CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125326Orig1s070

Trade Name:	KESIMPTA
Generic or Proper Name:	(ofatumumab)
Sponsor:	Novartis
Approval Date:	August 20, 2020
Indication:	KESIMPTA is a CD20-directed cytolytic antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

CENTER FOR DRUG EVALUATION AND RESEARCH

125326Orig1s070

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	
Non-Clinical Review(s)	**X**
Statistical Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326Orig1s070

APPROVAL LETTER

BLA 125326/S-70

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Lisa Perkins, MBA
Senior Global Program Regulatory Manager
One Health Plaza, Building 310 / Room 2132D
East Hanover, NJ 07936-1080

Dear Ms. Perkins:

Please refer to your supplemental biologics license application (sBLA), dated and received December 20, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Kesimpta (ofatumumab) injection.

We acknowledge receipt of your major amendment dated May 13, 2020, which extended the goal date by three months.

This Prior Approval sBLA provides for the subcutaneous administration of Kesimpta (ofatumumab) injection (20 mg/0.4 mL pre-filled syringe and pre-filled pen presentations) for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 125326/S-070**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for children 0 to less than 10 years of age because necessary studies are impossible or highly impracticable. This waiver is being granted because the number of children diagnosed with RMS in that age group is small.

We are deferring submission of your pediatric studies for children 10 to less than 18 years of age for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

3901-1 A two-part study of Kesimpta (ofatumumab) in pediatric patients with relapsing forms of multiple sclerosis (RMS) at least 10 years and less than 18 years of age. Part A is an open-label study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of Kesimpta (ofatumumab) in pediatric patients. Part A will include two cohorts, one with body weights less than 40 kg and the other with body weights 40 kg or more. The objective of Part A is to determine maintenance doses of Kesimpta (ofatumumab) that will result in PK and PD effects that are comparable to those of the dose administered to adult patients. Part B is a randomized, blinded, non-inferiority trial with Gilenya (fingolimod) as a comparator.

Draft Protocol Submission:	09/2020
Final Protocol Submission:	01/2021
Study Completion:	09/2025
Final Report Submission:	03/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 111116, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Kesimpta (ofatumumab) during pregnancy.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3901-2	Prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Kesimpta (ofatumumab) during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to Kesimpta (ofatumumab) before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on July 28, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2021
Final Protocol Submission:	02/2022
Annual Interim Report Submissions:	08/2023
	08/2024
	08/2025
	08/2026
	08/2027
	08/2028
	08/2029
	08/2030
	08/2031
	08/2032
Study Completion:	02/2033
Final Report Submission:	02/2034

3901-3	A pregnancy outcomes study using a different study design than provided for in PMR 3901-2 (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Kesimpta (ofatumumab) during pregnancy compared to an unexposed control population.

The timetable you submitted on July 28, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2021
Final Protocol Submission:	02/2022
Annual Interim Report Submissions:	08/2023
	08/2024
	08/2025
	08/2026
	08/2027
	08/2028
	08/2029
	08/2030
	08/2031
	08/2032
Study Completion:	02/2033
Final Report Submission:	02/2034

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of diminished serum immunoglobulin levels and the potential for a resultant increased risk of infections, particularly opportunistic infections.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

3901-4	A safety trial to monitor serum immunoglobulin G and M levels in patients with relapsing forms of multiple sclerosis during treatment with Kesimpta (ofatumumab) to establish the nadir in circulating immunoglobulins during chronic treatment, and to monitor patients after discontinuation of treatment with Kesimpta (ofatumumab) in order to ascertain the time needed to ensure restoration of pre-treatment baseline circulating serum levels of immunoglobulins G and M. This trial also should be designed to capture rates of infections, especially opportunistic and recurrent infections associated with immune suppression, and there should be monitoring of B-cell counts throughout treatment and after discontinuation until repletion of immunoglobulin levels.

The timetable you submitted on July 23, 2020, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	05/2021
Final Protocol Submission:	01/2022
Trial Completion:	05/2028
Final Report Submission:	05/2029

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

Submit the protocols to your IND 111116, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Submission of the protocols for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to

[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70 We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3901-5	Conduct a study to evaluate the presence of leachables in pre-filled syringe drug product material that is representative of the commercial process and stored in the intended pre-filled syringe at long-term storage conditions (5±3°C) up to the proposed expiry date (b) (4).

The timetable you submitted on August 4, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	10/2021
Final Report Submission:	12/2021

Submit clinical protocols to your IND 111116 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[6]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[7] Information and Instructions for completing the form can be found at FDA.gov.[8]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Candido Alicea, Regulatory Project Manager, at (240) 402-8310.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Acting Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

[6] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[8] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICHOLAS A KOZAUER
08/20/2020 10:36:51 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326Orig1s070

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KESIMPTA safely and effectively. See full prescribing information for KESIMPTA.

KESIMPTA® (ofatumumab) injection, for subcutaneous use
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------
KESIMPTA is a CD20-directed cytolytic antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. (1)

----------DOSAGE AND ADMINISTRATION----------
- Hepatitis B virus (HBV) and quantitative serum immunoglobulins screening are required before the first dose. (2.1)
- Administer KESIMPTA by subcutaneous injection only. (2.2, 2.3)
- Initial Dosing: 20 mg administered at Week 0, 1, and 2. (2.2)
- Subsequent Dosing: 20 mg administered monthly starting at Week 4. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 20 mg/0.4 mL solution in a single-dose prefilled Sensoready® pen (3)
- Injection: 20 mg/0.4 mL solution in a single-dose prefilled syringe (3)

----------CONTRAINDICATIONS----------
- Active HBV infection. (4)

----------WARNINGS AND PRECAUTIONS----------
- Infections: Delay KESIMPTA administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with KESIMPTA and after discontinuation, until B-cell repletion. (5.1)
- Injection-Related Reactions: Management for injection-related reactions depends on the type and severity of the reaction. (5.2)
- Reduction in Immunoglobulins: Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with KESIMPTA until B-cell repletion. Consider discontinuing KESIMPTA if a patient develops a serious opportunistic infection or recurrent infections if immunoglobulin levels indicate immune compromise. (5.3)
- Fetal Risk: May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping KESIMPTA. (5.4, 8.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence greater than 10%) are upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KESIMPTA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to First Dose of KESIMPTA

Hepatitis B Virus Screening

Prior to initiating KESIMPTA, perform Hepatitis B virus (HBV) screening. KESIMPTA is contraindicated in patients with active HBV confirmed by positive results for Hepatitis B surface antigen [HBsAg] and anti-HBV tests. For patients who are negative for HBsAg and positive for Hepatitis B core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment with KESIMPTA *[see Warnings and Precautions (5.1)]*.

Serum Immunoglobulins

Prior to initiating KESIMPTA, perform testing for quantitative serum immunoglobulins *[see Warnings and Precautions (5.3)]*. For patients with low serum immunoglobulins, consult immunology experts before initiating treatment with KESIMPTA.

Vaccinations

Because vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation until B-cell repletion, administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of KESIMPTA for live or live-attenuated vaccines, and whenever possible, at least 2 weeks prior to initiation of KESIMPTA for inactivated vaccines *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage

The recommended dosage of KESIMPTA is:

- initial dosing of 20 mg by subcutaneous injection at Weeks 0, 1, and 2, followed by
- subsequent dosing of 20 mg by subcutaneous injection once monthly starting at Week 4.

Missed Doses

If an injection of KESIMPTA is missed, it should be administered as soon as possible without waiting until the next scheduled dose. Subsequent doses should be administered at the recommended intervals.

2.3 Administration Instructions

Administer by subcutaneous injection only.

KESIMPTA is intended for patient self-administration by subcutaneous injection.

Administer KESIMPTA in the abdomen, thigh, or outer upper arm subcutaneously. Do not give injection into moles, scars, stretch marks or areas where the skin is tender, bruised, red, scaly or hard.

The first injection of KESIMPTA should be performed under the guidance of a healthcare professional *[see Warnings and Precautions (5.2)]*.

KESIMPTA Sensoready® pens and syringes are for one-time use only and should be discarded after use. See Instructions for Use for complete administration instructions.

2.4 Preparation of KESIMPTA

The KESIMPTA "Instructions for Use" for each presentation contains more detailed instructions on the preparation of KESIMPTA.

Before administration, remove KESIMPTA Sensoready pen or KESIMPTA prefilled syringe from the refrigerator and allow KESIMPTA to reach room temperature for about 15 to 30 minutes. DO NOT remove the needle cover while allowing the prefilled syringe to reach room temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the liquid contains visible particles or is cloudy.

3 DOSAGE FORMS AND STRENGTHS

KESIMPTA is a clear to slightly opalescent, and colorless to slightly brownish-yellow solution available as follows:

- Injection: 20 mg/0.4 mL in a single-dose prefilled Sensoready pen
- Injection: 20 mg/0.4 mL in a single-dose prefilled syringe

4 CONTRAINDICATIONS

KESIMPTA is contraindicated in patients with:

- Active HBV infection *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies.

KESIMPTA has the potential for an increased risk of infections, including serious bacterial, fungal, and new or reactivated viral infections; some of these infections have been fatal in patients treated with other anti-CD20 antibodies. In Study 1 and Study 2 *[see Clincial Studies (14)]*, the overall rate of infections and serious infections in patients treated with KESIMPTA was similar to patients who were treated with teriflunomide (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively). The most common infections reported by KESIMPTA-treated patients in the randomized clinical relapsing MS (RMS) trials included upper respiratory tract infection (39%) and urinary tract infection (10%). Delay KESIMPTA administration in patients with an active infection until the infection is resolved.

Possible Increased Risk of Immunosuppressant Effects with Other Immunosuppressants

When initiating KESIMPTA after an immunosuppressive therapy or initiating an immunosuppressive therapy after KESIMPTA, consider the potential for increased immunosuppressive effects *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*. KESIMPTA has not been studied in combination with other MS therapies.

Hepatitis B Virus

Reactivation

There were no reports of HBV reactivation in patients with MS treated with KESIMPTA. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients being treated with ofatumumab for chronic lymphocytic leukemia (CLL) (at higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment) and in patients treated with other anti-CD20 antibodies.

Infection

KESIMPTA is contraindicated in patients with active hepatitis B disease. Fatal infections caused by HBV in patients who have not been previously infected have occurred in patients being treated with ofatumumab for CLL (at higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment). HBV screening should be performed in all patients before initiation of treatment with KESIMPTA. At a minimum, screening should include Hepatitis B surface antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb) testing. These can be complemented with other appropriate markers as per local guidelines. For patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment with KESIMPTA. These patients should be monitored and managed following local medical standards to prevent HBV infection or reactivation.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability.

Although no cases of PML have been reported for KESIMPTA in the RMS clinical studies, PML resulting in death has occurred in patients being treated with ofatumumab for CLL (at substantially higher intravenous doses than the recommended dose in MS but for a shorter duration of treatment). In addition, JCV infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies. At the first sign or symptom suggestive of PML, withhold KESIMPTA and perform an appropriate diagnostic evaluation. Magnetic reasonance imaging (MRI) findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

If PML is confirmed, treatment with KESIMPTA should be discontinued.

Vaccinations

Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of KESIMPTA for live or live-attenuated vaccines, and whenever possible, at least 2 weeks prior to initiation of KESIMPTA for inactivated vaccines.

KESIMPTA may interfere with the effectiveness of inactivated vaccines.

The safety of immunization with live or live-attenuated vaccines following KESIMPTA therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion *[see Clinical Pharmacology (12.2)]*.

Vaccination of Infants Born to Mothers Treated with KESIMPTA During Pregnancy

In infants of mothers treated with KESIMPTA during pregnancy, do not administer live or live-attenuated vaccines before confirming the recovery of B-cell counts. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines.

Inactivated vaccines may be administered, as indicated, prior to recovery from B-cell depletion, but an assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted.

5.2 Injection-Related Reactions

In Study 1 and Study 2, systemic and local injection reactions were reported in 21% and 11% of patients treated with KESIMPTA compared to 15% and 6% of patients treated with teriflunomide who received matching placebo injections, respectively *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

Injection-related reactions with systemic symptoms observed in clinical studies occurred most commonly within 24 hours of the first injection, but were also observed with later injections. Symptoms observed included fever, headache, myalgia, chills, and fatigue, and were predominantly (99.8%) mild to moderate in severity. There were no life-threatening injection reactions in the RMS clinical studies.

Local injection-site reaction symptoms observed in clinical studies included erythema, swelling, itching, and pain.

Only limited benefit of premedication with corticosteroids, antihistamines, or acetaminophen was observed in RMS clinical studies. The first injection of KESIMPTA should be performed under the guidance of an appropriately trained healthcare professional. If injection-related reactions occur, symptomatic treatment is recommended.

5.3 Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Decrease in immunoglobulin M (IgM) was reported in 7.7% of patients treated with KESIMPTA compared to 3.1% of patients treated with teriflunomide in RMS clinical trials *[see Adverse Reactions (6.1)]*. Treatment was discontinued because of decreased immunoglobulins in 3.4% of patients treated with KESIMPTA and in 0.8% of patients treated with teriflunomide. No decline in immunoglobulin G (IgG) was observed at the end of the study. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections, and after discontinuation of therapy until B-cell repletion. Consider discontinuing KESIMPTA therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

5.4 Fetal Risk

Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA in utero. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail elsewhere in the labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Injection-Related Reactions *[see Warnings and Precautions (5.2)]*
- Reduction in Immunoglobulins *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Approximately 1500 patients with RMS received KESIMPTA in clinical studies. In Study 1 and Study 2, 1882 patients with RMS were randomized, 946 of whom were treated with KESIMPTA for a median duration of 85 weeks; 33% of patients receiving KESIMPTA were treated for up to 120 weeks *[see Clinical Studies (14.1)]*. The most common adverse reactions occurring in greater than 10% of patients treated with KESIMPTA and more frequently than in patients treated with teriflunomide were upper respiratory tract infections, injection-related reactions (systemic), headache, and injection-site reactions (local). The most common cause of discontinuation in patients treated with KESIMPTA was low immunoglobulin M (3.3%), defined in trial protocols as IgM at 10% below the lower limit of normal (LLN).

Table 1 summarizes the adverse drug reactions that occurred in Study 1 and Study 2.

Table 1: Adverse Reactions in Patients with RMS with an Incidence of at Least 5% with KESIMPTA and a Greater Incidence Than Teriflunomide (Pooled Study 1 and Study 2)

Adverse Reactions	KESIMPTA 20 mg N = 946 %	Teriflunomide 14 mg N = 936 %
Upper respiratory tract infections[a]	39	38
Injection-related reactions (systemic)	21	15
Headache	13	12
Injection-site reactions (local)	11	6
Urinary tract infection	10	8
Back pain	8	6
Blood immunoglobulin M decreased	6	2

[a]Includes the following: nasopharyngitis, upper respiratory tract infection, influenza, sinusitis, pharyngitis, rhinitis, viral upper respiratory infection, tonsillitis, acute sinusitis, pharyngotonsillitis, laryngitis, pharyngitis streptococcal, viral rhinitis, sinusitis bacterial, tonsillitis bacterial, viral pharyngitis, viral tonsillitis, chronic sinusitis, nasal herpes, tracheitis.

Injection-Related Reactions and Injection-Site Reactions

The incidence of injection-related reactions (systemic) was highest with the first injection (14.4%), decreasing with subsequent injections (4.4% with second, less than 3% with third injection). Injection-related reactions were mostly (99.8%) mild to moderate in severity. Two (0.2%) patients treated with KESIMPTA reported serious injection-related

reactions. There were no life-threatening injection-related reactions. Most frequently reported symptoms (2% or greater) included fever, headache, myalgia, chills, and fatigue.

In addition to systemic injection-related reactions, local reactions at the administration site were very common. Local injection-site reactions were all mild to moderate in severity. The most frequently reported symptoms (2% or greater) included erythema, pain, itching, and swelling *[see Warnings and Precautions (5.2)]*.

Laboratory Abnormalities

Immunoglobulins

In Study 1 and Study 2, a decrease in the mean level of IgM was observed in KESIMPTA-treated patients but was not associated with an increased risk of infections *[see Warnings and Precautions (5.3)]*. In 14.3% of patients in Study 1 and Study 2, treatment with KESIMPTA resulted in a decrease in a serum IgM that reached a value below 0.34 g/dL. KESIMPTA was associated with a decrease of 4.3% in mean IgG levels after 48 weeks of treatment and an increase of 2.2% after 96 weeks.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medication, and the underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other ofatumumab products may be misleading.

