA for drugs with high intra-subject variability and is also based on a cross-over design and not a parallel design. High intra-subject variability was especially seen in the thigh group, who consisted of a low number of patients**.**).

The methodology is considered adequate and bioequivalence between NSD and AI is considered demonstrated.

Distribution

Serum ofatumumab PK parameters (Study OMS115102) following the first and second infusions of ofatumumab in both Treatment Periods (Week 0- 24 and week 24- 48) are summarized by treatment and infusion in Table 2-8 and Table 2-9 (below), ranging from 2.15 to 2.74 L. The Applicant states that: in the two higher dose levels (300 and 700 mg) following the second IV infusions, Vss were approximately 2.4 L for the 300 mg dose 2.2 L and 19 days for the 700 mg dose. Furthermore, in the final popPK model, Vp was fixed to 2.8 L as the Applicant states that this value has been reported to be in the range of typical values for the peripheral volume of distribution. In the 2-compartment popPK model central volume of distribution was estimated to 2.8 L and Vss was estimated to 5.6

Table 10

Table 2-8 Summary of serum ofatumumab concentrations following first i.v. infusions in OMS115102 (FAS Population)

Treatment	N	Cmax mg/L	AUC(0-t) mg.h/L	Tmax hr
		Geometric mean (Coefficient of variation %)		Median (range)
		Treatment Period 1		
100 mg	8	36.8 (13.1)	153 (19.4)	5.33 (4.00-8.60)
300 mg	10	124 (23.6)	498 (18.6)	5.88 (4.17-7.67)
700 mg	6	346 (24.0)	1528 (20.7)	6.00 (5.17-9.42)
		Treatment Period 2		
100 mg	4	33.2 (13.7)	123 (8.6)	4.42 (4.08-6.00)
300 mg	3	137 (40.7)	624 (32.7)	6.00 (4.17-6.92)
700 mg	4	312 (24.5)	1347 (29.1)	6.54 (4.13-8.17)

Table 11

Table 2-9 Summary of serum ofatumumab concentrations following second i.v. infusions in OMS115102 (FAS Population)

Treatment	N	Cmax mg/L	AUCinf mg.h/L	CL L/hr	Vss L	T1/2 hr	Tmax hr
		Geometric mean (Coefficient of variation %)					Median (range)
Treatment Period 1							
100 mg	8	47.7 (14.7)	15559 (34.4)	0.006 (34.2)	2.48 (20.4)	246 (16.1)	4.25 (3.42-5.58)
300 mg	10	157 (25.9)	63165 (40.6)	0.005 (41.0)	2.61 (42.0)	331 (35.2)	4.33 (3.52-6.13)
700 mg	6	452 (28.5)	225876 (30.4)	0.003 (30.8)	2.19 (21.3)	452 (28.4)	3.83 (3.67-4.50)
Treatment Period 2							
100 mg	4	43.5 (25.2)	12763 (29.3)	0.008 (29.5)	2.74 (6.54)	241 (23.6)	3.67 (3.58-6.00)
300 mg	3	210 (54.1)	71041 (54.9)	0.004 (54.4)	2.20 (68.0)	342 (16.3)	5.17 (4.08-5.50)
700 mg	4	416 (24.6)	217757 (44.5)	0.003 (44.4)	2.15 (20.8)	453 (49.9)	4.50 (3.75-5.50)

In clinical studies with ofatumumab in other indications, the volume of distribution at steady state ranged from 1.7 to 8.1 L across studies, dose levels, and infusion number, and the expected Vd for a monoclonal antibody administered IV is approximately 5 L. In study 5102, the AUC might have been overestimated and thereby Vd underestimated, due to the short time interval relative to the long t½ between the infusions, which explains the differences in Vd.

Elimination

Based on simulations using the popPK model, the elimination profiles in men and women dosed to steady-state and following withdrawal of treatment showed an approximate half-life of ofatumumab of 14.9 days in men and 17.1 days in women.

Ofatumumab is eliminated through a non-linear, target-mediated route as well as a target-independent route-mediated by non-specific endocytosis followed by intracellular catabolism. Higher baseline B-cell count results in greater contribution of target-mediated elimination and shorter ofatumumab half-life at the start of treatment. Ofatumumab dosing leads to potent depletion of B-cells resulting in reduced overall CL at later cycles. As ofatumumab disposition does not involve the typical P450-mediated pathways of metabolism and excretion, no clinical or non-clinical ADME studies have been conducted.

Excretion and metabolism

The Applicant states that as other monoclonal antibodies, ofatumumab is expected to be degraded to small peptides and amino acids by ubiquitous proteolytic enzymes. It is agreed that antibodies are cleared principally through protein degradation processes, and thus classic xenobiotics metabolism pathways do not contribute to the CL of ofatumumab.

Dose proportionality and time dependency

Study OMS115102 was the first study with IV administration of ofatumumab to patients with RRMS, with the main purpose to evaluate the safety of ofatumumab. This study gave first evidence of profound B-cell depletion at relatively lower doses of ofatumumab in the target population.

The three dose cohorts were:

Table 12

Table 2-6 Treatment regimen in OMS115102

Sequential cohorts	Treatment sequence	1st Infusion (Week 0)	2nd infusion (Week 2)	3rd Infusion (Week 24)	4th infusion (Week 26)
Cohort 1	1	100 mg ofa	100 mg ofa	Placebo	Placebo
	2	Placebo	placebo	100 mg ofa	100 mg ofa
Cohort 2	1	300 mg ofa	300 mg ofa	Placebo	Placebo
	2	Placebo	placebo	300 mg ofa	300 mg ofa
Cohort 3	1	700 mg ofa	700 mg ofa	Placebo	Placebo
	2	Placebo	Placebo	700 mg ofa	700 mg ofa

Serum ofatumumab PK parameters following the first and second infusions of ofatumumab in both Treatment Periods are summarized by treatment and infusion in Table 2-8 and Table 2-9, (above).

Ofatumumab exhibited non-linear pharmacokinetics in doses below 100 mg. However, C_{max} and AUC increased 10-fold and 14-fold when the dose was increased from 100 mg to 700 mg. Hence, dose-proportionality in the range 100 mg -700 mg ofatumumab iv was not demonstrated, indicating saturation of the target-mediated elimination pathway in this dose range.

A lower dose of 20 mg SC monthly is tested in the phase 3 studies and proposed in the SmPC after a 3-time loading dose of 20 mg SC

In study OMS115102, higher PK-parameters were shown after the second infusion, which considered to be caused by a higher trough concentration before 2nd dose than 1st dose (no ofatumumab administered). Thus, time dependency for the doses 100-700 mg was demonstrated.

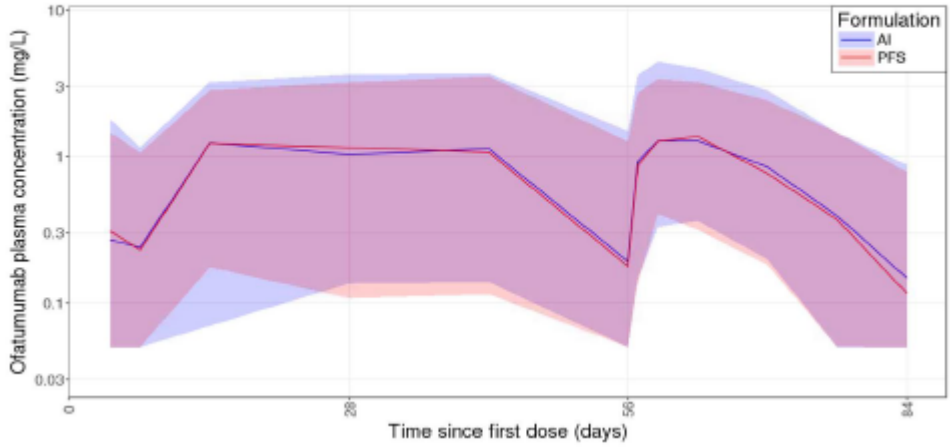
Furthermore, in study 2301 and 2302 an accumulation factor of ~3 was seen from month 3 to month 24.

Intra- and inter-individual variability

High inter-subject variability was shown in the bioequivalence study (G2102) time-wise ranging over approximately 1.5 orders of magnitude (fig 2-7 below). No intrasubject variability analysis was conducted.

Figure 7

Figure 2-7 Median and 2.5th - 97.5th percentiles of observed concentration-time data from AI and PFS in study G2102 - log scale



Pharmacokinetics in target population

The PK studies were conducted in RRMS patients and in RMS patients. No PK studies were conducted in healthy volunteers. In the pop-PK modelling, data from the phase 3 studies were included.

Special populations

No studies in hepatic and renal impaired patients have been conducted. The Applicant states that changes in renal or hepatic function are unlikely to affect the elimination of ofatumumab. This is agreed.

- **Gender**

Based on the popPK model, the bioavailability was estimated to be lower for women than men resulting in a 20% lower estimated AUC and C_{max} at steady state for women compared with men of similar bodyweight. This difference is considered small and is furthermore outweighed by a higher exposure with lower bodyweight. No differences in dosing between gender is recommended in the SmPC, which is agreed.

- **Race**

The Applicant found race not to be a significant covariate in the models. It should although be noted that only 112 out of a total of 1451 patient included in the 5 studies were non-Caucasians.

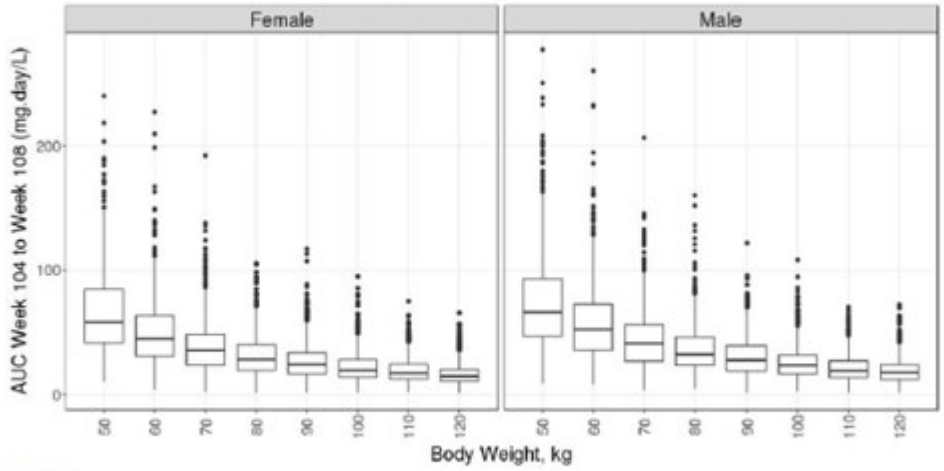
- **Weight**

Bodyweight was a significant covariate in the popPK model with a reduced exposure (AUC) of more than 50% in women above the 95% percentile bodyweight and an increased exposure of more than 50% in women below the 5% percentile bodyweight compared with women with the median bodyweight (65.5 kg). Among men, a similar pattern was seen.

Comparing a female patient of 60 kg with a female patient of 100 kg and a male patient of 60 kg with a male patient of 100 kg, more than a 2-fold higher AUC and C_{max} is observed. For the more extreme bodyweight values, the differences are even larger.

Figure 8

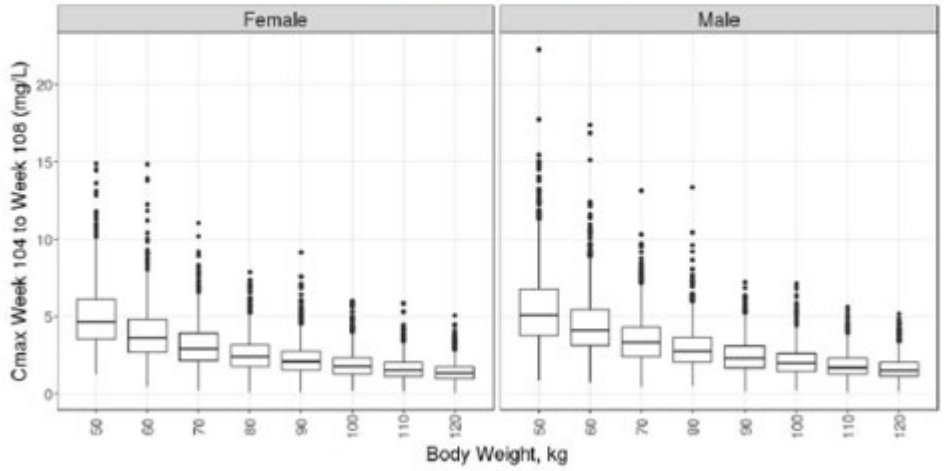
Figure 5-20 Simulated steady state AUC day 728-756 by weight and stratified by sex assuming the phase 3 dosage regimen and PFS administration



Source:
Script: TASK_03_Simulation/ OMB157_PK_simulations.Rmd
Output: TASK_03_Simulation/ OMB157_PK_simulations.docx

Figure 9

Figure 5-21 Simulated steady state Cmax day 728-756 by weight and stratified by sex assuming the phase 3 dosage regimen and PFS administration



The variability was extensive but no effect on efficacy and safety was observed due to the variability in exposure between the extreme values of bodyweight and a flat dose is considered acceptable. .

The impact of bodyweight on PK is reflected in the SmPC, section 5.2.

- **Elderly**

No studies in patients older than 56 years were conducted. Based on limited data available, no dose adjustment is considered necessary in elderly patients, which is adequately reflected in the SmPC.

- **Children**

No PK studies in children were performed. A PIP has been adopted.

Interactions

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

2.4.3. Pharmacodynamics

Ofatumumab is a monoclonal antibody that binds CD20. CD20 is a calcium channel protein expressed on late pre-B cells, mature -cells and memory B-cells. CD20 binding induces B-cell lysis primarily through complement-dependent cytotoxicity, and, to a lesser extent, by antibody-dependent T cell-mediated cytotoxicity.

B-cell count is used as the PD outcome in the pharmacology programme, which is considered an adequate marker of PD of ofatumumab.

Primary pharmacology

In study OMS115102, in which high IV doses were used, b-cell depletion was seen after 2 weeks after first dose (Fig 2.9 below). B-cell depletion was seen for most of the subjects up to week 48 (fig 2-10 below) for all dose levels. The recovery started earlier for the lowest dose, however, only a few subjects had recovered after 46 weeks post-dose. The median time to recovery of B-cells is 24 weeks in the phase 3 studies.

Figure 10

Figure 2-9 Blood B-cells (Week 0-24) in OMS115102 (FAS population)

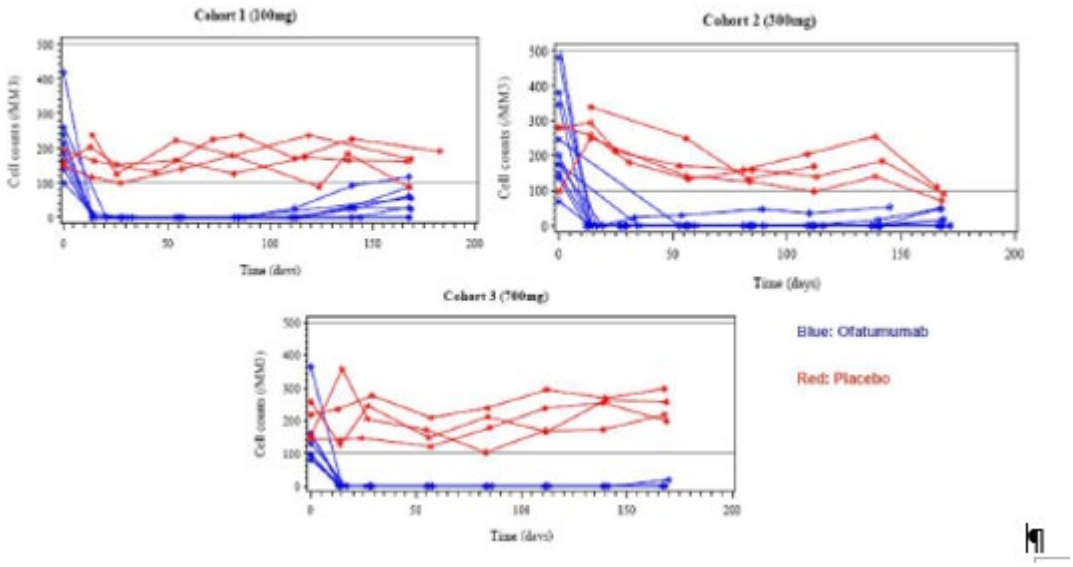
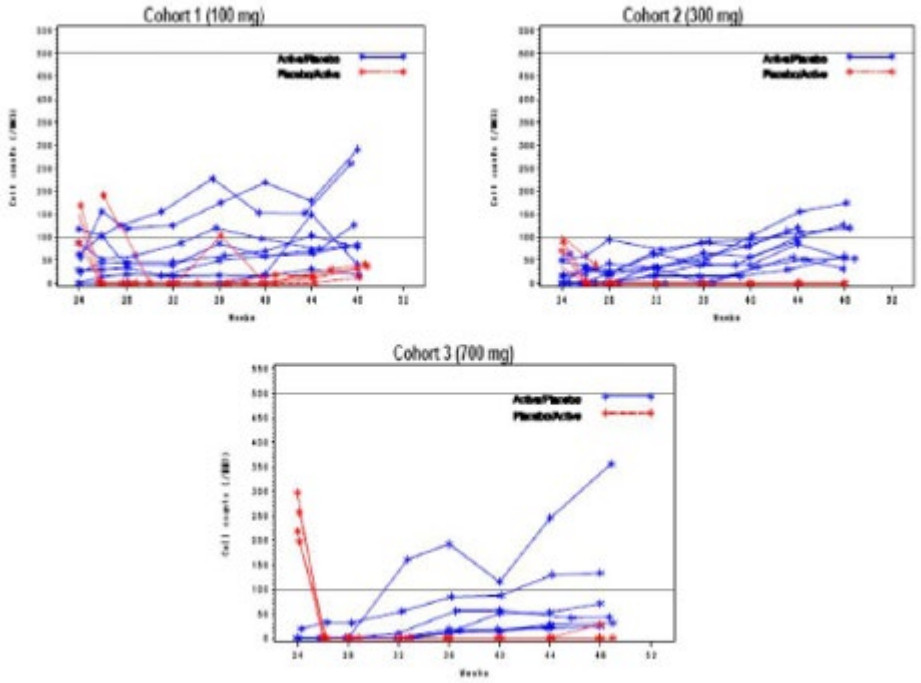


Figure 11

Figure 2-10 Blood B-cells (Week 24-48) in OMS115102 (FAS population)

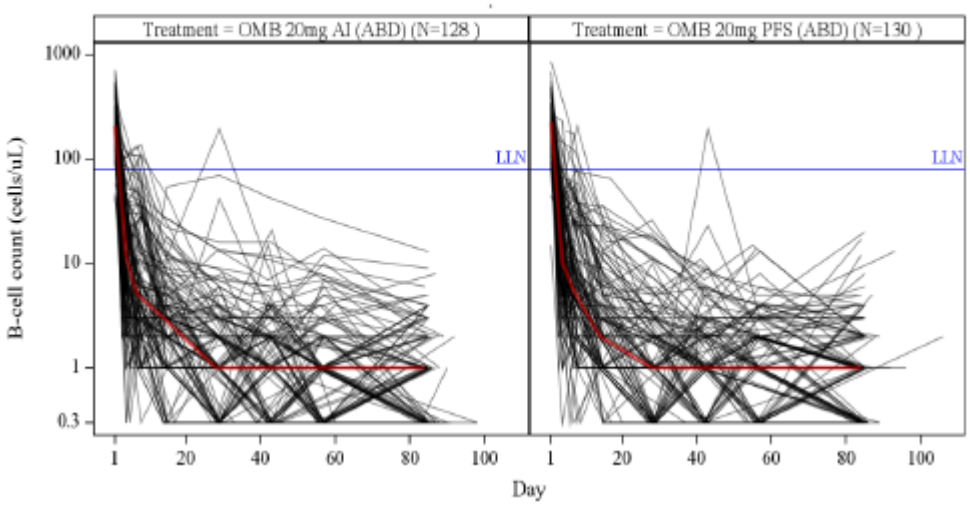


Red line: Placebo/Active; Blue line: Active/placebo

In Study G2102 the treatment period consisted of an initial loading phase (3 loading doses of 20 mg SC each on Days 1, 7 and 14) followed by a maintenance dose of 20 mg SC every 4 weeks, starting on Week 4. Depletion of b-cells was seen after the first injection and continued to decrease with subsequent injections. The proportion of patients that were below the lower limit of normal (LLN) of 80 cells /microliter after the three loading doses was 100%. The median b-cell count was 1/microliter after the end of the loading regimen (week 4), see fig 2-8 below. The treatment regimen is considered to deplete b-cells adequately.

Figure 12

Figure 2-8 Spaghetti plot of time to B-cell depletion on study drug (log scale) (Safety set)



Study OMS112831

Depletion of B-cells was rapid and dose-dependent at lower doses.

Studies G2301 and G2302

In pivotal studies, clinical activity of ofatumumab toward B-cell was shown. The loading dose regimen of 20 mg at days 1, 7 and 14, followed by maintenance regimen, every month administration of 20 mg, resulted in rapid and sustained depletion of B-cell in major of patients from week 2 of the treatment. Below LLN B-cell level (40 cells/µL) was observed for 96% of patients for as long as the treatment period continued. Discontinuation of treatment led to the repletion – (defined as valued above LLN or baseline) of B-cells. At week 60, repletion was 84.6% and 97.4% for Asclepios I and II, respectively.

In Phase II study OMS112831, depletion of B-cells below 32 cells/µL have no impact on lesions reduction. Main concern arises from different settings of B-cell limits which were used for division of patients according ofatumumab response toward B-cell depletion. First, the Applicant confirmed the target number of cells is ≤ 8 cells/µL. However, the lower limit for this study used for division of patients according to the number of B-cells after treatment was LLN, so 40 cells for 1 µL. Further, for pooled data analysis from studies G2301 and G2301 the cut-off was 10 cells/µL. The use of the ≤ 8 cells/µL as a target number was based upon understanding the relationship between B-cell depletion and the GdE T1 lesions volume. Lower B-cell count were associated with lower cumulative GdE T1 lesions volumes, not lesion count. Additionally, 32 cells/µL was appropriate for lowering GdE T1 volume lesions from week 4 to 12, whereas the T1 volume was lower between 12 and 24 weeks of treatment when the B cells were 8 cells/µL.

Secondary pharmacology

QTc

No dedicated QTc studies were performed. Monoclonal antibodies are not likely to cause QTc interval prolongation, and no QTc prolongation was seen in the pre-clinical studies, in the phase 3 studies in RMS patients or in the pre-clinical, clinical and post-marketing studies in oncology. Hence, ofatumumab is not considered to cause Qtc prolongation. According to ICH E14 Questions and Answers, R3, 2017 it is acceptable that no dedicated QTc studies have been conducted.

As the teriflunomide is not considered as drug that may cause QT interval prolongation of clinical significance, the Applicant was asked why patient with a QT prolongation in history was excluded from the study (OMS112831). Study OMS112831 was planned and executed by GlaxoSmithKline (GSK) with a CSR effective date 15-Dec-2015. The Applicant informed that the rationale for the individual inclusion / exclusion criteria are not documented and unknown to Novartis. In the Novartis Phase III studies, this exclusion criterion was not applied.

Antidrug antibodies

In 24 out 1476 subjects, antidrug-antibodies were identified, Table 2-1 (below). Of those, 17 subjects had pre-existing antidrug-antibodies and 7 subjects had induced antidrug-antibodies. Furthermore, in 10 subjects the analysis of antidrug-antibodies was inconclusive. In total, 20 samples were analysed for neutralising antibodies, and none of those were positive. The assay for evaluation of ADA in study 5102 was inconclusive due to low drug tolerance. The assays for evaluation of ADA and NAb in the phase 3 studies are considered valid, hence the prevalence and incidence of antibodies in the phase 3 studies are considered low.

Table 13

Table 2-1 Frequency distribution of integrated ADA status in ofatumumab-treated patients with RMS

Integrated ADA Status	OMS115102	OMS112831	OMB157G2102	OMB157G2301	OMB157G2302	Total
ADA negative or ADA positive with no boost	**38**	**231**	**284**	**454**	**469**	**1476**
ADA negative	38	227	278	449	462	1454
ADA positive with no boost	0/38	4/231	7/284	5/454*	8/469*	24/1476
Persistent ADA	0/38	0/231	1/284	1/454	2/469	4/1476
Pre-existing ADA	**0/38**	**0/229**	**6/281***	**4/442**	**7/460**	**17/1450**
Induced or Enhanced	**0/38**	**4/231**	**1/284**	**1/454**	**1/469**	**7/1476**
Induced (pre-existing ADA negative)	0/38	4/231	1/284	1/454	1/469	7/1476
Enhanced (pre-existing ADA positive)	0/38	0/231	0/284	0/454	0/469	0/1476
ADA inconclusive (exposure above DT)	10/38**	0/231	0/284	0/454	0/469	10/1476
Subjects analyzed in nAb assay	**0**	**0**	**7**	**5**	**8**	**20**
NAb positive	0/0	0/0	0/7	0/5	0/7	0/20
Missing ADA data at Pre-dose	0/38	2/231	3/284	12/454	9/469	27/1476

- n = Number of subjects satisfying the condition.
- M = Total number of subjects satisfying the appropriate subgroup with a pre-dose and at least one post-dose ADA data available.

*includes patients with persistent ADA.

** [Study OMS115102-Listing 48] and [Study OMS115102-Listing 49]

DT=Drug tolerance

ADA titers and PK

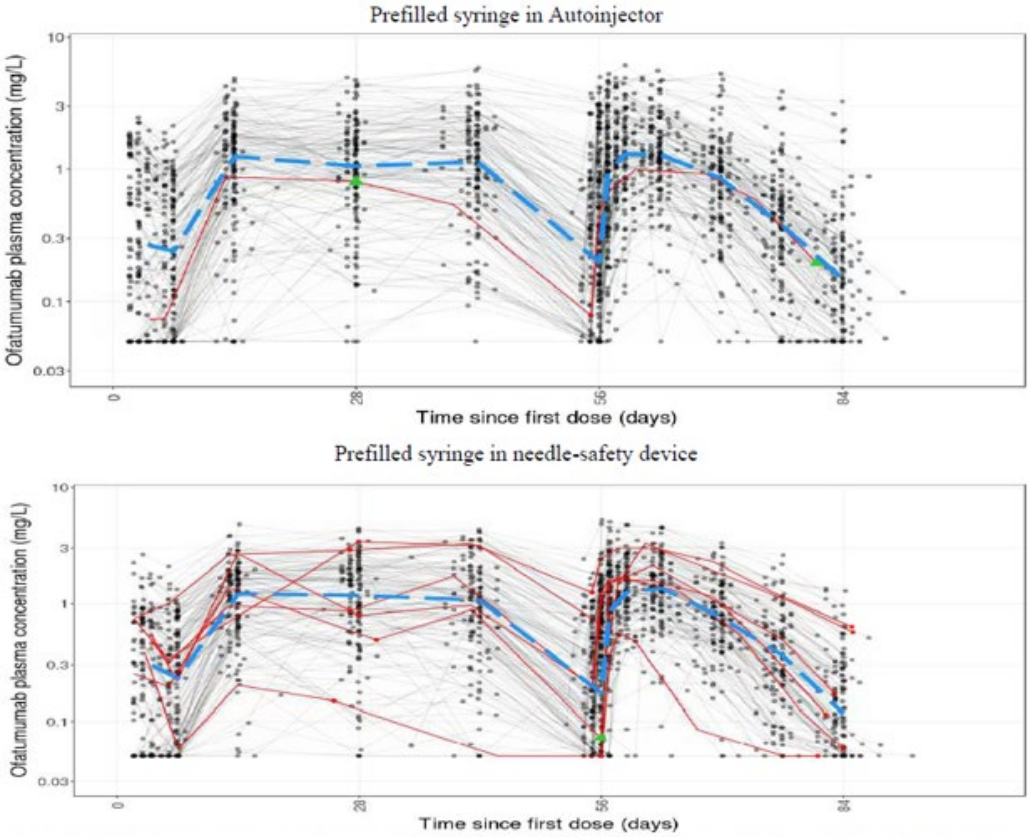
Individual plasma concentrations were plotted for subjects in studies G2102, G2301 and G2302, and the course of ofatumumab plasma concentrations for subjects with antidrug-antibodies (ADAs) were highlighted. There was no clear tendency of a lower plasma concentration in subjects with positive antidrug-antibodies, although one of the subjects in study G2102 had minimum trough concentrations at 3 time points. No neutralising antibodies were detected.

In all three studies, several subjects experienced minimal ofatumumab plasma concentrations. As no neutralising antibodies were detected, the low ofatumumab concentration in some of the patients is not due to NAb.

Figure 2-1, Figure 2-2 and Figure 2-3 (below) plot the course of ADA measures in ADA-positive patients in studies G2102, G2301 and G2302, respectively

Figure 13

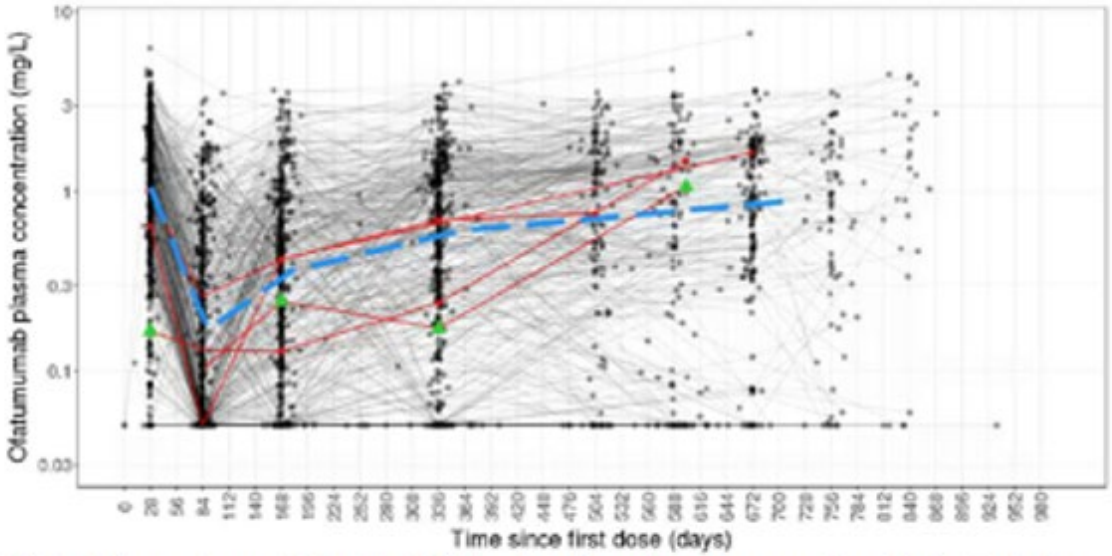
Figure 2-1 **Spaghetti plot of ofatumumab PK concentrations vs time with superimposed data from ADA-positive patients in Study G2102 from (semi-log scale)**



Black points are observed data without ADA; red points and lines correspond to patients who had an ADA at any time; green triangles are the points in time at which the ADA was recorded; blue line is median.

Figure 14

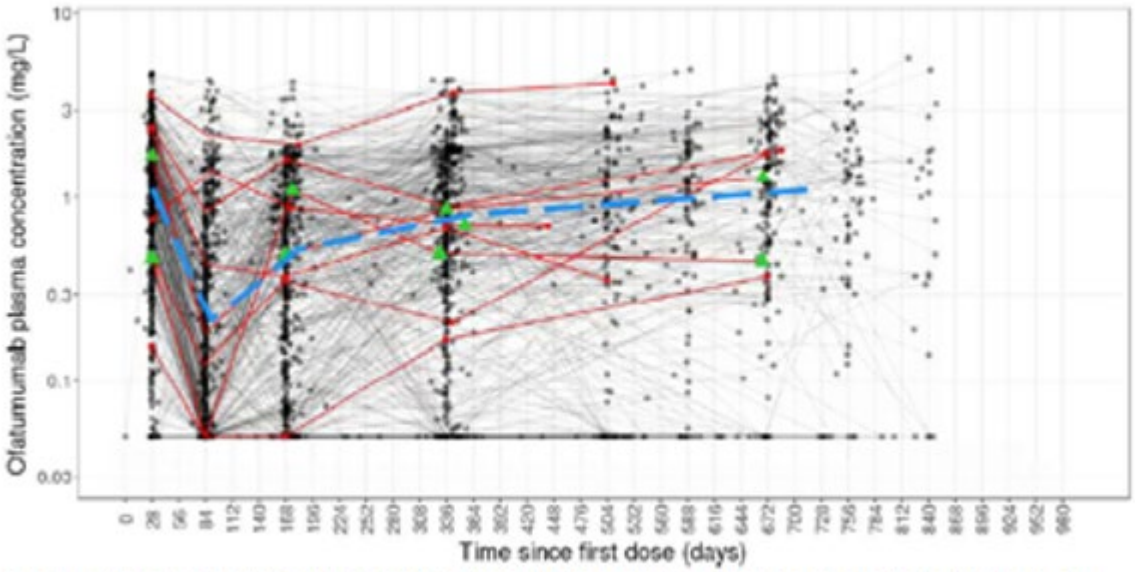
Figure 2-2 **Spaghetti plot of ofatumumab PK concentrations vs time with superimposed data from ADA-positive patients in Study G2301 (semi-log scale)**



Black points are observed data without ADA; red points and lines correspond to patients who had an ADA at any time; green triangles are the points in time at which the ADA was recorded; blue line is median.

Figure 15

Figure 2-3 **Spaghetti plot of ofatumumab PK concentrations vs time with superimposed data from ADA-positive patients in Study G2302 (semi-log scale)**



Black points are observed data without ADA; red points and lines correspond to patients who had an ADA at any time; green triangles are the points in time at which the ADA was recorded; blue line is median.

ADA and B-cell kinetics

The Applicant has plotted the levels of CD19+ B-cell count for study G2102, G2301 and G2302. There is no tendency that subjects with anti-drug antibodies have a lower depletion of B-cells. However, 2.4 % of the patients do not experience a depletion in B-cells. Even though the B-cell depletion was incomplete, the efficacy was higher in the 23 patients with insufficient b-cell response compared with the teriflunomide group.

The course of ADA overlaid on B-cell counts in Studies G2102, G2301 and G2302 are shown in Figure 2-4, Figure 2-5 and Figure 2-6. The plots indicate no impact of positive and high titers of ADA on B-cell kinetics in patients with RMS.

Figure 16

Figure 2-4 **Plot of B-cell count over time overlaid with ADA data in Study G2102 (semi-log scale)**

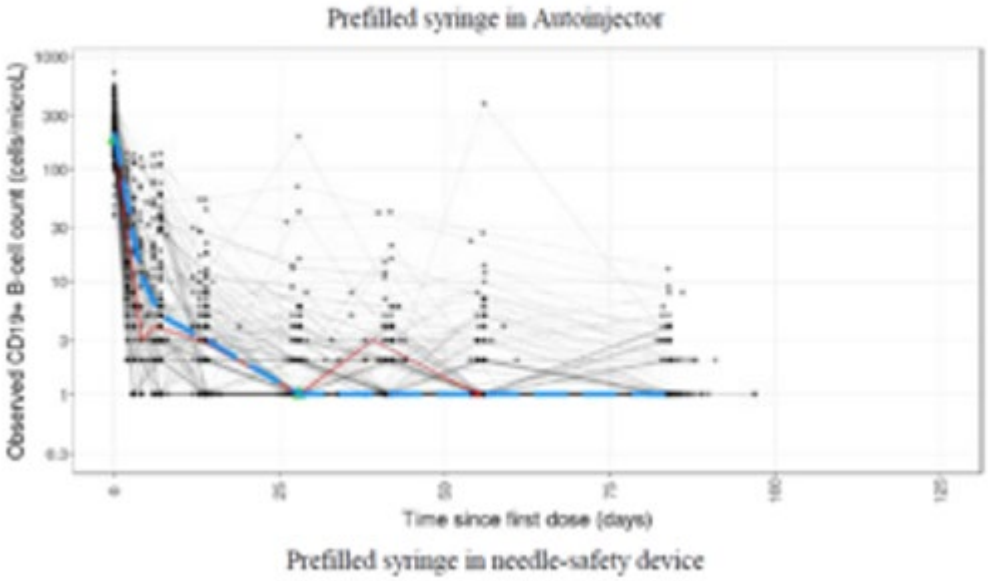
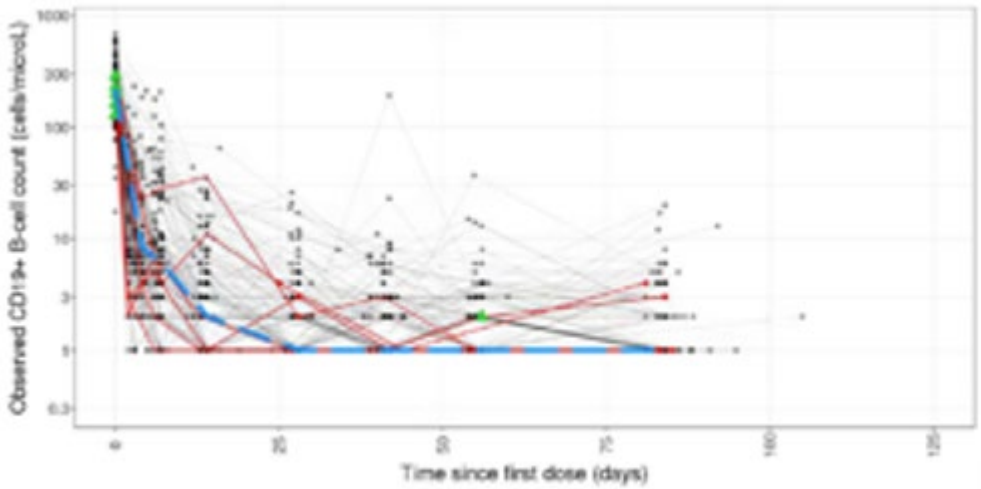


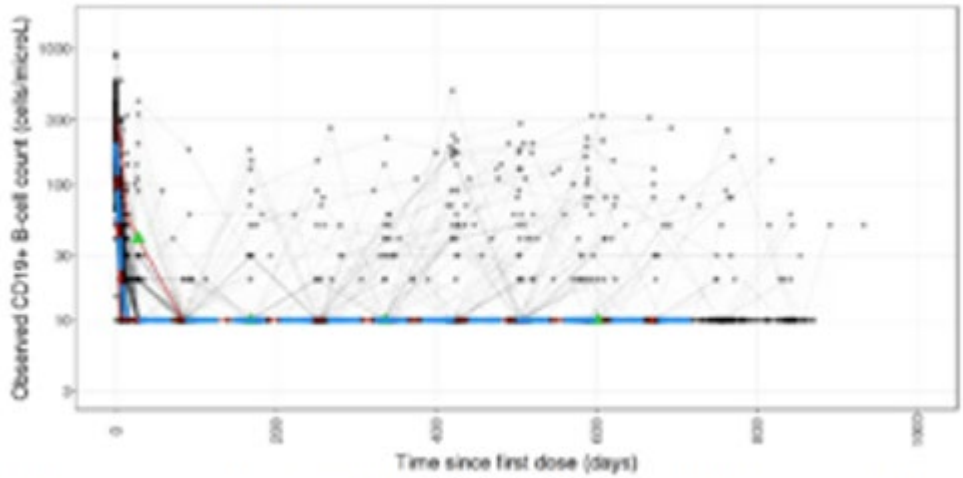
Figure 17



Black points are observed data without ADA; red points and lines correspond to patients who had an ADA at any time; green triangles are the points in time at which the ADA was recorded; blue line is median.

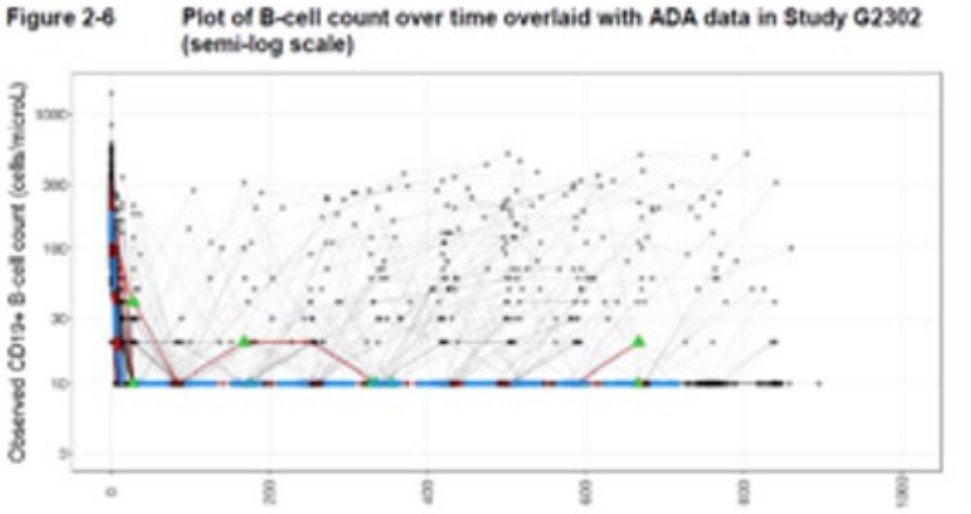
Figure 18

Figure 2-5 Plot of B-cell count over time overlaid with ADA data in Study G2301 (semi-log scale)



Black points are observed data without ADA; red points and lines correspond to patients who had an ADA at any time; green triangles are the points in time at which the ADA was recorded; blue line is median.

Figure 19



Relationship between plasma concentration and effect

In the dose finding study, depletion of b-cells was associated with dose – the higher dose, the greater depletion of b-cells. Simulation results suggested that the phase 3 regimen achieves and maintains target B-cell depletion in nearly all patients within 4 to 8 weeks (fig. 5-11, below). In addition, enabling recovery of B-cells for the median patient within 40 weeks of a dosing halt. Based on the results, the Applicant suggest the lower 20mg Q4W maintenance dose.

Depletion model simulations for phase 3 dose regimen selection:
Simulations of the percentage of patients attaining the target B-cells depletion (⩽8 cells/μL) for different doses and number of loading doses are shown in Table 5-8. Single doses of up to 60 mg achieved target depletion in 66% of patients. 20mg given 4 times is predicted to reach target depletion in nearly all patients. When the Applicant grouped three initial 20mg loading doses into a single 60mg dose and follow up with an additional 20mg dose, then it was suggested that nearly all (98%) patients attaining target depletion.

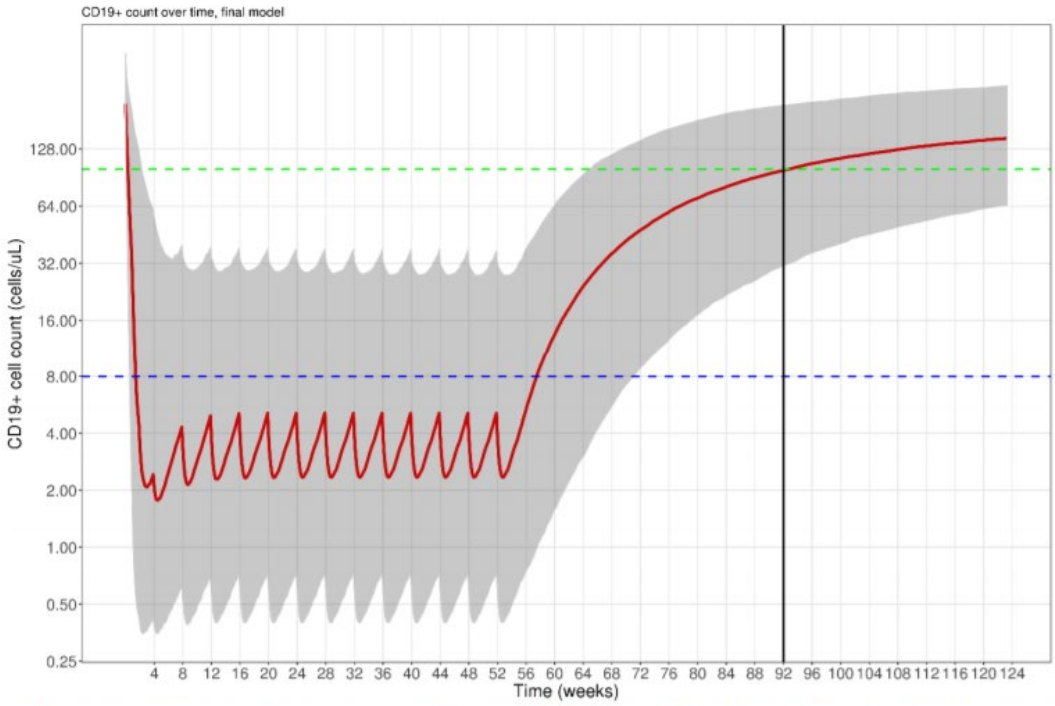
Table 14

Table 5-8 Depletion model simulation results of patients attaining B-cell count target (≤ 8 cells/μL) versus initial ofatumumab dose(s)

Ofatumumab Dose (mg)	Number of doses	Time period	% attaining target B-cell count (8 cells/μL)
3mg	1	4 weeks	3%
10mg	1	4 weeks	18%
20mg	1	4 weeks	37%
60mg	1	4 weeks	66%
20mg	2	4 weeks	94%
20mg	3	4 weeks	99%
20mg	4	4 weeks	>99%
60mg (loading), then additional 20mg after 4 weeks	1 (combined) + 1	8 weeks	98%

Figure 20

Figure 5-11 Simulated B-cell profiles in MS patients after 52 weeks of continuous treatment with 20mg weekly loading doses for the first 3 weeks, followed by 20 mg q4w starting from week 4 until week 52, and 72 weeks after dosing stop (1000 patients simulated)



Red line - population median; grey area - 90% prediction interval; blue dashed line - 8 cells/µL depletion threshold, green dashed line – lower limit of normal 100 cells/µL

Across the phase 3 studies, besides the loading phase, weak correlation between serum ofatumumab concentration and B-cells depletion has been found. When patients exhibited the lowest (observed in month 3) and the highest (observed in month 1) serum ofatumumab concentration, high depletion of B-cells seen in above 96% of patients, independently upon ofatumumab level was noted.

A simulation was performed to assess whether a lower dose of ofatumumab could have a potency to adequately decrease B-cell count. The result showed that median count of B-cell was similar for both the 20 mg and 10 mg maintenance doses (1.4 cells/µL and 1.5 cells/µL, respectively). However, the proportion of patients reaching target B-cell depletion were lower with the 10 mg maintenance dose (10% of patients have above 10 cell/µL in 10 mg maintenance dose compared to 5% in simulated patients after 20 mg of ofatumumab). Also, higher and variable count of B-cell after loading phase and higher B-cell count are associated with suboptimal efficacy (OMS112831-Figure 17).

Baseline B-cell count has no impact on B-cell depletion. Rapid and complete B-cell depletion was seen across the studies irrespective of baseline B-cell count, which ranged from below the LLN to above 1000 cell/µL. Besides B-cell depletion, no influence of baseline B-cell count was seen on efficacy and safety after ofatumumab administration

2.4.4. Discussion on clinical pharmacology

The pharmacology programme included three phase 2 studies and two phase 3 studies. From the phase 2 studies PK and PD were evaluated and bioequivalence were assessed, and the data from the phase 3 studies were included in the population PK analysis.

The PK of ofatumumab in patients with RMS has been evaluated based on data from 5 studies (OMS115102, OMS112831, G2301, G2302 and G2102). Both conventional non-compartmental and model-based analyses were used.

Methods to quantifyofatumumab, antidrug antibodies, and neutralizing antibodies were validated. Furthermore, the assay for quantification of ofatumumab had a LLQ of 100 ng/ml, hence the ofatumumab concentrations could not be measured for the majority of doses used in the dose-response study. For the highest dose (60 mg q4) and in the phase 3 study (20 mg q4) there was an accumulation ratio of 1.75 to 3, which is due to the depletion of B-cells and thereby a lower degradation of ofatumumab. The increased plasma concentration is not considered a safety concern.

The multiple dose studies showed non-linear pharmacokinetics. Hence, ofatumumab C_{max} increased 10-fold, and AUC increased 14-fold for a 7-fold increase in dose (from 100 mg to 700 mg). A lower dose of 20 mg was used in the phase 3 studies, where ofatumumab concentrations were measured as trough values at steady state.

Bioequivalence was demonstrated between the PFS assembled with a needle safety device (NSD) used in the Phase III studies and PFS assembled in an autoinjector (AI) device for commercial use. The Applicant states that SC injection can be in the thigh, abdomen and upper arm. No bioequivalence studies were conducted in order to show whether absorption differed between injections sites. However, the Applicant states that in the phase 3 studies upper arm, thigh and abdomen were used as injection sites. 552 patients (58.4 % of the study population) had at least one injection in the upper arm. 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.

A target-mediated drug-disposition model was selected to describe the ofatumumab concentration-time data. The PK parameter estimates have been specified as follows: a CL estimate of 0.156 L/day, the central volume of distribution estimated to 2.8 L, and the absorption rate constant estimated to 0.328 days -1, giving a steady state time to maximum concentration of 4-5 days post dose.

The inter-subject variability on the model parameters and the variability in the concentration data within patients described well the variability observed between patients, with concentrations at steady state ranging over 1-1.5 orders of magnitude given the phase 3 dose regimen.

Due to the degradation to small peptides and amino acids, no impact of hepatic insufficiency or renal impairment are expected. The Applicant furthermore states that data from Arzerra used in oncology shows that baseline creatinine CL is not associated with inter-individual variability in ofatumumab pharmacokinetics for CLcr values above 26ml/min, which is accepted.

The POP PK analysis (Population pharmacokinetics of ofatumumab in RMS patients Modelling Report) suggested a quasi-steady state approximation of the target mediated drug-disposition model with two PK compartments and a first order process for the SC administration. After the loading phase, ofatumumab concentrations decreased to a minimum and then increased to steady state after 2 years. This was captured in the model by a time-dependent effect on the receptor synthesis rate. The covariates that were selected in the final model

included weight effects on the absorption rate, CL, intercompartmental CL, central volume, complex elimination rate constant and the baseline receptor synthesis rate, a sex effect on bioavailability, an AI effect on complex elimination rate constant, and an IV formulation effect on baseline receptor synthesis rate. The covariates anti-drug antibodies, age, race and baseline B-cell count were found not to be related to any of the PK parameters.

The majority of the data came from patients given the phase 3 dosing regimen of 3 weekly loading doses of 20 mg followed by 20 mg given every 4 weeks starting from day 28, corresponding to 1196 patients with 7874 observed concentrations. Dose ranging information came from the IV study OMS115102 and the phase 2 study OMS112831. While OMS112831 provided 650 observations from 219 patients administered doses between 3 and 60 mg, 70.9% of the observations were BLOQ. This meant that most of the rich PK data with dose ranging information came from study OMS115102, although at doses higher than are possibly relevant for RMS patients. However, PK data after administration of 3, 30 and 60 mg allowed the characterisation of the PK across different dose levels and the result from study OMS115102 was included in the popPK analysis.

The population PK model shows that bioavailability for women is 20% lower than for men of similar body weight, which is not considered clinically relevant and no dose adjustment is recommended in the SmPC. On the other hand, body weight was a significant covariate in the population PK analysis. Hence, for women in the top 5% or lowest 5% of the body weight distribution, a 50% decrease or 50% increase was shown. Among men, a similar pattern was seen. The variability in exposure was extensive but no effect on efficacy and safety was observed between the extreme values of bodyweight, and a flat dose is considered acceptable.

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 monoclonal antibodies is degraded to small peptides and amino acids and are not metabolised by the cytochrome p450 system.

PD were assessed using three phase 2 studies and two phase 3 studies.

In study OMS115102, in which high IV doses were used, b-cell depletion was seen after 2 weeks after first dose. B-cell depletion was seen for most of the subjects up to week 48. Recovery started earlier for the lowest dose, however, only a few subjects had recovered after 46 weeks post-dose. The median time to recovery of B-cells is 24 weeks in the phase 3 study in which the proposed dose has been used. This is reflected in the SmPC section 4.4.

In study G2102, in which the proposed dose of 20 mg q4 post loading was used, adequate depletion of b-cells was seen after 4 weeks. Across the phase 3 studies, besides the loading phase, weak correlation between serum ofatumumab concentration and B-cells depletion has been found. When patients exhibited the lowest (observed in month 3) and the highest (observed in month 1) serum ofatumumab concentration, high depletion of B-cells seen in above 96% of patients, independently upon ofatumumab level was noted.

A simulation was performed to assess whether a lower dose of ofatumumab could have a potency to adequately decrease B-cell count. The result showed that median count of B-cell was similar for both the 20 mg and 10 mg maintenance doses (1.4 cells/µL and 1.5 cells/µL, respectively). However, the proportion of patients reaching target B-cell depletion were lower with the 10 mg maintenance dose (10% of patients have above 10 cell/µL in 10 mg maintenance dose compared to 5% in simulated patients after 20 mg of ofatumumab). Also, higher and variable count of B-cell after loading phase and higher B-cell count are associated with suboptimal efficacy (OMS112831-Figure 17).

Baseline B-cell count has no impact on B-cell depletion. Rapid and complete B-cell depletion was seen across the studies irrespective of baseline B-cell count, which ranged from below the LLN to above 1000 cell/µL. Besides B-cell depletion, no influence of baseline B-cell count was seen on efficacy and safety after ofatumumab administration.

No dedicated QT study was conducted; however, monoclonal antibodies are not likely to cause QTc interval prolongation, and no QTc prolongation was seen in the pre-clinical studies, in the phase 3 studies in RMS patients or in the pre-clinical, clinical and post-marketing studies in oncology. Hence, ofatumumab is not considered to cause QTc prolongation, and it is considered acceptable that no dedicated QTc study was conducted.

Few subjects had developed antidrug antibodies, however, 17 subjects had pre-existing antidrug antibodies, and 10 samples were inconclusive. The assay for evaluation of ADA in study 5102 was inconclusive due to low drug tolerance. The assays for evaluation of ADA and NAb in the phase 3 studies are considered valid, hence the prevalence and incidence of antibodies in the phase 3 studies are considered low. No neutralising antibodies were detected in the phase 3 studies, therefore the lack of B-cell depletion in several of the patients in the phase 3 studies is not considered to be caused by NAb. A tendency towards a lower effect in 23 patients with incomplete B-cell response was seen, however, the effect was higher than compared with the teriflunomide group.

2.4.5. Conclusions on clinical pharmacology

In conclusion, the clinical pharmacology programme describes adequately the pharmacokinetics of ofatumumab and the proposed dosing regimen: 20 mg weekly loading dose for 3 weeks followed by 20mg Q4W maintenance dose. Ofatumumab showed adequate depletion of b-cells using the proposed dosing regimen, however, the effect was higher than compared with the teriflunomide group. In conclusion, the clinical pharmacology is considered acceptable.

2.5. Clinical efficacy

The Phase III studies COMB157G2301 (hereafter referred to as Study 2301) and COMB157G2302 (hereafter referred to as Study 2302) are the key studies supporting the registration of ofatumumab 20 mg SC in patients with active RMS. Studies 2301 and 2302 had a flexible duration design: The treatment duration for an individual patient was variable and based on when the End of Study (EOS) was declared. 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 study-specific data cut-off date was 05-Jul-2019 for Study 2301 and 10-Jul-2019 for Study 2302.

Study COMB157G2399 is the open-label, single-arm, multi-center extension study enrolling patients completing other ofatumumab MS clinical studies (including studies 2301 and 2302). The study will be evaluating further long-term safety, tolerability and effectiveness of ofatumumab in patients with RMS. Limited data were available at the time of submission and were therefore not included.

Table 15

Table 1-1 Overview of studies or sources of data

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

Table 16

Table 1-3 Summary of pivotal Phase III 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)				

ARR= annualized relapse rate, MS= multiple sclerosis, RMS= relapsing multiple sclerosis, s.c.= subcutaneous(ly).

2.5.1. Dose-selection study

The ofatumumab dose and regimen for use in the pivotal Phase III studies was determined based on PK/PD modelling of data from the Phase II Study OMS112831, which investigated different doses (3 mg, 30 mg, and 60 mg) and different dosing intervals (Q12W and Q4W) of ofatumumab SC in patients with RRMS. Based on the results of the PK/PD modelling, the Applicant selected a loading dose regimen of 20 mg ofatumumab SC at Day 1, 7, and 14, and a maintenance dose regimen of 20 mg every 4 weeks starting at Week 4.