Treatment induced anti-drug antibodies (ADAs) were detected in 2 of 914 (0.2%) KESIMPTA-treated patients; no patients with treatment enhancing or neutralizing ADAs were identified. There was no impact of positive ADA titers on PK, safety profile or B-cell kinetics in any patient; however, these data are not adequate to assess the impact of ADAs on the safety and efficacy of KESIMPTA.

7 DRUG INTERACTIONS

7.1 Immunosuppressive or Immune-Modulating Therapies

Concomitant usage of KESIMPTA with immunosuppressant drugs, including systemic corticosteroids, may increase the risk of infection. Consider the risk of additive immune system effects when coadministering immunosuppressive therapies with KESIMPTA.

When switching from therapies with immune effects, the duration and mechanism of action of these therapies should be taken into account because of potential additive immunosuppressive effects when initiating KESIMPTA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of KESIMPTA in pregnant women. Ofatumumab may cross the placenta and cause fetal B-cell depletion based on findings from animal studies *(see Data)*.

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to KESIMPTA have not been studied in clinical trials. The potential duration of B-cell depletion in infants exposed to ofatumumab *in utero*, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown. Avoid administering live vaccines to neonates and infants exposed to KESIMPTA *in utero* until B-cell recovery occurs *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

Following administration of ofatumumab to pregnant monkeys, increased mortality, depletion of B-cell populations, and impaired immune function were observed in the offspring, in the absence of maternal toxicity, at plasma levels substantially higher than that in humans *(see Data)*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Intravenous administration of ofatumumab (weekly doses of 0, 20, or 100 mg/kg) to pregnant monkeys during the period of organogenesis (gestations days 20 to 50) resulted in no adverse effects on embryofetal development; however, B-cell depletion was observed in fetuses at both doses when assessed on gestation day 100. Plasma exposure (C_{ave}) at the no-effect dose (100 mg/kg) for adverse effects on embryofetal development was greater than 5000 times that in humans at the recommended human maintenance dose of 20 mg. A no-effect dose for effects on B-cells was not identified; plasma exposure (C_{ave}) at the low-effect dose (20 mg/kg) was approximately 780 times that in humans at the recommended human maintenance dose (RHMD) of 20 mg/month.

Intravenous administration of ofatumumab (5 weekly doses of 0, 10, and 100 mg/kg, followed by biweekly doses of 0, 3, and 20 mg/kg) to pregnant monkeys throughout pregnancy resulted in no adverse effects on the development of the offspring. However, postnatal death, B-cell depletion, and impaired immune function were observed in the offspring at the high dose. The deaths at the high dose were considered secondary to B-cell depletion. Plasma exposure (C_{ave}) in dams at the no-effect dose (100/20 mg/kg) for adverse developmental effects was approximately 500 times that in humans at RHMD. A no-effect level for mortality and immune effects in offspring was not established because of the limited number of evaluable offspring at the low dose.

8.2 Lactation

Risk Summary

There are no data on the presence of ofatumumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Human IgG is excreted in human milk, and the potential for absorption of ofatumumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KESIMPTA and any potential adverse effects on the breastfed infant from KESIMPTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Females of childbearing potential should use effective contraception while receiving KESIMPTA and for 6 months after the last treatment of KESIMPTA *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of KESIMPTA did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Ofatumumab is a recombinant human monoclonal immunoglobulin G1 (IgG1) antibody that binds to human CD20 expressed on B-cells. Ofatumumab is produced in a murine NS0 cell line and consists of two IgG1 heavy chains and two kappa light chains with a molecular weight of approximately 146 kDa.

KESIMPTA (ofatumumab) injection is a sterile, preservative-free solution for subcutaneous use.

Each 20 mg/0.4 mL KESIMPTA Sensoready pen or prefilled syringe delivers 0.4 mL of solution. Each 0.4 mL contains 20 mg of ofatumumab, and arginine (4 mg), disodium edetate (0.007 mg), polysorbate 80 (0.08 mg), sodium acetate trihydrate (2.722 mg), sodium chloride (1.192 mg), and Water for Injection, USP with a pH of 5.5. Hydrochloric acid may have been added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which ofatumumab exerts its therapeutic effects in multiple sclerosis is unknown, but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ofatumumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.

12.2 Pharmacodynamics

B-cell Depletion

For B-cell counts, assays for CD19+ B-cells are used because the presence of KESIMPTA interferes with the CD20 assay. In Study 1 and Study 2, KESIMPTA administered as recommended, resulted in a reduction of CD19+ B-cells to below the LLN in 77.0% and 78.8% of patients, respectively, one week after treatment initiation, and in 95.0% and 95.8% of patients, respectively, two weeks after treatment initiation *[see Dosage and Administration (2.2) and Clinical Studies (14)]*. In Study 1 and Study 2, at Week 12, 99.3% to 99.5% of patients had CD19+ B-cell counts below LLN. The CD19+ B-cell counts remained below LLN for approximately 97% of patients in Study 1 and 92% of patients in Study 2 from 12 weeks through 120 weeks while on KESIMPTA treatment.

In a study of bioequivalence using the same dosing regimen as in Study 1 and Study 2, before initiation of the maintenance phase, total CD19+ B-cell levels below the defined threshold of 10 cells/µL were achieved in 94% of patients starting at Week 4 and 98% of patients at Week 12.

B-cell Repletion

Data from RMS clinical studies indicate B-cell recoveries over the LLN in at least 50% of patients in 24 to 36 weeks post treatment discontinuation. Modeling and simulation for B-cell repletion corroborates these data, predicting median time to B-cell recovery of 40 weeks post treatment discontinuation.

12.3 Pharmacokinetics

Absorption

A subcutaneous dose of 20 mg every 4 weeks leads to a mean AUC_{tau} of 483 mcg h/mL and a mean C_{max} of 1.43 mcg/mL at steady state.

After subcutaneous administration, ofatumumab is believed to be predominantly absorbed via the lymphatic system similarly to other therapeutic monoclonal antibodies.

Distribution

The volume of distribution at steady-state was estimated to be 5.42 L following subcutaneous administration of repeated KESIMPTA 20 mg dose.

Elimination

Metabolism

Ofatumumab is a protein for which the expected metabolic pathway is degradation to small peptides and amino acids by ubiquitous proteolytic enzymes.

Excretion

Ofatumumab is eliminated in two ways: a target-independent route as with other IgG molecules and a target-mediated route that is related to binding to B-cells. Higher baseline B-cell count results in greater component of target-mediated elimination clearance and shorter ofatumumab half-life at the start of therapy. Following B cell depletion, clearance was estimated to be 0.34 L/day following repeated subcutaneous administration of KESIMPTA 20 mg injections. The half-life at steady state was estimated to be approximately 16 days following subcutaneous administration of repeated KESIMPTA 20 mg dose.

Specific Populations

The following population characteristics do not have a clinically meaningful effect on the pharmacokinetics of ofatumumab: body weight, sex, age, race, or baseline B-cell count.

Patients with Renal/Hepatic Impairment

Pharmacokinetics of ofatumumab in patients with renal or hepatic impairment have not been studied.

Drug Interaction Studies

Ofatumumab does not share a common clearance pathway with chemical drugs that are metabolized by the cytochrome P450 system or other drug metabolizing enzymes. Additionally, there is no evidence that CD20 monoclonal antibodies are involved in the regulation of the expression of drug metabolizing enzymes. Interactions between KESIMPTA and other medicinal products have not been investigated in formal studies.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No carcinogenicity studies have been conducted to assess the carcinogenic potential of ofatumumab.

Mutagenesis

No studies have been conducted to assess the mutagenic potential of ofatumumab. As an antibody, ofatumumab is not expected to interact directly with DNA.

Impairment of Fertility

No effects on reproductive parameters, including hormones, menstrual cycle, sperm analysis, or histopathological evaluation of reproductive organs, were observed in male or female monkeys administered ofatumumab by intravenous injection (5 weekly doses of 0, 10, and 100 mg/kg, followed by biweekly doses of 0, 3, and 20 mg/kg). Plasma exposures (C_{ave}) at the high dose tested in monkey are greater than 500 times that in humans at the recommended human maintenance dose of 20 mg/month.

14 CLINICAL STUDIES

The efficacy of KESIMPTA was demonstrated in two randomized, double-blind, double-dummy, active comparator-controlled clinical trials of identical design, in patients with relapsing forms of MS [Study 1 (NCT02792218) and Study 2 (NCT02792231)]. Both studies enrolled patients with at least one relapse in the previous year, 2 relapses in the previous 2 years, or the presence of a T1 gadolinium-enhancing (GdE) lesion in the previous year. Patients were also required to have an Expanded Disability Status Scale (EDSS) score from 0 to 5.5.

Patients were randomized to receive either KESIMPTA, 20 mg subcutaneously on Days 1, 7, and 14, followed by 20 mg every 4 weeks thereafter starting at Week 4 with a daily oral placebo, or the active comparator, teriflunomide, at a dose of 14 mg orally once daily with a placebo administered subcutaneously on Days 1, 7, 14, and every 4 weeks thereafter. The treatment duration for an individual patient was variable based on when the end of study criteria were met. The maximal duration of treatment for an individual patient was 120 weeks. Neurologic evaluations were performed at baseline, every 3 months during blinded treatment, and at the time of a suspected relapse. Brain MRI scans were performed at baseline, 1 and 2 years.

The primary endpoint of both trials was the annualized relapse rate (ARR) over the treatment period. Additional outcome measures included: 1) the time to 3-month confirmed disability progression for the pooled populations, 2) the number of T1 GdE lesions per scan at Weeks 24, 48, and 96, and 3) the annualized rate of new or enlarging T2 MRI lesions. Disability progression was defined as an increase in EDSS of at least 1.5, 1, or 0.5 points in patients with a baseline EDSS of 0, 1 to 5, or 5.5 or greater, respectively.

In Study 1, a total of 927 patients were randomized to receive KESIMPTA (n = 465) or teriflunomide (n = 462). Of those randomized to KESIMPTA, 90% completed the study; of those randomized to teriflunomide, 81% completed the study. Demographics and disease characteristics were balanced across treatment arms. The mean age was 38 years, 89% were White, and 69% were female. The mean time since MS diagnosis was 5.7 years and the median EDSS score at baseline was 3.0; 60% had been treated with a non-steroid therapy for MS. At baseline, the mean number of relapses in the previous year was 1 and the mean number of T1 GdE lesions on MRI scan was 1.5.

In Study 2, a total of 955 patients were randomized to receive KESIMPTA (n = 481) or teriflunomide (n = 474). Of those randomized to KESIMPTA, 83% completed the study; of those randomized to teriflunomide, 82% completed the study.

Demographics and disease characteristics were balanced across treatment arms. The mean age was 38 years, 87% were White, and 67% were female. The mean time since MS diagnosis was 5.5 years and the median EDSS score at baseline was 2.5; 61% had been treated with a non-steroid therapy for MS. At baseline, the mean number of relapses in the previous year was 1.3, and the mean number of T1 GdE lesions on MRI scan was 1.6.

In both studies, KESIMPTA significantly lowered the ARR compared to teriflunomide.

KESIMPTA significantly reduced the risk of 3-month confirmed disability progression compared to teriflunomide.

KESIMPTA significantly reduced the number of T1 GdE lesions and the rate of new or enlarging T2 lesions in both studies.

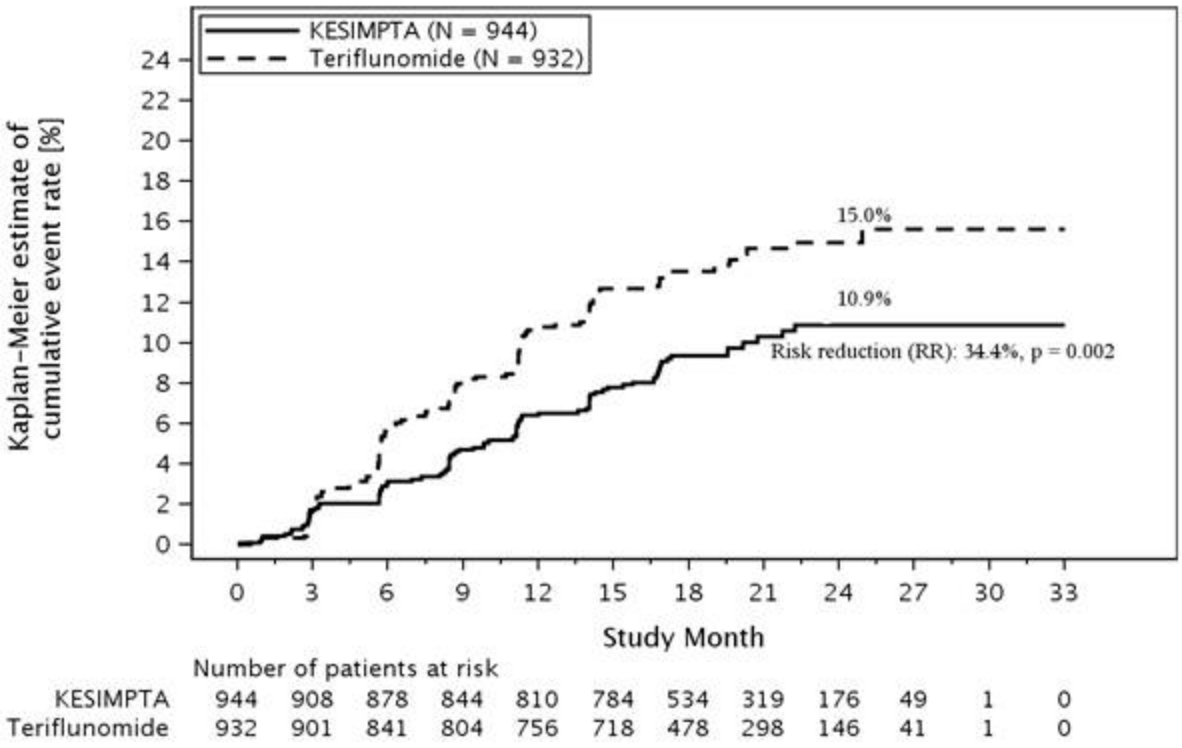
Key results for Study 1 and Study 2 are presented in Table 2 and Figure 1.

Table 2: Key Clinical and MRI Endpoints From Study 1 and Study 2

Endpoints	**Study 1**		**Study 2**	
	KESIMPTA 20 mg (n = 465)	Teriflunomide 14 mg (n = 462)	KESIMPTA 20 mg (n = 481)	Teriflunomide 14 mg (n = 474)
Clinical Endpoints				
Annualized relapse rate (Primary Endpoint)	0.11	0.22	0.10	0.25
Relative Reduction	51% ($p < 0.001$)		59% ($p < 0.001$)	
Proportion of Patients with 3-month Confirmed Disability Progression[a,b]	10.9% KESIMPTA vs 15.0% teriflunomide			
Relative Risk Reduction	34.4% ($p = 0.002$)			
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI scan	0.01	0.45	0.03	0.51
Relative Reduction	98% ($p < 0.001$)		94% ($p < 0.001$)	
Number of new or enlarging T2 lesions per year	0.72	4.00	0.64	4.15
Relative Reduction	82% ($p < 0.001$)		85% ($p < 0.001$)	

[a]Disability progression was defined as an increase in EDSS of at least 1.5, 1, or 0.5 points in patients with a baseline EDSS of 0, 1 to 5, or 5.5 or greater, respectively.
[b]Prospective pooled analysis of Studies 1 and 2. Proportion of patients with 3-month confirmed disability progression refers to Kaplan-Meier estimates at Month 24.

Figure 1: Time to First 3-month Confirmed Disability Progression by Treatment Full Analysis Set



A similar effect of KESIMPTA on the key efficacy results compared to teriflunomide was observed across the two studies in exploratory subgroups defined by sex, age, body weight, prior non-steroid MS therapy, and baseline disability and disease activity.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

KESIMPTA (ofatumumab) injection is a preservative-free, clear to slightly opalescent and colorless to slightly brownish-yellow solution for subcutaneous administration, which is supplied as follows:

KESIMPTA Sensoready Pen:

Carton of one 20 mg/0.4 mL single-dose prefilled Sensoready pen NDC 0078-1007-68

KESIMPTA Prefilled Syringe:

Carton of one 20 mg/0.4 mL single-dose prefilled syringe NDC 0078-1007-69

16.2 Storage and Handling

KESIMPTA Sensoready pens and prefilled syringes must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Keep the product in the original carton to protect from light until the time of use. Do not freeze. To avoid foaming, do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infections

Advise patients to contact their healthcare provider for any signs of infection during treatment or after the last dose. Signs include fever, chills, constant cough, or dysuria *[see Warnings and Precautions (5.1)]*.

Advise patients that KESIMPTA may cause reactivation of hepatitis B infection and that monitoring will be required if they are at risk *[see Warnings and Precautions (5.1)]*.

Advise patients that PML has happened with an intravenous form of ofatumumab administered at a higher intravenous dosage in patients with CLL, as well as with drugs that are similar to KESIMPTA, and may happen with KESIMPTA. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient of the importance of contacting their healthcare provider if they develop any symptoms suggestive of PML. Inform the patient that typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes *[see Warnings and Precautions (5.1)]*.

Vaccinations

Advise patients to complete any required live or live-attenuated vaccinations at least 4 weeks and, whenever possible at least 2 weeks prior to initiation of KESIMPTA for inactivated vaccines.

Administration of live-attenuated or live vaccines is not recommended during KESIMPTA treatment and until B-cell recovery *[see Warnings and Precautions (5.1)]*.

Injection-Related Reactions

Inform patients about the signs and symptoms of injection-related reactions, and that these reactions generally occur within 24 hours and predominantly following the first injection. Advise patients to contact their healthcare provider if they experience signs or symptoms of injection-related reactions *[see Warnings and Precautions (5.2)]*.

Contraception

Advise females of childbearing potential to use effective contraception while receiving KESIMPTA and for 6 months after the last treatment of KESIMPTA *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.3)]*.

Instruction on Injection Technique

Patients or caregivers should be instructed by a healthcare professional on how to administer KESIMPTA *[see Instructions for Use]*.

Instruct patients or caregivers in the technique of proper syringe and needle disposal, and advise them not to reuse these items. Instruct patients to inject the full amount of KESIMPTA according to the directions provided in the Instructions for Use. Dispose of pens and syringes in a puncture-resistant container.

Manufactured by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936
U.S. License No.: 1244

KESIMPTA and SENSOREADY is a [registered] trademark of Novartis AG.

MEDICATION GUIDE

KESIMPTA® (KEY-simp-ta)
(ofatumumab)
injection, for subcutaneous use

What is the most important information I should know about KESIMPTA?

KESIMPTA can cause serious side effects, including:

Infections. Serious infections can happen during treatment with KESIMPTA. If you have an active infection, your healthcare provider should delay your treatment with KESIMPTA until your infection is gone. KESIMPTA taken before or after other medicines that weaken the immune system may increase your risk of getting infections.

Tell your healthcare provider right away if you have any infections or get any symptoms, including painful and frequent urination, nasal congestion, runny nose, sore throat, fever, chills, cough, or body aches.

- **Hepatitis B virus (HBV) reactivation.** Before starting treatment with KESIMPTA, your healthcare provider will do blood tests to check for HBV. If you have ever had HBV infection, the HBV may become active again during or after treatment with KESIMPTA. Hepatitis B virus becoming active again (called reactivation) may cause serious liver problems, including liver failure or death. You should not receive KESIMPTA if you have active hepatitis B liver disease. Your healthcare provider will monitor you for HBV infection during and after you stop using KESIMPTA.

Tell your healthcare provider right away if you get worsening tiredness or yellowing of your skin or white part of your eyes during treatment with KESIMPTA.

- **Progressive Multifocal Leukoencephalopathy (PML)**. PML may happen with KESIMPTA. PML is a rare, serious brain infection caused by a virus that may get worse over days or weeks. PML can result in death or severe disability. Tell your healthcare provider right away if you have any new or worsening neurologic signs or symptoms. These may include weakness on one side of your body, loss of coordination in arms and legs, vision problems, changes in thinking and memory which may lead to confusion and personality changes.
- **Weakened immune system**. KESIMPTA taken before or after other medicines that weaken the immune system could increase your risk of getting infections.

What is KESIMPTA?

KESIMPTA is a prescription medicine used to treat adults with relapsing forms of multiple sclerosis (MS) including:

- clinically isolated syndrome
- relapsing-remitting disease
- active secondary progressive disease

It is not known if KESIMPTA is safe or effective in children.

Do not use KESIMPTA if you:

- have active hepatitis B virus infection.

Before using KESIMPTA, tell your healthcare provider about all of your medical conditions, including if you:

- have or think you have an infection including HBV or PML. See **"What is the most important information I should know about KESIMPTA?"**
- have ever taken, currently take, or plan to take medicines that affect your immune system. These medicines could increase your risk of getting an infection.
- have had a recent vaccination or are scheduled to receive any vaccinations.
    - **You should receive any required 'live' or 'live-attenuated' vaccines at least 4 weeks before you start treatment with KESIMPTA**. You **should not receive** 'live' or 'live-attenuated' vaccines while you are being treated with KESIMPTA and until your healthcare provider tells you that your immune system is no longer weakened.
    - **Whenever possible, you should receive any 'non-live' vaccines at least 2 weeks before you start treatment with KESIMPTA**.
    - Talk to your healthcare provider about vaccinations for your baby if you used KESIMPTA during your pregnancy.
- are pregnant, think that you might be pregnant, or plan to become pregnant. It is not known if KESIMPTA will harm your unborn baby. Females who can become pregnant should use birth control (contraception) during treatment

with KESIMPTA and for 6 months after your last treatment. Talk with your healthcare provider about what birth control method is right for you during this time.

- are breastfeeding or plan to breastfeed. It is not known if KESIMPTA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take KESIMPTA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use KESIMPTA?

See the detailed Instructions for Use that comes with KESIMPTA for information about how to prepare and inject a dose of KESIMPTA and how to properly throw away (dispose of) used KESIMPTA Sensoready pens or prefilled syringes.

- Use KESIMPTA exactly as your healthcare provider tells you to use it.
- KESIMPTA is given as an injection under your skin (subcutaneous injection), in your thigh or stomach-area (abdomen) by you or a caregiver. A caregiver may also give you an injection of KESIMPTA in your upper outer arm.
- Your healthcare provider will show you how to prepare and inject KESIMPTA the right way before you use it for the first time.
- **Do not** inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with moles, scars or stretch marks.
- The initial dosing is 20 mg of KESIMPTA given by subcutaneous injection at Weeks 0, 1, and 2. There is no injection at Week 3. Starting at Week 4 and then every month, the recommended dose is 20 mg of KESIMPTA administered by subcutaneous injection.
- If you miss an injection of KESIMPTA at Week 0, 1, or 2, talk to your healthcare provider. If you miss a monthly injection, give it as soon as possible without waiting until the next scheduled dose. After that, give your KESIMPTA injections a month apart.

What are the possible side effects of KESIMPTA?

KESIMPTA may cause serious side effects, including:

See **"What is the most important information I should know about KESIMPTA?"**

- **Injection-related reactions.** Injection-related reactions is a common side effect of KESIMPTA. Injecting KESIMPTA can cause injection-related reactions that can happen within 24 hours (1 day) following the first injections and with later injections. Talk with your healthcare provider if you have any of these signs and symptoms:
    - **at or near the injection site**: redness of the skin, swelling, itching and pain or
    - **that may happen when certain substances are released in your body**: fever, headache, pain in the muscles, chills, and tiredness.
- **Low immunoglobulins**. KESIMPTA may cause a decrease in some types of antibodies. Your healthcare provider will do blood tests to check your blood immunoglobulin levels.

The most common side effects of KESIMPTA include:

- upper respiratory tract infection, with symptoms such as sore throat and runny nose, and headache. See "**What is the most important information I should know about KESIMPTA?"**
- headache

These are not all the possible side effects of KESIMPTA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KESIMPTA?

- Store KESIMPTA in a refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep KESIMPTA in the original carton until ready for use to protect from light.
- Do not freeze KESIMPTA.
- Do not shake KESIMPTA.

Keep KESIMPTA and all medicines out of the reach of children.

General information about the safe and effective use of KESIMPTA.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use KESIMPTA for a condition for which it was not prescribed. Do not give KESIMPTA to other people, even if they have the same symptoms that you have. It may harm them.You can ask your pharmacist or healthcare provider for information about KESIMPTA that is written for health professionals.

What are the ingredients in KESIMPTA?
Active ingredient: ofatumumab
Inactive ingredients: Sensoready pen and prefilled syringe: arginine, disodium edetate, polysorbate 80, sodium acetate trihydrate, sodium chloride, and Water for Injection. Hydrochloric acid may be added.

Distributed by: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936

For more information, go to www.novartis.us.com or call 1-888-669-6682.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approved: 08/2020

INSTRUCTIONS FOR USE
KESIMPTA® [KEY-simp-ta]
(ofatumumab)
injection, for subcutaneous use
Sensoready® Pen

This Instructions for Use contains information on how to inject **KESIMPTA Sensoready Pen**.

Be sure that you read, understand, and follow this Instructions for Use before injecting KESIMPTA. Your healthcare provider should show you how to prepare and inject KESIMPTA the right way using the Sensoready Pen before you use it for the first time. Talk to your healthcare provider if you have any questions before you use KESIMPTA for the first time.

Important Information You Need to Know Before Injecting KESIMPTA Sensoready Pen.

- **Do not use** the KESIMPTA Sensoready Pen if either the seal on the outer carton or the seal on the KESIMPTA Sensoready Pen is broken. Keep the KESIMPTA Sensoready Pen in the sealed outer carton until you are ready to use it.
- **Do not shake** the KESIMPTA Sensoready Pen.
- If you drop your KESIMPTA Sensoready Pen, **do not use** it if it looks damaged, or if you dropped it with the cap removed.

Throw away (dispose of) the used KESIMPTA Sensoready Pen right away after use. **Do not re-use a KESIMPTA Sensoready Pen**. See "**How should I dispose of used KESIMPTA Sensoready Pens?**" at the end of this Instructions for Use.

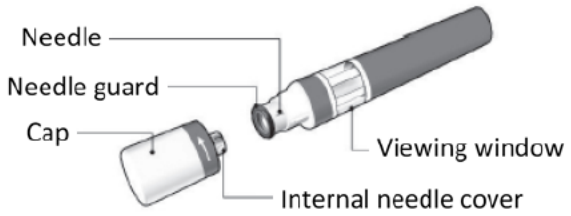
How should I store KESIMPTA Sensoready Pen?

- Store your carton of KESIMPTA Sensoready Pen in a refrigerator, between 36ºF to 46ºF (2°C to 8°C).
- Keep KESIMPTA Sensoready Pen in the original carton until ready to use to protect from light.
- **Do not freeze** KESIMPTA Sensoready Pen.

Keep KESIMPTA Sensoready Pen and all medicines out of the reach of children.

KESIMPTA Sensoready Pen parts (see Figure A):

Figure A



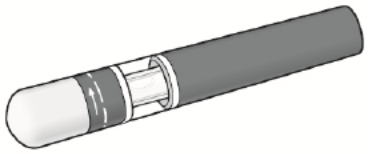
The KESIMPTA Sensoready Pen is shown with the cap removed. **Do not** remove the cap until you are ready to inject.

What you need for your injection:

Included in the carton:

A new KESIMPTA Sensoready Pen **(see Figure B)**.

Figure B



Not included in the carton **(see Figure C)**:

- 1 alcohol wipe
- 1 cotton ball or gauze
- Sharps disposal container

Figure C

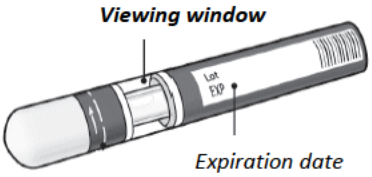
See "**How should I dispose of used KESIMPTA Sensoready Pens?**" at the end of this Instructions for Use.

Before your injection

Take the KESIMPTA Sensoready Pen out of the refrigerator **15 to 30 minutes before injecting** to allow it to reach room temperature.

Step 1. Important safety checks before you inject (see Figure D):

Figure D

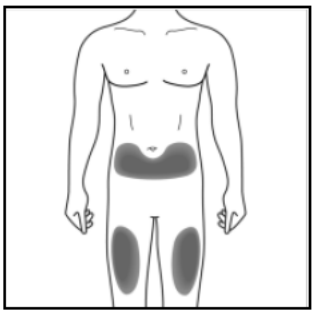


- Look through the viewing window. The liquid should be clear to slightly cloudy.
  Do not use if the liquid contains visible particles or is cloudy.
  You may see a small air bubble, which is normal.
- Look at the **expiration date (EXP)** on your KESIMPTA Sensoready Pen. **Do not use** your pen if the expiration date has passed.

Contact your pharmacist or healthcare provider if your pen fails any of these checks.

Step 2. Choose your injection site:

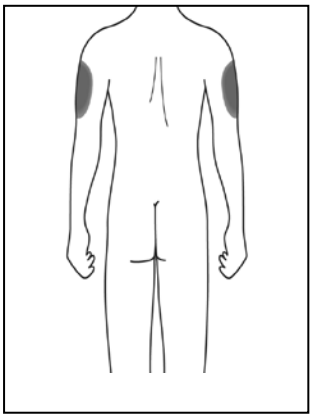
Figure E



- The recommended site is the front of the thighs. You may also use the lower stomach area (lower abdomen), but **not** the area 2 inches around the navel (belly button) **(see Figure E)**.
- **Do not** inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with moles, scars or stretch marks.

- If a **caregiver** or **healthcare provider** is giving you your injection, they may also inject into your outer upper arm **(see Figure F)**.

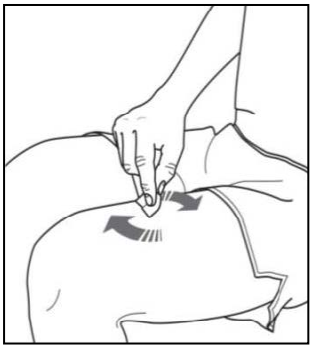
Figure F (Caregiver and healthcare provider only)



Step 3. Clean your injection site:

- Wash your hands with soap and water.
- Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting **(see Figure G)**.
- Do not touch the cleaned area again before injecting.

Figure G



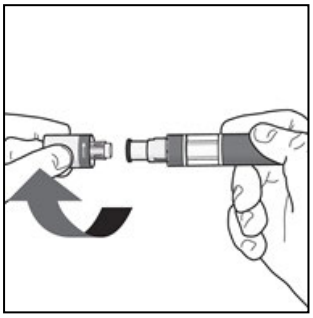
Your injection

Step 4. Remove the cap:

- Only remove the cap when you are ready to use the KESIMPTA Sensoready Pen.
- Twist off the cap in the direction of the arrow **(see Figure H)**.
- Throw away the cap. **Do not try to re-attach the cap.**
- Use the KESIMPTA Sensoready Pen within 5 minutes of removing the cap.

You may see a few drops of medicine come out of the needle. This is normal.

Figure H



Step 5. Hold your KESIMPTA Sensoready Pen:

- Hold the KESIMPTA Sensoready Pen at 90 degrees to the cleaned injection site **(see Figure I)**.

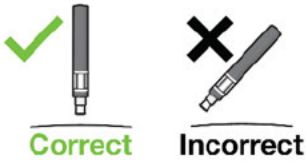


Figure I

Important: During the injection you will hear **2 loud clicks:**

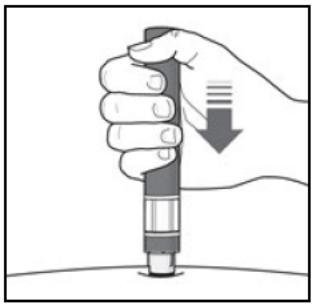
- The **1st click** indicates that **the injection has started**
- A **2nd click** will indicate that **the injection is almost complete**

You must keep holding the KESIMPTA Sensoready Pen firmly against the skin until the **green indicator** fills the window and stops moving.

Step 6. Start your injection:

- Press the KESIMPTA Sensoready Pen firmly against the skin to start the injection **(see Figure J)**.
- The **1st click** indicates the injection has started.
- **Keep holding** the KESIMPTA Sensoready Pen firmly against your skin.
- The **green indicator** shows the progress of the injection.