Study OMS112831 was a Phase II, randomized, multicenter, double-blind, placebo-controlled, parallel-group study to assess the MRI efficacy, safety, and tolerability of a range of ofatumumab doses administered SC in patients with RRMS. The study consisted of 4 phases: Screening, 24-week Treatment (Weeks 0-12 were placebo-controlled; at Week 12 placebo patients received ofatumumab 3 mg (Table 2-2), 24-week Follow-up, and individualised follow-up every 12 weeks until B-cell repletion. Patients could participate in a PK-sub-study if they signed a separate informed consent.

The study met the primary endpoint, as demonstrated by a reduction in cumulative new Gd-enhancing T1 lesions for all ofatumumab groups compared to placebo following 12 weeks of treatment. There was a rapid and dose-dependent reduction in CD19 +B-cells. During Weeks 0-12, the reduction in the cumulative number of new Gd-enhancing T1 lesions (primary endpoint) was 65% for all ofatumumab dose groups compared to placebo.

Table 17

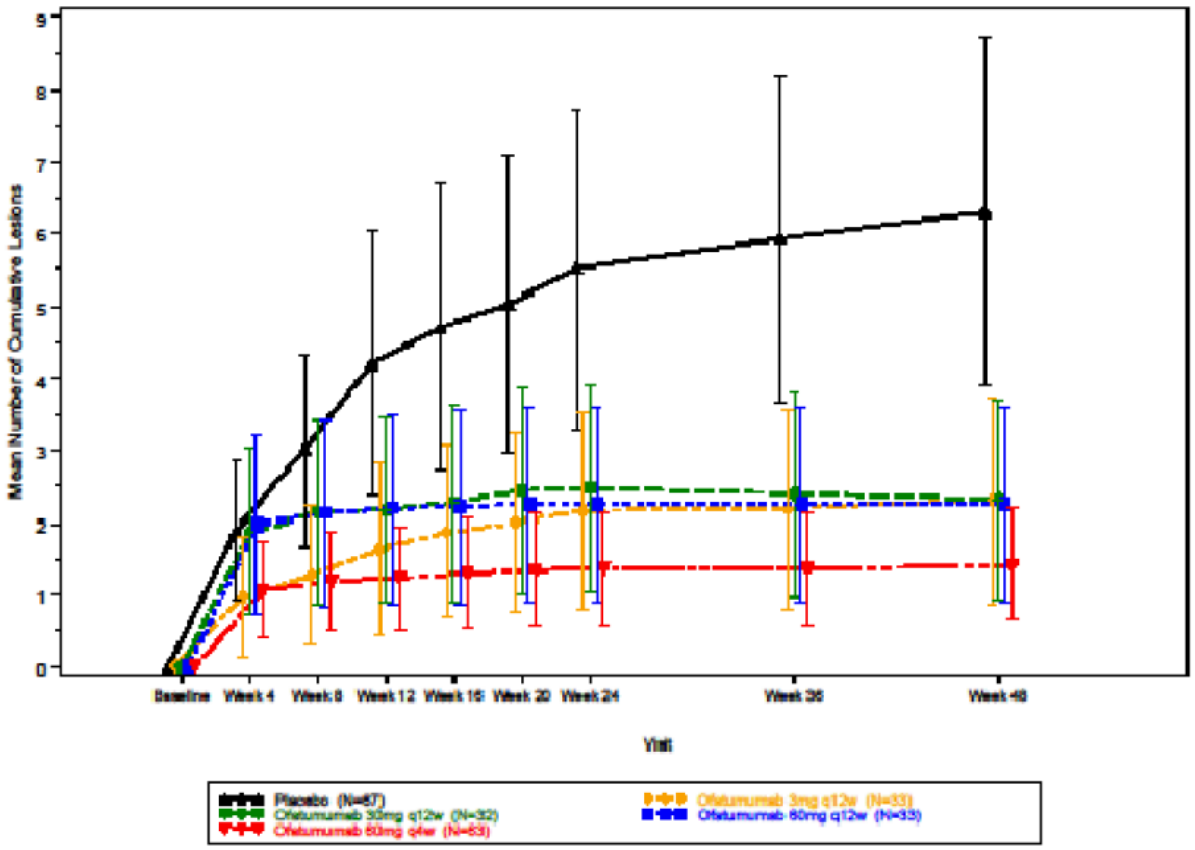
Table 21 Summary of Statistical Analysis of the Cumulative Number of New Gadolinium-Enhancing T1 Lesions Weeks 0-12 (ITT Population, AES Dataset): EMAX Model

				Treatment Comparisons[c]		
Treatment	N	n	Mean Rate [b]	Rate Ratio	95% Confidence Interval	P-value
Placebo[a]	67	67	0.99	1.00		
Ofatumumab 3mg q12w	33	33	0.35	0.35	(0.221, 0.548)	<0.001
Ofatumumab 30mg q12w	32	30	0.35	0.35	(0.221, 0.548)	<0.001
Ofatumumab 60mg q12w	33	33	0.35	0.35	(0.221, 0.548)	<0.001
Ofatumumab 60mg q4w	63	63	0.35	0.35	(0.221, 0.548)	<0.001

Data Source: Table 7.07
Note: n = Number of subjects contributing to the analysis.
Note: Emax model fitted was E0+Emax*dose/(ED50+dose)+baseline GdE lesion status.
a. Subjects randomised to placebo group received 3mg ofatumumab at Week 12.
b. Rate of the Cumulative Number of New Gadolinium-Enhancing T1 Lesions per scan
c. Ratios (Ofatumumab/ Placebo).

Figure 21

Figure 5 Mean Cumulative Number of New Gadolinium-Enhancing T1 Lesic by Treatment Phase, Dose Group and Visit (ITT Population, AES Dataset)



A clear dose-response relationship was not demonstrated. Thus, all doses tested (3 mg, 30 mg, 60 mg) in the MIRROR study (OMS112831) led to the same (65%) reduction in the cumulative number of new Gd-enhancing T1 lesions compared to placebo. A slightly higher median percentage B-cell reduction from baseline was observed in the 30 mg group (89.32%) as compared to the 3 mg group (77.93%) at Week 24. This led to the assumption that a lower dose than 30 mg and higher dose than 3 mg would be sufficient to achieve the desired efficacy. Furthermore, the dose regimens of 60 mg Q12W and Q4W were associated with more AEs than the lower dose regimens of 3 mg or 30 mg Q12W between Week 0 and Week 12. PK/PD modelling based on the study data suggested that a loading regimen of 3 separate 20 mg injections of ofatumumab (at weeks 0, 1 and 2) was required to attain a target depletion of $\leq$ 8 cells/μ L in > 95% of patients. Furthermore, an ofatumumab dose of 20 mg appeared to be sufficient to either maintain or to further deplete B-cells in > 95% of patients with previously depleted B-cell levels. Thus, this dosing regimen was selected for Phase III.

2.5.2. Main studies

Methods

The pivotal studies 2301 and 2302 were of identical design and will be addressed together in the methods section.

Study Participants

The study population in both studies consisted of adult patients with relapsing MS fulfilling all the eligibility criteria stated in the study protocols.

Inclusion criteria

1. Male or female patients aged 18 to 55 years (inclusive) at Screening.
2. Diagnosis of MS according to the 2010 Revised McDonald criteria (Polman et al 2011)
3. Relapsing MS: relapsing-remitting course (RRMS), or secondary progressive (SPMS) course with disease activity.
4. Disability status at Screening with an expanded disability status scale (EDSS) score of 0 to 5.5 (inclusive).
5. Documentation of at least: 1 relapse during the previous 1 year OR 2 relapses during the previous 2 years prior to Screening OR a positive Gd-enhancing MRI scan during the year prior to randomisation.
6. Neurologically stable within 1 month prior to randomisation.

Key Exclusion criteria

1. Patients with PPMS or SPMS without disease activity.
2. Patients meeting criteria for neuromyelitis optica.
3. Disease duration of more than 10 years in patients with an EDSS score of 2 or less.
4. Pregnant or nursing (lactating) women.
5. Women of child-bearing potential unless using highly effective methods of contraception during study drug dosing and for 12 months post-dosing.
6. Sexually active males unless they agree to use condom during intercourse while on study drug.
7. Patients with an active chronic disease of the immune system other than MS or with immunodeficiency syndrome.
8. Patients with neurological findings consistent with PML or confirmed PML.
9. Patients at risk of developing or having reactivation of hepatitis: positive results at Screening for serology markers for hepatitis A, B, C and E (HAV, HBV, HCV, and HEV) indicating acute or chronic infection.
10. Patients with active systemic infections or known to have AIDS or to test positive for HIV antibody at Screening.

11. Patients at risk of developing or having reactivation of syphilis or tuberculosis.
12. Have received any live or live-attenuated vaccines within 2 months prior to randomisation.
13. Have been treated with medications as specified or within timeframes specified (e.g. corticosteroids, ofatumumab, rituximab, ocrelizumab, alemtuzumab, natalizumab, cyclophosphamide, teriflunomide, leflunomide, etc.).
14. Any other disease or condition that could interfere with participation in the study according to the study protocol, or with the ability of the patients to cooperate and comply with the study procedures.

Treatments

The studies included 2 treatment groups:

- Ofatumumab group: ofatumumab 20 mg SC injections on Days 1, 7, 14, Week 4 (Study month 1) and every 4 weeks thereafter + teriflunomide-matching placebo capsule orally once daily.
- Teriflunomide group: teriflunomide 14 mg capsule orally once daily + ofatumumab matching placebo injections on Days 1, 7, 14, Week 4 (Study month 1) and every 4 weeks thereafter.

Ofatumumab is clear to opalescent, colourless to pale yellow, essentially particle-free liquid in a PFS. Ofatumumab 20 mg PFS for SC administration was supplied to the Investigators. The matching placebo to ofatumumab PFS had the same appearance as the investigational drug.

The control treatment, teriflunomide (Aubagio®) 14 mg for oral administration was provided as over-encapsulated tablets (either a hard gelatine capsule or a vegetarian-based hydroxy propyl methyl cellulose capsule was used, referred to as capsule hereafter). Teriflunomide-matching placebo capsule (capsule containing placebo-tablet) had the same appearance as the active comparator. Teriflunomide and teriflunomide-matching placebo capsules were provided in blisters.

Objectives

Primary objective

- To demonstrate that ofatumumab 20 mg SC once every 4 weeks is superior to teriflunomide 14 mg p.o. once daily in reducing the frequency of confirmed relapses as evaluated by the ARR in patients with RMS.

Key Secondary objectives

- To evaluate if ofatumumab 20 mg SC q4 weeks is superior to teriflunomide 14 mg p.o. once daily on the following efficacy measures:
    - Time to disability worsening as measured by 3-month confirmed disability worsening (3mCDW) on the 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 disability improvement (6mCDI) on EDSS
    - Number of T1 Gd-enhancing 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

Note: Disability-related key-secondary objectives are reported separately in a combined data (meta-analysis) report. All other key secondary objectives are addressed separately based on data from each individual study.

Outcomes/endpoints

Primary endpoint

The primary endpoint was the ARR, which was defined as the number of confirmed MS relapses in a year. Relapses were confirmed based on the EDSS by the independent EDSS Rater.

- MS relapse definition: appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. The abnormality must have been present for at least 24 hours and occurred in the absence of fever (< 37.5°C) or known infection.
- Confirmation of MS relapse: the definition of a confirmed MS relapse is one accompanied by a clinically relevant change in the EDSS performed by the Independent EDSS Rater, i.e. an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two functional scores (FSs) or 2 points on one FS, excluding changes involving bowel/bladder or cerebral FS compared to the previous available rating (the last EDSS rating that did not occur during a relapse).

The primary analysis used a treatment policy strategy e.g. the Applicant compared the treatment effect in term of ARR between ofatumumab and teriflunomide regardless of treatment discontinuation or short treatment to alleviate the symptoms of relapses.

Key-secondary efficacy endpoints

Disability worsening (3-month or 6-month confirmed)

A 3mCDW was defined as an increase from baseline in EDSS sustained for at least 3 months (Table 9-6). Analogously, a 6mCDW is defined as an increase from baseline in EDSS sustained for at least 6 months. This means that after a scheduled or unscheduled visit at which the patient fulfils the disability worsening criterion, all EDSS assessments (scheduled or unscheduled) need to also fulfil the worsening criteria until the worsening ("the event") can be confirmed at the first scheduled visit that occurs 3-months (or 6 months) after the onset of the worsening, or later.

Table 18

Table 9-6 Criterion for disability worsening based on change in EDSS score

Total EDSS at baseline*	"Disability worsening" criterion
0	≥+1.5
1 to 5	≥+1
≥5.5	≥+0.5

EDSS=Expanded Disability Status Scale

A 3-month confirmed disability worsening (3mCDW) can have an onset at any scheduled or unscheduled visit if the disability worsening criterion is met. A disability worsening can only be confirmed at a scheduled visit if, over a period of 3 months (≥90 days=3*30) time interval, all assessments meet the worsening criterion.

A 6-month confirmed disability worsening (6-mCDW) can have an onset at any scheduled or unscheduled visit if the disability worsening criterion is met. A disability worsening event can only be confirmed at a scheduled visit if, over a period of 6 months (≥166 days=6*30-14) time interval, all assessments meet the worsening criterion.

If a patients dies due to MS (EDSS=10 at any time), it is considered a confirmed disability worsening regardless of the baseline EDSS or the change in EDSS.

* Baseline EDSS is defined as the last EDSS assessment prior to the first dose of study treatment (protocol inclusion criterion is EDSS 0-5.5)

Disability improvement (6-month confirmed)

A 6mCDI is defined as a decrease from baseline EDSS sustained for at least 6 months. Censoring occurs in patients who did not experience a 6mCDI event in the study.

Number of T1 Gd-enhancing lesions per scan

Comparison of the number of Gd-enhancing lesions per scan between ofatumumab 20 mg SC and teriflunomide 14 mg p.o.

Annualised rate of new or enlarging T2 lesions

Comparison of the number of new or enlarging T2 lesions between ofatumumab 20 mg SC and teriflunomide 14 mg p.o.

Neurofilament light chain

NfL is hypothesised to be a putative biomarker to indicate treatment response and to predict disability worsening in patients with MS. Comparison is performed of the NfL concentration between ofatumumab and 20 mg SC teriflunomide 14 mg p.o. by Month 3.

Superiority of ofatumumab 20 mg SC over teriflunomide 14 mg p.o. was concluded if NfL levels were already lower at Month 3 in patients treated with ofatumumab compared with teriflunomide.

Brain volume loss

The BVL between ofatumumab 20 mg SC and teriflunomide 14 mg p.o. will be compared.

Randomisation

Eligible patients were randomised to receive either ofatumumab 20 mg sc injections once every 4 weeks (after initial loading regimen) or teriflunomide 14 mg orally once daily. The randomisation was stratified by geographical region (Western Europe, Eastern Europe, North America and Australia, Asia Pacific, Latin America, Others) and by MS subtype (RRMS, SPMS) to ensure a balance between covariates with potential impact on

the primary endpoint. All eligible subjects were randomised via Interactive Response Technology (IRT) by NIRT, using a block randomisation schedule (block size=4) by region.

The definition of region could be modified if that is indicated based on statistical criteria (e.g., non-convergence). For statistical analysis where region is adjusted in the statistical models, regions "Asia Pacific" and "Latin America" were combined with region "Other" due to small number of patients in these 2 regions.

No minimum number of SPMS patients was defined.

Study sites could only participate in one of the 2 studies to ensure independence of each study.

Blinding (masking)

A double-dummy design was used because the identity of the study drug cannot be disguised, as the drug products utilise different formulations.

Patients, Investigator staff, persons performing the assessments, and data analysts would remain blinded to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data kept strictly confidential until the time of unblinding, and not accessible by anyone involved in the study with the following exceptions: Data Monitoring Committee (DMC) members, Independent Statisticians and Independent Programmers. (2) The identity of the treatments would be concealed by the use of investigational treatment that are all identical in packaging, labelling, schedule of administration, appearance, taste and odour.

The randomisation codes associated with PK samples were disclosed to the Bioanalysts who should keep PK and ADA results confidential until data base lock.

The following measures were taken to protect the blinding of the Independent EDSS Rater (Rater):

- Prohibited access to patients' study data
- Separate binders of worksheets and CRF materials for Investigator and the Rater
- Prohibited cross-over of Investigator and Rater
- Use of appropriate clothing by patients to cover potential injection sites during neurological examinations
- Limited interactions between Rater and patient: permitting only a minimum required to perform the EDSS rating.

Additionally, potentially unblinding laboratory parameters (e.g. B-cell counts, teriflunomide plasma level results) were not to be communicated to the Investigator or other study staff.

Unblinding would only occur in the case of patient emergencies and at the conclusion of the core study.

Statistical methods

The efficacy analyses were performed using the full analysis set (FAS), which included all randomized patients according to the assigned treatment. The per-protocol set was used in supportive analysis. The use of the FAS

for the primary analyses is endorsed. It is worth noticing that the statistical models used for the primary and key secondary endpoints included covariates. Some patients had missing covariate values and therefore were excluded from the primary analyses (21 and 17 patients were excluded in study 2301 and 2302, respectively). This is not endorsed since it violates the ITT-principle. Imputation of missing covariate values would have been preferred in order to include all subjects in the analysis. The Applicant performed supplementary analyses where the covariates with missing values were excluded from the model and thus all patients were included. These analyses had similar results to those corresponding to the primary analyses.

The primary endpoint of both studies was the ARR. 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 Gd-enhancing 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. The variable region was redefined from that originally planned due to too few patients/relapses in some regions. This model assumes that the relapse rate is constant within patient. Patients who discontinued the study contributed only with the observed time and it was assumed that the relapse rate for those patients would not be affected by treatment discontinuation (missing at random assumption). Sensitivity analyses included the use of all relapses (confirmed and unconfirmed) and a tipping point analysis. To further support the primary analyses, a Cox model comparing the time to the first relapse was implemented. In order to assess whether the relapse rate could change between and after 8 weeks (onset period of both drugs), a piecewise negative binomial regression model was implemented. The model implemented to analyse the primary endpoint and the supportive analyses are considered adequate.

The number of Gd-lesions per MRI-scan and the number of new or enlarging T2 lesions will be compared using a negative binomial regression model with log-link. The total number of Gd-enhancing T1 lesions and the number of new or enlarging T2 lesions will be used as the response variable, and the natural log of the number of MRI-scans as offset. The covariates of the model are treatment and region, and age, and number of Gd enhancing T1 lesions or volume of T2 lesions at baseline. These models assume noninformative drop-out and constant intensity of lesion formation over time.

The model implemented to compare the number of Gd-enhancing T1 lesions between ofatumumab and teriflunomide is endorsed. Only scheduled MRI scans with non-missing values for the number of Gd-enhancing T1 and T2 lesions were considered in the analysis. It is understood that most unscheduled MRI scans would be performed during the onset of a relapse.

The model implemented to compare the number of new or enlarged T2 lesions between ofatumumab and teriflunomide is endorsed. Only scheduled MRI scans with non-missing values for T2 lesions were considered in the analysis.

The geometric mean of NfL concentration of the two treatment arms will be compared at month 3 using a mixed model for repeated measures. The response variable is the log-transformed values of the NfL level. The model covariates are treatment, region, visit, age, number of Gd-enhancing lesions at baseline, baseline T2 lesion volume and the log-transformed NfL baseline value. The model will also include a treatment-by-timepoint interaction and an unstructured covariance matrix will be used. The model implemented to compare the mean concentration of NfL between ofatumumab and teriflunomide is endorsed. The model for the NfL concentration assumes missing at random.

A random coefficients model will be used as main analysis for brain volume loss. The random coefficients model will include treatment, region, time, number of Gd-enhancing lesions at baseline, baseline T2 volume, and normalized brain volume at baseline and treatment by time interaction. The model will also contain random a

random slope and a random intercept. Under the assumption of linearity of the percentage brain volume change over time, the model corrects for missing values. Overall, the model used for the calculation of the difference in brain volume loss across treatment is agreed.

The disability endpoints (3mCDP, 6mCDP and 6mCDI) were analysed using a Cox-model stratified by study. The variables of the model were treatment, region and baseline EDSS. Between study heterogeneity was tested using a Cox-model including a treatment-by-study interaction. Patients who did not experience an event during observation were censored. For 3mCDP and 6mCDP sensitivity analyses assuming that patients who discontinue the study due to "Lack of efficacy" had an event were performed in both arms or only on the ofatumumab arm. Several supportive analyses were also planned. The statistical methods used for analysing the disability endpoints are overall agreed. It is not considered adequate to apply the non-informative censoring assumption in the primary analysis. Sensitivity analyses were presented challenging this assumption and are endorsed.

Type I error control

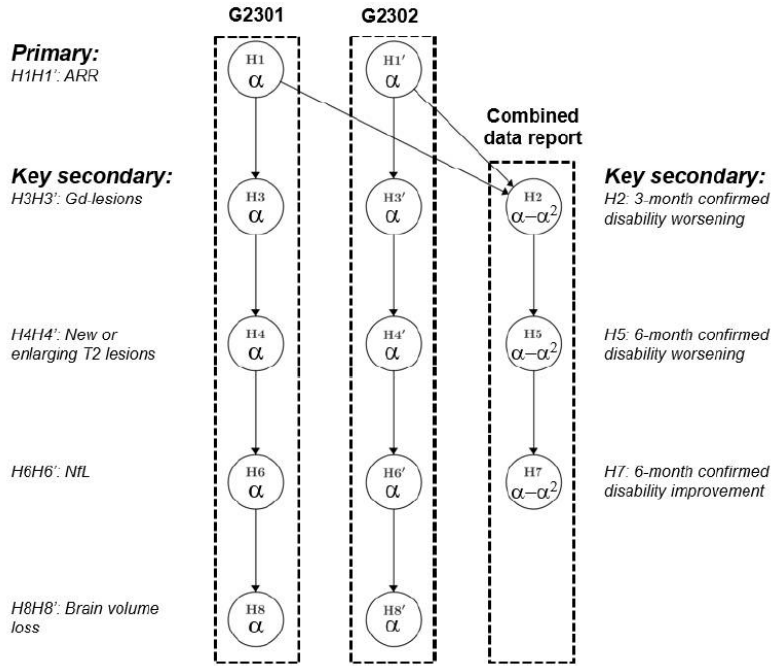
Each study has one primary endpoint and several key secondary endpoints. Furthermore, some key secondary endpoints will be obtained by pooling both studies. The studies were planned in order to allow for pooling of the data in order to achieve reasonable power to detect a treatment effect in the disability endpoints. Planning of the analyses adds credibility to the results, and it was encouraged by the CHMP as mentioned in the SA given in 2016 (EMA/CHMP/SAWP/207022/2016). There is no established methodological approach to control for multiplicity in a pooling set-up.

Power calculation

A negative binomial distribution of relapses was assumed for the primary analysis; this is a common assumption in MS. The demonstration of a relative reduction of the ARR in patients treated with ofatumumab ($\lambda ofa=0.168$) compared with those treated with teriflunomide ($\lambda ter=0.28$) by 40% ($\lambda ofa / \lambda ter =0.6$) with a power of 90% at a one-sided alpha-level of 0.025 in a study with 1.5 years follow-up and under the assumption of a dispersion parameter $\kappa=0.82$ requires a sample size of 322 completers per treatment group (644 completers for the study). Allowing for 20% uninformative dropouts equally distributed across treatment groups, a total sample size of 805 randomized patients was required for the study to demonstrate superiority of ofatumumab based on ARR. A sample size of 900 patients per study (driven by the 3mCDW endpoint), under otherwise the same assumptions as before, would provide approximately 95% power for the demonstration of superiority of ofatumumab over teriflunomide at a one-sided alpha level of 0.000625 (=0.0252) using the pooled data from 2 studies of identical design. The formula proposed by Keene et al (2007) was used for the sample size calculation for the primary endpoint.

Figure 22

Figure 2-1 Multiple testing procedure



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. If 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 hypotheses 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 type-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.

The Applicant designed the strategy to control for multiplicity based on the approach presented by Brezt and Xi in Commentary on "Statistics at the FDA: Reflection on the Past Six Years" (Statistics in Biopharmaceutical Research, 2019, vol 11). Briefly, Bretz and Xi proposed that if the primary endpoint within study is met and the studies are homogenous, a secondary endpoint could be tested by pooling the data from the two studies (see figure from Bretz et al.).

According to Brezt and Xi, this testing strategy controls the FWER at level α = 0.025 for each trial, the submission-wise error rate (SWER) at level α2 = 0.000625 for the primary endpoint across both trials and achieves independent substantiation at the submission level.

However, the Applicant's testing situation is different from that presented in Brezt and Xi. The Applicant aims also to control for multiplicity key secondary endpoints within each study in addition to the pooled endpoints. In other words, the Applicant aims to control for multiplicity in 3 different branches simultaneously (key secondary endpoints within study and key secondary endpoints across studies). It is not clear that the current strategy effectively controls for multiplicity across all key secondary endpoints. Similar concerns were mentioned by the PEI in the SA received in 2016 "The considerations of the Sponsor regarding multiple testing are considered correct if the success of each of the null hypothesis H3, H4 and H6 is only given if both studies rejected the corresponding null hypothesis, i.e. if only "super hypotheses" are considered. As this is not the case, i.e. a hypothesis can be rejected in each of the studies irrespective of the results of the other study, this

leads to a successful claim and continued testing within that respective study…Hence the Sponsor does not look at a sequence of "super hypothesis" but independent hypothesis within each study. The considerations under the global null, as presented by the Sponsor are in general not relevant for the family wise error control (which must hold under arbitrary situations). Thus, control of the type I error within each study and over both studies is considered doubtful."

The Biostatistics working party (BSWP) was consulted on the issue during the assessment. The BSWP expressed the opinion that in principle, the approach to a pooled analysis is acceptable and although the testing procedure can be criticized, type I error is controlled for the primary endpoint ARR in the individual studies and the disability endpoint can be assessed at the significance level achieved in the pooled study data.

Results

Study G2301

Participant flow

Screening epoch

A total of 1277 patients were screened, of whom 350 patients (27.4%) discontinued Screening epoch prior to the randomisation for the primary reasons shown in Table 10-1. The most common reasons for discontinuing the Screening epoch were screen failures (n=325, 25.5%) related to the inclusion/exclusion criteria.