Figure J



Step 7. Complete your injection:

- Listen for the **2nd click**. This indicates that the injection is **almost** complete.
- Check to see if the **green indicator** fills the window and has stopped moving **(see Figure K)**.
- The KESIMPTA Sensoready Pen can now be removed **(see Figure L)**.

Figure K

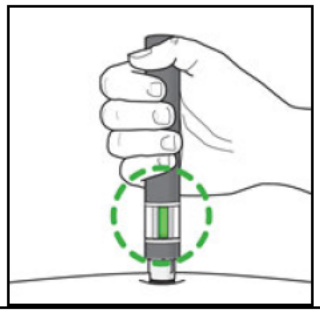


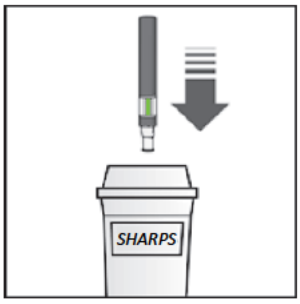
Figure L

After your injection

- In case the green indicator does not fill the window, it means the medicine has not been delivered. Contact your healthcare provider if the green indicator is not visible.
- There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

How should I dispose of used KESIMPTA Sensoready® Pens?

Figure M



Step 8. Put your used KESIMPTA Sensoready Pen in a FDA-cleared sharps disposal container right away after use **(see Figure M)**. **Do not throw away (dispose of)** your used KESIMPTA Sensoready Pen in your household trash.

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes and pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

Keep the sharps container out of the reach of children.

Manufactured by:

Novartis Pharmaceuticals Corporation

East Hanover, NJ 07936

U.S. License No.: 1244

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: 8/2020

INSTRUCTIONS FOR USE
KESIMPTA® [KEY-simp-ta]
(ofatumumab)
injection, for subcutaneous use
Prefilled Syringe

This Instructions for Use contains information on how to inject **KESIMPTA Prefilled Syringe**.

Be sure that you read, understand, and follow this Instructions for Use before injecting KESIMPTA prefilled syringe. Your healthcare provider should show you how to prepare and inject KESIMPTA the right way before using the prefilled syringe the first time. Talk to your healthcare provider if you have any questions.

Important Information You Need to Know Before Injecting KESIMPTA prefilled syringe.

- **Do not use** the KESIMPTA prefilled syringe if either the seal on the outer carton or the seal of the blister is broken. Keep the KESIMPTA prefilled syringe in the sealed carton until you are ready to use it.
- **Do not shake** the KESIMPTA prefilled syringe.
- The KESIMPTA prefilled syringe has a needle guard that will be activated to cover the needle after the injection is finished. The needle guard will help to prevent needle stick injuries to anyone who handles the KESIMPTA prefilled syringe after injection.
- Do not remove the needle cap until just before you give the injection.
- Avoid touching the syringe guard wings before use. Touching them may cause the needle guard to be activated too early.
- Throw away (dispose of) the used KESIMPTA prefilled syringe right away after use. **Do not re-use a KESIMPTA prefilled syringe**. See "**How should I dispose of used KESIMPTA prefilled syringe?**" at the end of these Instructions for Use.

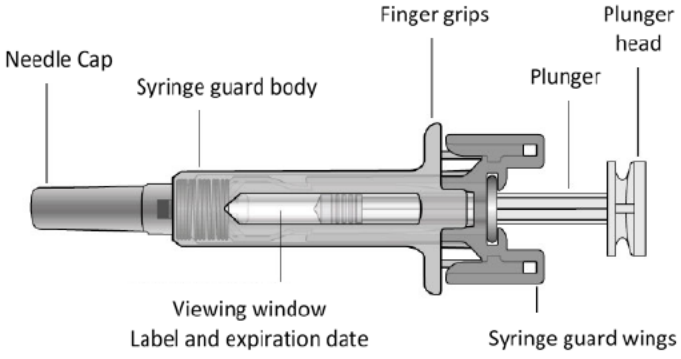
How should I store KESIMPTA Prefilled Syringe?

- Store your carton of the KESIMPTA prefilled syringe in a refrigerator, between 36°F to 46°F (2°C to 8°C).
- Keep the KESIMPTA prefilled syringe in the original carton until ready to use to protect from light.
- **Do not freeze** the KESIMPTA prefilled syringe.

Keep KESIMPTA Prefilled Syringe and all medicines out of the reach of children.

KESIMPTA prefilled syringe parts (see Figure A):

Figure A



What you need for your injection

Included in the carton:

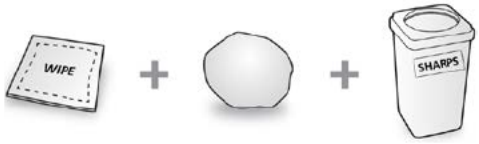
A new KESIMPTA prefilled syringe.

Not included in the carton **(see Figure B)**:

- 1 alcohol wipe
- 1 cotton ball or gauze
- Sharps disposal container

See "**How should I dispose of used KESIMPTA prefilled syringe?**" at the end of these Instructions for Use.

Figure B



Prepare the KESIMPTA prefilled syringe

Step 1. Find a clean, well-lit, flat work surface.

Step 2. Take the carton containing the KESIMPTA prefilled syringe out of the refrigerator and leave it **unopened** on your work surface for about 15 to 30 minutes so that it reaches room temperature.

Step 3. Wash your hands well with soap and water.

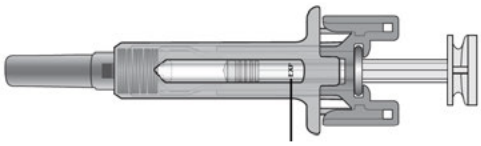
Step 4. Remove the KESIMPTA prefilled syringe from the outer carton and take it out of the blister by holding the syringe guard body.

Step 5. Look through the viewing window on the KESIMPTA prefilled syringe. The liquid inside should be clear to slightly cloudy. You may see a small air bubble in the liquid, which is normal. **Do not use** the KESIMPTA prefilled syringe if the liquid contains particles or is cloudy.

Step 6. Do not use the KESIMPTA prefilled syringe if it is broken. Return the KESIMPTA prefilled syringe and the package it came in to the pharmacy.

Step 7. Do not use the KESIMPTA prefilled syringe if the expiration date has passed **(see Figure C)**. Return the expired KESIMPTA prefilled syringe and the package it came in to the pharmacy.

Figure C

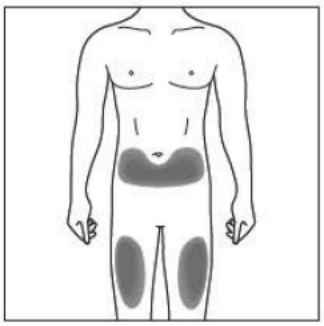


Expiration date

Choose and clean the injection site

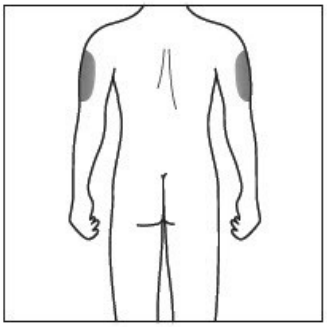
- Areas of your body that you may use as injection sites include:
  - the front of your thighs **(see Figure D)**
  - the lower stomach-area (abdomen), but not the area 2 inches around your navel (belly button) **(see Figure D)**
  - your outer upper arms, if a healthcare provider or caregiver is giving you the injection **(see Figure E)**.
- **Do not inject** into areas where the skin is tender, bruised, red, scaly, or hard. Avoid areas with moles, scars or stretch marks.

Figure D



Step 8. Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting. Do not touch the cleaned area again before injecting.

Figure E (Caregiver and healthcare provider only)



Giving your injection

Figure F

Step 9. Carefully remove the needle cap from the KESIMPTA prefilled syringe **(see Figure F)**. Throw away the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

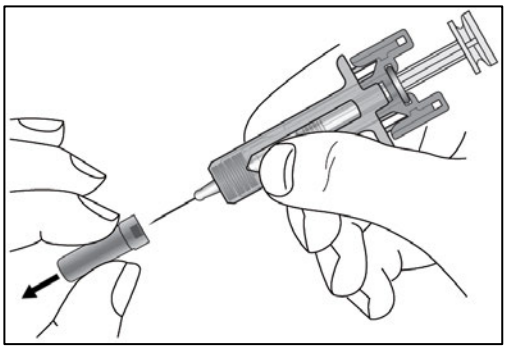
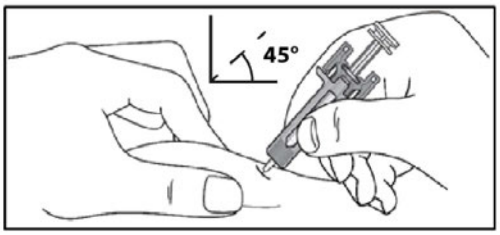


Figure G

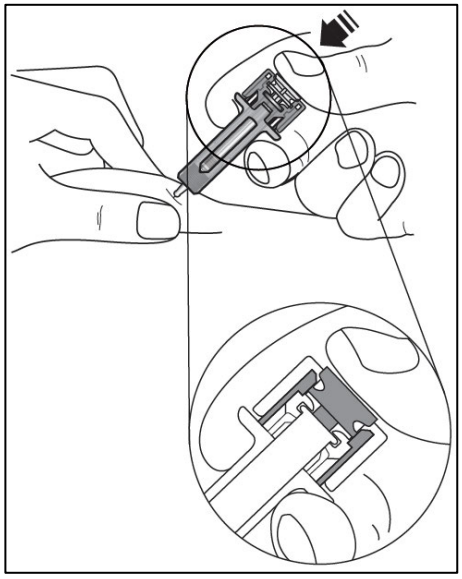
Step 10. With one hand, gently pinch the skin at the injection site. With your other hand insert the needle into your skin at an angle of about 45 degrees as shown **(see Figure G)**. Push the needle all the way in to make sure that you inject your full dose.



Step 11. Hold the KESIMPTA prefilled syringe finger grips as shown **(see Figure H)**. Slowly press down on the plunger head as far as it will go, so that the plunger head is completely between the syringe guard wings.

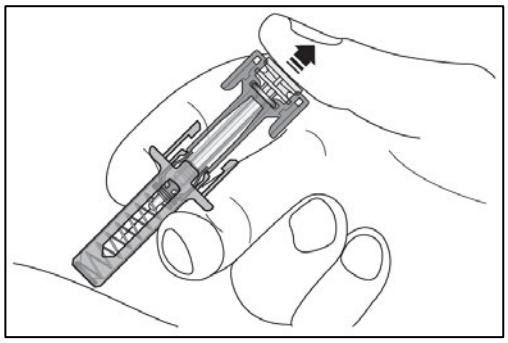
Continue to press fully on the plunger head for an additional 5 seconds. Hold the syringe in place for the full 5 seconds.

Figure H



Step 12. Slowly release the plunger head until the needle is covered **(see Figure I)**, and then remove the syringe from the injection site.

Figure I

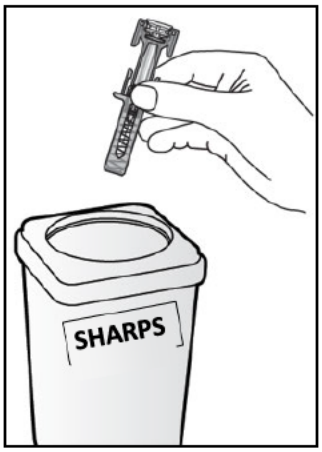


Step 13. There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

How should I dispose of used KESIMPTA prefilled syringe?

Step 14. Put your used KESIMPTA prefilled syringe in a FDA-cleared sharps disposal container right away after use **(see Figure J)**. **Do not throw away (dispose of)** your used KESIMPTA prefilled syringe in your household trash. Never try to reuse your KESIMPTA prefilled syringe.

Figure J



If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes and prefilled syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

Keep the sharps container out of the reach of children.

Manufactured by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

U.S. License No.: 1244

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: 8/2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326Orig1s070

SUMMARY REVIEW

Summary Review

Date	August 20, 2020
From	Paul R. Lee, MD, PhD, Acting Deputy Director, Division of Neurology 2 (DN2) Nick Kozauer, MD, Acting Director, DN2
Subject	Summary Review
sBLA #	125326
Applicant	Novartis
Date of Submission	February 7, 2020
PDUFA Goal Date	September 20, 2020
Proprietary Name	Kesimpta
Established or Proper Name	Ofatumumab
Dosage Form(s)	20 mg/4mL for subcutaneous injection
Applicant Proposed Indication(s)/Population(s)	Adults with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.
Applicant Proposed Dosing Regimen(s)	Initial dose: 20 mg subcutaneous at Weeks 0, 1, and 2, 20 mg subcutaneous monthly starting at Week 4
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adults with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.
Recommended Dosing Regimen(s) (if applicable)	Initial dose: 20 mg subcutaneous at Weeks 0, 1, and 2, 20 mg subcutaneous monthly starting at Week 4

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Ofatumumab is a fully-human anti-CD20 monoclonal antibody that targets an epitope of the B-lymphocyte antigen CD20 expressed on the cell membranes of lymphocytes. After binding to CD20, ofatumumab induces B-cell destruction primarily by complement-dependent cytotoxicity and by antibody-dependent cell-mediated cytotoxicity. This monoclonal antibody was approved on April 19, 2010, for the treatment of chronic lymphocytic leukemia refractory to alemtuzumab and fludarabine and is marketed for this indication as Arzerra. Ocrevus (ocrelizumab) is a humanized murine monoclonal anti-CD20 therapy that is approved for the relapsing and primary progressive forms of multiple sclerosis (MS). Rituxan (rituximab), a chimeric murine/human monoclonal antibody directed against CD20, which is approved to treat several malignancies and rheumatologic autoimmune diseases, is sometimes used to treat MS but has not been demonstrated to be safe and effective for the treatment of MS.

Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (secondary progressive MS with relapses), are phenotypes of the chronic and potentially disabling central nervous system disease of apparent autoimmune etiology termed "multiple sclerosis." In the relapsing forms of MS, patients experience episodes of focal neurological deficits and disseminated lesions of demyelination within the brain. Symptoms of relapsing forms of MS commonly include recurrent paroxysms of diminished sensory or motor function that can be temporarily or permanently disabling. Over time, many, but not all, patients with relapsing forms of MS experience some degree of persistent disability that may gradually worsen over years. Over fifteen therapies have been approved for the treatment of relapsing forms of MS, and all these approved therapies share a basic common feature of modifying the immune response. The mechanism of action of anti-CD20 therapy in the treatment of relapsing forms of MS is unknown but presumably is linked to depletion of B-cells and immunosuppression.

The applicant presents the results from two adequate and well-controlled Phase 3 clinical trials, Studies COMB157G2301 and COMB157G2302 (Studies G2301 and G2302 hereafter) as the basis of a supplemental application to support a claim of safety and efficacy in the treatment of relapsing forms of MS. Studies G2301 and G2302 were both randomized, double-blind, double-dummy, active-controlled trials that compared 20 mg subcutaneous ofatumumab (Kesimpta) to 14 mg teriflunomide (Aubagio). The two studies were identical in design with the same primary efficacy outcome measure, the frequency of confirmed relapses, as well as the same secondary outcome measures enumerated in hierarchical order as follows: 3-month confirmed disability worsening, the number of gadolinium-enhancing T1 lesions, the number of new or enlarging T2 lesions, 6-month confirmed disability worsening, serum level of neurofilament light chain at month 3, brain volume loss, and 6-month confirmed disability improvement. The analyses of disability worsening were based on the pooled disability data from the two studies.

In both studies, treatment with Kesimpta resulted in statistically significant reductions in relapse rates and disability worsening compared to

treatment with teriflunomide. These significant results in Studies G2301 and G2302 were achieved relative to an active comparator, teriflunomide, a therapy itself approved for relapsing forms of MS based upon significant treatment effects on relapse frequency and disability worsening in placebo-controlled studies. With respect to the primary efficacy outcome finding, in Study G2301, Kesimpta-treated patients had a significant ($p<0.001$) reduction of 50.5% in annualized relapse rate (ARR) as compared to teriflunomide-treated patients' ARR. In Study G2302, the relative reduction in ARR was 58.5% in Kesimpta treatment relative to teriflunomide treatment and was statistically significant ($p<0.001$). A comparison of pooled data from Studies G2301 and G2302 demonstrated that 3-month and 6-month risk of confirmed disability worsening was reduced significantly (34.4% and 32.5%, $p<0.002$ and $p<0.012$, respectively) with Kesimpta relative to teriflunomide. There were also significant findings on gadolinium-enhancing T1 and T2 lesion outcomes for Kesimpta that provide further evidence to support the significant treatment effect observed in the clinical outcome findings.