Table 19

Table 10-1 Screening epoch patient disposition (All screened patients)

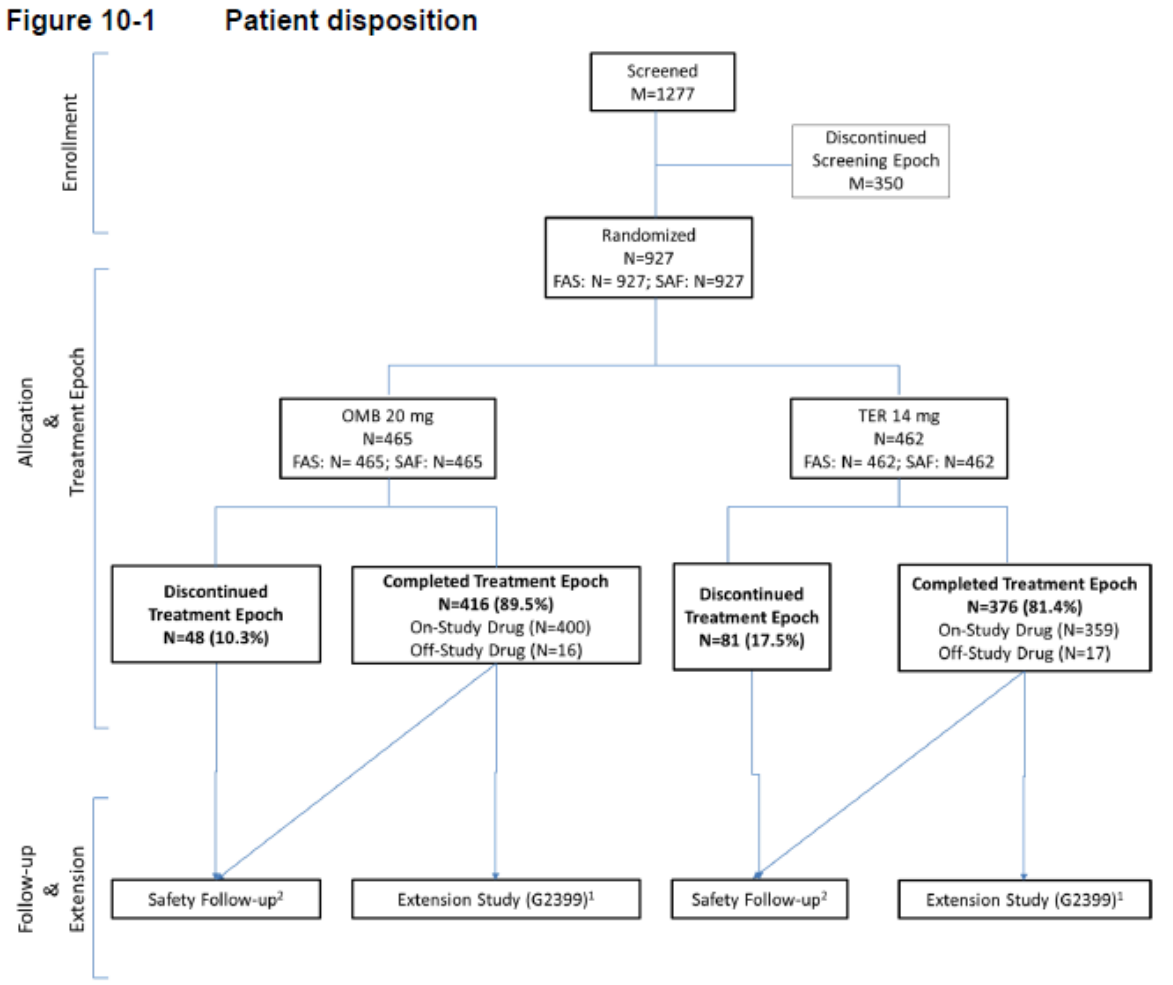
Disposition/Reason	Total N=1277 n (%)
Completed screening epoch	927 (72.6)
Discontinued prior to screening epoch completion	350 (27.4)
Primary reason for not completing screening epoch	
Adverse event	0
Death	0
Lost to follow-up	1 (0.1)
Patient/guardian decision	22 (1.7)
Pregnancy	0
Screen failure	325 (25.5)
Technical problems	2 (0.2)

Percentage is out of total number screened.

Treatment epoch

An overview of patient disposition during the study is provided in Figure 10-1.

Figure 23



-The following 6 patients (1 in ofatumumab and 5 in teriflunomide treatment group) are considered 'ongoing' (i.e. study completion occured after the data cut-off date of 05-Jul-2019): 5 patients completed the study treatment prior to the cutoff date (IDs: G2301-4041-001, G2301-4041-002, G2301-4001-018, G2301-4002-029, G2301-4002-038), 1 patient discontinued study drug and study prematurely (ID: G2301-2000-005).
[1] Patients who completed the double-blind Treatment epoch were eligible to enter an open-label ofatumumab Extension study (Study G2399). This extension study is planned to collect data from 2 to 5 years of treatment per patient. This extension will be reported separately.
[2]Patients who completed the double-blind Treatment epoch and did not enter the planned Extension study (G2399) or who prematurely discontinued study drug and did not agree to complete the study Treatment epoch or had less than 9 months of follow up after study drug discontinuation, entered the Safety FU epoch.

A total of 927 patients were randomised into the study; 465 patients to the ofatumumab treatment group and 462 patients to the teriflunomide treatment group (Table 10-2). A total of 416 patients (89.5%) randomised to ofatumumab completed the Treatment epoch compared with 376 patients (81.4%) randomised to teriflunomide. In total, 129 patients (13.9%) discontinued from the Treatment epoch. The most common reasons for discontinuation in the Treatment epoch were patient/guardian decision (6.3%) and adverse event (3.0%). A higher proportion of patients in the teriflunomide treatment group (17.5%) discontinued prematurely from the Treatment epoch as compared to the ofatumumab treatment group (10.3%). The difference was mainly due to discontinuation for patient/guardian decision (9.1% vs 3.4%) in the teriflunomide treatment group vs the ofatumumab treatment group. Overall, 163 patients (17.6%) discontinued study drug (ofatumumab 14% patients, teriflunomide 21.2% patients). The 3 most common reasons for discontinuing

study drugs were: patient/guardian decision (ofatumumab 4.9% patients, teriflunomide 8.2% patients), AE (ofatumumab 5.2% patients, teriflunomide 5.0% patients) and physician decision (ofatumumab 2.2% patients, teriflunomide 6.5% patients). The Applicant subsequently discussed the higher discontinuation rate in the teriflunomide arm, especially in the categories "patient/guardian decision" and "physician decision" including an evaluation of patient characteristics (SPMS, patients with confirmed disease worsening, patients with protocol deviations). No obvious pattern of patient characteristics in terms of the selected aspects was observed for those who discontinued study due to patient/guardian decision or due to physician decision. Investigators' comments would often indicate perceived lack of efficacy as the reason behind 'patient/guardian decision'. However, this would not necessarily imply an 'objective' lack of efficacy.

Table 20

Table 10-2 Treatment epoch patient disposition (Full analysis set)

Disposition/Reason	OMB 20 mg N=465 n (%)	TER 14 mg N=462 n (%)	All Patients N=927 n (%)
Completed treatment epoch*	**416 (89.5)**	**376 (81.4)**	**792 (85.4)**
On study drug	400 (86.0)	359 (77.7)	759 (81.9)
Off study drug	16 (3.4)	17 (3.7)	33 (3.6)
Discontinued treatment epoch	**48 (10.3)**	**81 (17.5)**	**129 (13.9)**
Primary reason for discontinuing treatment epoch			
Patient/guardian decision	16 (3.4)	42 (9.1)	58 (6.3)
Adverse event	14 (3.0)	14 (3.0)	28 (3.0)
Lost to follow-up	10 (2.2)	5 (1.1)	15 (1.6)
Lack of efficacy	1 (0.2)	12 (2.6)	13 (1.4)
Physician decision	3 (0.6)	4 (0.9)	7 (0.8)
Protocol deviation	3 (0.6)	2 (0.4)	5 (0.5)

Disposition/Reason	OMB 20 mg N=465 n (%)	TER 14 mg N=462 n (%)	All Patients N=927 n (%)
New therapy for study indication	0	1 (0.2)	1 (0.1)
Non-compliance with study treatment	0	1 (0.2)	1 (0.1)
Pregnancy	1 (0.2)	0	1 (0.1)

- N = Number of patients entered the treatment epoch; All percentages are calculated based on the number of patients in full analysis set.
- Number of patients (%) who completed the treatment epoch includes those who discontinued study drug and were followed up until end of treatment epoch.
- 'On study drug': Patients who took study drug until the treatment epoch completion.
- 'Off study drug': Patients who completed the treatment epoch but discontinued study drug prematurely.
- The discontinuation reason is the primary reason from the Study Phase Completion page. Data is sorted in the descending frequency in column "All patients" (except for "Missing" category).
* The following six patients are considered 'ongoing' (i.e. study completion >cutoff date = 05-July 2019): five completed the study treatment prior to the cutoff date (IDs: 4041001, 4041002, 4001018, 4002029, 4002038), one discontinued study drug and study prematurely (ID: 2000005).

Baseline data

The study population consisted of a broad RMS patient population as it included a substantial number of treatment-naïve patients (373 patients [40.2%]), as well as patients with EDSS scores at screening ranging from 0-5.5, and 55 patients (5.9%) of the population having SPMS at study entry. Treatment groups were balanced with respect to baseline data such as age, gender, duration of MS, EDSS etc.

Table 21

Table 10-6 Patient demographics (Full analysis set)

Characteristic	OMB 20 mg N=465	TER 14 mg N=462	All Patients N=927
Age (years)			
n	465	462	927
Mean	38.9	37.8	38.4
SD	8.77	8.95	8.87
Min	19	18	18
Median	40.0	38.0	39.0
Max*	56	55	56
Sex - n (%)			
Male	147 (31.6)	145 (31.4)	292 (31.5)
Female	318 (68.4)	317 (68.6)	635 (68.5)
Race - n (%)			
Asian	15 (3.2)	16 (3.5)	31 (3.3)
Black or African American	15 (3.2)	20 (4.3)	35 (3.8)
White	411 (88.4)	412 (89.2)	823 (88.8)
Other	22 (4.7)	14 (3.0)	36 (3.9)
Unknown	2 (0.4)	0	2 (0.2)
Ethnicity - n (%)			
Hispanic or Latino	37 (8.0)	36 (7.8)	73 (7.9)
Not Hispanic or Latino	360 (77.4)	355 (76.8)	715 (77.1)
Not Reported	30 (6.5)	34 (7.4)	64 (6.9)
Unknown	38 (8.2)	37 (8.0)	75 (8.1)
Weight (kg)			
n	465	462	927
Mean	74.84	75.47	75.15
SD	19.896	20.002	19.941
Min	41.2	41.7	41.2
Median	70.20	72.00	71.50
Max	171.5	170.3	171.5
BMI (kg/m^2)			
n	465	461	926
Mean	26.21	26.18	26.20
SD	6.413	6.110	6.260
Min	15.4	14.4	14.4
Median	24.77	25.22	24.87
Max	57.8	53.9	57.8

Age is calculated from date of first administration of study drug and date of birth.

* For 1 patient the calculated age was displayed as 56 years. As the age was calculated from the date of first administration of study drug and date of birth, the calculation provided an age of 56 years, because only the year of birth (but not day and month) was recorded. The Investigator confirmed that these patients were actually still 55 years of age at the time of inclusion in the study and randomization.

Weight is taken from screening vital signs evaluations.

BMI: body mass index is calculated based on raw data measurements.

Table 22

Table 10-7 Multiple Sclerosis (MS) disease history (Full analysis set)

	OMB 20 mg N=465	TER 14 mg N=462	All Patients N=927
Duration of MS since diagnosis (years), n (%)			
n	465	462	927
Mean	5.77	5.64	5.71
SD	6.048	6.197	6.120
Min	0.1	0.1	0.1
Median	3.94	3.49	3.71
Max	29.0	35.8	35.8
Duration of MS since first symptom (years), n (%)			
n	465	462	927
Mean	8.36	8.18	8.27
SD	6.841	7.207	7.022
Min	0.1	0.2	0.1
Median	6.41	6.69	6.52
Max	38.7	35.8	38.7
Number of relapses in the last 12 months prior to screening, n (%)			
n	465	462	927
Mean	1.2	1.3	1.2
SD	0.63	0.69	0.66
Min	0	0	0
Median	1.0	1.0	1.0
Max	4	5	5
Number of relapses in the 12 to 24 months prior to screening, n (%)			
n	465	462	927
Mean	0.9	0.9	0.9
SD	0.95	1.21	1.09
Min	0	0	0
Median	1.0	1.0	1.0
Max	5	12	12
Time since onset of the most recent relapse (months)			
n	465	462	927
Mean	7.13	7.94	7.53
SD	10.491	16.082	13.568
Min	1.2	1.2	1.2
Median	4.86	5.34	5.16
Max	119.2	264.8	264.8
Type of MS at study entry, n (%)			
RRMS	438 (94.2)	434 (93.9)	872 (94.1)
SPMS	27 (5.8)	28 (6.1)	55 (5.9)
Time since onset of SPMS (years)			
n	24	27	51
Mean	4.33	3.79	4.04
SD	3.957	3.947	3.922
Min	0.2	0.3	0.2
Median	2.90	2.27	2.50
Max	15.9	15.6	15.9

- Duration of MS since diagnosis (years) is derived [(first dose date – MS diagnosis start date + 1)/365.25].
- Duration of MS since first symptom (years) is derived as [(first dose date – first MS symptom date +1)/365.25].
- Time since onset of SPMS (years) is derived as [(first dose date – conversion to SPMS date+1)/365.25].
- Time since onset of most recent relapse (months) is derived as [(first dose date – most recent relapse onset date + 1)/365.25/12].

Table 23

Table 10-9 Prior use of MS disease-modifying therapies (Full analysis set)

	OMB 20 mg N=465 n (%)	TER 14 mg N=462 n (%)	All Patients N=927 n (%)
Treatment-naïve patients*	**191 (41.1)**	**182 (39.4)**	**373 (40.2)**
Previously treated patients	**274 (58.9)**	**280 (60.6)**	**554 (59.8)**
Any interferon beta	175 (37.6)	181 (39.2)	356 (38.4)
- IFN beta	6 (1.3)	10 (2.2)	16 (1.7)
- IFN beta-1a	121 (26.0)	117 (25.3)	238 (25.7)
- IFN beta-1b	62 (13.3)	66 (14.3)	128 (13.8)
Glatiramer Acetate	124 (26.7)	106 (22.9)	230 (24.8)
Dimethyl-fumarate	36 (7.7)	37 (8.0)	73 (7.9)
Teriflunomide	8 (1.7)	6 (1.3)	14 (1.5)
Daclizumab	5 (1.1)	12 (2.6)	17 (1.8)
Fingolimod	27 (5.8)	44 (9.5)	71 (7.7)
Natalizumab	31 (6.7)	36 (7.8)	67 (7.2)
Any B-cell therapy	2 (0.4)	3 (0.6)	5 (0.5)
- Rituximab	0	1 (0.2)	1 (0.1)
- Ocrelizumab	2 (0.4)	2 (0.4)	4 (0.4)
Laquinimod	5 (1.1)	4 (0.9)	9 (1.0)
Other DMT**	31 (6.7)	36 (7.8)	67 (7.2)

- DMT: disease-modifying therapy. IFN: Interferon
- A patient can be counted in multiple categories.
- *Treatment-naïve patients are those who have not received a prior multiple sclerosis disease modifying therapy.
- **Category "other DMT" contains all medications that were labeled by the Investigator as a multiple sclerosis disease-modifying therapy but are not part of the listed medications

Numbers analysed

In total, 927 (100%) randomised patients were included in the FAS and safety set (SAF) populations. The FAS and SAF populations for this study happened to have 100% overlap because all patients were treated as intended and hence were identical. The PPS population included all FAS patients who were compliant with the study protocol; 864 (93.2%) patients were included in this population. For analyses performed on the PPS, only efficacy data assessed during the on-treatment period was included. The FAS was used for the summary of demography and baseline characteristics as well as for all efficacy analyses. The SAF was used for all safety analyses. The PPS was used for the supportive analyses of the primary efficacy variable and selected key secondary variables. A PK analysis set was not defined: PK analysis were performed on the subset of ofatumumab patients from the FAS.

Outcomes and estimation

Primary efficacy results

Patients treated with ofatumumab experienced 90 confirmed relapses in 769 patient-years of exposure, compared with teriflunomide patients who experienced 177 confirmed relapses in 741 patient-years. Analysis of the ARR using a negative binomial model for confirmed relapses demonstrated a significantly lower ARR for the ofatumumab treatment group compared to the teriflunomide treatment group, with ARR estimates of 0.11 vs 0.22, respectively. This corresponded to a statistically significant reduction of 50.5% in ARR estimates (ARR ratio 0.495, p<0.001).

Table 24

Table 11-1 Annualized relapse rate (ARR) (confirmed relapses) (Full analysis set)

		Between-treatment comparison			
Treatment	Adjusted ARR (95% CI)	Comparison	Rate reduction	ARR ratio (95% CI)	P-value
OMB 20 mg N=454	0.11 (0.09, 0.14)	vs TER 14 mg	50.5%	0.495 (0.374, 0.654)	<0.001*
TER 14 mg N=452	0.22 (0.18, 0.26)				

- N: Total number of patients included in the analysis.
- Confirmed relapses are those accompanied by a clinically relevant change in the EDSS.
- Obtained from fitting a negative binomial regression model with log-link to the number of relapses, adjusted for treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd-enhancing lesions and the patient's age at baseline as covariates. The natural log of the time-in-study was used as offset to annualize the relapse rate.
* Indicates statistical significance (2-sided) at the 0.05 level.

The analysis of all relapses (confirmed and unconfirmed) showed that patients treated with ofatumumab experienced a total of 122 all relapses in 769 patient-years of exposure, compared with teriflunomide patients who experienced a total of 234 relapses in 741 patient-years. Analysis of the ARR for all relapses (confirmed and unconfirmed) demonstrated a rate reduction of 49.7% in the ofatumumab vs the teriflunomide treatment group (ARR ratio 0.503, p<0.001) in the FAS.

A sensitivity analysis was performed to investigate the potential impact of missing not-at random (MNAR) on ARR estimates and treatment effects on ARR. The ARR analysis accounts for missing data during the period after premature study discontinuation using different MNAR imputations.

Table 25

Table C2 1.3.3-6b (Page 1 of 2)
Estimated annual relapse rate (ARR) ratio with 95% confidence intervals by study using different MNAR assumptions for the missing data
Full analysis set

		ARR Ratio	LCL	UCL
G2301				
	Table 14.2-1.1[a]	0.4948	0.3742	0.6543
	Factor 1[b]	0.4877	0.3714	0.6404
	Factor 2	0.4622	0.3502	0.6099
	Factor 3	0.4460	0.3359	0.5921
	Factor 4	0.4280	0.3186	0.5749
	Factor 5	0.4314	0.3205	0.5805

Results are consolidated using Rubin's rule based on 1000 multiply imputed datasets.
[a] Results from analysis of primary endpoint in CSR Table 14.2-1.1.
[b] It is assumed that the relapse rates increase by a factor (e.g. 2.0, 3.0, T) once a patient discontinues from the study.

Characteristics of MS relapses

Patients treated with ofatumumab experienced 90 confirmed relapses in 769 patient-years of exposure, compared with teriflunomide patients who experienced 177 confirmed relapses in 741 patient-years. See table below for the characteristics of such relapses (note that for a patient with multiple relapses only the worst relapse is described in the table).

Patients treated with ofatumumab had fewer relapses of moderate and severe severity, fewer relapses leading to the hospitalization, and fewer relapses requiring steroid treatment compared with patients treated with teriflunomide.

Table 26

Table 11-3 Characteristics of MS relapses (confirmed relapses) (Full analysis set)

MS Relapse Characteristics	OMB 20 mg N=465 n (%)	TER 14 mg N=462 n (%)
Severity		
Mild	21 (4.5)	21 (4.5)
Moderate	41 (8.8)	81 (17.5)
Severe	17 (3.7)	30 (6.5)
Hospitalization		
Yes	19 (4.1)	29 (6.3)
No	60 (12.9)	103 (22.3)
Recovery as assessed by primary Investigator		
None	3 (0.6)	5 (1.1)
Partial	19 (4.1)	33 (7.1)
Complete	57 (12.3)	94 (20.3)
Steroid treatment		

Yes	73 (15.7)	123 (26.6)
No	6 (1.3)	9 (1.9)

Confirmed relapses are those accompanied by a clinically relevant change in the EDSS.
Mild relapse: EDSS increase of 0.5 point (or) 1 point functional score (FS) change in 1 to 3 systems.
Moderate relapse: EDSS increase of 1 or 2 points (or) 2-point FS change in 1 or 2 systems (or) 1-point change in 4 or more systems.
Severe relapse: Exceeding moderate criteria.
For each MS relapse characteristic, a patient with multiple relapses was counted only once using the worst category observed. %=n/N.

Table 14.2-1.10 (Page 1 of 1)
Proportion of patients with confirmed relapses of selected characteristics by treatment - Chi-square test
Full analysis set

Endpoint	Treatment	n/N (%)	Comparison	P-value
Proportion of patients hospitalized for relapses	OMB 20mg	19/465 (4.1)	vs. TER 14mg	0.132
	TER 14mg	29/462 (6.3)		
Proportion of patients with severe relapses	OMB 20mg	17/465 (3.7)	vs. TER 14mg	0.049*
	TER 14mg	30/462 (6.5)		

n: Total number of patients with the specified relapses.
N: Total number of patients included in the analysis.
Confirmed relapses are those accompanied by a clinically relevant change in the EDSS.
- P-values are obtained from a Chi-square test.
*** Indicates statistical significance (2-sided) at the 0.05 level.**

Secondary efficacy results

Although not prespecified, the 6mCDW for each individual study will be presented first since it is considered the analysis closest to CHMP guideline requirements.

6-month CDW, individual study (not prespecified)

Ofatumumab reduced the risk of 6mCDW compared with teriflunomide (39%).

Table 27

G2301						
OMB 20mg	7.5 (5.4,10.4)	8.2 (6.0,11.3)	35/465 (7.5)	0.607 (0.396, 0.930)	39.3	0.022[4]
TER 14mg	11.5 (8.9,14.9)	13.0 (10.0,16.9)	53/459 (11.5)			
Log-Rank test						0.031[4]

Table 14.2-14.1 (Page 3 of 3)
Time to first 6-month confirmed disability worsening (6mCDW) during treatment epoch by treatment (G2301 and G2302 pooled)
Full analysis set

For the prespecified pooled analyses - please see "Analysis performed across trials (pooled analyses AND meta-analysis)".

Number of T1 Gd-enhancing lesions per scan

Treatment with ofatumumab compared with teriflunomide, reduced the mean number of Gd-enhancing T1 lesions per scan (0.0115vs 0.4523) by 97.5%.

Table 28

Table 11-4 Number of Gd-enhancing T1 lesions per scan - Rate ratio estimate of treatment effect from negative binomial regression (Full analysis set)

				Between-treatment comparison				
Treatment	N	Adjusted mean number of Gd-enhancing lesions per scan	(95% CI)	Comparison	Rate reduction	Rate ratio	(95% CI)	P-value
OMB 20 mg	432	0.0115	(0.006, 0.022)	vs TER 14 mg	97.5%	0.025	(0.013, 0.049)	<.001*
TER 14 mg	422	0.4523	(0.356, 0.575)					

- N: Total number of patients included in the analysis.
- Gd-enhancing lesion counts from scans collected within 30 days after termination of steroid therapy were excluded from the analysis.
- The model includes adjustment for treatment and region (factors), and age, and number of Gd-enhancing lesions at baseline as continuous covariates.
- The natural log of the number of MRI-scans with evaluable Gd-enhancing lesion counts was used as the offset to obtain the lesion rate per scan.
* Indicates statistical significance (2-sided) at the 0.05 level.

Annualised rate of new or enlarging T2 lesions

Treatment with ofatumumab, compared to teriflunomide, reduced the mean number of new or enlarging T2 lesions per year between baseline and EOS (0.72 vs 4.00) by 81.9%. The mean number of new or enlarging T2 lesions per year between baseline and Month 12 (1.13 vs 4.30), and between baseline and Month 24 (0.72 vs 3.21) were reduced in the ofatumumab vs the teriflunomide treatment group by 73.8% and 77.6%, respectively.

Table 29: Number of new or enlarging T2 lesions per year (relative to baseline) - Rate ratio estimate of treatment effect from negative binomial regression model (Full analysis set)

						Between-treatment comparison			
Visit-window	Treatment	N	Adjusted annualized mean rate of new or enlarging T2 lesions	(95% CI)	Comparison	Rate reduction	Rate ratio	(95% CI)	P-value
Month 12	OMB 20 mg	420	1.13	(0.95, 1.33)	vs TER 14 mg	73.8%	0.26	(0.21, 0.33)	<.001*
	TER 14 mg	407	4.30	(3.71, 4.98)					
Month 24	OMB 20 mg	103	0.72	(0.53, 0.98)	vs TER 14 mg	77.6%	0.22	(0.15, 0.34)	<.001*
	TER 14 mg	93	3.21	(2.42, 4.24)					
EOS**	OMB 20 mg	440	0.72	(0.61, 0.85)	vs TER 14 mg	81.9%	0.18	(0.15, 0.22)	<.001*

						Between-treatment comparison			
Visit-window	Treatment	N	Adjusted annualized mean rate of new or enlarging T2 lesions	(95% CI)	Comparison	Rate reduction	Rate ratio	(95% CI)	P-value
	TER 14 mg	431	4.00	(3.47, 4.61)					

- N: Total number of patients included in the analysis.
- The number of new or enlarging T2 lesions (compared to baseline) is analyzed in a negative binomial model with adjustments for treatment and region (factors), and age, and baseline volume of T2 lesions as continuous covariates.
- The natural log of the time from the screening scan (in years) is used as the offset.
* Indicates statistical significance (2-sided) at the 0.05 level.
**Last scan in the double blind treatment epoch

The mean number of new or enlarging T2 lesions (relative to baseline) analysed by visit window were lower in the ofatumumab treatment group than in the teriflunomide treatment group at Month 12 (1.4 ofatumumab, 5.9 teriflunomide) and Month 24 (1.6 ofatumumab, 7.7 teriflunomide) in the FAS.

Neurofilament light chain

Ofatumumab 20 mg was superior to teriflunomide 14 mg in reducing the NfL concentration in serum at Month 3 (and at all subsequent assessments). At Month 3, the first post-baseline assessment of NfL concentrations in serum in the ofatumumab vs the teriflunomide treatment group demonstrated a relative reduction in NfL concentration by 7%. A further relative reduction in NfL concentration by 27% at Month 12 and by 23% at Month 24 in the ofatumumab vs teriflunomide treatment group was observed.

Brain volume loss

The rate of brain volume loss appeared similar or slightly larger in the ofatumumab treatment group as compared to the teriflunomide treatment group.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the B/R (see later sections).

Table 30: ***Efficacy overview table for study COMB157G2301***

Title: A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis (ASCLEPIOS I)			
Study identifier	COMB157G2301 (EudraCT no. 2015-005418-31)		
Design	Randomized, double-blind, double-dummy, active comparator-controlled, parallel-group, multi-center study with variable treatment duration in patients with relapsing multiple sclerosis (MS)		
	Duration of main phase:		The Treatment epoch was variable for each patient. Individual patients were treated until the End of Study (EOS) was declared or for a maximum of 30 study months. The EOS was declared when, based on blinded data, sufficient data became available to provide the required power for the statistical tests for the primary endpoint (ARR) and for key secondary endpoints related to disability worsening (3mCDW, 6mCDW). Note: The Safety follow-up epoch of the study is still ongoing.
Hypothesis	Superiority		
Treatments groups	Ofatumumab 20 mg (OMB 20 mg)		OMB 20 mg Median duration of exposure: 613.0 days Cumulative exposure: 745.9 patient-years % of patients with cumulative exposure>12 months: 90.1 % % of patients with cumulative exposure >2 years: 34.0 % N= 465 randomized
	Teriflunomide 14 mg (TER 14 mg)		TER 14 mg Median duration of exposure: 580.0 days Cumulative exposure: 695.7 patient-years % of patients with cumulative exposure>12 months 87.9% % of patients with cumulative exposure >2 years: 24.9% N= 462 randomized
Endpoints and definitions	Primary endpoint	Annualized relapse rate (ARR)	Number of confirmed MS relapses in a year
	Key secondary endpoint	3-month confirmed disability worsening (3mCDW)	• Time to disability worsening as measured by 3-month confirmed worsening (3mCDW) on the Expanded Disability Status Scale (EDSS) Note: Disability-related key secondary efficacy endpoints were analysed in a pre-specified analysis of the combined data of studies COMB157G2301 and COMB157G2302.

	Key secondary endpoint	6-month confirmed disability worsening (6mCDW)	• Time to disability worsening as measured by 6-month confirmed worsening (6mCDW) on EDSS Note: Disability-related key secondary efficacy endpoints were analysed in a pre-specified analysis of the combined data of studies COMB157G2301 and COMB157G2302.
	Key secondary endpoint	6-month confirmed disability improvement (6mCDI)	• Time to disability improvement as measured by 6-month confirmed improvement (6mCDI) on EDSS Note: Disability-related key secondary efficacy endpoints were analysed in a pre-specified analysis of the combined data of studies COMB157G2301 and COMB157G2302.
	Key secondary endpoint	Gd-enhancing T1 lesions	• Number of Gd-enhancing T1 lesions per MRI scan
	Key secondary endpoint	T2 lesions	• Annualized rate of new or enlarging T2 lesions on MRI
	Key secondary endpoint	Neurofilament light chain (NfL)	• Neurofilament light chain (NfL) concentration in serum
Database lock	Data cut-off: 05-Jul-2019		

Results and Analysis

Note: The primary and all key-secondary endpoints were tested according to a statistical testing procedure.

Analysis description	**Primary Analysis: ARR**		
Analysis population and time point description	Full analysis set (FAS): following the intent-to-treat principle, included all patients with randomization numbers assigned. Data up to end of study (EOS)		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	454	452
	Adjusted ARR (95% CI)	0.11 (0.09, 0.14)	0.22 (0.18, 0.26)
Analysis description	**Key Secondary Analysis: 3mCDW***		
Analysis population and time point description	FAS/intent-to-treat Data up to EOS		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	944	931
	KM estimate at Month 24 (95% CI)	10.9 (8.8, 13.4)	15.0 (12.6, 17.7)
Analysis description	**Key Secondary Analysis: 6mCDW***		
Analysis population and time point description	FAS/intent-to-treat Data up to EOS		

Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	944	931
	KM estimate at Month 24 (95% CI)	8.1 (6.5, 10.2)	12.0 (9.9, 14.5)
Analysis description	**Key Secondary Analysis: 6mCDI***		
Analysis population and time point description	FAS/intent-to-treat Data up to EOS		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	749	723
	KM estimate at Month 24 (95% CI)	11.0 (8.8, 13.7)	8.1 (6.2, 10.6)
Analysis description	**Key Secondary Analysis: Gd-enhancing T1 lesions**		
Analysis population and time point description	FAS/intent-to-treat Data up to EOS		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	432	422
	No. of lesions per scan (95% CI)	0.01 (0.006, 0.022)	0.45 (0.356, 0.575)
Analysis description	**Key Secondary Analysis: T2 lesions**		
Analysis population and time point description	FAS/intent-to-treat Data up to EOS		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	440	431
	No. of new/enlarging lesions per year (95% CI)	0.72 (0.61, 0.85)	4.00 (3.47, 4.61)
Analysis description	**Key Secondary Analysis: NfL**		
Analysis population and time point description	FAS/intent-to-treat Month 3; Month 12, Month 24		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	436	412
	NfL concentration at Month 3 (95% CI)	8.80 (8.48, 9.12)	9.41 (9.06, 9.77)
	NfL concentration at Month 12 (95% CI)	7.02 (6.73, 7.32)	9.62 (9.22, 10.05)

	NfL concentration at Month 24 (95% CI)	6.90 (6.57, 7.24)	8.99 (8.55, 9.45)

*Disability-related key secondary efficacy endpoints (i.e. 3mCDW, 6mCDW and 6mCDI) were analysed based on a pre-specified analysis of the combined data for the two studies COMB157G2301 and COMB157G2302. Results shown here are based on the analysis of the combined data.

Study G2302

Participant flow

Screening epoch

A total of 1280 patients were screened, of whom 325 patients (25.4%) discontinued Screening epoch prior to randomisation for the primary reasons shown in Table 10-1. The most common reasons for discontinuing the Screening epoch were screen failures (n=306, 23.9%) based on inclusion/exclusion criteria.

Table 31

Table 10-1 Screening epoch patient disposition (All screened patients)

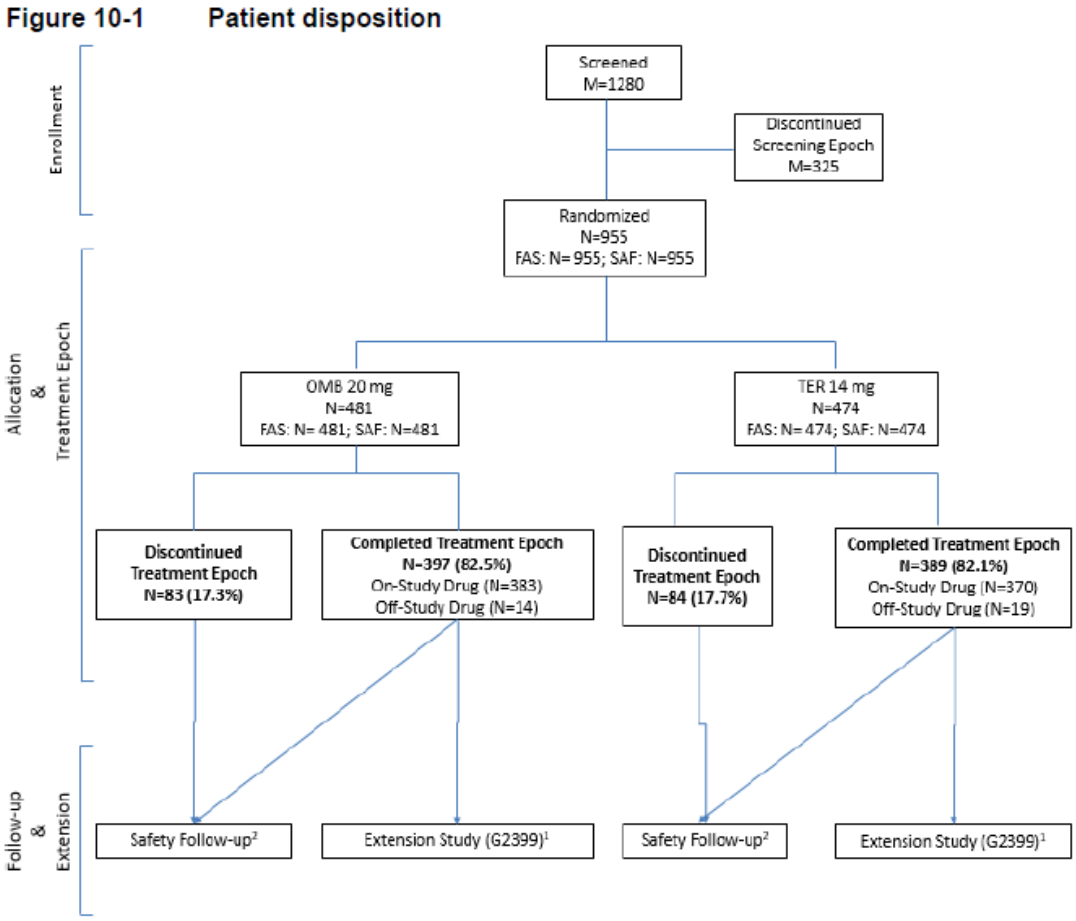
Disposition/Reason	Total N=1280 n (%)
Completed screening epoch	955 (74.6)
Discontinued prior to screening epoch completion	325 (25.4)
Primary reason for not completing screening epoch	
Adverse event	0
Death	0
Lost to follow-up	0
Patient/guardian decision	18 (1.4)
Pregnancy	0
Screen failure	306 (23.9)
Technical problems	1 (0.1)

Percentage is out of total number screened.

Treatment epoch

An overview of patient disposition during the study is provided in Figure 10-1.

Figure 24



- The following two patients (1 in each treatment group) are considered 'ongoing' (i.e. study completion occurred after the data cut-off date of 10-Jul-2019); all patients completed the study treatment prior to the cutoff date (IDs: G2302-5022-012, G2302-7042-005).

[1]Patients who completed the double-blind Treatment epoch were eligible to enter an open-label ofatumumab extension study (Study G2399). This extension study is planned to collect data from 2 to 5 years of treatment per patient. This extension will be reported separately.

[2]Patients who completed the double-blind Treatment epoch and did not enter the planned Extension study (G2399) or who prematurely discontinued study drug and did not agree to complete the study Treatment epoch or had less than 9 months of follow up after study drug discontinuation, entered the Safety FU epoch.

A total of 955 patients were randomised into the study; 481 patients to the ofatumumab group and 474 patients to the teriflunomide group (Table 10-2). A total of 397 patients (82.5%) randomised to ofatumumab compared with 389 patients (82.1%) randomised to teriflunomide completed the Treatment epoch. In total, 167 patients (17.5%) discontinued from the Treatment epoch. The most common reasons for discontinuation in the Treatment epoch were patient/guardian decision (7.6%) and AE (3.0%). A similar proportion of patients in the teriflunomide treatment group (17.7%) discontinued prematurely from the Treatment epoch as compared to the ofatumumab treatment group (17.3%). Overall, 198 patients (20.7%) discontinued study drug (ofatumumab 20% patients, teriflunomide 21.5% patients). The 3 most common reasons for discontinuing study drugs were: patient/guardian decision (ofatumumab 7.3% patients, teriflunomide 7.8% patients), AE (ofatumumab 5.6% patients, teriflunomide 4.9% patients) and physician decision (ofatumumab 5.2% patients, teriflunomide 6.8% patients).

Table 32

Table 10-2 Treatment epoch patient disposition (Full analysis set)

Disposition/Reason	OMB 20 mg N=481 n (%)	TER 14 mg N=474 n (%)	All Patients N=955 n (%)
Completed Treatment epoch*	**397 (82.5)**	**389 (82.1)**	**786 (82.3)**
On study drug	383 (79.6)	370 (78.1)	753 (78.8)
Off study drug	14 (2.9)	19 (4.0)	33 (3.5)
Discontinued Treatment epoch	**83 (17.3)**	**84 (17.7)**	**167 (17.5)**
Primary reason for discontinuing Treatment epoch			
Patient/guardian decision	32 (6.7)	41 (8.6)	73 (7.6)
Adverse event	16 (3.3)	13 (2.7)	29 (3.0)
Physician decision	14 (2.9)	11 (2.3)	25 (2.6)
Lack of efficacy	7 (1.5)	9 (1.9)	16 (1.7)
Lost to follow-up	9 (1.9)	5 (1.1)	14 (1.5)
Pregnancy	1 (0.2)	3 (0.6)	4 (0.4)
Non-compliance with study treatment	2 (0.4)	1 (0.2)	3 (0.3)
Protocol deviation	2 (0.4)	0	2 (0.2)
Technical problems	0	1 (0.2)	1 (0.1)
Disposition/Reason	**OMB 20 mg N=481 n (%)**	**TER 14 mg N=474 n (%)**	**All Patients N=955 n (%)**

- N = Number of patients entered the Treatment epoch; All percentages are calculated based on the number of patients in full analysis set.
- Number of patients (%) who completed the Treatment epoch includes those who discontinued study drug and were followed up until end of Treatment epoch.
- 'On study drug': Patients who took study drug until the Treatment epoch completion.
- 'Off study drug': Patients who completed the Treatment epoch but discontinued study drug prematurely.
- The discontinuation reason is the primary reason from the Study Phase Completion page. Data is sorted in the descending frequency in column "All patients" (except for "Missing" category).

* The following two patients are considered 'ongoing' (i.e. study completion >cutoff date = 10-July2019); all completed the study treatment prior to the cutoff date (IDs: 5022012, 7042005).

Baseline data

The study population consisted of a broad RMS patient population as it included a substantial number of treatment-naïve patients (376 patients [39.4%]), as well as patients with EDSS scores at screening ranging from 0-5.5, and 53 patients (5.5%) of the population having SPMS at study entry. Treatment groups were balanced with respect to baseline data such as age, gender, duration of MS, EDSS etc.

Table 33

Table 10-6 Patient demographics (Full analysis set)

Characteristic	OMB 20 mg N=481	TER 14 mg N=474	All Patients N=955
Age (years)			
N	481	474	955
Mean	38.0	38.2	38.1
SD	9.28	9.47	9.37
Min	18	18	18
Median	38.0	38.0	38.0
Max*	56	56	56
Sex - n (%)			
Male	162 (33.7)	155 (32.7)	317 (33.2)
Female	319 (66.3)	319 (67.3)	638 (66.8)
Race - n (%)			
Asian	21 (4.4)	19 (4.0)	40 (4.2)
Black or African American	13 (2.7)	18 (3.8)	31 (3.2)
White	418 (86.9)	417 (88.0)	835 (87.4)
Other	20 (4.2)	14 (3.0)	34 (3.6)
Unknown	9 (1.9)	6 (1.3)	15 (1.6)
Ethnicity - n (%)			
Hispanic or Latino	39 (8.1)	35 (7.4)	74 (7.7)
Not Hispanic or Latino	351 (73.0)	364 (76.8)	715 (74.9)
Not Reported	62 (12.9)	52 (11.0)	114 (11.9)
Unknown	29 (6.0)	23 (4.9)	52 (5.4)
Weight (kg)			
N	481	474	955
Mean	73.62	73.97	73.79
SD	19.008	17.879	18.448
Min	40.5	39.5	39.5
Median	70.00	71.00	70.30
Max	157.9	143.1	157.9
Body Mass Index (kg/m^2)			
N	481	473	954
Mean	25.52	25.69	25.60
SD	6.009	5.931	5.968
Min	16.1	14.6	14.6
Median	24.15	24.53	24.28
Max	54.5	55.4	55.4

Age is calculated from date of first administration of study drug and date of birth.

*For 3 patients the calculated age was displayed as 56 years. As the age was calculated from the date of first administration of study drug and date of birth, the calculation provided an age of 56 years, because only the year of birth (but not day and month) was recorded. The Investigator confirmed that these patients were actually still 55 years of age at the time of inclusion in the study and randomization.
Weight is taken from screening vital signs evaluations.
Body mass index is calculated based on raw data measurements.

Table 34

Table 10-7 Multiple Sclerosis (MS) disease history (Full analysis set)

	OMB 20 mg N=481	TER 14 mg N=474	All Patients N=955
Duration of MS since diagnosis (years), n (%)			
n	481	474	955
Mean	5.59	5.48	5.54
SD	6.375	6.003	6.190
Min	0.1	0.1	0.1
Median	3.15	3.10	3.11
Max	31.8	33.5	33.5
Duration of MS since first symptom (years), n (%)			
n	481	473	954
Mean	8.20	8.19	8.19
SD	7.404	7.376	7.386
Min	0.1	0.2	0.1
Median	5.70	6.30	6.20
Max	34.5	36.1	36.1
Number of relapses in the last 12 months prior to screening, n (%)			
n	481	474	955
Mean	1.3	1.3	1.3
SD	0.74	0.73	0.74
Min	0	0	0
Median	1.0	1.0	1.0
Max	7	6	7
Number of relapses in the 12 to 24 months prior to screening, n (%)			
n	480	473	953
Mean	0.7	0.8	0.7
SD	0.95	1.02	0.98
Min	0	0	0
Median	0.0	0.0	0.0
Max	5	6	6

Time since onset of the most recent relapse (months)			
n	480	474	954
Mean	7.79	7.66	7.73
SD	14.990	11.090	13.190
Min	1.3	1.2	1.2
Median	5.17	5.22	5.19
Max	261.5	150.3	261.5
Type of MS at study entry, n (%)			
RRMS	452 (94.0)	450 (94.9)	902 (94.5)
SPMS	29 (6.0)	24 (5.1)	53 (5.5)
Time since onset of SPMS (years)			
n	29	24	53
Mean	3.89	3.56	3.74
SD	3.999	3.101	3.591
Min	0.5	0.4	0.4
Median	2.82	3.13	2.86
Max	19.3	11.0	19.3

- Duration of MS since diagnosis (years) is derived [(first dose date – MS diagnosis start date + 1)/365.25].
- Duration of MS since first symptom (years) is derived as [(first dose date – first MS symptom date +1)/365.25].
- Time since onset of SPMS (years) is derived as [(first dose date – conversion to SPMS date+1)/365.25].
- Time since onset of most recent relapse (months) is derived as [(first dose date – most recent relapse onset date + 1)/365.25/12].

Table 35

Table 10-9 Prior use of MS disease-modifying therapies (Full analysis set)

	OMB 20 mg N=481 n (%)	TER 14 mg N=474 n (%)	All Patients N=955 n (%)
Treatment-naïve patients*	**195 (40.5)**	**181 (38.2)**	**376 (39.4)**
Previously treated patients	**286 (59.5)**	**293 (61.8)**	**579 (60.6)**
Any interferon beta	182 (37.8)	180 (38.3)	362 (37.9)
interferon beta	10 (2.1)	9 (1.9)	19 (2.0)
interferon beta-1a	126 (26.2)	131 (27.6)	257 (26.9)
interferon beta-1b	61 (12.7)	53 (11.2)	114 (11.9)
Glatiramer Acetate	118 (24.5)	149 (31.4)	267 (28.0)
Dimethyl-fumarate	36 (7.5)	44 (9.3)	80 (8.4)
Teriflunomide	13 (2.7)	9 (1.9)	22 (2.3)
Daclizumab	8 (1.7)	7 (1.5)	15 (1.6)
Fingolimod	39 (8.1)	43 (9.1)	82 (8.6)
Natalizumab	26 (5.4)	20 (4.2)	46 (4.8)
Laquinimod	2 (0.4)	7 (1.5)	9 (0.9)
Other DMT**	41 (8.5)	46 (9.7)	87 (9.1)

- DMT: disease-modifying therapy.
- A patient can be counted in multiple categories.
- *Treatment-naïve patients are those who have not received a prior multiple sclerosis DMT.
- **Category "other DMT" contains all medications that were labeled by the Investigator as a multiple sclerosis DMT but are not part of the listed medications

Numbers analysed

In total, 955 (100%) randomised patients were included in the FAS and SAF populations. The FAS and SAF populations for this study happened to have 100% overlap because all patients were treated as intended and hence were identical.

The PPS population included all FAS patients who were compliant with the study protocol; 893 (93.5%) patients were included in this population. For analyses performed on the PPS, only efficacy data assessed during the on-treatment period was included. The FAS was used for the summary of demography and baseline characteristics as well as for all efficacy analyses. The SAF was used for all safety analyses. The PPS was used for the supportive analyses of the primary efficacy variable and selected key secondary variables. A PK analysis set was not defined: PK analysis were performed on the subset of ofatumumab patients from the FAS.

Outcomes and estimation

Primary efficacy results

Patients treated with ofatumumab experienced 95 confirmed relapses in 768 patient-years of exposure, compared with teriflunomide patients who experienced 198 confirmed relapses in 750 patient-years. Analysis of the ARR using a negative binomial model for confirmed relapses demonstrated a significantly lower ARR for the ofatumumab treatment group compared to the teriflunomide treatment group, with ARR estimates of 0.10 vs 0.25, respectively. This corresponded to a statistically significant reduction of 58.5% in ARR estimates (ARR ratio 0.415, p<0.001).

Primary analysis

Table 36

Table 11-1 Annualized relapse rate (ARR) (confirmed relapses) (Full analysis set)

		Between-treatment comparison			
Treatment	Adjusted ARR (95% CI)	Comparison	Rate reduction	ARR ratio (95% CI)	P-value
OMB 20 mg N=469	0.10 (0.08, 0.13)	vs TER 14 mg	58.5%	0.415 (0.308, 0.559)	<0.001*
TER 14 mg N=469	0.25 (0.21, 0.30)				

		Between-treatment comparison			
Treatment	Adjusted ARR (95% CI)	Comparison	Rate reduction	ARR ratio (95% CI)	P-value

- N: Total number of patients included in the analysis.
- Confirmed relapses are those accompanied by a clinically relevant change in the EDSS.
- Obtained from fitting a negative binomial regression model with log-link to the number of relapses, adjusted for treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd-enhancing lesions and the patient's age at baseline as covariates. The natural log of the time-in-study was used as offset to annualize the relapse rate.
* Indicates statistical significance (2-sided) at the 0.05 level.

The analysis of all relapses (confirmed and unconfirmed) showed that patients treated with ofatumumab experienced a total of 131 relapses in 768 patient-years of exposure, compared with teriflunomide patients who experienced a total of 250 relapses in 750 patient-years. Analysis of the ARR for all relapses (confirmed and unconfirmed) demonstrated a rate reduction of 54.6% in the ofatumumab vs the teriflunomide treatment group (ARR ratio 0.454, p<0.001) in the FAS.

A sensitivity analysis was performed to investigate the potential impact of missing not-at random (MNAR) on ARR estimates and treatment effects on ARR. The ARR analysis accounts for missing data during the period after premature study discontinuation using different MNAR imputations.

Table 37

Table C2 1.3.3-6b (Page 1 of 2)
Estimated annual relapse rate (ARR) ratio with 95% confidence intervals by study using different MNAR assumptions for the missing data
Full analysis set

		ARR Ratio	LCL	UCL
G2302				
	Table 14.2-1.1[a]	0.4152	0.3085	0.5589
	Factor 1[b]	0.4227	0.3165	0.5644
	Factor 2	0.4158	0.3077	0.5620
	Factor 3	0.4059	0.2954	0.5577
	Factor 4	0.3993	0.2873	0.5550
	Factor 5	0.3946	0.2807	0.5547

Results are consolidated using Rubin's rule based on 1000 multiply imputed datasets.
[a] Results from analysis of primary endpoint in CSR Table 14.2-1.1.
[b] It is assumed that the relapse rates increase by a factor (e.g. 2.0, 3.0, T) once a patient discontinues from the study.

Characteristics of MS relapses

Patients treated with ofatumumab experienced 95 confirmed relapses in 768 patient-years of exposure, compared with teriflunomide patients who experienced 198 confirmed relapses in 750 patient-years. See table below for the characteristics of such relapses (note that for a patient with multiple relapses only the worst relapse is described in the table).

Patients treated with ofatumumab had fewer relapses across all severity levels, fewer relapses leading to the hospitalization, and fewer relapses requiring steroid treatment compared with patients treated with teriflunomide.

Table 38

Table 11-3 Characteristics of MS relapses (confirmed relapses) (Full analysis set)

MS Relapse Characteristics	OMB 20 mg N=481 n (%)	TER 14 mg N=474 n (%)
Severity		
Mild	15 (3.1)	23 (4.9)
Moderate	42 (8.7)	94 (19.8)
Severe	15 (3.1)	21 (4.4)
Hospitalization		
Yes	22 (4.6)	46 (9.7)
No	50 (10.4)	92 (19.4)
Recovery as assessed by primary Investigator		
None	3 (0.6)	3 (0.6)
Partial	21 (4.4)	37 (7.8)
Complete	48 (10.0)	98 (20.7)
Steroid treatment		
Yes	65 (13.5)	126 (26.6)

Table 39

Table 14.2-1.10 (Page 1 of 1)
Proportion of patients with confirmed relapses of selected characteristics by treatment - Chi-square test
Full analysis set

Endpoint	Treatment	n/N (%)	Comparison	P-value
Proportion of patients hospitalized for relapses	OMB 20mg	22/481 (4.6)	vs. TER 14mg	0.002*
	TER 14mg	46/474 (9.7)		
Proportion of patients with severe relapses	OMB 20mg	15/481 (3.1)	vs. TER 14mg	0.287
	TER 14mg	21/474 (4.4)		

n: Total number of patients with the specified relapses.
N: Total number of patients included in the analysis.
Confirmed relapses are those accompanied by a clinically relevant change in the EDSS.
- P-values are obtained from a Chi-square test.
* Indicates statistical significance (2-sided) at the 0.05 level.

Secondary efficacy results

Although not prespecified, the 6-month CDW for each individual study will be presented first since it is considered the analysis closest to CHMP guideline requirements.

6mCDW, individual study (not prespecified)

Ofatumumab did not significantly reduce the risk of 6mCDW compared with teriflunomide although a trend in favour of ofatumumab was observed.

Table 40

Table 14.2-14.1 (Page 3 of 3)
Time to first 6-month confirmed disability worsening (6mCDW) during treatment epoch by treatment (G2301 and G2302 pooled)
Full analysis set

	Kaplan-Meier estimate (with event),% (95% CI)					
Data source	Month 18	Month 24	n/N (%)	Hazard ratio (95% CI)	Risk reduction %	P-value
G2302						
OMB 20mg	8.0 (5.9,11.0)	8.0 (5.9,11.0)	36/479 (7.5)	0.756 (0.489, 1.170)	24.4	0.209[4]
TER 14mg	10.0 (7.5,13.2)	10.9 (8.2,14.4)	46/472 (9.7)			
Log-Rank test						0.215[4]

For the prespecified pooled analyses - please see "Analysis performed across trials (pooled analyses AND meta-analysis)".

Number of T1 Gd-enhancing lesions per scan

Treatment with ofatumumab, compared with teriflunomide, reduced the mean number of Gd-enhancing T1 lesions per scan (0.0317 vs 0.5141) by 93.8%.

Table 41

Table 11-4 Number of Gd-enhancing T1 lesions per scan - Rate ratio estimate of treatment effect from negative binomial regression (Full analysis set)

				Between-treatment comparison			
Treatment	N	Adjusted mean number of Gd-enhancing lesions per scan	(95% CI)	Comparison	Rate reduction	Rate ratio	(95% CI)	P-value
OMB 20 mg	439	0.0317	(0.021, 0.048)	vs TER 14 mg	93.8%	0.062	(0.037, 0.101)	<.001*
TER 14 mg	434	0.5141	(0.402, 0.658)					

- N: Total number of patients included in the analysis.
- Gd-enhancing lesion counts from scans collected within 30 days after termination of steroid therapy were excluded from the analysis.
- The model includes adjustment for treatment and region (factors), and age, and number of Gd-enhancing lesions at baseline as continuous covariates.
- The natural log of the number of MRI-scans with evaluable Gd-enhancing lesion counts was used as the offset to obtain the lesion rate per scan.
* Indicates statistical significance (2-sided) at the 0.05 level.

Annualised rate of new or enlarging T2 lesions

Treatment with ofatumumab, compared to teriflunomide, significantly reduced the mean number of new or enlarging T2 lesions per year between baseline and EOS (0.64 vs 4.15) by 84.5%. The mean number of new or enlarging T2 lesions per year between baseline and Month 12 (0.94 vs 4.41), and between baseline and Month 24 (0.72 vs 3.72) were reduced in the ofatumumab vs the teriflunomide treatment group by 78.6% and 80.6%, respectively.

Table 42

Table 11-5 Number of new or enlarging T2 lesions per year (relative to baseline) - Rate ratio estimate of treatment effect from negative binomial regression model (Full analysis set)

						Between-treatment comparison			
Visit-window	Treatment	N	Adjusted annualized mean rate of new or enlarging T2 lesions	(95% CI)	Comparison	Rate reduction	Rate ratio	(95% CI)	P-value
Month 12	OMB 20 mg	422	0.94	(0.80, 1.11)	vs TER 14 mg	78.6%	0.21	(0.17, 0.27)	<.001*
	TER 14 mg	410	4.41	(3.83, 5.08)					
Month 24	OMB 20 mg	90	0.72	(0.51, 1.02)	vs TER 14 mg	80.6%	0.19	(0.12, 0.31)	<.001*
	TER 14 mg	76	3.72	(2.68, 5.18)					
EOS**	OMB 20 mg	448	0.64	(0.55, 0.75)	vs TER 14 mg	84.5%	0.15	(0.13, 0.19)	<.001*
	TER 14 mg	443	4.15	(3.64, 4.74)					

- N: Total number of patients included in the analysis.
- The number of new or enlarging T2 lesions (compared to baseline) is analyzed in a negative binomial model with adjustments for treatment and region (factors), and age, and baseline volume of T2 lesions as continuous covariates.
- The natural log of the time from the screening scan (in years) is used as the offset.
* Indicates statistical significance (2-sided) at the 0.05 level.
**Last scan in the double blind Treatment epoch

The mean number of new or enlarging T2 lesions (relative to baseline) analysed by visit window were lower in the ofatumumab treatment group than in the teriflunomide treatment group at Month 12 (1.2 ofatumumab, 5.8 teriflunomide) and Month 24 (1.3 ofatumumab, 8.1 teriflunomide) in the FAS.

Neurofilament light chain

Ofatumumab 20 mg was superior to teriflunomide 14 mg in reducing the NfL concentration in serum at Month 3 (and at all subsequent assessments). At Month 3, the first post-baseline assessment of NfL concentrations in serum in the ofatumumab vs the teriflunomide treatment group demonstrated a relative reduction in NfL concentration by 11%. A further relative reduction in NfL concentration by 26% at Month 12 and by 24% at Month 24 in the ofatumumab vs teriflunomide treatment group was observed.

Brain volume loss

The rate of brain volume loss appeared similar or slightly larger in the ofatumumab treatment group as compared to the teriflunomide treatment group.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the B/R assessment (see later sections).