Anti-CD20 therapies like ofatumumab reduce the number of B-cells available to prevent and combat infection and are immune suppressants. The safety findings for Kesimpta in patients with relapsing forms of MS were similar to reported safety outcomes with other anti-CD20 therapies in MS. The findings for Kesimpta are similar and supplemental to the safety database used to support approval of Arzerra in the treatment of patients with chronic lymphocytic leukemia. The most common treatment-emergent adverse event and serious adverse event associated with Kesimpta was an increased risk of infections. Serious, potentially fatal opportunistic infections such as progressive multifocal leukoencephalopathy have been reported in chronic lymphocytic leukemia patients treated with Arzerra; there were no cases of PML in patients with MS treated in these trials but the potential for PML infection exists with Kesimpta. Injection-related reactions occurred in approximately 20% of patients treated with Kesimpta and were not usually serious. A fraction of patients treated with Kesimpta had a sustained, progressive decline in immunoglobulin M which could predispose to possible infection risk, and a postmarketing evaluation will be requested to explore this safety issue.

The overall benefit-risk profile of Kesimpta supports approval. The labeling for Kesimpta will include a warning regarding infection risk, including the known risk of serious opportunistic infections identified with the use of ofatumumab in patients with chronic lymphocytic leukemia and a warning of reduced immunoglobulins with chronic use.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (SPMS with relapses), are phenotypes of the chronic and potentially disabling central nervous system disease known as MS, a disease of apparent autoimmune etiology which in its relapsing form is characterized by episodes of worsening focal neurological deficits and disseminated lesions representing demyelination. • The usual age of onset of relapsing forms of MS is 20 to 50 years old. Symptoms commonly include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. Over time, many, but not all, patients with relapsing forms of MS experience some degree of persistent disability that may gradually worsen over years. Some patients may have a relatively benign manifestation with few discrete relapse events; others may become severely disabled after only a few years. There are no reliable biomarkers or predictors of outcome.	Relapsing forms of MS are serious and disabling. The defining symptom of relapsing forms of MS are paroxysms of focal neurological deficits termed "relapses" which can be disabling and reduce quality of life.
Current Treatment Options	• There are eighteen unique therapies approved to treat relapsing forms of MS. All of these therapies reduce patient relapse rates, and many include disability progression outcomes in their labeling. All except glatiramer acetate and mitoxantrone include at least one trial that showed a statistically significant treatment effect for a disability progression outcome versus a placebo comparator.	All therapies approved for the treatment of relapsing forms of MS reduce the frequency of relapses and some of these therapies also reduce accumulation of disability.
Benefit	• The annualized relapse rate in Kesimpta-treated patients was 0.11 and 0.10, vs. 0.22 and 0.25 for teriflunomide-treated patients. Based on the results of Studies G2301 and G2302, the percent reduction in relapse rate associated with Kesimpta	Two adequate and well-controlled trials provided substantial evidence of efficacy in significantly reduced likelihood of experiencing a relapse and significantly

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment relative to teriflunomide treatment was 50.5% and 58.5%, respectively. The overall mean reduction in relapses estimated for patients with relapsing forms of MS based on these trials would be approximately 0.12 fewer relapses per year on Kesimpta treatment as compared teriflunomide treatment and treating approximately 8 patients with Kesimpta would prevent one clinical relapse that might have otherwise occurred on teriflunomide treatment. • Kesimpta treatment reduced the relative risks of 3-month and 6-month confirmed disability worsening by 34.4% and 32.5%, respectively, as compared to teriflunomide.	reduced the likelihood of disability worsening relative to an active comparator. The pooled results from two adequate and well-controlled trials provided substantial evidence of efficacy that Kesimpta reduced the likelihood of accumulation of disability in patients with relapsing forms of MS relative to an active comparator with a significant effect on disability worsening.
Risk and Risk Management	• Ofatumumab, a monoclonal antibody targeting CD20, causes immune suppression by selectively reducing the number of B-cells. Findings from studies in oncology patients identified that ofatumumab primarily is associated with a higher risk of infections. In comparison with the safety profiles of two other approved anti-CD20 therapies (rituximab and ocrelizumab), ofatumumab has a safety profile that is similar and consistent with these other therapies which cause immune suppression via reduction in B-cell counts. • The MS development program did not reveal any previously unidentified risks associated with ofatumumab treatment. The most common treatment-emergent adverse events reported in patients treated with Kesimpta were nasopharyngitis (17.6%), injection site reaction (16.3%), headache (12.3%), and upper respiratory infection (10.3%). • Injection-related reactions appear lower in patients treated with subcutaneous administration of ofatumumab (21%) as compared	The safety data from the ofatumumab MS development program support approval and are consistent with ofatumumab's established safety profile for its approved intravenous form for oncology indications. Most adverse events associated with subcutaneous ofatumumab (Kesimpta) were treatable, not medically serious, or reversible upon discontinuation. Immunosuppression using anti-CD20 therapies has a known association with increased infection risk. Most of the injection-related reactions occurred on the first day of treatment in both treatment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to the rates reported with the intravenous route (67%). The majority of injection-related reactions associated with Kesimpta were mild and all reactions were managed without a need for hospitalization. Premedication reduced injection-related reactions to the same extent for Kesimpta (6.9% with corticosteroids, 4.5% with nonsteroidal anti-inflammatory agents) as it did for placebo administration (6.9% with corticosteroids, 4.4% with nonsteroidal anti-inflammatory agents).	groups (84% for Kesimpta, ~100% of placebo). Premedication did not appear to significantly impact Kesimpta injection-related reactions.
	• Severe adverse events associated with treatment occurred in approximately 10% of patients treated with Kesimpta and approximately 8% of patients treated with the active comparator, teriflunomide. The most common serious adverse events in Kesimpta-treated patients were isolated cases of serious infections (2.5%); the most often reported serious infection was appendicitis (reported in 8 patients, or 1.8%). • There were no deaths reported in Kesimpta-treated patients in the Phase 3 clinical trials. • In Studies G2301 and G2302, the rate of adverse events leading to Kesimpta discontinuation were 5.2% and 5.6% as compared to 5.0% and 4.9% in the teriflunomide treatment arms. The most common reason for discontinuation of Kesimpta was low immunoglobulins. The median reduction in immunoglobulin M in Kesimpta-treated patients during the clinical trial period was 29% compared to 17% for teriflunomide. • Nonclinical studies demonstrated that offspring exposed to ofatumumab before birth had depletion of B-cells and impaired	Increased risk of serious infections is a known risk of B-cell depleting therapies. The labeling for Arzerra has a boxed warning for hepatitis B reactivation and progressive multifocal leukoencephalopathy. These warnings will be included in Kesimpta's labeling even though no cases of either of these serious infections were observed in clinical trials because of the known risks associated with ofatumumab in the treatment of leukemia and other anti-CD20 monoclonal antibody therapies. Immunoglobulin screening before initiation and during Kesimpta therapy will be a labeling warning because of low immunoglobulin levels observed during clinical trials. There are published data form other B-cell depleting therapies that long-term use is associated with decreased immunoglobulins and possible increased risk of infections. There will be a postmarketing requirement to study the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	T-cell responses to a novel antigen. Whether long-term impaired immune function occurs in infants exposed to Kesimpta *in utero* is unclear.	relationship between low immunoglobulins and risk of infection for Kesimpta. Labeling will warn that animal studies suggested risk of fetal harm and advise continuous use of adequate contraception. There will be a required postmarketing pregnancy registry and a required postmarketing pregnancy outcomes study.

2. Background

This application contains data in support of the safety and effectiveness of Kesimpta (ofatumumab), a fully human anti-CD20 monoclonal antibody (mAb) that selectively targets an epitope of the CD20 molecule on the cell membrane of B-cells. Ofatumumab is administered subcutaneously once weekly for three consecutive weeks then continued monthly as a maintenance dose. In 2010, ofatumumab (as Arzerra) was approved for the intravenous treatment of chronic lymphocytic leukemia (CLL) refractory to alemtuzumab and fludarabine. This application was submitted as a supplement to the approved Biologics License Application (BLA) for Arzerra.

Relapsing forms of multiple sclerosis (MS), which include clinically isolated syndrome, relapsing-remitting disease, and secondary progressive MS with relapses (active secondary progressive disease), are related phenotypes of a chronic and potentially disabling central nervous system disease of apparent autoimmune etiology characterized by episodes of worsening focal neurological deficits and disseminated lesions of demyelination. Patients diagnosed with relapsing forms of MS are typically White women between 20 to 50 years of age. Symptoms commonly include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. As disease duration increases, many, but not all, patients with relapsing disease experience some degree of persistent disability that may gradually worsen over years as a result of incomplete recovery of the disability that resulted from MS relapses. In some patients, disability may accrue progressively with clear independence from acutely disabling relapse events, a process termed secondary progressive disease.

There is no widely accepted biomarker to assess disease status in patients with relapsing forms of MS. The diagnosis of relapsing forms of MS relies on clinical criteria, and the ongoing evaluation of patients with MS is reliant on clinical investigation. To support an indication for the treatment of relapsing forms of MS, clinical trials should demonstrate that a therapy is associated with a significant, clinically meaningful decrease in the frequency of MS-associated relapses, typically measured as an annual relapse rate (ARR). Some therapies approved for the treatment of relapsing forms of MS, including another anti-CD20 therapy, have also demonstrated an additional significant reduction of the accrual of disability over three-month or six-month observational periods.

In 2017, Ocrevus (ocrelizumab) was the first anti-CD20 therapy approved for the treatment of relapsing forms of MS (as well the first approved therapy for primary progressive MS) in adults. Ocrelizumab is a humanized murine anti-CD20 mAb and is administered as an initial 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion, with subsequent doses of 600 mg intravenously infused every 6 months. Rituxan (rituximab), an anti-CD20 chimeric murine-human mAb, became the first anti-CD20 mAb therapy approved for any indication in 1997. Rituximab is not indicated for the treatment of MS but is sometimes used to treat MS and other neuroimmune diseases on an "off-label" basis. Rituximab's relatively higher antigenicity is a consideration in its safety and efficacy. Ofatumumab is a fully human antibody and therefore is predicted to have less antigenicity than chimeric or partially humanized antibodies. Kesimpta is presented as a subcutaneous administration for home use, a key difference from these other anti-CD20 therapies and from ofatumumab's Arzerra presentation which require administration via intravenous infusions in a monitored medical setting.

The CD20 antigen is a transmembrane calcium channel that is expressed on the surfaces of B-cells beginning in the late pre-B-cell stage of maturation through the fully matured memory B-cell. Administration of mAb anti-CD20 therapies such as ofatumumab reduces B-cell counts in serum via B-cell lysis by complement-dependent cytotoxicity (CDC) and by antibody-dependent cell-mediated cytotoxicity (ADCC). The precise mechanism by which ofatumumab exerts its therapeutic effects in MS is not known, but immune suppression by a variety of treatments that target B-cells, including the other approved anti-CD20 mAb therapy ocrelizumab, appears to prevent relapses and accumulation of significant disability in patients with various forms of MS.

The applicant presents results from two adequate and well-controlled Phase 3 clinical trials as the basis of support for the effectiveness of ofatumumab for the treatment of relapsing forms of MS. These two efficacy and safety studies, Studies COMB157G2301 and COMB157G2302, were both randomized, double-blind, double-dummy, active-controlled studies comparing ofatumumab to teriflunomide treatment in adult patients with relapsing forms of MS. These trials were identical in design with the same primary efficacy outcome measure, ARR, along with the same secondary endpoints (3-month confirmed disability worsening, the number of gadolinium-enhancing T1 lesions, the number of new or enlarging

T2 lesions, 6-month confirmed disability worsening, serum neurofilament light chain levels at 3 months, brain volume loss, and 6-month confirmed disability improvement) that were analyzed in a hierarchical analysis.

Regulatory History

Dr. Lawrence Rodichok's clinical review provides the full regulatory history of the development program for ofatumumab for the treatment of relapsing forms of MS. Ofatumumab is currently marketed worldwide as Arzerra. Ofatumumab (as Arzerra) was granted accelerated approval as on October 26, 2009, for the treatment of CLL refractory to alemtuzumab and fludarabine. Since its original action, Arzerra has been approved, in combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate and for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL.

This submission is a supplemental BLA (sBLA) to BLA 125326, the original Arzerra BLA, approved in 2009. In this sBLA, the applicant proposes a new proprietary name for the MS indication ("Kesimpta") because of the new proposed subcutaneous route of administration (Arzerra is administered intravenously) and the need to differentiate the labeling for the MS indication given the anticipated differences from the labeling for the oncology indication.

The applicant opened IND 111116 for ofatumumab for the treatment of MS on April 29, 2011. There was an end-of-Phase 2 meeting held on March 25, 2014, with much of the discussion relating to the design of the Phase 3 trials and how best to reference product quality data from the existing BLA in a future application. The applicant submitted an initial pediatric study plan on August 30, 2018, with the Agency's subsequent agreement. A pre-BLA meeting with the applicant was held on October 2, 2019, and it was at this meeting that the applicant stated an intention to propose a standalone, different tradename for ofatumumab for the MS indication. The applicant submitted notification of an intention to use a priority review voucher (PRV 208711) on September 17, 2019. The sBLA for ofatumumab (Kesimpta) was submitted on September 20, 2019, and was filed for a priority review on February 18, 2020. The basis for the priority review was the applicant's use of a rare tropical disease priority review voucher.

On June 1, 2020, after review of the applicant's May 13, 2020, response to an Information Request sent by the Agency regarding chemistry-manufacturing, and control issues, the Agency notified the applicant that the submission dated May 13, 2020, constituted a major amendment to the application. As a result of this major amendment, the review goal date was extended by three months to September 20, 2020.

3. Product Quality

The Office of Biotechnology Products (OBP) provided an integrated review. The primary, secondary, and tertiary clinical reviewers from were Drs. Anshu Rastogi, Brian Janelsins, and Rachel Novak, respectively. Refer to the OBP review for the full listing of the OBP review team. The OBP team recommends approval.

The drug substance, ofatumumab, is approved as Arzerra for intravenous infusion, but ofatumumab presented as Kesimpta is formulated for subcutaneous administration. Thus, while Kesimpta contains the same drug substance (ofatumumab) as Arzerra, the proposed new subcutaneous route necessitates changes in the drug product from Arzerra's formulation with subsequent changes in manufacturing. The OBP review therefore focused on the changes in chemistry, manufacturing, controls issues associated with the Kesimpta formulation.

General Product Quality Considerations

Kesimpta is formulated as a 20 mg/0.4 mL solution for injection in two new subcutaneous delivery systems, a pre-filled syringe with a needle safety device, and a pre-filled syringe assembled into an autoinjector. The concentration of ofatumumab in Kesimpta is higher (50 mg/ml) than in Arzerra (20 mg/ml); there is no change to the rest of the formulation (i.e., excipients). Stability of the Kesimpta formulation was evaluated at long term (2 – 8°C), at accelerated (25°C), and stressed (40°C) storage conditions. Formulations containing minimal and maximal amounts of excipients within the tested ranges showed comparable stability. The ranges tested for the excipients, pH, and protein concentration did not impact the quality attributes of Kesimpta within 12 months at 5°C and up to 6 months at 25°C.

The OBP team noted that the leachables study data for the pre-filled syringe submitted in the sNDA only included data for up to 3 months at long-term storage conditions, but the applicant proposes a product shelf-life of (b) (4). OBP

determined that a postmarketing commitment (PMC) needed to be issued for the applicant to perform a leachable assessment for Kesimpta in its proposed primary container closure system at the intended storage conditions for up to the proposed (b) (4) self-life. The applicant clarified that the leachables study is ongoing and is intended to provide the shelf-life assessment requested in the PMC. The applicant provided the study protocol of the ongoing study as well as data from the 6-month time point which showed leachable levels were not exceeding the safety concern threshold. The OBP team concluded that the protocol and timelines of the ongoing study were acceptable; hence the agreed upon PMC does not have goal dates for a draft and final protocol submissions, and the completion/report goal dates align with the projected dates of the ongoing leachables study (see Section 11).