***Table 43**:* Efficacy overview table for study COMB157G2302

Title: A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis (ASCLEPIOS II)			
Study identifier	COMB157G2302, EudraCT no. 2015-005419-33		
Design	Randomized, double-blind, double-dummy, active comparator-controlled, parallel-group, multi-center study with variable treatment duration in patients with relapsing multiple sclerosis (MS)		
	Duration of main phase:		The Treatment epoch was variable for each patient. Individual patients were treated until the End of Study (EOS) was declared or for a maximum of 30 study months. The EOS was declared when, based on blinded data, sufficient data became available to provide the required power for the statistical tests for the primary endpoint (ARR) and for key secondary endpoints related to disability worsening (3mCDW, 6mCDW). Note: The Safety follow-up epoch of the study is still ongoing.
Hypothesis	Superiority		
Treatments groups	Ofatumumab 20 mg (OMB 20 mg)		OMB 20 mg Median duration of exposure: 589.0 days Cumulative exposure: 740.8 patient-years % of patients with cumulative exposure>1 months : 85.7% % of patients with cumulative exposure > years: 32.0% N= 481 randomized
	Teriflunomide 14 mg (TER 14 mg)		TER 14 mg Median duration of exposure: 573.5 days Cumulative exposure: 702.1 patient-years % of patients with cumulative exposure>1 months : 86.3% % of patients with cumulative exposure > years: 21.5% N= 474 randomized
Endpoints and definitions	Primary endpoint	Annualized relapse rate (ARR)	Number of confirmed MS relapses in a year
	Key secondary endpoint	3-month confirmed disability worsening (3mCDW)	• Time to disability worsening as measured by 3-month confirmed worsening (3mCDW) on the Expanded Disability Status Scale (EDSS) Note: Disability-related key secondary efficacy endpoints were analysed in a pre-specified analysis of the combined data of studies COMB157G2301 and COMB157G2302.

	Key secondary endpoint	6-month confirmed disability worsening (6mCDW)	• Time to disability worsening as measured by 6-month confirmed worsening (6mCDW) on EDSS Note: Disability-related key secondary efficacy endpoints were analysed in a pre-specified analysis of the combined data of studies COMB157G2301 and COMB157G2302.
	Key secondary endpoint	6-month confirmed disability improvement (6mCDI)	• Time to disability improvement as measured by 6-month confirmed improvement (6mCDI) on EDSS Note: Disability-related key secondary efficacy endpoints were analysed in a pre-specified analysis of the combined data of studies COMB157G2301 and COMB157G2302.
	Key secondary endpoint	Gd-enhancing T1 lesions	• Number of Gd-enhancing T1 lesions per MRI scan
	Key secondary endpoint	T2 lesions	• Annualized rate of new or enlarging T2 lesions on MRI
	Key secondary endpoint	Neurofilament light chain (NfL)	• Neurofilament light chain (NfL) concentration in serum
Database lock	Data cut-off: 10-Jul-2019		

Results and Analysis

Note: The primary and all key-secondary endpoints were tested according to a statistical testing procedure.

Analysis description	**Primary Analysis: ARR**		
Analysis population and time point description	Full analysis set (FAS): following the intent-to-treat principle, included all patients with randomization numbers assigned. Data up to end of study (EOS)		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	469	469
	Adjusted ARR (95% CI)	0.10 (0.08, 0.13)	0.25 (0.21, 0.30)
Analysis description	**Key Secondary Analysis: 3mCDW***		
Analysis population and time point description	FAS/intent-to-treat Data up to EOS		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	944	931
	KM estimate at Month 24 (95% CI)	10.9 (8.8, 13.4)	15.0 (12.6, 17.7)
Analysis description	**Key Secondary Analysis: 6mCDW***		

Analysis population and time point description	FAS/intent-to-treat Data up to EOS		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	944	931
	KM estimate at Month 24 (95% CI)	8.1 (6.5, 10.2)	12.0 (9.9, 14.5)
Analysis description	**Key Secondary Analysis: 6mCDI***		
Analysis population and time point description	FAS/intent-to-treat Data up to EOS		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	749	723
	KM estimate at Month 24 (95% CI)	11.0 (8.8, 13.7)	8.1 (6.2, 10.6)
Analysis description	**Key Secondary Analysis: Gd-enhancing T1 lesions**		
Analysis population and time point description	FAS/intent-to-treat Data up to EOS		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	439	434
	No. of lesions per scan (95% CI)	0.03 (0.021, 0.048)	0.51 (0.402, 0.658)
Analysis description	**Key Secondary Analysis: T2 lesions**		
Analysis population and time point description	FAS/intent-to-treat Data up to EOS		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	448	443
	No. of new/enlarging lesions per year (95% CI)	0.64 (0.55, 0.75)	4.15 (3.64, 4.74)
Analysis description	**Key Secondary Analysis: NfL**		
Analysis population and time point description	FAS/intent-to-treat Month 3; Month 12, Month 24		
Descriptive statistics and estimate variability	Treatment group	OMB 20 mg	TER 14 mg
	Number of subjects	430	427
	NfL concentration at Month 3 (95%CI)	8.92 (8.62, 9.23)	10.02 (9.68, 10.36)

	NfL concentration at Month 12 (95%CI)	7.06 (6.77, 7.37)	9.53 (9.13, 9.95)
	NfL concentration at Month 24 (95%CI)	6.80 (6.47, 7.13)	8.99 (8.57, 9.44)

*Disability-related key secondary efficacy endpoints (i.e. 3mCDW, 6mCDW and 6mCDI) were analysed based on a pre-specified analysis of the combined data for the two studies COMB157G2301 and COMB157G2302. Results shown here are based on the analysis of the combined data.

Analysis performed across trials (pooled analyses and meta-analysis)

A meta-analysis was performed combining data from studies 2301 and 2302 with the primary purpose to evaluate the pre-defined disability-related key secondary study objectives.

The key disability-related objectives were to evaluate if ofatumumab 20 mg SC every 4 weeks was superior to teriflunomide 14 mg p.o. once daily on the following efficacy measures:

1. Time to disability worsening as measured by 3mCDW on the EDSS
2. Time to disability worsening as measured by 6mCDW on EDSS
3. Time to disability improvement as measured by 6mCDI on EDSS

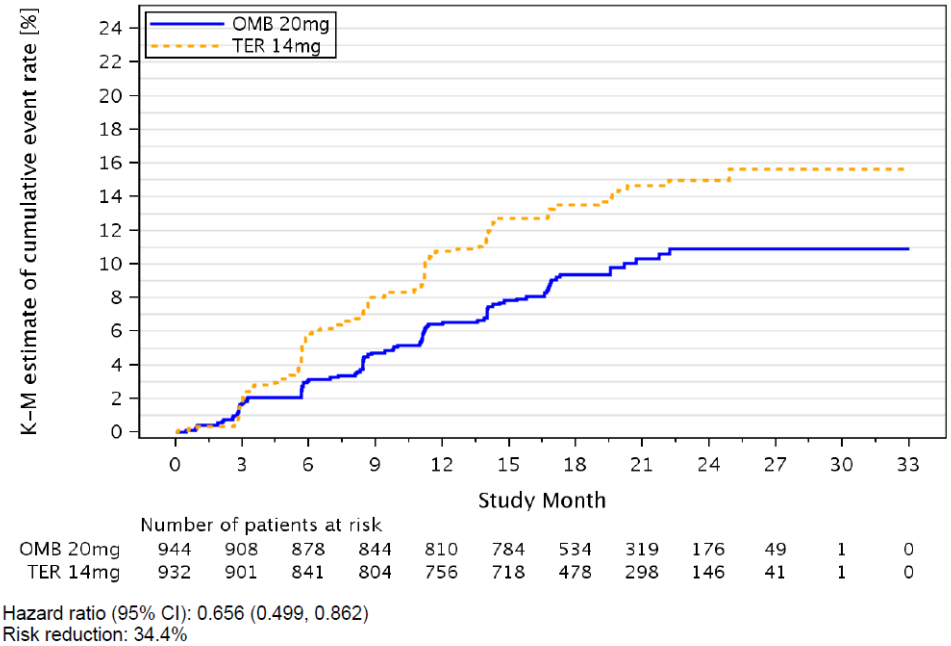
Results

Time to 3mCDW based on EDSS

Ofatumumab appeared to lower the risk of a 3mCDW by 34.4% vs teriflunomide:

Figure 25

Figure 11-2 Time to first 3mCDW during treatment epoch by treatment G2301 and G2302 combined (FAS)



Hazard ratio (95% CI): 0.656 (0.499, 0.862)
Risk reduction: 34.4%

Table 44

Table 11-1 Time to first 3mCDW during treatment epoch by treatment G2301 and G2302 combined (FAS)

Data source	Kaplan-Meier estimate (with event),% (95% CI) Month 18	Month 24	n/N (%)	Hazard ratio (95% CI)	Risk reduction %	P-value
Combined data G2301 + G2302[1]						
OMB 20mg	9.4 (7.6,11.5)	10.9 (8.8,13.4)	88/944 (9.3)	0.656 (0.499, 0.862)	34.4	**0.002[3]**
TER 14mg	13.5 (11.4,16.0)	15.0 (12.6,17.7)	125/931 (13.4)			
Heterogeneity test[2]						0.967[4]
Log-Rank test						0.004[4]
By study[2]						
G2301						
OMB 20mg	9.4 (7.0,12.6)	11.3 (8.4,15.1)	45/465 (9.7)	0.652 (0.445, 0.957)	34.8	0.029[4]
TER 14mg	13.9 (10.9,17.5)	15.4 (12.1,19.4)	63/459 (13.7)			
Log-Rank test						0.042[4]
G2302						
OMB 20mg	9.3 (6.9,12.5)	10.5 (7.8,14.1)	43/479 (9.0)	0.660 (0.447, 0.974)	34.0	0.036[4]
TER 14mg	13.2 (10.3,16.7)	14.6 (11.5,18.6)	62/472 (13.1)			
Log-Rank test						0.038[4]

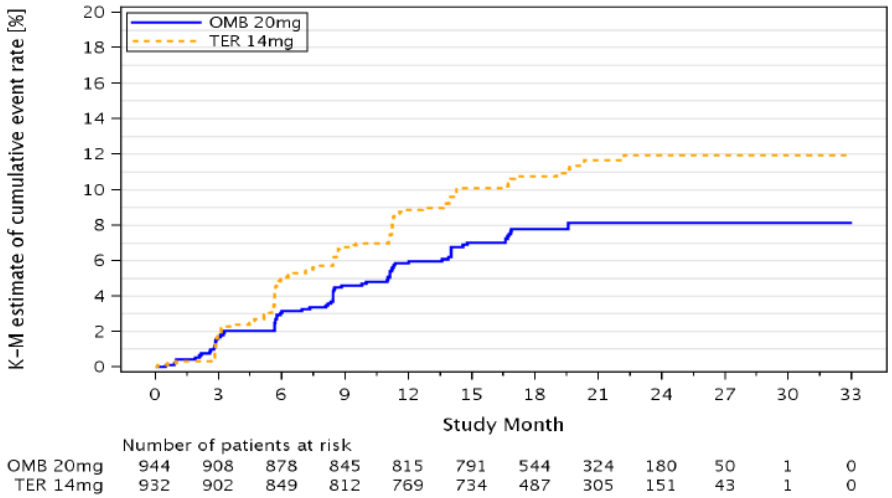
[1] Results of treatment comparison obtained from a Cox regression adjusted for study as stratum, treatment, and region as factors and baseline EDSS as a continuous covariate.
[2] Treatment-by-study interaction added to the main model to obtain by study treatment comparison results and test of heterogeneity (i.e., statistical test of the treatment-by-study interaction; if significant the treatment effect differs between studies).
[3] Statistical test uses significance (2-sided) level at 0.04875 between treatments according to the multiplicity procedure. (The p-value related to the key secondary hypothesis is part of the testing strategy).
[4] Statistical test uses significance (2-sided) level of 0.05.
N: Total number of patients included in the analysis. n: Number of patients with the specified event. %=n/N.

Time to 6mCDW based on EDSS

Ofatumumab lowered the risk of a 6mCDW by 32.5% vs teriflunomide:

Figure 26

Figure 11-3 Time to first 6mCDW during treatment epoch by treatment G2301 and G2302 combined (FAS)



Hazard ratio (95% CI): 0.675 (0.498, 0.916)
Risk reduction: 32.5%

Table 45

Table 11-2 Time to first 6mCDW during treatment epoch by treatment G2301 and G2302 combined (FAS)

Data source	Kaplan-Meier estimate (with event),% (95% CI) Month 18	Month 24	n/N (%)	Hazard ratio (95% CI)	Risk reduction %	P-value
Combined data G2301 + G2302[1]						
OMB 20mg	7.8 (6.2,9.7)	8.1 (6.5,10.2)	71/944 (7.5)	0.675 (0.498, 0.916)	32.5	**0.012[3]**
TER 14mg	10.7 (8.9,13.0)	12.0 (9.9,14.5)	99/931 (10.6)			
Heterogeneity test[2]						0.480[4]
Log-Rank test						0.016[4]
By study[2]						
G2301						
OMB 20mg	7.5 (5.4,10.4)	8.2 (6.0,11.3)	35/465 (7.5)	0.607 (0.396, 0.930)	39.3	0.022[4]
TER 14mg	11.5 (8.9,14.9)	13.0 (10.0,16.9)	53/459 (11.5)			
Log-Rank test						0.031[4]
G2302						
OMB 20mg	8.0 (5.9,11.0)	8.0 (5.9,11.0)	36/479 (7.5)	0.756 (0.489, 1.170)	24.4	0.209[4]
TER 14mg	10.0 (7.5,13.2)	10.9 (8.2,14.4)	46/472 (9.7)			
Log-Rank test						0.215[4]

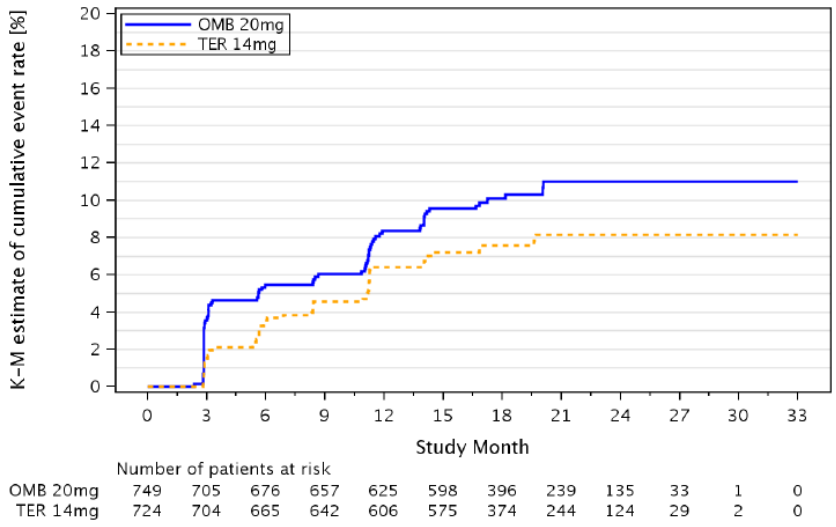
[1] Results of treatment comparison obtained from a Cox regression adjusted for study as stratum, treatment, and region as factors and baseline EDSS as a continuous covariate.
[2] Treatment-by-study interaction added to the main model to obtain by study treatment comparison results and test of heterogeneity (i.e., statistical test of the treatment-by-study interaction; if significant the treatment effect differs between studies).
[3] Statistical test uses significance (2-sided) level at 0.04875 between treatments according to the multiplicity procedure.
[4] Statistical test uses significance (2-sided) level of 0.05.
N: Total number of patients included in the analysis. n: Number of patients with the specified event. %=n/N.

Time to 6mCDI based on EDSS

Ofatumumab appeared to numerically increase the probability of a 6mCDI by 35.2% compared with teriflunomide. The difference was not significant in the prespecified test (risk reduction = −35.2%, p=0.094):

Figure 27

Figure 11-4 Time to first 6mCDI during treatment epoch by treatment G2301 and G2302 combined (FAS)



Number of patients at risk

OMB 20mg	749	705	676	657	625	598	396	239	135	33	1	0
TER 14mg	724	704	665	642	606	575	374	244	124	29	2	0

Patients with Baseline EDSS score of 0 to 1.5 were excluded from the analysis as no disability improvement was possible for these patients as described in Section 9.6.4.1.2.

Hazard ratio (95% CI): 1.352 (0.950, 1.924)

Risk reduction: -35.2%

Table 46

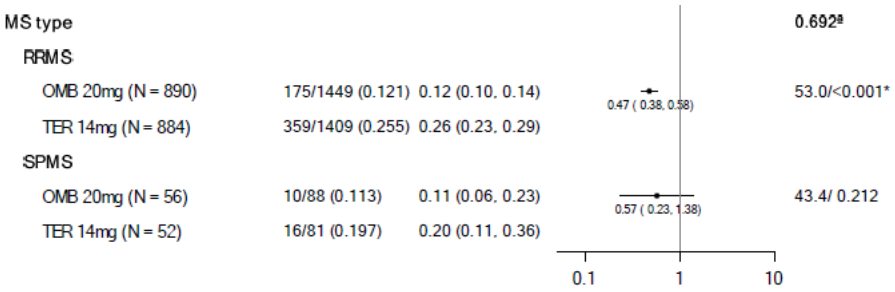
Table 11-3 Time to first 6mCDI during treatment epoch by treatment (G2301 and G2302 combined) (FAS)

Data source	Kaplan-Meier estimate (with event),% (95% CI) Month 18	Month 24	n/N (%)	Hazard ratio (95% CI)	Risk reduction %	P-value
Combined data G2301 + G2302[1]						
OMB 20mg	10.1 (8.1,12.6)	11.0 (8.8,13.7)	74/749 (9.9)	1.352 (0.950, 1.924)	-35.2	**0.094[3]**
TER 14mg	7.6 (5.8,9.8)	8.1 (6.2,10.6)	53/723 (7.3)			
Heterogeneity test[2]						0.497[4]
Log-Rank test						0.081[4]
By study[2]						
G2301						
OMB 20mg	9.1 (6.5,12.7)	9.7 (7.0,13.5)	33/375 (8.8)	1.186 (0.709, 1.984)	-18.6	0.515[4]
TER 14mg	7.1 (4.8,10.3)	8.2 (5.6,11.9)	26/363 (7.2)			
Log-Rank test						0.429[4]
G2302						
OMB 20mg	11.1 (8.2,14.8)	12.3 (9.1,16.5)	41/374 (11.0)	1.516 (0.932, 2.466)	-51.6	0.094[4]
TER 14mg	8.1 (5.6,11.6)	8.1 (5.6,11.6)	27/360 (7.5)			
Log-Rank test						0.099[4]

[1] Results of treatment comparison obtained from a Cox regression adjusted for study as stratum, treatment, and region as factors and baseline EDSS as a continuous covariate.
[2] Treatment-by-study interaction added to the main model to obtain by study treatment comparison results and test of heterogeneity (i.e., statistical test of the treatment-by-study interaction; if significant the treatment effect differs between studies).
[3] Statistical test uses significance (2-sided) level at 0.04875 between treatments according to the multiplicity procedure.
[4] Statistical test uses significance (2-sided) level of 0.05.
N: Total number of patients included in the analysis. n: Number of patients with the specified event. %=n/N. Patients with Baseline Total EDSS score 0, 1 or 1.5 are excluded from analyses as no disability improvement is possible for these patients.

Exploratory pooled subgroup analyses, SPMS:

ARR, SPMS



6-month CDW, SPMS

Ofatumumab numerically reduced the risk of 6mCDP compared with teriflunomide (risk reduction of 6mCDP = 44%, p=0.228)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Demonstration of the clinical efficacy of ofatumumab 20 mg SC vs. teriflunomide in patients with active RMS was based on two randomised 1:1 double-blind double-dummy Phase III studies of identical design (2301 and 2302). 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 design is considered acceptable and the Sponsor had in place adequate measures to protect the blinding of the study.

The studies were designed before the publication of the ICH E9 addendum. However, the Applicant defined the estimand's attributes of the studies to facilitate the review of this marketing authorisation application. The Applicant compared the treatment effect in term of annualized relapse rate between ofatumumab and teriflunomide regardless of treatment discontinuation or short treatment to alleviate the symptoms of relapses. This estimand is considered of clinical relevance and is endorsed.

The patient population consisted of adult patients with RMS, activity as evidenced by relapses or MRI findings, and an EDSS score of 0-5.5. The patient population in clinical studies should be guiding the future clinical use and indication in SmPC, also in line with similar products. Both RRMS and 'active SPMS' patients were eligible but no minimum number of SPMS patients was prespecified. The rationale for including both RRMS and SPMS patients with no minimum number defined and assumption of similar treatment effect for 3mCDW and 6mCDW in all subgroups presents some challenges for the analyses and the interpretation of results.

The choice of teriflunomide as active comparator is accepted and in accordance with previous scientific advice (EMEA/H/SA/1049/6/FU/1/2016/II). The primary endpoint (ARR) for each study is considered relevant. As for the key secondary endpoints the most important should have been not the 3mCDW but the 6mCDW as per guideline and multiple scientific advices (e.g. EMEA/H/SA/1049/6/FU/1/2016/II). The secondary endpoints appear reasonable.

The studies were planned in order to allow for pooling of the data in order to achieve reasonable power to detect a treatment effect in the disability endpoints. Therefore, the sample size calculations are primarily driven by the pooling of the disability endpoints. Of note, the sample size calculation assumed the same treatment effect in RRMS and SPMS for 3mCDW and 6mCDW

The efficacy analyses were performed using the FAS, which included all randomized patients according to the assigned treatment. This is endorsed.

The statistical methods used to analyse the endpoints are overall considered adequate. 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 Gd-enhancing 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. This model assumes that the relapse rate is constant within patient. Patients who discontinued the study contributed only with the observed time and it was assumed that the relapse rate for those patients would not be affected by treatment discontinuation (missing at random assumption). The validity of the assumption was not discussed by the Applicant. However, several sensitivity and supportive analyses were planned to assess the robustness of the results and departures from the MAR assumption. The number of Gd-lesions and the number of new or enlarging T2 per MRI-scan will be compared

using a negative binomial regression model with log-link. The geometric mean of NfL concentration of the two treatment arms was compared at month 3 using a mixed model for repeated measures, which assumes missing at random. A random coefficients model was used in the main analysis for brain volume loss, which is agreed. The disability endpoints (3mCDW, 6mCDW and 6mCDI) were analysed using a Cox-model stratified by study. The variables of the model were treatment, region and baseline EDSS. Between study heterogeneity was tested using a Cox-model including a treatment-by-study interaction. Patients who did not experience an event during observation were censored. It is not considered adequate to apply the non-informative censoring assumption in the primary analysis. However, sensitivity analyses were presented challenging this assumption and are endorsed.

The main methodological concern regards the procedure implemented to control for multiplicity for the secondary endpoints. There is no established methodological approach to control for multiplicity in a pooling set-up. While planning of the analyses adds credibility to the results, this does not guarantee that the type I error is overall controlled. The Applicant aims to control for multiplicity in 3 different branches simultaneously. If the primary endpoint within study is met, the alpha would be transferred to the secondary endpoints in a hierarchical fashion. If both primary endpoints were met, the pooled endpoints would be tested with significance level α - α2. Type I error is controlled for the primary endpoint ARR in the individual studies and the disability endpoint can be assessed at the significance level achieved in the pooled study data, however it is not clear if the current strategy effectively controls for multiplicity for other key secondary endpoints.

As a note, aspects of the clinical investigational plan (inclusion of SPMS patients, median treatment duration, choice of 3mCDW as most important secondary endpoint, and the loading dose regimen) were questioned in the 2016 scientific advice but no changes appear to have been subsequently implemented by the Applicant.

The choice of the final dose for pivotal studies is not entirely clear. The dosing regimen with an initial 20 mg SC of ofatumumab every week for a first 3 week, following a maintenance administration of 20 mg SC from week 4 is based on study OMS112831. Replacing 60 mg initial dose with 3 weekly doses of 20 mg was a result of better tolerability profile observed in Phase II (with doses of ofatumumab below 30 mg). 20 mg SC is perceived as a dose regimen being the lowest to assure reliable and constant B-cell depletion in MS patients. It was also approved by the EMA before starting Phase III studies. The results of the dose response analysis show that the cumulative dose of 60 mg ofatumumab administered over 12 weeks provided maximal benefit, with no additional suppression of GdE T1 lesions at higher cumulative doses. The OMS112831 study did not show significant differences in clinical efficacy e.g., between doses, even though the rate of depletion of B cells was different (e.g., for a 60 mg dose administered every 4 and 12 weeks). Also, the analysis after 24 weeks showed that the efficacy of ofatumumab concerning the cumulative number of new GdET1 Lesions (Week 24) administered at 3 mg every 12 weeks, 30 mg every 12 weeks and 60 mg every 4 weeks is almost identical. In addition, the use of a lower maintenance dose, 10 mg, gives only a marginal reduction in drug concentration, there are no data from the clinical trial on AAR and other efficacy parameters, and the modelling of CD19+ cell level reduction has been assumed to be equivalent to efficacy. In this context, the Applicant's explanations are not entirely convincing, but given the favourable safety profile of the dose used in the G2301 and G2302 studies, the rationale regarding the use of the dose of 20 mg, can be accepted.

Efficacy data and additional analyses

Both studies 2301 and 2302 met the primary endpoint with clinically relevant ARR reductions of 50.5% (study 2301) and 58.5% (study 2302), respectively. Sensitivity and supportive analyses were consistent with the results of the primary analysis.

In the combined data from studies 2301 and 2302 the risk of 6mCDW and 3mCDW was reduced by 32.5% (6mCDW) and 34.4% (3mCDW), respectively.

Regarding the MRI endpoints, ofatumumab reduced the number of Gd-enhancing T1 lesions by 97.5% (study 2301) and 93.8% (study 2302), respectively. The number of new or enlarging T2 lesions was reduced with a rate reduction of 81.9% (study 2301) and 84.5% (study 2302), respectively.

No difference in the annual BVL was demonstrated.

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

Subgroup analyses suggest larger effect size in young patients and in patients with mild disease. No studies in patients older than 56 years were conducted. Extrapolation to older individuals should be justified as also mentioned in the Clinical Pharmacology section. The point estimate for the SPMS subgroup was approximately similar to that of RRMS although this should be interpreted with caution since the SPMS group was very small and 95% CI was extending beyond 1.

Only one dose level was tested in Phase III. In the Phase II MIRROR study (OMS112831) all doses tested (3 mg, 30 mg, 60 mg) led to the same (65%) reduction in the cumulative number of new Gd-enhancing T1 lesions compared to placebo, however, a dose-dependent increase in efficacy was shown after excluding the initial 4 weeks data. Although the mentioned studies have explored different doses of ofatumumab, the dose-response relationship has not been fully elucidated.

At the Oral Explanation, the Applicant has presented analyses in patients with different baseline characteristics including analyses for newly diagnosed naïve patients and analyses based on time since last relapse.

Newly diagnosed DMT naive patients were included in the studies as far as they fulfilled the inclusion criteria, including recent evidence of activity. In newly diagnosed patients if active, the benefits seem comparable to the ones observed in the overall population studied (see Table below).

Table 47

	Overall population* (N=1882)		Newly diagnosed, treatment-naive patients (N=615)	
Endpoint	**OMB 20mg**	**TER 14mg**	**OMB 20mg**	**TER 14mg**
ARR [1]	0.11 (N=946)	0.24 (N=936)	0.09 (N=314)	0.18 (N=301)
Treatment effect vs comparator	**52.6% reduction** ARR-ratio: 0.47 (0.39, 0.58) p<0.001		**50.3% reduction** ARR-ratio: 0.50 (0.33, 0.74) p<0.001	
3mCDW[2]	10.9% (N=944)	15.0% (N=932)	10.1% (N=312)	12.8% (N=300)
Treatment effect vs comparator	**33% risk reduction** HR [3]: 0.67 (0.51, 0.88) p=0.004		**38.0% risk reduction** HR [3]: 0.62 (0.37, 1.03) p=0.065	
6mCDW[2]	8.1% (N=944)	12.0% (N=932)	5.9% (N=312)	10.4% (N=300)
Treatment effect vs comparator	**31.0% risk reduction** HR [3]: 0.675 (0.51, 0.93) p=0.017		**46.0% risk reduction** HR [3]: 0.54 (0.30, 0.98) p=0.044	
Gd-enhancing T1 lesions[4] (number of lesions per scan)	0.03 (N=893)	0.69 (N=868)	0.02 (N=296)	0.39 (N=284)
Treatment effect vs comparator	**95.8% risk reduction** RR: 0.04 (0.03, 0.06) p<0.001		**95.4% risk reduction** RR: 0.05 (0.02, 0.10) p<0.001	
T2 lesions[5] (number of new or enlarging lesions per year)	0.88 (N=891)	5.12 (N=876)	0.86 (N=300)	4.78 (N=287)
Treatment effect vs comparator	**82.9% risk reduction** RR: 0.17 (0.15, 0.20) p<0.001		**82.0% risk reduction** RR: 0.18 (0.14, 0.24) p<0.001	

ARR=adjusted response rate, 3mCDW=3-month confirmed disability worsening, 6mCDW=6-month confirmed disability worsening, HR=hazard ratio; RR=rate reduction

* The results presented for the overall population in this table are slightly different than results presented in the Meta-analysis G2301/G2302 CSR due to use of a simplified model to be consistent with the subgroup analysis.