The manufacturing process of ofatumumab was revised extensively for the Kesimpta presentations. Significant changes included the institution of a main new manufacturing site, validation of new release and stability test methods for testing of the syringe and autoinjector, and transfer of the release and stability test methods (except for potency) to a new testing site. The OBP team sent several information requests to the applicant to clarify the manufacturing changes made to support the new presentations. An information request response from the applicant received on May 13, 2020, contained many clarifications and new details regarding numerous aspects of the manufacturing changes. Upon evaluation, this response was sufficiently extensive to necessitate additional review time and therefore constituted a major amendment to the sNDA (see Section 2). The OBP review concluded that the subsequent responses to manufacturing and related drug product inquiries provided by the applicant, taken together with the supplemental application's initial submission materials and earlier information request responses, provided an adequate basis for approval.

Facilities Review/Inspection

All facilities inspections have been completed, and the Office of Pharmaceutical Quality and Office of Compliance have determined these facilities to be acceptable.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Melissa Banks-Muckenfuss. Dr. Lois Freed provided a supervisory review. Dr. Banks-Muckenfuss recommends approval, and Dr. Freed concurs. The principal conclusions of Dr. Banks-Muckenfuss's and Dr. Freed's reviews are as follows:

- Based on the toxicology studies conducted to support Arzerra's approval, the following were identified as clinically-relevant risks: increased risk of infection, infusion-reaction/cytokine response, delayed onset anemia, fetal toxicity (i.e., decreased placental, fetal spleen, and fetal thymus weights), and clinical chemistry alterations (i.e., increased lactate dehydrogenase, increased C-reactive protein). These toxicities were deemed to be related to the anti-CD20 effects of ofatumumab.

- To support a new indication for chronic treatment of relapsing forms of MS using subcutaneous ofatumumab, the applicant provided nonclinical subcutaneous, fertility, and enhanced pre- and post-natal development studies.

- A subcutaneous administration study was conducted in female cynomolgus monkeys to support the proposed subcutaneous route of administration for Kesimpta. CD20+ B-cells were totally depleted, and CD40+ B-cells were markedly reduced, in all ofatumumab treatment groups regardless of administration route. Lymphocyte recovery was observed in all groups within the 33-week observation period after discontinuation of ofatumumab treatment.

- The applicant provided a fertility study conducted in cynomolgus monkeys who received ofatumumab (0, 10, or 100 mg/kg weekly for 5 weeks then 0, 3, or 20 mg/kg every 2 weeks) for 3 months followed by an 8-week recovery period. In all treated monkeys, CD20+ cells were depleted in the spleen and lymphatic tissues (with reduced CD3+ cells considered secondary to reduced germinal centers reflecting marked depletion of CD20+ cells). Anti-drug antibodies (ADAs) were observed at the high and low doses, and neutralizing ADAs were observed at the low dose. There was no clear drug effect on female reproductive tissues and inconclusive findings in the reproductive tissues of high-dose treated male monkeys.

- The enhanced prenatal and postnatal development studies demonstrated CD20+ B-cell depletion in maternal animals at all doses, and increased fetal loss in the low dose treatment group. In the high dose group, early postnatal losses appeared to be due to drug-dependent (infections) and drug-independent (accidents) causes; overall infant postnatal survival was reduced in the high dose group.

- Infants exposed to ofatumumab had initial CD20+ depletion and abnormal immune responses even after B-cell repletion, especially in the high dose exposed group. CD3+ and CD3+CD4+ T cells were increased in high dose female infants up to postnatal day 119. Immunoglobulin G levels were reduced in the high dose infants and while immunoglobulin levels recovered in males females did not show full recovery. The T-Cell-Dependent Antibody Response (TDAR) assay, using immunizations on PND119 and PND147, demonstrated persistent reductions in expected immune responsivity in the high dose offspring of ofatumumab-dosed females. A warning regarding avoidance of use during pregnancy is included in labeling based on these and the enhanced prenatal development study's findings. Such a warning is consistent with a warning in the labeling of another approved anti-CD20 mAb (i.e., rituximab.)

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) Review was written by Drs. Jagan Parepally (primary reviewer), Angela Men (the clinical pharmacology team leader), Vishnu Sharma (reviewer for Division of Pharmacometrics), and Atul Bhattaram (the Division of Pharmacometrics team leader). The OCP review notes that ofatumumab is approved as Arzerra (at a higher dose, via the intravenous route, for the treatment of CLL) and that the Kesimpta application contains two Phase 2 and two Phase 3 studies as well as a pharmacokinetic (PK) study comparing ofatumumab administered via pre-filled syringe assembled with a safety needle device and via pre-filled syringe assembled with an autoinjector to support the new proposed dose, proposed route of administration, indication, and chronicity of use. The OCP team found that for Kesimpta, the proposed 20 mg subcutaneous dose with initial dosing at Weeks 0, 1, and 2 followed by subsequent monthly dosing starting at Week 4 supported approval for the relapsing forms of MS indication. The OCP team recommends approval.

Ofatumumab is already approved (as Arzerra), and therefore, there has been extensive adequate and sufficient prior characterization to support approval of this anti-CD20 monoclonal antibody with respect to basic pharmacological properties (e.g., mechanism of action, metabolism, excretion) that would not be altered by the changes associated with the proposed Kesimpta formulation. The OCP review therefore focused on three topics relevant to ofatumumab as proposed for use as Kesimpta: (1) the relative bioavailability of ofatumumab comparing ofatumumab administered via pre-filled syringe assembled with a safety needle device and via pre-filled syringe assembled with an autoinjector, (2) whether a population pharmacokinetic analysis focusing patient specific characteristics on the pharmacokinetics of Kesimpta provided evidence of a need for dose adjustments based on these factors, and (3) immunogenicity of Kesimpta.

The OCP review major conclusions regarding these topics were as follows:

1. Ofatumumab administered by a pre-filled syringe assembled in an autoinjector device and via a pre-filled syringe assembled in a needle safety device are bioequivalent.

2. There is no need for dose adjustment of Kesimpta in patients with MS based on age, sex, body weight, race, or baseline B-cell count.

3. The overall incidence of positive ADAs in patients with relapsing forms of MS was low. Treatment-induced ADAs were detected in less than 1% of patients (2/923 patients) with relapsing forms of MS treated with Kesimpta in the two Phase 3 studies. No patients with treatment-enhanced ADAs were identified. No neutralizing antibodies were identified in ADA-positive samples from the Phase 2 and Phase 3 studies.

The labeling reviewers stated that the applicant's population PK analysis supported most of the labeling statements as proposed but recommended changes to the labeling language for Kesimpta as follows:

- Revisions to Sections 6.2 (Immunogenicity), 7 (Drug-Drug Interactions), and 12.3 (Pharmacokinetics) to align with the key conclusions discussed in their review.

- Deletion of [redacted] (b) (4) which was not needed.

- Need for inclusion of an explicit statement in Section 12.3 that the following population characteristics do not have a clinically meaningful effect on the pharmacokinetics of Kesimpta: body weight, sex, age, race and baseline B-cell count.

4. Clinical Microbiology

Not applicable.

5. Clinical/Statistical- Efficacy

Dr. Lawrence Rodichok was the clinical efficacy reviewer for this application. Dr. Xiang Ling was the biometrics reviewer, and Dr. Kun Jin was the biometrics team leader. Dr. Rodichok finds that the application provides substantial evidence of efficacy for ofatumumab in the treatment of patients with relapsing forms of MS. Drs. Ling and Jin agree that the application provides adequate statistically significant findings on the primary outcome measure and relevant clinical disability endpoints; the biometrics team recommends approval.

Study Design

The applicant submitted data from two adequate and well-controlled efficacy studies, Study COMB157G2301 (hereafter "Study G2301"), and Study COMB157G2302 (hereafter "Study G2302"). These studies were identical Phase 3, multinational, randomized, double-blind, double-dummy, parallel-group, active-controlled studies that evaluated 20 mg ofatumumab (subcutaneously once weekly for 3 weeks then monthly) compared to 15 mg oral teriflunomide administered daily.

The treatment durations for patients in both these studies was variable because patients received treatment in the controlled phase of the trial until sufficient blinded data were available to provide the pre-determined power for the key statistical outcomes. Patients enrolled in these trials were not permitted to receive other chronic immune treatments for

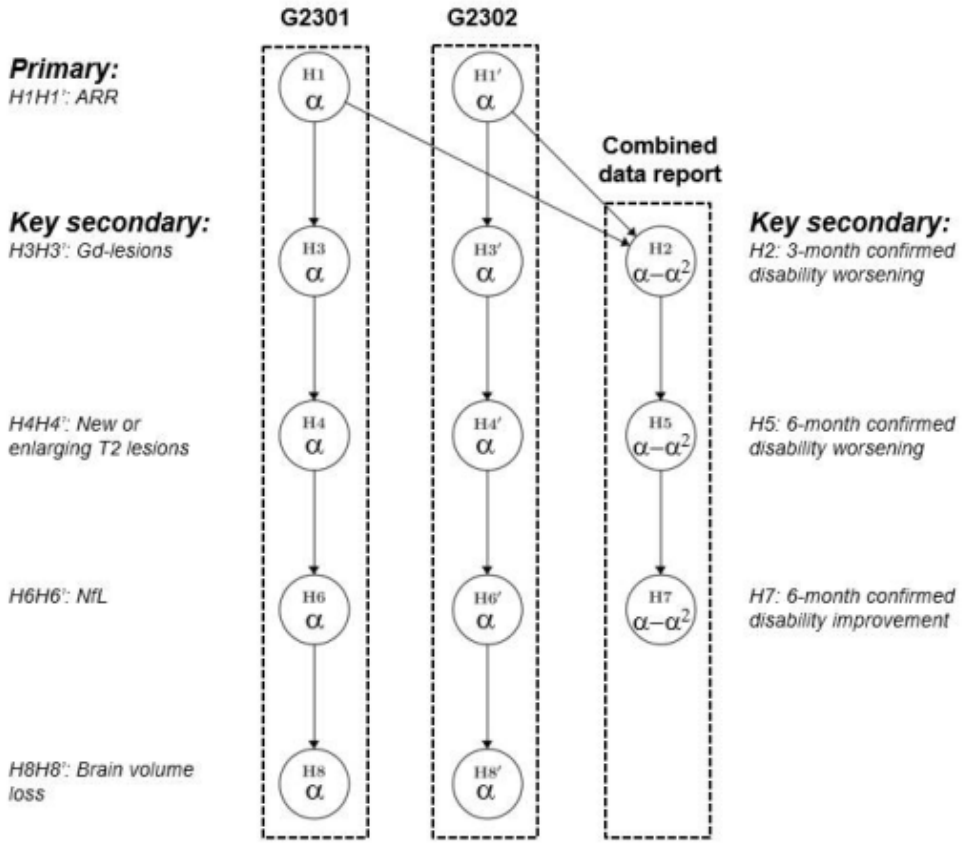
MS, and there were exclusion criteria and allowances for adequate treatment abstinence periods prior to randomization designed to prevent carry over of previous treatments' effects into the controlled trial phase. Patients could continue dalfampridine at a stable dose during the trial and corticosteroids could be administered for acute treatment of relapses and as premedication to prevent infusion-related reactions. The inclusion criteria for Studies G2301 and G2302 were a diagnosis of a relapsing form of MS using the standard international 2010 Revised McDonald criteria and 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 gadolinium-enhancing (GdE) T1 lesion on magnetic resonance imaging (MRI) scan during the year prior to randomization.

Relapses were assessed by independent raters who were the only study personnel allowed to provide disability scoring and were blinded with respect to patient treatment condition. Patients reporting a potential relapse event were evaluated at an unscheduled study visit using standardized procedures. Measures were taken to maintain rater blinding including covering potential injection sites and preventing independent raters from accessing patient data such as adverse event history and B-lymphocyte counts that might reveal treatment condition. Confirmation of MS relapse was done centrally based on the independent rater evaluation findings. A confirmed MS relapse required an increase of at least 0.5 points on the Expanded Disability Status Scale (EDSS) score, or an increase of 1 point on two functional scores (FS) or 2 points on one FS, excluding changes involving bowel/bladder or cerebral FS compared to the previously available rating (the last EDSS rating that did not occur during a relapse).

The primary efficacy endpoint for Studies G2301 and G2302 was the annualized relapse rate (ARR). The secondary endpoints of Studies G2301 and G2302, were analyzed in a closed sequential hierarchy as indicated in the figure below. Thus, within each study, the primary endpoint (ARR) was tested first, and if the null hypothesis could be rejected, the key secondary endpoints were tested according to the following hierarchy: the number of GdE T1 lesions, the number of new or enlarging T2 lesions, neurofilament light levels, and brain volume loss. A meta-analysis for the combined data (pooled from Studies G2301 and G2302) was prespecified for the key secondary disability-related endpoints, 3-month confirmed disability worsening, and 6-month confirmed disability worsening because the individual studies were not powered for these analyses. If both studies successfully rejected the null-hypothesis of the primary endpoint, disability-related

endpoints could be tested at 1-sided significance level of 0.024 using the combined data from both studies, regardless of the outcomes of MRI- and neurofilament-related endpoints.

Figure 1: Testing Procedure and Type-I Error Control in Studies G2301 and G2302



Source: Biometrics Review, Figure 2

Study G2301

Demographics

In Study G2301, the intention-to-treat (ITT) population, defined as every patient receiving at least one dose of treatment, comprised nine-hundred and twenty-seven (927) patients who were randomized to treatment, 465 to treatment with Kesimpta and 462 to treatment with teriflunomide. Patients enrolled from 170 centers in 28 countries worldwide. Most (68.5%) of the enrolled patients came from Eastern Europe, and 20.8% came from the United States.

The ITT population in Study G2301 was 68.5% female, had a median and mean age of 39.0 and 38.3 years old, respectively, and 88.8% of the patients were White. These demographic data are entirely consistent with the well-established demographics of the worldwide population diagnosed with a relapsing form of MS. The ITT population was adequately balanced between treatment arms with respect to key demographic and baseline disease variables.

Eighty-six percent of the Kesimpta-treated patients and 78.8% of the teriflunomide-treated patients completed Study G2301 on treatment. The two most frequent reasons for treatment discontinuation in the Kesimpta treatment arm were patient/guardian decision (4.9%), adverse event (5.2%), and physician decision (2.2%). Dr. Rodichok noted an overall higher rate of discontinuation in the teriflunomide treatment group (17.5% vs. 10.3%) which was the result of a much higher rate of discontinuation due to patient and physician decision (14.7% in teriflunomide versus 7.1% in Kesimpta). While this imbalance might suggest subject or physician level unblinding, this imbalance was only prominent in Study G2301, and there was broad consistency in the statistically significant efficacy outcome results from both trials, including independently evaluated clinical and radiological outcomes which would not be impacted by this potential unblinding. Aside from this numerical discrepancy, there is no evidence that there was patient or investigator unblinding nor that unblinding by any party significantly influenced the outcome results in these trials.

Primary Outcome Measure

ARR was analyzed using a negative binomial regression model with treatment and region as factors; the number of relapses in previous year, baseline EDSS score, baseline number of gadolinium-enhancing T1 lesions, and the patient's age

at baseline were covariates. The patient's time in study was calculated in a manner to correct for the fact that patients would not all be enrolled in the study for the same durations due to the study design.

In Study G2301, there were 79 patients treated with Kesimpta who experienced a total of 90 confirmed relapses during the randomized controlled trial; there were 132 patients treated with teriflunomide who had a total of 177 confirmed relapses. There was a similar rate of relapse confirmation in both treatment arms.

The following table, adapted from the biometrics review, provides the results of the primary efficacy analysis:

Table 1: Study G2301: Summary of Annualized Relapse Rate (ARR)

	Kesimpta 20 mg N=465	Teriflunomide 14 mg N=462
Adjusted ARR (95% confidence interval)	0.11 (0.09, 0.14)	0.22 (0.18, 0.26)
Rate ratio (95% confidence interval)	0.495 (0.374, 0.654)	
Percentage reduction	50.5%	
p-value*	<0.001	

*This endpoint was analyzed in a negative binomial model.
Source: Biometrics Review, Table 8

The primary efficacy analysis of Study G2301 was statistically significant (p<0.001) in favor of Kesimpta in patients with relapsing forms of MS. Drs. Rodichok and Ling agree that the ARR outcome of the primary efficacy analysis is convincing evidence of a significant treatment effect of Kesimpta that exceeds the established efficacy of teriflunomide in the prevention of relapses in MS.