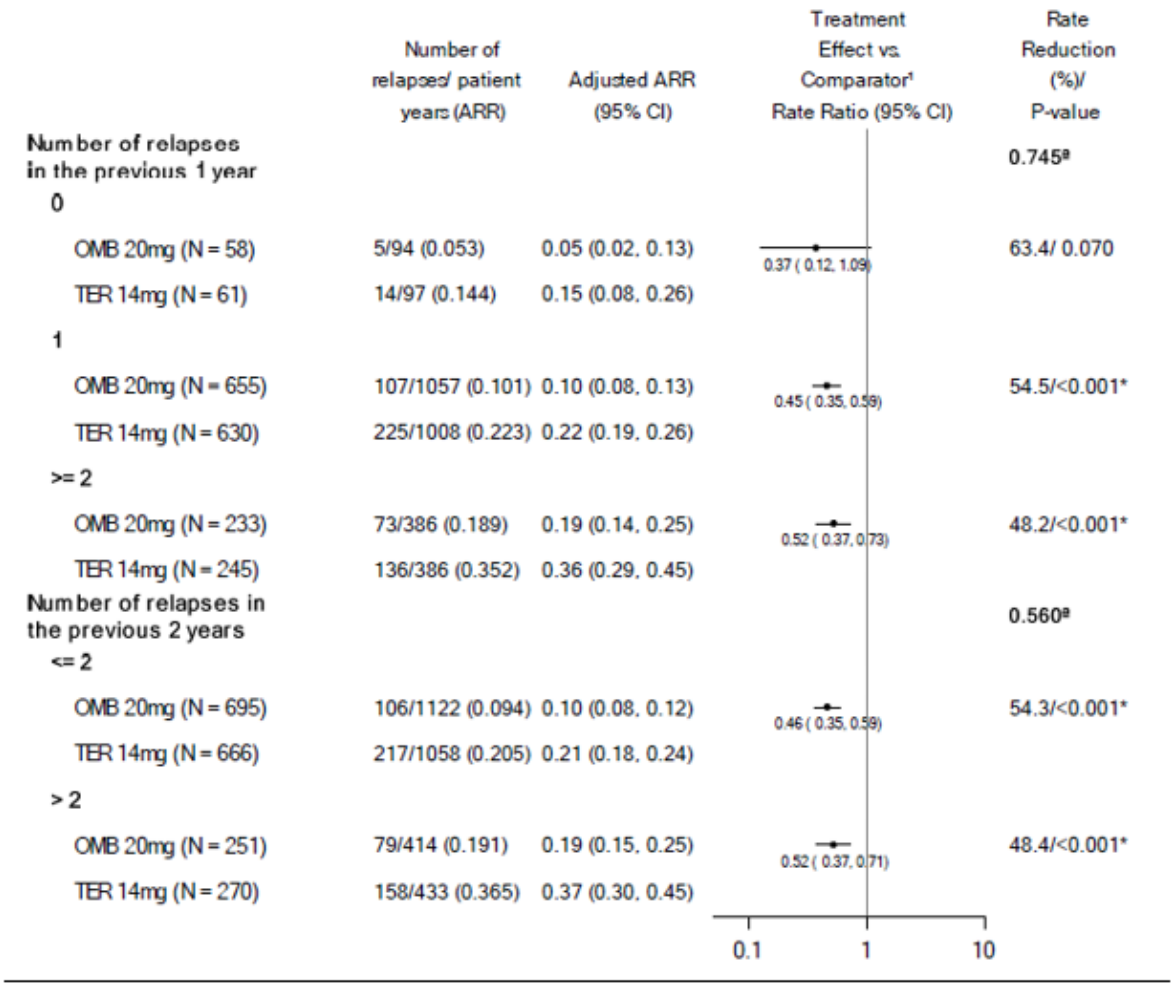
[1] ARR obtained from fitting a negative binomial regression model with log-link to the number of relapses, adjusted for study, treatment for the overall analysis, with additional co-factors of subgroup, treatment by subgroup interaction for the subgroup analysis. The natural log of the time-in-study was used as offset to annualize the relapse rate.; reported are the ARR, the ARR-ratio with 95% CI and p-value; the p-value indicates statistical significance (2-sided) at the 0.05 level.

[2] Kaplan-Meier estimates at Month 24; results of treatment comparison obtained from a Cox regression adjusted for study as stratum and treatment as factor for the overall analysis, with additional co-factors of subgroup, and treatment by subgroup interaction for the subgroup analysis; Indicates statistical significance (2-sided) at the 0.05 level.

[3] HR hazard ratio with 95% confidence interval

[4] Number of Gd-enhancing lesions per scan as analyzed in a negative binomial model; the model includes adjustment for study, treatment for the overall analysis, with additional co-factors of subgroup and treatment by subgroup interaction for the subgroup analysis; the natural log of the number of MRI-scans with evaluable Gd-enhancing lesion counts was used as the offset to obtain the lesion rate per scan; the p-value indicates statistical significance (2-sided) at the 0.05 level

For patients with less recent activity, the analyses presented (see below) do not demonstrate a lower level of efficacy.



However, it should be noted that at least 75% of patients had a relapse within the prior 8.2 months of enrollment in the Asclepios I and II according to the subgroup analyses based on time since last relapse (Q4 defined as time>8.2 months using P_{75} of the distribution). This is in line with inclusion criteria requiring the documentation of at least one of the following: (i) 1 relapse during the previous 1 year OR (ii) 2 relapses during the previous 2 years prior to Screening OR (ii) a positive Gd-enhancing MRI scan during the year prior to randomisation. Given the eligibility criteria, patients not meeting the "activity criterion" were not appropriately represented in the study. Hence, a conclusion on the magnitude of effect in patients not meeting the "activity" criterion cannot be drawn, but the benefit is assumed to be smaller due to the lower counterfactual risk.

2.5.4. Conclusions on clinical efficacy

Efficacy (of ofatumumab 20 mg SC vs. teriflunomide) on relapses in active RMS was demonstrated in two identical confirmatory studies of adequate design. The magnitude of the effect in a population not fulfilling the activity criteria at baseline has not been demonstrated, but it can be assumed to be smaller due to the smaller counterfactual risk.

2.6. Clinical safety

Patient exposure

At the time of finalization of safety summary, 2499 patients with MS have been treated in blinded or open-label studies in the ofatumumab MS clinical program, which consists of 2 ongoing studies (Study G1301 and Study G2399), 2 pivotal Phase-III studies (Study G2301 and Study G2302, Pool C2, n=1882) and 3 supportive Phase-II studies: one SC PK bioequivalence study (Study G2102), one SC efficacy study (Study OMS112831 or Pool C1), one IV dose finding study (Study OMS115102 or Pool C0). After exclusion of patients in ongoing studies G1301 and G2399, 1497 patients remained in the group who had received at least one dose of ofatumumab, any dose. The Applicant has excluded safety data from other indications (such as chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD), pemphigus vulgaris (PV)) in the analyses for this application.

The primary source of safety data with ofatumumab 20 mg SC (Pool L2), in the RMS target population, consists of the two pivotal Phase-III studies (main SAF or Pool C2) with supportive data from Phase-II bioequivalence study with autoinjector and prefilled syringes for administration (Study G2102). Number of all MS patients exposed to 20 mg SC formulation of ofatumumab in the clinical program is 1230 (94.4% of those are RRMS patients); with 946 patients from phase III pivotal studies (40.8 % of those are treatment naïve patients) and 284 from study G2102. The approaches for pooling the safety data in Pool C2 and Pool L2 are reasonable and appropriate. In main SAF, the demographics and exposure are adequately described, and study arms are balanced at baseline with regards to age, gender, race, body composition, and "disease characteristics/predictors/treatments". The safety package in phase III studies and amount of exposure to ofatumumab 20 mg SC dose is considered adequate for characterization of the short-term safety of ofatumumab 20 mg SC in RMS patients.

In small subset of patients who had a diagnosis of active SPMS at baseline, the patients were older (~45 years), had the disease for longer (~10 years), were more disabled (mean EDSS>4.5), had a substantially higher T2 lesion load on MRI (mean ~20 mm3), and a higher proportion of patients (>70%) had previously received at least one other DMT before entry into the G2301 and G2302 studies compared with RRMS patients. Total exposure (patient-years) was proportionately higher in patients with RRMS in both treatment groups (ofatumumab, 1400.6 patient-years; teriflunomide, 1321.7 patient years) compared with those with SPMS (ofatumumab, 86.1 patient years; teriflunomide, 76.1 patient years).

The choice of active comparator in main SAF is acceptable with the caveat of unblinding risk for some patients/investigators due to injection-related AEs. However, the fact that teriflunomide has its own side effect profile as an immune-modulating agent and there are certain monitoring rules which are both clearly reflected in its SmPC and Risk Management Plan (RMP), should be kept in mind during the evaluation of safety profile for ofatumumab in comparison to teriflunomide, especially in case of AEs/ serious AE (SAEs) which are similar between groups and have monitoring or risk management measures specified in teriflunomide SmPC/RMP.

Long-term safety data have been collected in accordance with requirements of ICH E1 guidance (CPMP/ICH/375/95). In main SAF, 832 patients were exposed to ofatumumab 20mg SC over 48 weeks, and 312 patients were exposed over 96 weeks. In this pool, 85.9% (813) of patients completed the double-blind treatment epoch while 13.8% (131) discontinued from the treatment epoch and 17% discontinued study drug. The number of patients exposed for more than 1 year were sufficient. Further long-term safety and tolerability data in patients with MS will be available after receiving results of the ongoing study G2399 which is not included in this submission. Study G2399 is an extension study which enrolled patients from Study G2301,

Study G2302, Study G2102, and Study G1301 who have transitioned and therefore have not been followed further in the original studies. A listing of SAEs available at the time of the submission cut-off date (15-Nov-2019) is provided in the appendix and includes SAEs such as myocardial infarction, acute heart failure, CIDP, acute cholecystitis, acute pancreatitis, acute appendicitis, depression, suicide attempt, emotional distress.

Adverse events

Overview of adverse events in main SAF does not signal an imbalance between treatment arms in number of AEs, despite a higher frequency noted in ofatumumab group for SAEs and AEs leading to drug discontinuation.

However, in the supportive analyses significantly higher number of treatment-emergent adverse events (TEAEs), SAEs, AEs leading to drug discontinuation is reported for ofatumumab. Specifically, in Pool C1, the incidence of SAEs in the ofatumumab group was 3%, no SAEs were reported in the placebo group, and all withdrawals from the study treatment (3 patients, 1%) were due to injection-related reactions with the 60-mg dose regimens. Therefore, phase III studies included a loading dose of 20 mg given three times weekly which was preferred over a loading dose of 60 mg given every 4 weeks due to more AEs/SAEs associated with 60 mg dose (in particular post-injection systemic reactions reported as SAEs on day 1).

The long-term safety profile of ofatumumab in clinical use for MS patients with proposed dosing regimen, loading regimen and cumulative exposure is unknown, so all the treatment emergent adverse events are considered to be potentially clinically important, despite the small number of patients in some groups in supplementary analyses. Despite the differences of patient population and dosing in other indications, a summary of studies in RA indication did not reveal any new safety signals compared to Arzerra. In RA, the higher burden of infusion reactions and anaphylactic reactions is due to the mode of administration (IV), higher doses and the initial lack of a standardized and effective premedication regimen. The most frequently reported infection AEs are upper respiratory tract infection, urinary tract infection, nasopharyngitis, and rhinitis. Neoplasms occurred in 0.2% patients (1 patient) of the 'All' OMB157 group and in 1.4% patients (4 patients) of the placebo group. One patient of the OMB157 700-mg group was diagnosed with breast cancer (PT serious, grade 4) 3 months after the first cycle of study drug. The incidence of neutropenia events was 2.9% overall and none in 300mg, 4,5% in 700mg, 13% in 1000/700mg groups, showing a dose dependent increase tendency.

In main SAF for RMS, the most frequently reported exposure adjusted TEAEs by PT were injection-related reaction (ofatumumab, 20.6%; teriflunomide, 15.3%) followed by nasopharyngitis (ofatumumab, 18.0%; teriflunomide, 16.7%), headache (ofatumumab, 13.3%; teriflunomide, 12.4%), injection site reaction (ofatumumab, 10.9%; teriflunomide, 5.6%) and all had OR >1. Other common TEAEs included but were not limited to urinary tract infection, back pain, influenza, blood IgM decreased, arthralgia, anxiety, dizziness, insomnia, pyrexia, oropharyngeal pain, pharyngitis, gastroenteritis, rhinitis, constipation, vertigo, muscular weakness, viral upper respiratory tract infection, influenza like illness, migraine, blood creatinine increased, cystitis. Exposure adjusted adverse event profile in pool C1 seems to be similar to main analysis pool in terms of most frequently reported AEs but also has similarities with Pool C0 and study G2102 (the studies with iv infusion and/or higher doses of ofatumumab and data not shown here).

In active SPMS sub-group of main SAF, 8 (14.3%) patients in the ofatumumab group and 4 (7.7%) patients in the teriflunomide group experienced at least one SAE. Overall percentage of patients with infections in RRMS (OFA 463 (52.0%), TER 473 (53.5%)) or active SPMS (OFA 25 (44.6%), TER 20 (38.5%)) groups were similar between two treatment arms, with a possible difference in herpes viral infections (OFA 4 (7.1%) vs TER 1 (1.9%)) which were more frequent in ofatumumab group in the overall results (OFA 42 (4.7%) vs TER 38

(4.3%)). In contrast to RRMS group (OFA 7 (0.8%), TER 30 (3.4%)), neutropenia events were more common with ofatumumab and at a similar level to teriflunomide in active SPMS group (OFA 2 (3.6%), TER 2 (3.8%)).

In Pool L2, which consists of only ofatumumab 20mg SC treated patients, of the 953 patients (77.5%) who experienced AEs, 83 patients (6.7%) experienced grade 3-4 AEs. The most frequently reported grade 3-4 AEs was appendicitis (8, 0.7%), urinary tract infection (4, 0.3%), decreased blood immunoglobulin M (IgM) (7, 0.6%), and injection-related reaction (3, 0.2%). Other grade 3-4 AEs occurring in two patients each (0.2%) were back pain, cholecystitis, depression, foot fracture, gastroenteritis, influenza, neutropenia, pneumonia, and tibia fracture. Limited number of SAEs from ongoing studies listed in appendix also show similarities with some of grade 3-4 AEs reported above.

It is noted that some of the most frequently reported grade 3-4 AEs are in line with the identified or potential risks in Arzerra SmPC or RMP, thus occurring even at much lower doses. All adverse events known for Arzerra and available data from prior clinical studies in non-oncology indications (RA, PV, COPD), were taken into consideration when evaluating the overall safety profile of ofatumumab in MS patients. Such potentially important risks from Arzerra include 'Infusion reactions, including cytokine release syndrome', 'HBV infection and reactivation', 'Cardiovascular events', 'Neutropenia' 'Cytopenia (excluding neutropenia)', 'Infections with PML, 'Severe mucocutaneous reactions', 'Effects on immunizations, including interactions with live vaccines', 'Immunogenicity'.

Adverse events of special interest

Analyses of adverse events of special interest (AESI) revealed that clinically important potential events such as injection-related reactions, upper respiratory tract infections, urinary infections, herpes or varicella-zoster infections, or suicidal ideation/behaviour were more common in the ofatumumab group than in the active comparator group.

In line with the safety profile described for anti-CD20 mAbs, the main safety issues with ofatumumab are the risk of injection related reactions, infections, decreased ability to mount an immune response to live or attenuated vaccines, coupled with the potential for infection following the administration of live vaccines, and decreased IgM levels. Vaccines and immunoglobulin levels are discussed later.

Injection-related reactions

Injection-related reactions with ofatumumab 20 mg SC are "very common" AEs in SmPC and an "identified" risk in RMP.

Injection-related reactions are common with the first and second ofatumumab injection and requires the first injection of ofatumumab to be given under the guidance of a healthcare professional. They comprise systemic reactions (e.g. fever, other systemic symptoms, headache, chills, myalgia, fatigue), 20.2% and injection-site reactions (e.g. erythema/redness, other site symptoms, pain, induration/swelling, warmth, itching), 10.8%. They appear to be independent of the administered dose and may not be predicted on beforehand.

Pre-treatment is not recommended. Steroids may reduce the frequency of fever, myalgia, chills, and nausea but conversely increase the occurrence of flushing, chest discomfort, hypertension, tachycardia and abdominal pain. If injection-related reactions occurred, they have been reported to be manageable. However, in supplementary pools there had been SAEs such as cytokine release syndrome, angioedema/urticaria or injection related reaction (IRR) events leading to withdrawal with higher doses than 20 mg SC.

In Study G2102, IRRs appear to be influenced by site of administration. However, this difference was not confirmed in phase III studies, where there were no differences in occurrence of injection systemic reactions at three sites (upper arm=13.3%, thigh=16.4%, abdomen=14.8%; Overall=14.4%).

Infections (including opportunistic infections)

A risk of infection, including opportunistic infections, is associated with the use of any anti-CD20 biological product (including ofatumumab) depleting B-cells and thereby lowering immunoglobulins.

The overall proportion of patients with infections was similar in the ofatumumab group and the teriflunomide treatment group (teriflunomide SmPC includes a contraindication for use in patients with severe active infection until resolution and warnings on this topic). The most commonly reported infections included but were not limited to nasopharyngitis (18.0%), upper respiratory tract infection (10.3%), urinary tract infection (10.3%), and influenza (6.6%). The occurrence of new or reactivated herpes infections, including ophthalmic infections, was increased in the ofatumumab group (46, 4.9% vs 39, 4.2% in the ofatumumab and teriflunomide groups). There were no observed cases of PML, cryptococcal infections, reactivation of hepatitis in MS studies and following patients were excluded from clinical studies: history of PML; risk of developing or having reactivation of hepatitis, syphilis or tuberculosis; impaired immune response including PML, hepatitis, syphilis, tuberculosis, acquired immunodeficiency syndrome; chronic disease of the immune system other than MS; significantly impaired bone marrow function or significant anaemia, leukopenia, neutropenia.

"Serious infections, including opportunistic infections (e.g., PML, HBV reactivation)" is an important potential risk in RMP and characterizes the serious infections related to decrease in immunoglobulins and lymphopenia or neutropenia. Furthermore, appendicitis being reported in 1% of the population and more frequently in the ofatumumab group was included in this broadened important potential risk of serious infections, to be further characterised in Post Authorisation Safety Studies (PASS) and monitored and reported in the future PSURs.

Malignancy or pre-malignant disorders

There was not an increased frequency of malignancy or pre-malignant disorders with ofatumumab compared to teriflunomide in the clinical trial experience with RMS patients. However, the time on the study and/or follow-up was short with regards to the development of neoplasms and sustained depletion of B-cells might affect the immune system´s ability to detect and eliminate cancer cells thus leading to an increased risk of developing solid tumours. Since the risk of malignancy is known to be increased with use of some other agents that affect the immune system (e.g. malignancies including breast cancer is included in AEs for ocrelizumab or skin cancers with sphingosine-1-phosphate modulators), the currently available data do not exclude that a similar risk apply to longer-term treatment with ofatumumab. The risk of malignancy is included as an important potential risk in the RMP and active malignancies is included as a contraindication in SmPC.

Serious adverse events and deaths

No deaths were reported during treatment with ofatumumab in main SAF or supplementary pools.

The total number of patients reporting SAEs in Pool C2 was slightly higher in the ofatumumab group (ofatumumab: 86, 9.1%; teriflunomide: 74, 7.9%). The most frequently reported SAE by SOC (incidences $\geq$ 2% of patients) in both treatment groups was 'infections and 'infestations' (ofatumumab: 24, 2.5%; teriflunomide: 17, 1.8%). The higher rate in the ofatumumab group compared to teriflunomide was driven by appendicitis reported in 8 patients (0.8%).

In the ofatumumab group, other SAEs were reported in the following SOCs (incidences ≥1.0%): 'injury, poisoning and procedural complications' (ofatumumab: 13, 1.4%; teriflunomide: 9, 1.0%), 'psychiatric disorders' (ofatumumab, 10, 1.1%; teriflunomide, 2, 0.2%), and 'neoplasms benign, malignant and unspecified (including cysts and polyps)' (ofatumumab: 9, 1.0%; teriflunomide: 4, 0.4%).

Pulmonary sarcoidosis was reported in 2 patients and grade-3 serious injection-related reaction was reported in one patient in the ofatumumab group.

The proportion of patients who discontinued study drug due to an SAE was higher in ofatumumab group (11 patients, 1.2% in the ofatumumab group and 8 patients, 0.8% in the teriflunomide group). Eight patients on ofatumumab, 0.8% and seven patients on teriflunomide, 0.7% experienced grade-4 SAEs.

SAEs in the supplementary studies were similar to the main SAF with highest frequency of SAEs in injection/infusion related reactions and infections categories. High frequency of SAEs reported after initiation of therapy resulted in a change in loading regimen with ofatumumab to current regimen used in phase III studies. In Pool C1, there were 3 additional events to be noted, all in 60mg dosing groups and each reported by 1 subject: cytokine release syndrome, cholelithiasis and hypokalaemia.

Laboratory findings

Cytopenia, including prolonged and late-onset neutropenia, have been reported during ofatumumab therapy in other indications and included in Arzerra RMP as identified or potential risks in the form of 'Neutropenia' and 'Cytopenia (excluding neutropenia)'. In ofatumumab group of main SAF, the overall incidence of neutropenia-related AEs was 1.0% compared to 3.4% in teriflunomide group, the patients with at least 2 consecutive post-baseline worsening of grade ≥ 1 in neutrophil or lymphocyte counts were respectively 2.6% (26 patients) and 1.5% (14 patients) in the ofatumumab group and 17.4% (162 patients) and 1.3% (12 patients) in teriflunomide group; despite close monitoring and measures in place in clinical trial environment 8 patients in ofatumumab group (0.8%) and 71 patients (7.6%) in teriflunomide group reported any AE term from the 'infection' SOC post-first-grade worsening of neutropenia and 8 patients in ofatumumab group (0.8%) and 6 patients (0.6%) in teriflunomide group reported any AE term from the 'infection' SOC post-first-grade worsening of lymphopenia; in the ofatumumab group, 3 patients reported SAE including a neutropenic sepsis, and 1 grade 3 AE led to discontinuation. In the Pool L2, overall incidence of cytopenia-related AEs was 2.3% with ofatumumab 20 mg SC Cytopenia including neutropenia is considered highly clinically relevant and is addressed in RMP as a potential risk. The physician is recommended to evaluate the patient's immune status prior to initiating therapy and Ofatumumab must not be given to patients in a severely immunocompromised state (e.g. significant neutropenia or lymphopenia).

In line with the mechanism of action of ofatumumab, B-cell depletion was achieved after 1 week in >75% of the patients during the initial loading regimen of ofatumumab (3 weekly 20 mg doses at Day 7, Day 14, and Day 21). A median time to B cell recovery of 24.6 weeks post treatment discontinuation is predicted which requires vigilance for infection for patients under risk throughout this period.

In the majority of patients, IgM levels decreased. In Pool C2, in the ofatumumab group, a decrease of 30.9% (-0.420 g/L) in mean IgM values from baseline was experienced by Week 48 completers (824 patients) and a decrease of 38.8% (-0.537 g/L) was experienced by Week 96 completers (304 patients). Treatment with ofatumumab resulting in a decrease in IgM that reached a value below 0.34 g/dL, more than 10% of LLN, was observed in 14.3% of patients, while a decrease of more than 30% or 50% of LLN was observed for respectively 3.8% or 2.1% of patients. Decreased blood IgM was amongst the most frequently reported grade 3-4 AEs and was the most frequently reported AE leading to withdrawal of study drug. Immunoglobulin

decrease/abnormality was reported as AEs leading to withdrawal for 35 patients in Pool C2 (3.7%) out of 54 patients who discontinued treatment due to AEs (5.7%). Additionally, 55 patients (5.8%) reported immunoglobulin decrease as AEs leading to treatment interruption (out of 9.1% of the patients in ofatumumab group who had treatment interruption due to AEs). In Pool C2, in the ofatumumab group, a decrease of 4.3% (-0.435 g/L) in mean IgG values from baseline was experienced by Week 48 completers (824 patients) and an increase of 2.2% (+0.249 g/L) was experienced by Week 96 completers (304 patients).

Vital signs in which patients in the ofatumumab group experienced ≥ 5% difference relative to teriflunomide group were pulse rate <60 bpm (+6.0%) and increase of ≥ 7% from baseline weight (+9.6%).

Cardiovascular events are known as identified risk for Arzerra and other CD20-mAbs, including both acute IRRs and non-IRR related events. In the Pool C2, overall 26 patients (2.7%) in ofatumumab group reported cardiac disorder AE compared to 33 patients (3.5%) in teriflunomide group; in the ofatumumab group, 8 patients (0.8%) reported within 24 hours of injection administration whereas 19 patients (2.0%) beyond 24 hours reported cardiac disorder AEs compared to 12 patients (1.3) within 24 hours of injection administration and 24 patients (2.6%) beyond 24 hours reported cardiac disorder AEs in teriflunomide group. Tachycardia (6 patients, 0.6%) is the only AE that occurred within 24 hours of injection administration and reported in more than one patient. The proportion of patients with AEs related to cardiac arrhythmia was 0.4% vs 0.5% in the ofatumumab and teriflunomide groups. In the ofatumumab group, 1 patient (0.1%) reported an AE related to cardiac arrhythmia within 24 hours of injection administration compared to 3 patients (0.3%) beyond 24 hours. For the patient who reported an AE in less than 24 hours in the ofatumumab group, a non-serious, and grade-2, atrioventricular block second degree occurred on Day 757. In Study G2102, one patient reported a non-serious grad-1 sinus arrhythmia on Day 85, within 24 hours of injection administration.

Other laboratory parameters (not discussed above) including clinical chemistry, urinalysis and electrocardiogram did not show any consistent abnormalities or clinically relevant differences compared to active control group. High incidences (≥ 10% of patients in ofatumumab group) of new or worsening biochemistry abnormalities were high serum cholesterol, high triglycerides, high ALT (alanine aminotransferase), high AST (aspartate aminotransferase), and high creatinine.

Safety in special populations

Subgroups were evaluated for main SAF. Patients aged 18-55 years and mostly Caucasians were included in the studies, hence, the safety profile is not known for other age groups and races.

The differences in safety profile across gender and previous treatment status could be expected due to different severity or stage of disease between these subgroups.

Use of ofatumumab during pregnancy and lactation may increase the risk of B-cell depletion in utero, transient peripheral B-cell depletion and lymphocytopenia in infants after birth and, hence, infections in the off-spring or unknown safety and efficacy profile of vaccinations in the new-born. Therefore, women of childbearing potential should use effective contraception while treated with ofatumumab, treatment with ofatumumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. It is unknown whether ofatumumab is excreted in human milk. In humans, excretion of IgG antibodies in milk occurs during the first few days after birth, which is decreasing to low concentrations soon afterwards. Consequently, a risk to the breastfed child cannot be excluded during this short period. Afterwards, ofatumumab could be used during breast-feeding if clinically needed. When treatment has occurred up to the last few months of pregnancy, breastfeeding can be started immediately after birth.

There was no pattern of treatment differences between the sub-groups by region and status of financial interest.

There does not appear to be an increased risk for hepatic or renal safety, or drug abuse and dependence, withdrawal and rebound with ofatumumab in the clinical trial experience with RMS patients in main SAF.

Immunological events

It is considered that development of clinically significant ADAs is not a current concern in relation to ofatumumab 20 mg Q4W according to the results presented.

Safety related to drug-drug interactions and other interactions

There are no known clinically significant interactions with other medicinal products, and it has not been in evaluated in dedicated drug-drug interaction studies.

Safety and effectiveness of vaccination is impacted by administration of ofatumumab and other antiCD20 antibodies. Study G2399 and vaccination sub-study are included as an additional pharmacovigilance activity part of the proposed RMP to further characterize the risk of impaired immunization response.

Discontinuation due to AES

AE's leading to withdrawal was reported for 54 patients in main SAF (5.7%), 35 of whom (3.7%) were due to immunoglobulin levels. Pulmonary sarcoidosis (2 patients, 0.2%) and ALT or AST increase (1 patient each) were the other treatment emergent AEs causing drug discontinuation in ofatumumab group. AEs leading to treatment interruption was reported for 9.1% (47 patients) of the patients in ofatumumab group in main SAF. Besides immunoglobulin levels (55 patients, 5.8%), infections-infestations, blood and lymphatic system disorders, gastrointestinal disorders, psychiatric disorders, general disorders and administration site conditions, reproductive system and breast disorders were listed in TEAEs causing drug interruption in more than 2 patients for ofatumumab group.

2.6.1. Discussion on clinical safety

The Applicant has excluded safety data from ongoing studies in MS and studies in other indications in the analyses for this application. The primary source of safety data in the MS target population consists of the two pivotal Phase-III studies (main SAF or Pool C2). Supportive data from phase II studies in MS is presented separately.

Number of all MS patients exposed to 20 mg SC formulation of ofatumumab (forming Pool L2) in the clinical program is 1230 (94.4% of those are RRMS patients); with 946 patients from phase III pivotal studies (40.8 % of those are treatment naïve patients) and 284 from Phase II bioequivalence study (Study G2102). The safety package in phase III studies and amount of exposure to ofatumumab 20 mg SC dose is considered adequate for characterization of the short-term safety of ofatumumab 20 mg SC in active RMS patients.

Long-term safety data have been collected in accordance with requirements of ICH E1 guidance (CPMP/ICH/375/95). In main SAF, 832 patients were exposed to ofatumumab 20mg SC over 48 weeks, 312 patients were exposed over 96 weeks and the number of patients exposed for more than 1 year were sufficient.

Further long-term safety and tolerability data in patients with MS will be available after receiving results of the ongoing study G2399 which is not included in this submission.

Overview of adverse events in main SAF does not signal an imbalance between treatment arms in number of AEs but a slightly higher frequency noted in ofatumumab group for SAEs and AEs leading to drug discontinuation. However, in the supportive analyses higher number of TEAEs, SAEs, AEs leading to drug discontinuation is reported for ofatumumab. Therefore, phase III studies included a loading dose of 20 mg given three times weekly which was preferred over a loading dose of 60 mg given every 4 weeks due to more AEs/SAEs associated with 60 mg dose (in particular post-injection systemic reactions reported as SAEs on day 1). It is noted that some of the most frequently reported grade 3-4 AEs are in line with the identified or potential risks in Arzerra SmPC or RMP.

In line with the safety profile described for anti-CD20 mAbs, the main safety issues with ofatumumab are the risk of injection related reactions, infections, decreased ability to mount an immune response to live or attenuated vaccines, coupled with the potential for infection following the administration of live vaccines, and decreased IgM levels.

Analyses of AESI revealed that clinically important potential events such as IRRs, upper respiratory tract infections, urinary infections, herpes or varicella-zoster infections were more common in the ofatumumab group than in the active comparator group.

Injection-related reactions with ofatumumab 20 mg SC are "very common" AEs in SmPC. Injection-related reactions are common with the first and second ofatumumab injection and requires the first injection of ofatumumab to be given under the guidance of a healthcare professional. They comprise systemic reactions (e.g. fever, other systemic symptoms, headache, chills, myalgia, fatigue), 20.2%, and injection-site reactions (e.g. erythema/redness, other site symptoms, pain, induration/swelling, warmth, itching), 10.8%. They appear to be independent of the administered dose and may not be predicted on beforehand. Pre-treatment is not recommended. If occur, they are reported to be manageable in general, despite a small number of SAEs or IRR events leading to withdrawal in MS studies. Injection-related reactions appear to be influenced by method of administration (AI or PFS). In study G2102, a significant difference is noted in the incidence of drug related AEs and injection-related reactions between the AI-abdomen group (43% and 32%) and the PFS-abdomen group (36.2% and 22.3%).

A risk of infection, including opportunistic infections, is associated with the use of any anti-CD20 biological product (including ofatumumab) depleting B-cells and thereby lowering immunoglobulins. The overall proportion of patients with infections was similar in the ofatumumab and the teriflunomide treatment groups. Teriflunomide SmPC includes a contraindication for use in patients with severe active infection until resolution and warnings on this topic and ofatumumab SmPC is updated with warnings and information in sections 4.4 and 4.8 and a contraindication for severe infection until resolution is implemented. Active malignancy and patients in a severely immunocompromised state are added as contraindications in ofatumumab SmPC. The most commonly reported infections included but were not limited to nasopharyngitis (18.0%), upper respiratory tract infection (10.3%), urinary tract infection (10.3%), and influenza (6.6%). The occurrence of new or reactivated herpes infections, including ophthalmic infections, was increased in the ofatumumab group (46, 4.9% vs 39, 4.2% in the ofatumumab and teriflunomide groups. There were no observed cases of PML, cryptococcal infections, reactivation of hepatitis in MS studies (although these are included in warnings for this class and Arzerra) and patients at risk of immunocompromised status or infections were excluded from clinical studies. "Serious infections, including opportunistic infections (e.g., PML, HBV reactivation)" is an important potential risk in RMP and characterizes the serious infections related to decrease in immunoglobulins and lymphopenia or neutropenia. Furthermore, appendicitis being reported in 1% of the population and more

frequently in the ofatumumab group was included in the monitoring for this important potential risk of serious infections.

No deaths were reported during treatment with ofatumumab in main SAF or supplementary pools. Most frequently reported SAE with ofatumumab were 'infections and 'infestations' (24, 2.5%), 'injury, poisoning and procedural complications' (13, 1.4%), 'psychiatric disorders' (10, 1.1%), and 'neoplasms benign, malignant and unspecified (including cysts and polyps)' (9, 1.0%). The proportion of patients who discontinued study drug due to an SAE was possibly higher in ofatumumab group (ofatumumab: 11 patients, 1.2%; teriflunomide: 8 patients, 0.8%).

In laboratory parameters, cytopenia and immunoglobulin abnormalities were noted. Cytopenia including prolonged and late-onset neutropenia are identified or potential risks with Arzerra. In main SAF, the overall incidence of neutropenia-related AEs was 1.0% with ofatumumab, the patients with at least 2 consecutive post-baseline worsening of grade ≥ 1 in neutrophil or lymphocyte counts were respectively 2.6% (26 patients) and 1.5% (14 patients). Despite close monitoring and measures in place in clinical trial environment, 8 patients in each group (0.8%) reported any AE term from the 'infection' SOC post-first-grade worsening, 3 patients reported SAE including a neutropenic sepsis, and 1 grade 3 AE led to discontinuation. In the Pool L2, overall incidence of cytopenia-related AEs was 2.3% with ofatumumab 20 mg SC Cytopenia including neutropenia is considered highly clinically relevant and is addressed in RMP as a potential risk. The physician is recommended to evaluate the patient's immune status prior to initiating therapy and Ofatumumab must not be given to patients in a severely immunocompromised state (e.g. significant neutropenia or lymphopenia).

In line with the mechanism of action of ofatumumab, B-cell depletion was achieved after 1 week in >75% of the patients during the initial loading regimen of ofatumumab (3 weekly 20 mg doses at Day 7, Day 14, and Day 21). A median time to B cell recovery of 40 weeks post treatment discontinuation is predicted which requires vigilance for infection for patients under risk throughout this period.

In the majority of patients, mean IgM levels decreased with ofatumumab (30.9% decrease by Week 48, 38.8% decrease by Week 96). Treatment with ofatumumab resulting in a decrease in IgM that reached a value below 0.34 g/dL, more than 10% of LLN, was observed in 14.3% of patients, while a decrease of more than 30% or 50% of LLN was observed for respectively 3.8% or 2.1% of patients. Immunoglobulin decrease/abnormality was amongst the most frequently reported grade 3 or 4 AEs and was the most frequently reported AE leading to withdrawal of study drug (3.7%) or treatment interruption (5.8%). Precaution for immunoglobulins will be necessary with ofatumumab in clinical use.

Safety and effectiveness of vaccination is impacted by administration of ofatumumab and other antiCD20 antibodies. Use of ofatumumab during pregnancy and lactation may increase the risk of B-cell depletion in utero, transient peripheral B-cell depletion and lymphocytopenia in infants after birth and, hence, infections in the off-spring or unknown safety and efficacy profile of vaccinations in the new-born. Therefore, women of childbearing potential should use effective contraception while treated with ofatumumab, treatment with ofatumumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.

It is considered that development of clinically significant ADAs is not a current concern in relation to ofatumumab 20 mg Q4W according to the results presented.

At the Oral Explanation, the Applicant claimed that no data with ofatumumab in studied RMS population supports the inclusion of the contraindication for *'Severe active infection until resolution'.* However, it was unanimously concluded during the oral explanation and subsequent discussion that initiation of treatment with a medicine whose mechanisms of action is as for ofatumumab (immunosupressant through anti-CD20 mediated

B depletion) should not be considered in patients with severe active infection until resolution. While the argument that most experts would already be aware of this is acknowledged, a contraindication is consistent with this position, as well as with labels of related products and was included in section 4.3 of SmPC.

2.6.2. Conclusions on clinical safety

The safety package in phase III studies and amount of exposure to ofatumumab 20 mg SC dose is considered adequate, with 946 patients treated with the target dose of ofatumumab in phase III and 832 patients for more than 48 weeks, for characterization of the safety of ofatumumab 20 mg SC in active RMS patients.

Ofatumumab causes prolonged B cell depletion primarily through CDC and, to a lesser extent, by ADCC. In line with the safety profile described for anti-CD20 mAbs, the main safety issues with ofatumumab are the risk of injection related reactions, infections, decreased ability to mount an immune response to live or attenuated vaccines, coupled with the potential for infection following the administration of live vaccines, and decreased immunoglobulin levels. The majority of these events were manageable although they were amongst most common grade 3-4 AEs, AEs leading to treatment interruptions and discontinuations. Contraindication for severe active infection until resolution is included in SmPC.

In conclusion, ofatumumab 20 mg/Q4W SC appear to have a manageable safety profile for treatment of active RMS patients with a 5.7% discontinuation rate in phase III studies.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns

Important identified risks	None
Important potential risks	Serious infections, including opportunistic infections (e.g., PML, HBV reactivation)
	Malignancy
	Impaired Immunization Response, including vaccination of newborns after exposure in utero
Missing information	Safety in pregnancy and lactation
	Long-term safety of ofatumumab treatment
	Use in pediatric population
	Use in patients >55 years and Elderly population

Pharmacovigilance plan

On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization.				
None Proposed				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
None Proposed				
Category 3 - Required additional pharmacovigilance activities				
Pregnancy outcomes Intensive Monitoring (PRIM; Category 3 PASS) Status: Planned	Primary Objective: To estimate the proportion of major congenital malformations associated with exposure to ofatumumab during pregnancy among a) live births and b) live births, stillbirths and termination of pregnancy for fetal anomaly (TOPFA).	Safety in pregnancy and lactation	Protocol submission	30-Sep-2021
			Start of the study Data from the PRIM will be reported on an annual basis.	01-Oct-2021
	Key Secondary Objective: To estimate the proportion of minor congenital malformations associated with exposure to ofatumumab during pregnancy among a) live births and b) live births, still births and TOPFA.		Final report	10 years post approval or 500 live births, whichever occurs first
Post-Authorization long term Safety Study in multiple sclerosis patients treated with ofatumumab in real world settings	The primary objective is to estimate the event rates of malignancy and serious infections following ofatumumab	• Malignancy • Serious infections, including opportunistic infections (e.g., PML, HBV	Protocol submission	30-Jun-2022
			Start of the study	01-Jul-2022

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
(Category 3 PASS) Status: Planned	treatment in patients with MS. The secondary objective is to compare the incidence of each serious safety event between ofatumumab-exposed patients with RMS and patients with RMS exposed to other approved disease modifying therapies (DMTs).	reactivation) Long term safety of ofatumumab treatment. • Use in patients >55 years and Elderly population	Data will be provided cumulatively in standalone reports at regular intervals that will be defined in the final protocol.	Approximately 10 years.
ALITHIOS Study (COMB157G2399) : An open-label, single arm, multi-center extension study evaluating long-term safety, tolerability and effectiveness of ofatumumab in subjects with relapsing multiple sclerosis (RMS) (Category 3 PASS) Status: Ongoing	The ALITHIOS study will allow patients to continue treatment with open-label ofatumumab for 5 years and aims to provide additional long-term safety data as well as additional information on tolerability.	• Serious infections, including opportunistic infections (e.g., PML, HBV reactivation) • Malignancy • Long term Safety of ofatumumab treatment • Use in patients >55 years and Elderly population	Interim annual report Final report	Data from the study will be reported on an annual basis. 05-Apr-2029
COMB157G2399 Sub Study: A sub-study to evaluate the effects of ofatumumab subcutaneous treatment on the immune responses following vaccination in patients with relapsing forms of multiple sclerosis. (Category 3 PASS) Status: Ongoing	The study will characterize the humoral immune response to the below vaccines, in subjects with RMS who are treated with ofatumumab 20 mg sc once every 4 weeks. • tetanus-toxoid (TT) vaccine • 13-valent pneumococcal conjugate vaccine (13-PCV) • 23-valent pneumococcal polysaccharide	Impaired immunization response, including vaccination of newborns after exposure in utero	Final Report	31-Mar-2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	vaccine (23-PPV) • KLH neo-antigen seasonal quadrivalent influenza vaccine			

Risk minimisation measures

Summary of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious infections, including opportunistic infections (e.g., PML, HBV reactivation)	**Routine risk minimization measures:** SmPC Sections 4.3, 4.4 and 4.8 Patient Leaflet (PL) Section 2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist will be used for PML Independent review of cases of suspected PML by External Adjudication Committee **Additional pharmacovigilance activities**: ALITHIOS study (COMB157G2399) Post-Authorization long term Safety Study in multiple sclerosis patients treated with ofatumumab in real world settings (Category 3 PASS).
Malignancy	**Routine risk minimization measures:** SmPC Section 4.3, PL section 2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities**: ALITHIOS study (COMB157G2399) Post-Authorization long term Safety Study in multiple sclerosis patients treated with ofatumumab in real world settings (Category 3 PASS).
Impaired Immunization Response, including vaccination of newborns after exposure in utero	**Routine risk minimization measures**: SmPC Sections 4.4 and 4.5 PL Section 2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** COMB157G2399 Sub-study (Category 3 PASS)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Safety in pregnancy and lactation	**Routine risk minimization measures:** SmPC Section 4.6 and PL Section 2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: **Additional pharmacovigilance activities:** Pregnancy outcomes Intensive Monitoring (PRIM; Category 3 PASS)
Long-term safety of ofatumumab treatment	**Routine risk minimization measures:** None **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ALITHIOS study (COMB157G2399) Post-Authorization long term Safety Study in multiple sclerosis patients treated with ofatumumab in real world settings (Category 3 PASS).
Use in pediatric population	**Routine risk minimization measures:** SmPC Sections 4.2 and 5.2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Use in patients >55 years and Elderly population	**Routine risk minimization measures:** SmPC Sections 4.2 and 5.2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** ALITHIOS study (COMB157G2399) Post-Authorization long term Safety Study in multiple sclerosis patients treated with ofatumumab in real world settings (Category 3 PASS)

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the Applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The Applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Quick Response (QR) code

A request to include a QR code in the outer package and package leaflet has been submitted by the Applicant and has been found acceptable.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kesimpta (ofatumumab) is included in the additional monitoring list.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The **indication** for Kesimpta (ofatumumab) is:

Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see section 5.1),

The recommended dosing regimen is administered by SC injection with initial dosing at weeks 0, 1 and 2, followed by subsequent monthly dosing, starting at week 4.

MS is a chronic, immune-mediated disease of the CNS characterised by inflammation, demyelination, and axonal/neuronal destruction, ultimately leading to severe disability. Relapsing MS includes CIS, RRMS, active SPMS. At the time of their first MS diagnosis, 80% to 85% of adult patients present with RRMS, characterised by recurrent acute exacerbations (relapses) of neurological dysfunction followed by a variable state of complete or incomplete recovery. Most patients with RRMS may progress to SPMS, which is a stage of the disease characterized by continuous worsening of disability with or without superimposed relapses.

3.1.2. Available therapies and unmet medical need

The current therapeutic approach involves symptomatic treatment, treatment of acute relapses, and disease modifying therapies. The standard of care for acute relapses is methylprednisolone IV. Methylprednisolone 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. Several DMTs/DMT classes are currently available and approved for use in RMS, which vary in their mechanism of action, efficacy, safety, mode of administration and ease of use. 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.

mAbs directed against proteins expressed by B-cells, e.g. anti-CD20 antibodies, such as ocrelizumab and rituximab, are high-efficacy therapies offering the same high efficacy as other highly efficacious DMTs, including (but not limited to) mAbs like natalizumab and alemtuzumab, but at the same time show a better safety profile. Despite the availability of several DMT 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.

3.1.3. Main clinical studies

3.2. Favourable effects

Ofatumumab 20 mg SC was investigated in 1882 RMS patients from 2 Phase III randomized, double-blind, double-dummy, active-comparator (teriflunomide) controlled, parallel-group, multi-center studies of identical design ([Study G2301] (ASCLEPIOS I) and [Study G2302] (ASCLEPIOS II)). The Phase III studies enrolled treatment naïve or previously treated, male or female patients, aged 18 to 55, with relapsing form of MS (RRMS or SPMS), with disease activity as defined by Lublin et al 2014, and an EDSS score of 0 to 5.5 at screening. Patients had to have active MS defined by at least 1 relapse in the year prior to screening, 2 relapses in the 2 years prior to screening, or a positive T1 Gd-enhancing MRI scan within a year prior to randomization, and to be neurologically stable within 1 month prior to randomization. The primary endpoint, ARR, is defined as the number of EDSS-confirmed MS relapses in a year. The treatment duration for an individual patient was flexible and up to 30 study months (approximately 2.5 years). The study-specific data cut-off date was 05-Jul-2019 for Study G2301 and 10-Jul-2019 for Study G2302.

3.3. Uncertainties and limitations about favourable effects

The population studied in the clinical efficacy package were adult patients with RMS with active disease defined by clinical or imaging features. Both naïve and previously treated patients were included. Given the eligibility criteria, patients not meeting the "activity criterion" were not appropriately represented in the studies. Hence, a conclusion on the magnitude of effect in these patients cannot be drawn, but the benefit is assumed to be smaller due to the lower counterfactual risk.

The RMS population included only 69 active SPMS patients (no specific predefined number or statistical analysis). The point estimate for disability related endpoints in SPMS group showed a similar pattern to RRMS group, however too broad confidence intervals extended beyond 1.

Studies were not individually powered for the analysis of 6mCDW; nevertheless, consistent trends in favour of ofatumumab were seen in both studies (reaching statistical significance in Study G2301).

A lack of B-cell depletion is observed with a small group of patients (2.4 %) and long-term consequences related to incomplete B-cell depletion in terms of efficacy are not known. In a post hoc analysis, the Applicant shows that the number of Gd-enhancing T1 lesions per scan and the number of new or enlarging T2 lesions per year were higher in those with low B-cell depletion compared with those with sufficient B-cell depletion, although still lower than the teriflunomide treated patients.

3.4. Unfavourable effects

IRR include systemic (e.g. fever, headache, myalgia, chills, fatigue and flushing) and local site reactions (e.g. itching, erythema, pain, oedema, pruritus and swelling), and are very common with ofatumumab SC reported at higher proportions than with matching placebo injections in the teriflunomide treatment group (injection-systemic reactions 20.2% vs 15.0%; injection-site reactions 10.8% vs 5.6%).

Infections, including opportunistic infections, are a known safety concern based on mechanism of action and experience from other anti-CD20 indications and previous use of ofatumumab in other indications. The most commonly reported infections by PTs were nasopharyngitis (18.0%), upper respiratory tract infection (10.3%),

urinary tract infection (10.3%), influenza (6.6%), and others. The occurrence of new or reactivated herpes infections, including ophthalmic infections, was increased in the ofatumumab group (46, 4.9% vs 39, 4.2% in the ofatumumab and teriflunomide groups.

Patients with active infection are not necessarily immunosuppressed/compromised prior to starting ofatumumab therapy but they will be under the risk of worsening with ofatumumab therapy. Therefore, the administration of ofatumumab should be delayed until a severe infection is resolved and a contraindication for 'Severe active infection until resolution' is included in the SmPC.

In the majority of patients, IgM levels decreased. In Pool C2, in the ofatumumab group, a decrease of 30.9% (-0.420 g/L) in mean IgM values from baseline was experienced by Week 48 completers (824 patients) and a decrease of 38.8% (-0.537 g/L) was experienced by Week 96 completers (304 patients). Treatment with ofatumumab resulting in a decrease in IgM that reached a value below 0.34 g/dL, more than 10% of LLN, was observed in 14.3% of patients, while a decrease of more than 30% or 50% of LLN was observed for respectively 3.8% or 2.1% of patients. Decreased blood IgM was amongst the most frequently reported grade 3-4 AEs and was the most frequently reported AE leading to withdrawal of study drug. Immunoglobulin decrease/abnormality was reported as AEs leading to withdrawal for 35 patients in Pool C2 (3.7%) out of 54 patients who discontinued treatment due to AEs (5.7%). Additionally, 55 patients (5.8%) reported immunoglobulin decrease as AEs leading to treatment interruption (out of 9.1% of the patients in ofatumumab group who had treatment interruption due to AEs).

3.5. Uncertainties and limitations about unfavourable effects

"Serious infections, including opportunistic infections (e.g., PML, HBV reactivation)", "Malignancy", and "Impaired Immunization Response, including vaccination of newborns after exposure in utero" are added in RMP as potential risks. From previous use of Arzerra, IRRs, infections, decreased ability to mount an immune response to live or attenuated vaccines, decreased IgM levels, neutropenia, and malignant/pre-malignant disorders, thus most of above-mentioned AEs, were observed. It is uncertain if these AEs also apply to ofatumumab since ofatumumab is dosed differently, however, AEs known for Arzerra should be kept in mind while evaluating the safety data from MS patients.

IRRs are most frequently seen in relation to the first two injections, there is currently no proposed pre-treatment, thus, the patients need to remain in hospital /under observation during the initial injections.

Infections, including opportunistic infections, are a known safety concern based on mechanism of action and experience from other anti-CD20 indications and previous use of ofatumumab in other indications. There were no observed cases of PML or reactivation of hepatitis in MS studies, but these are identified risks for Arzerra and other anti-CD20 therapies.

There was not an increased frequency of malignancy or pre-malignant disorders with ofatumumab compared to teriflunomide in the clinical trial experience with RMS patients. However, the time on the study and/or follow-up was short with regards to the development of neoplasms and sustained depletion of B-cells might affect the immune system´s ability to detect and eliminate cancer cells thus leading to an increased risk of developing solid tumours.

The uncertainties above are considered acceptable and will be reduced by monitoring in the PSUR and in a PASS.

3.6. Effects Table

***Table 48**. Effects Table for Ofatumumab in RMS.*

Effect	Short Description	Unit	Ofatumumab	Teriflunomide	Uncertainties/ Strength of evidence	References
Favourable Effects						
ARR	Annualized relapse rate. Number of confirmed MS relapses in a year		0.11 (0.09, 0.13)	0.24 (0.21, 0.27)	RMS population with only 69 active SPMS patients (no predefined number or analysis).	1
6mCDW	Time to disability worsening as measured by 6-month confirmed worsening (6mCDW) on EDSS	KM estimate at Month 24 (95% CI)	8.1 (6.5, 10.2)	12.0 (9.9, 14.5)	Pivotal studies were not individually powered for the analysis of 6mCDW. Hazard ratio (95% CI): 0.675 (0.498, 0.916) Risk reduction: 32.5% P-value =0.012	1
Unfavourable Effects						
IRRs	Systemic reactions	%	20.2	15.0	Identified risk	2
	Injection site reactions	%	10.9	5.6	Identified risk	2
Infections	Infection or infestations (SOC)	%	51.6	52.7	Teriflunomide has contraindications related to infections and immune status of the patient.	2
	Herpes viral infections	%	4.9	4.2	The occurrence of new or reactivated herpes infections, including ophthalmic infections, was increased in the ofatumumab group.	

Abbreviations:
ARR: annualized relapse rate; 6mCDP: 6month confirmed disability progression;
IRR: Injection related reactions; SOC: system organ class; SMQ: systematic MedDRA query; PT: preferred term.
Notes:
(1) Combined data from Studies G2301 and G2302
(2) Data from the Controlled Pool consisting of the placebo-controlled studies G2301 and G2302

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Ofatumumab significantly decreased the risk of relapses in active RMS patients. The risk reduction was considerable and thus considered clinically relevant. The ARR was less than half that of the active comparator

teriflunomide. The effect on relapses translated into a reduction in risk of worsening of disability (6mCDW). The analyses presented showed that time to first 6mCDW was delayed to a clinically meaningful extent. All in all, the favourable effects of ofatumumab on active RMS patients are well-documented.

In line with the safety profile described for anti-CD20 mAbs, the main safety issues with ofatumumab are the risk of injection related reactions, infections, decreased ability to mount an immune response to live or attenuated vaccines, coupled with the potential for infection following the administration of live vaccines, and decreased immunoglobulin levels. These concerns are serious but manageable provided that the product information provides relevant information to the prescriber/patient about the contraindications and precautions necessary to minimize risk.

3.7.2. Balance of benefits and risks

A clinically relevant effect on relapses has been demonstrated in a study population consisting of mainly RRMS patients and a smaller number of SPMS with relapses. However, this DMT intends to modify inflammatory activity in MS and it is considered 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. Extrapolation of the effect on disability will not be considered appropriate as pathophysiology is different. In this regard, the point estimate for disability related endpoints in SPMS group showed a similar pattern to RRMS group, however too broad confidence intervals extended beyond 1.

A smaller magnitude of benefit – not sufficient to outweigh the risks - can be expected in patients without activity at baseline. This consideration is relevant for patients not receiving any DMD and showing no inflammatory activity.

In fact, extensive discussions during the assessment have been held about the wording of the indication. The Applicant focussed in particular on two patients' populations:

a. Patients who are newly diagnosed.

b. Patients treated with a different DMT who decide to switch from the current DMT due to lack of efficacy, or safety or tolerability considerations

To clarify the target population for ofatumumab with more precision the Applicant has proposed to add "newly diagnosed patients and patients switching from their current treatment due to lack of efficacy, or safety or tolerability considerations" in the indication statement in section 4.1 of the SmPC together with the requested "active disease" wording. The proposed indication wording is "Kesimpta is indicated for the treatment of adult patients with RMS with active disease defined by clinical or imaging features (see section 5.1), *including newly diagnosed patients and patients switching from their current treatment due to lack of efficacy, or safety or tolerability considerations*."

a. Given the current practice in the EU; a significant number of newly diagnosed patients would fulfil the "activity" phenotype criterion. Similarly, patients switching their DMT due to lack of efficacy should be fulfilling the indication with activity criterion, thus their inclusion in the indication would be redundant. However, it has been agreed that section 5.1 should adequately reflect the inclusion criteria, stating that newly diagnosed patients were also included in the studies.

b. It is acknowledged that patients treated with a different DMT who decide to switch from the current DMT due to safety or tolerability considerations would not formally fulfil the "activity" criterion at the time of switching the DMT (otherwise, the switch would be due to efficacy failure). However, the fact that these patients

are currently receiving a DMT for controlling the MS inflammatory activity could be considered as a "proxy" of fulfilment of an "activity" criterion because it can be assumed that (i) these patients needed to be active at the time the first DMT was prescribed and (ii) a patient whose inflammatory activity is adequately controlled by a DMT intended to control this activity might not be without. Therefore, even if a conclusion on the magnitude of effect in patients not meeting the "activity" criterion cannot be directly drawn from the results in this study population (all active as per eligibility criteria), it could be agreed that patients switching from their current DMT due to safety or tolerability considerations could have also a positive B/R.

As per regards of the wording of the indication in section 4.1, it is concluded that it should not deviate from comparable products.

The balance of benefits and risks is considered positive in adult patients with RMS fulfilling the activity specifier.

3.8. Conclusions

The overall B/R of Kesimpta is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kesimpta is favourable in the following indication:

Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see section 5.1)

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.