Dr. Ling confirmed the findings of all of the applicant's pre-planned sensitivity analyses. The statistical analysis plan stipulated that primary analysis was to be repeated to include all reported MS relapses (confirmed or unconfirmed). The primary analysis was also repeated using a "per-protocol" data set to provide an analysis of on-treatment data from

patients who had no major protocol violations. In this analysis, only relapses with a start date during the on-treatment period were included, in comparison with the primary analysis which used all available data up to the end of treatment epoch date, irrespective of on or off study treatment. Additionally, the time-to-first relapse was analyzed in a Cox proportional hazards model. Dr. Ling confirmed that the ARR results remained highly significant in all of these prespecified analyses and confirmed that the analysis of time-to-first relapse showed significantly longer time-to-first relapse in Kesimpta-treated patients.

The biometrics reviewer also confirmed the applicant's results from exploratory subgroup analyses for age, gender, race, and region. The confirmed findings demonstrate that Kesimpta treatment had a significantly greater treatment effect on ARR than teriflunomide in all of these subgroups, and the subgroup findings were consistent with the overall primary outcome analysis.

Secondary Outcome Measures

GdE T1 Lesions and New or Enlarging T2 Lesions

The following tables, adapted from the biometrics review, provides the confirmed results of the secondary outcome efficacy analyses of MRI outcomes (T1 GdE lesions and new or enlarging T2 lesions):

Table 2: Study G2301: Summary of GdE T1 Lesions

	Kesimpta 20 mg N=465	Teriflunomide 14 mg N=462
Adjusted Mean Number of T1 GdE Lesions per Scan (95% confidence interval)	0.01 (0.006, 0.022)	0.45 (0.356, 0.575)
Rate ratio (95% confidence interval)	0.025 (0.013, 0.049)	
Percentage rate reduction	97.5%	
p-value*	<0.001	

*This endpoint was analyzed in a negative binomial model.

Source: Biometrics Review, Table 9

Table 3: Study G2301: Summary of New or Enlarging T2 Lesions

	Kesimpta 20 mg N=465	Teriflunomide 14 mg N=462
Adjusted Mean Number of New/enlarging T2 lesions per Scan (95% confidence interval)	0.72 (0.61, 0.85)	4.00 (3.47, 4.61)
Rate ratio (95% confidence interval)	0.18 (0.15, 0.22)	
Percentage rate reduction	82.0%	
p-value*	<0.001	

*This endpoint was analyzed in a negative binomial model.
Source: Biometrics Review, Table 10

The MRI outcome findings show a robust statistically significant treatment effect of Kesimpta on GdE T1 and new or enlarging T2 lesions on MRI scans. These MRI outcomes provide additional support for a treatment effect of Kesimpta as evidenced by the highly significant primary outcome analysis finding of a reduction in ARR and the prevention of disability worsening discussed below.

Neurofilament Light Chain
The following table, taken from the biometrics review, summarizes the findings of neurofilament light chain serum concentrations at month 3:

Table 4: Study G2301: Neurofilament Light Chain Concentrations at Month 3

	Kesimpta 20 mg N=465	Teriflunomide 14 mg N=462
Adjusted Mean Concentration at Month 3 (95% confidence interval)	8.80 (8.48, 9.12)	9.41 (9.06, 9.77)
Ratio (95% confidence interval)	0.93 (0.89, 0.98)	
p-value*	0.011	

*This endpoint was analyzed using a repeated measures mixed effects model.
Source: Biometrics Review, Table 11

The applicant provided data demonstrating that serum levels of neurofilament light chain at month 3 were statistically different between the two treatment arms. The use of neurofilament light chain as a potential serum marker of neuronal injury is speculative. The specificity and interpretability of serum neurofilament levels are not clear because many neurological diseases and insults yield similar changes in serum neurofilament light chain levels, and there is no consensus opinion regarding what represents an "abnormal" finding in this laboratory assessment. Serum measurement

of neurofilament light chain is not an established, accepted biomarker for MS. This finding is reported for completeness because it was within the applicant's hierarchical analysis, but discussion of this finding is not an endorsement of this measurement as an acceptable regulatory endpoint nor is this finding considered to represent substantial evidence of efficacy.

Percent Change in Brain Volume from Baseline
The following table, taken from the biometrics review, summarizes the change in brain volume from baseline:

Table 5: Study G2301: Percent Change in Brain Volume from Baseline

	Kesimpta 20 mg N=465	Teriflunomide 14 mg N=462
Annual Rate of Change from Baseline (95% confidence interval)	-0.28 (-0.34, -0.22)	-0.35 (-0.41, -0.29)
Difference (95% confidence interval)	0.07 (-0.02, 0.15)	
p-value*	0.116	

*This endpoint was analyzed using a random coefficients model.
Source: Biometrics Review, Table 12

The percent change in brain volume was not statistically different between the Kesimpta and teriflunomide treatment arms.

Study G2302

Demographics
In Study G2302, the ITT population comprised nine hundred and fifty-five (955) patients who were randomized to treatment, 481 to treatment with Kesimpta and 474 to treatment with teriflunomide. Patients enrolled from 180 centers in

30 countries worldwide. Most (69.9%) of the enrolled patients came from Eastern Europe, and 20.9% came from the United States.

The ITT population in Study G2302 was 66.8% female, had both a median and a mean age of approximately 38 years old, and 87.4% of the patients were White. These demographic data are entirely consistent with the well-established demographics of the worldwide population diagnosed with a relapsing form of MS. The ITT population were adequately balanced between treatment arms with respect to key demographic and baseline disease variables.

In this study, 80% of the Kesimpta group and 78.5% of the teriflunomide group, respectively, completed study on treatment. As in Study G2301, the most frequent reasons for treatment discontinuation in the Kesimpta treatment arm in Study G2302 were patient/guardian decision (7.3%), physician decision (5.2%), and adverse event (5.6%). There was less of an imbalance between the overall discontinuation rates (20.0% and 21.5%) in the Kesimpta and teriflunomide conditions, as well as a relative lack of discrepancy between the combined physician and subject decision discontinuation rates (12.7% and 14.6%) in Study G2302.

Primary Outcome Measure

ARR was analyzed using a negative binomial regression model with treatment and region as factors; the number of relapses in previous year, baseline EDSS score, baseline number of GdE T1 lesions, and the patient's age at baseline were covariates. The patient's time in study was calculated in a manner to correct for the fact that patients would not all be enrolled in the study for the same durations due to the study design.

In Study G2302, there were 72 patients treated with Kesimpta who experienced a total of 95 confirmed relapses during the randomized controlled trial; there were 138 patients treated with teriflunomide who had a total of 198 confirmed relapses. The relapse confirmation rate was similar in both treatment arms.

The following table, adapted from the biometrics review, provides the results of the primary efficacy analysis:

Table 6: Study G2302: Summary of Annualized Relapse Rate (ARR)

	Kesimpta 20 mg N=465	Teriflunomide 14 mg N=462
Adjusted ARR (95% confidence interval)	0.10 (0.08, 0.13)	0.25 (0.21, 0.30)
Rate ratio (95% confidence interval)	0.415 (0.308, 0.559)	
Percentage reduction	58.5%	
p-value*	<0.001	

*This endpoint was analyzed in a negative binomial model.
Source: Biometrics Review, Table 13

The primary efficacy analysis of Study G2302 was statistically significant ($p<0.001$) in favor of Kesimpta in patients with relapsing forms of MS. Drs. Rodichok and Ling agree that the ARR outcome of the primary efficacy analysis is convincing evidence of a significant treatment effect of Kesimpta that exceeds the established efficacy of teriflunomide in the prevention of relapses in MS. The findings are nearly identical to the findings from Study G2301 which confirms the treatment effect is robust and consistent.

Dr. Ling confirmed the findings of all of the applicant's pre-planned sensitivity analyses. The statistical analysis plan stipulated that primary analysis was to be repeated to include all reported MS relapses (confirmed or unconfirmed). The primary analysis was also repeated using a "per-protocol" data set to provide an analysis of on-treatment data from patients who had no major protocol violations. In this analysis, only relapses with a start date during the on-treatment period were included, in comparison with the primary analysis which used all available data up to the end of treatment epoch date, irrespective of on or off study treatment. Additionally, the time-to-first relapse was analyzed in a Cox proportional hazards model. Dr. Ling confirmed that the ARR results remained highly significant in all of these prespecified analyses and confirmed that the analysis of time-to-first relapse showed significantly longer time-to-first relapse in Kesimpta-treated patients.

The biometrics reviewer also confirmed the applicant's results from exploratory subgroup analyses for age, gender, race, and region. The confirmed findings demonstrate that Kesimpta treatment had a significantly greater treatment effect on ARR than teriflunomide in all of these subgroups, and the subgroup findings were consistent with the overall primary outcome analysis.

Secondary Outcome Measures

GdE T1 Lesions and New or Enlarging T2 Lesions

The following tables, adapted from the biometrics review, provides the confirmed results of the secondary outcome efficacy analyses of MRI outcomes (T1 GdE lesions and new or enlarging T2 lesions):

Table 7: Study G2302: Summary of GdE T1 Lesions

	Kesimpta 20 mg N=465	Teriflunomide 14 mg N=462
Adjusted Mean Number of T1 GdE Lesions per Scan (95% confidence interval)	0.03 (0.021, 0.048)	0.51 (0.402, 0.658)
Rate ratio (95% confidence interval)	0.062 (0.037, 0.101)	
Percentage rate reduction	93.8%	
p-value*	<0.001	

*This endpoint was analyzed in a negative binomial model.

Source: Biometrics Review, Table 14

Table 8: Study G2302: Summary of New or Enlarging T2 Lesions

	Kesimpta 20 mg N=465	Teriflunomide 14 mg N=462
Adjusted Mean Number of New/enlarging T2 lesions per Scan (95% confidence interval)	0.64 (0.55, 0.75)	4.15 (3.64, 4.74)
Rate ratio (95% confidence interval)	0.15 (0.13, 0.19)	
Percentage rate reduction	84.5%	
p-value*	<0.001	

*This endpoint was analyzed in a negative binomial model.
Source: Biometrics Review, Table 15

As in Study G2302, the MRI outcome findings for Study G2302 demonstrate a robust, statistically significant treatment effect of Kesimpta on GdE T1 and new or enlarging T2 lesions on MRI scans. These MRI outcomes provide additional support for a treatment effect of Kesimpta as evidenced by the highly significant replicated primary outcome analysis finding of a reduction in ARR and the prevention of disability worsening discussed below.

Neurofilament Light Chain
The following table, taken from the biometrics review, summarizes the findings of neurofilament light chain serum concentrations at month 3:

Table 9: Study G2302: Neurofilament Light Chain Concentrations at Month 3

	Kesimpta 20 mg N=465	Teriflunomide 14 mg N=462
Adjusted Mean Concentration at Month 3 (95% confidence interval)	8.92 (8.62, 9.23)	10.02 (9.68, 10.36)
Ratio (95% confidence interval)	0.89 (0.85, 0.93)	
p-value*	<0.001	

*This endpoint was analyzed using a repeated measures mixed effects model.
Source: Biometrics Review, Table 16

The applicant provided data demonstrating that serum levels of neurofilament light chain at month 3 were statistically different between the two treatment arms. This laboratory assessment is not an accepted outcome measure providing meaningful information regarding any aspect of relapsing forms of MS. Refer to the discussion of this outcome measure in Study G2301 for further elaboration.

Percent Change in Brain Volume from Baseline

The following table, taken from the biometrics review, summarizes the change in brain volume from baseline:

Table 10: Study G2302: Percent Change in Brain Volume from Baseline

	Kesimpta 20 mg N=465	Teriflunomide 14 mg N=462
Annual Rate of Change from Baseline (95% confidence interval)	-0.29 (-0.35, -0.23)	-0.35 (-0.42, -0.29)
Difference (95% confidence interval)	0.07 (-0.02, 0.15)	
p-value*	0.129	

*This endpoint was analyzed using a random coefficients model.

Source: Biometrics Review, Table 17

The percent change in brain volume was not statistically different between the Kesimpta and teriflunomide treatment arms.

Pooled Disability Outcome Findings

As per prior agreement, the disability-related key secondary outcome assessments of disability at 3-month and 6-months were to be based on analyses of the pooled data from Studies G2301 and G2302 because each individual trial would not be adequately powered to provide individual study outcome analyses of these relatively small number of outcomes.

3-month Confirmed Disability Worsening

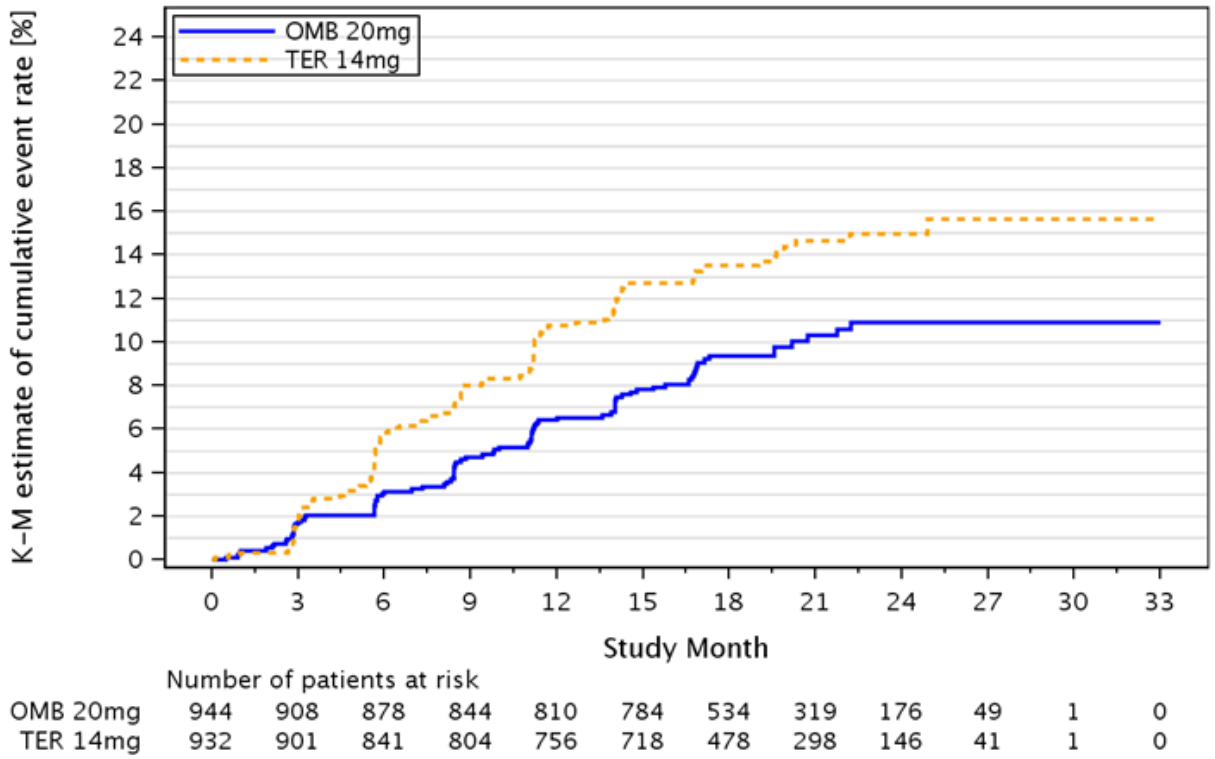
The following table and figure, taken from the biometrics review, summarizes the time to 3-month confirmed disability worsening in both trials:

Table 11: Studies G2301 and G2302: Time to 3-month Confirmed Disability Worsening

Studies G2301 + G2302	KM Estimate at Month 24 (95% Confidence Interval)	n/N (%)	Hazard Ratio (95% Confidence Interval)	Risk Reduction	p-value
Kesimpta 20 mg	10.9 (8.8, 13.4)	88/944 (9.3%)	0.656 (0.499, 0.862)	34.4%	0.002
Teriflunomide 14 mg	15.0 (12.6, 17.7)	125/931 (13.4%)			

Source: Biometrics review, Table 18

Figure 2: Studies G2301 and G2302: Time to 3-Month Confirmed Disability Worsening



Source: Biometrics review, Figure 3

The time to 3-month disability worsening was statistically significant (p=0.002) in favor of Kesimpta treatment. Patients treated with Kesimpta had a lower rate of confirmed 3-month disability worsening as compared to patients treated with teriflunomide. Even though the individual studies were not powered for this endpoint, analysis of Study G2301 and G2302 individually yielded statistically significant results for the 3-month disability worsening endpoint (p=0.029 and p=0.036, respectively.) In prior clinical trials, teriflunomide reduced the confirmed disability progression at a 3-month interval relative to placebo; Kesimpta is therefore demonstrating superiority over a treatment that has a significant effect on disability progression in relapsing forms of MS.

The biometrics reviewer confirmed the findings of the pre-specified secondary outcome analysis and several sensitivity analyses including a "worst-case" analysis in which Kesimpta-treated patients who discontinued from the study due to lack of efficacy were considered as having a confirmed 3-month disability worsening outcome (a risk reduction for ofatumumab vs. teriflunomide of 32.9%, p=0.004). The confirmed sensitivity analyses replicated the pre-specified analysis result, which is a significant effect on prevention of 3-month disability worsening in patients treated with Kesimpta.

6-month Confirmed Disability Worsening

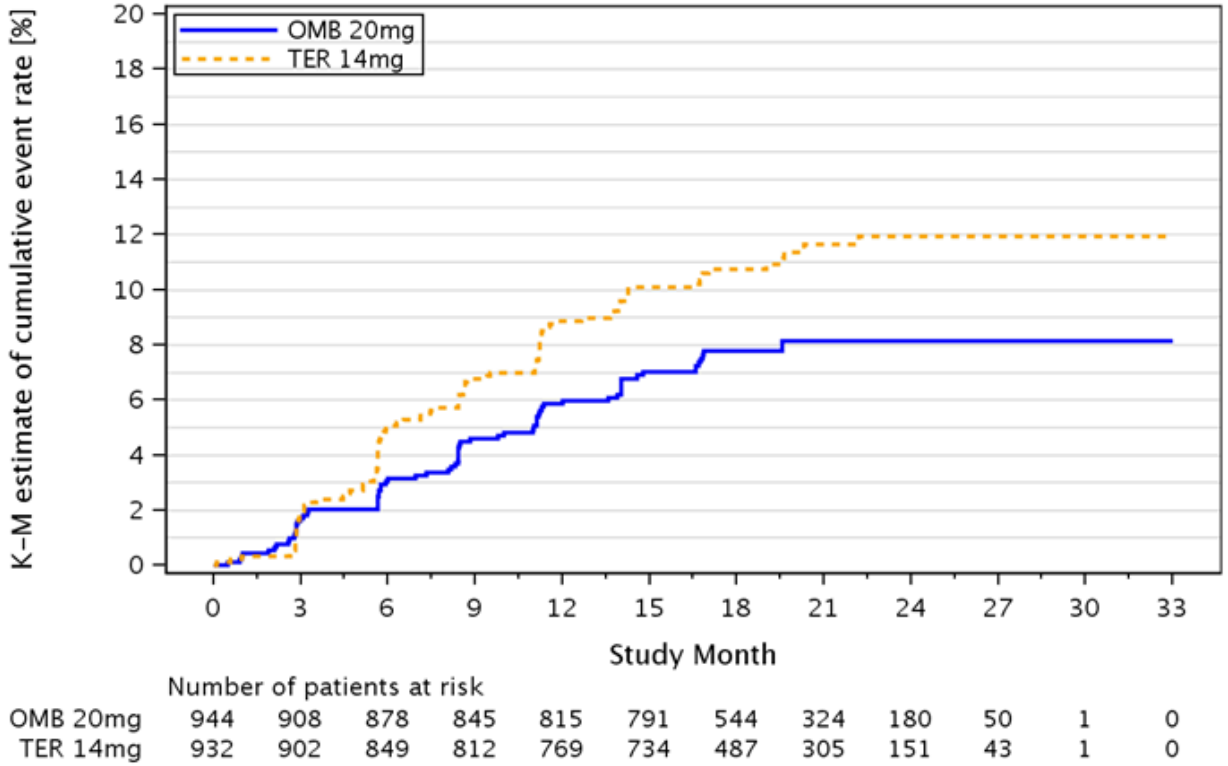
The following table and figure, taken from the biometrics review, summarizes the time to 6-month confirmed disability worsening in both trials:

Table 12: Studies G2301 and G2302: Time to 6-month Confirmed Disability Worsening

Studies G2301 + G2302	KM Estimate at Month 24 (95% Confidence Interval)	n/N (%)	Hazard Ratio (95% Confidence Interval)	Risk Reduction	p-value
Kesimpta 20 mg	8.1 (6.5, 10.2)	71/944 (7.5%)	0.675 (0.498, 0.916)	32.5%	0.012
Teriflunomide 14 mg	12.0 (9.9, 14.5)	99/931 (10.6%)			

Source: Biometrics review, Table 18

Figure 3: Studies G2301 and G2302: Time to 6-Month Confirmed Disability Worsening



Source: Biometrics review, Table 4

The time to 6-month disability worsening was statistically significant (p=0.012) in favor of Kesimpta treatment. Patients treated with Kesimpta had a lower rate of confirmed 6-month disability worsening as compared to patients treated with teriflunomide. Even though the individual studies were not powered for this endpoint, analysis of Study G2301 and G2302 individually yielded statistically significant results for the 6-month disability worsening endpoint for Study G2301 (p=0.022) but the result for Study G2302 was not significant (p=0.209). In clinical trials, teriflunomide reduced the confirmed disability worsening relative to placebo; in the pooled analysis, Kesimpta is therefore demonstrating superiority over a treatment that has a significant effect on disability worsening in relapsing forms of MS.

The biometrics reviewer confirmed the findings of the pre-specified secondary outcome analysis and several sensitivity analyses including a "worst-case" analysis in which Kesimpta-treated patients who discontinued from the study due to lack of efficacy were considered as having a confirmed 6-month disability worsening outcome (a risk reduction for ofatumumab vs. teriflunomide of 29.6%, p=0.022). The confirmed sensitivity analyses largely replicated the pre-specified analysis result, which is a significant effect on prevention of 6-month disability worsening in patients treated with Kesimpta.

6-month Confirmed Disability Improvement

The following table and figure, taken from the biometrics review, summarizes the time to 6-month confirmed disability improvement in both trials:

Table 13: Studies G2301 and G2302: Time to 6-month Confirmed Disability Improvement

Studies G2301 + G2302	KM Estimate at Month 24 (95% Confidence Interval)	n/N (%)	Hazard Ratio (95% Confidence Interval)	Risk Reduction	p-value
Kesimpta 20 mg	11.0 (8.8, 13.7)	74/749 (9.9%)	1.352 (0.950, 1.924)	-35.2	0.094
Teriflunomide 14 mg	8.1 (6.2, 10.6)	53/723 (7.3%)			

Source: Biometrics review, Table 22

The analysis of confirmed disability improvement at 6-months was not statistically significant (p=0.094).

Conclusions on the Substantial Evidence of Effectiveness

Approval for Kesimpta (ofatumumab) for relapsing forms of MS is supported by efficacy findings from two adequate and well-controlled clinical trials, Studies G2301 and G2302. These studies demonstrated that Kesimpta treatment yielded consistent statistically significant reductions of over 50% (50.5% and 58.5%) in ARR relative to an active comparator,

teriflunomide. A reduction of over 50% in ARR is a robust and meaningful outcome for a therapeutic to treat relapsing forms of MS; in these studies, a significant treatment effect on ARR is established relative to teriflunomide, an active comparator with its own significant treatment effect on ARR. The significant MRI findings in these two studies provide additional supportive findings for the primary clinical outcome analysis. With respect to the primary efficacy endpoint, these studies have provided substantial evidence of effectiveness for Kesimpta in the treatment of patients with relapsing forms of MS and a strong treatment effect on relapses.

The disability assessment outcomes from Studies G2301 and G2302 support the conclusion that Kesimpta is superior to the active comparator with respect to reducing the likelihood of confirmed disability worsening. Various sensitivity analyses demonstrate that this effect on disability worsening is independent of relapse occurrences in the trial and is maintained through more conservative sensitivity analyses that assume worsening with missing final confirmation assessments. Drs. Rodichok and Ling note that the applicant's methodology for calculating disability "worsening" at both time points differed from the conventions used for some historical assessments of confirmed disability "progression" in other development programs. Dr. Rodichok asked for, via an information request, an exploratory analysis from the applicant that utilized calculation methods excluding patient relapse visits as events that initiated or confirmed EDSS progression assessment and assumed patients with any worsening, but without confirmation of disability visits, had confirmed disability progression. The results of this exploratory analysis were confirmed by Dr. Ling and are discussed in the biometrics review. This confirmed disability progression analysis is conservative, even more so than the "worst case" scenario in the applicant's sensitivity analyses, but the findings from this analysis remained significant for the 3-month confirmed disability progression endpoint (nominal p=0.012) and revealed a strong trend (nominal p=0.074) for the 6-month confirmed disability progression endpoint. Thus, the requested exploratory analysis of outcomes using this conservative approach were consistent with the applicant's primary analysis and did not suggest that the applicant's findings regarding disability worsening were driven entirely by relapses and absent confirmatory visits. Finally, the Division requested an analysis that allowed a clinical relapse to occur at the initiation of a disability progression, but excluded relapses that occurred within 30 days of a disability worsening confirmation visit for the 3- month disability confirmation endpoint. This analysis, verified by biometrics reviewer, again demonstrates a significant effect of Kesimpta on disability progression at 3 months (relative risk reduction of 34.9%, nominal p=0.002) in comparison to teriflunomide. The findings of this exploratory analysis are nearly identical to the prespecified primary analysis findings, and this

analysis aligns with the Division's current approach to disability outcome assessment. Thus, there is confidence that the robust treatment effect on disability progression from the applicant's pre-specified primary analysis that is described in Section 14 of the labeling is comparable to the disability progression outcomes obtained in both historical and contemporary analyses, regardless of the differences in the definition of progression and how relapses were considered within the analytical methods.

Furthermore, disability worsening or progression as an endpoint is considered to be a singular concept. A treatment effect that prevents an increase in disability as measured by EDSS over 3 months and 6 months represents only a difference in time of observed persistence, not an achievement of a treatment effect on two entirely unrelated, unique, clinically relevant outcomes. Achieving a significant finding on a single disability outcome, or both 3-month and 6-month outcomes, represents the same fundamental finding, that is, a relative prevention of a clinically relevant accumulation of disability over a quantum of time. (b) (4)

(b) (4)

6. Safety

According to Dr. Rodichok's review, 1230 unique patients with MS were exposed to at least one dose of Kesimpta of at least 20 mg via any route in the MS development program. Of these 1230 patients, 946 patients in Studies G2301 and G2302 were exposed to the 20 mg subcutaneous dose proposed for the treatment of relapsing forms of MS; the remaining 284 patients were exposed to Kesimpta in the other antecedent studies within this program, at doses ranging from 20-60 mg. The comparator in Studies G2301 and G2302 was teriflunomide, an approved therapy for relapsing forms of MS with its own well characterized safety profile. While ofatumumab is approved for treatment of CLL, Dr. Rodichok's safety review focused on any safety signals in patients with relapsing forms of MS because the studies in CLL used to support ofatumumab's use in CLL were obtained in the setting of a substantially higher intravenous dose along with the

concurrent use of multiple potent immune suppressing agents, and, therefore, the applicability of the existing labeled warnings and safety findings was limited.

The following table, adapted from a table in Dr. Rodichok's review, summarizes the extent of exposure to Kesimpta in the applicant's development program for relapsing forms of MS:

Table 14: Kesimpta Safety Population Duration of Exposure

Duration of Exposure	Kesimpta (N=1230)
≥ 6 months	889
≥ 12 months	824
≥ 18 months	551
All Exposed ≥ 1 dose	1230

Source: Clinical Safety Review, Table 57

The safety database consisting of 1230 exposed patients is adequate with respect to number exposed and duration of exposure (824 patients exposed for at least 1 year and 1555 patient-years of cumulative experience overall) for generating meaningful safety conclusions regarding the MS indication. Two-thirds (66.7%) of the patients in these studies were women, 58.1% were less than 40 years old, and 88.1% were White, all of which are to be expected for studies of relapsing forms of MS because of the disease's typical and well-known demographics.

Deaths

There were no deaths reported in ofatumumab-exposed patients in the MS development program.

Serious Adverse Events

Despite identical designs and largely similar serious adverse event (SAE) findings, Studies G2301 and G2302 are discussed separately due to a notable difference in the findings between the two studies.

Study G2301

In Study G2301, SAEs occurred in 48/466 patients (10.3%) treated with Kesimpta and in 38/463 patients (8.2%) treated with teriflunomide. The most frequently reported SAEs, categorically, were infections and infestations (2.6% vs. 1.5% in teriflunomide comparator arm), psychiatric disorders (1.9% vs. 0%), and injury, poisoning, and procedural complications (1.3% vs. 0.2%). The most often reported infections were appendicitis (which occurred in three patients treated with Kesimpta and one patient treated with teriflunomide) and gastroenteritis (which occurred in two patients treated with Kesimpta versus no teriflunomide-treated patients). Increased risk of infections, including serious infections, is a known consequence of immune suppression achieved with anti-CD20 treatments, generally, and with ofatumumab, specifically. Labeling for risks of infection and warning against the use of Kesimpta in patients with active infections should be adequate to mitigate this serious issue. The increased rate of procedural complications was attributable to a higher rate of injection-related reactions in the Kesimpta treatment group, which is expected in comparison to a comparator arm which featured an inert injection.

There were nine serious psychiatric adverse events in the Kesimpta treatment arm of Study G2301, but no serious psychiatric events were reported in the teriflunomide treatment arm. Two of the psychiatric SAEs were suicidal ideation; the remaining psychiatric SAEs were isolated events such as stress, suicidal depression, depression, and a suicide attempt. There were no deaths by suicide in the MS development program, and suicide assessments collected routinely during these trials did not reveal an increased suicidality signal in Kesimpta-treated patients. Dr. Rodichok also notes that there was not a disproportionate number of psychiatric SAEs for Kesimpta-treated patients in the other MS and non-MS trials with ofatumumab which argues against ofatumumab as the specific unique explanation for this outcome. Monoclonal antibody anti-CD20 therapies would not be expected to cross the blood-brain barrier and directly interact with the central nervous system to potentiate a centrally-mediated neuropsychiatric adverse event. Additionally, high dose ofatumumab has not been associated with more psychiatric adverse events in CLL patients treated with Arzerra. In response to an information request, the applicant provided an analysis of psychiatric adverse events that confirmed Dr. Rodichok's analysis and did not support the hypothesis that Kesimpta was associated with increased risk of psychiatric adverse events. Depression, anxiety, and suicide are common in patients with the diagnosis of MS and are reported to be several-fold more likely to occur in patients with MS than in the general population. Therefore, this apparent increase in

psychiatric SAE findings appears reflective of the known psychiatric sequelae of MS, overrepresented by chance in the Kesimpta treatment arm, and very unlikely to be a treatment-emergent effect.

Study G2302

In Study G2302, SAEs occurred in 38/481 patients (7.9%) treated with Kesimpta and in 36/474 patients (7.6%) treated with teriflunomide. As in Study G2301, two of the most common categories of SAEs were infections and procedural complications (injection-site reactions), but the risks of these categories of SAEs were more balanced in this study than in Study G2301 between the Kesimpta and teriflunomide treatment arms at 2.5% vs. 2.1%, and 1.5% vs. 1.7%, respectively. Appendicitis was again the most common infection noted in 5 patients treated with Kesimpta and 1 patient treated with teriflunomide. As discussed, an imbalance in suicidal depression/ideation in Kesimpta-treated patients was not reported in Study G2302.

Most SAEs in these trials were isolated events, and, aside from the general patterns noted above, the safety database did not identify other broad categories of serious risks nor any new signals previously unseen in association with ofatumumab.

Interruptions and Discontinuations

During Studies G2301 and G2302, 5.8% of patients treated with Kesimpta and 5.2% of patients treated with teriflunomide discontinued treatment. The most common reason for discontinuation of therapy, reported in over half of the 5.8% of patients who discontinued Kesimpta treatment in both studies, was decreased serum immunoglobulins. By contrast, less than 1% of patients ended teriflunomide because of low serum immunoglobulins. Per protocol, patients with serum immunoglobulin M (IgM) less than 10% of the lower limit of normal or immunoglobulin G (IgG) less than 20% of the lower limit of normal were to discontinue treatment. A reduction in serum immunoglobulins is not unexpected with anti-CD20 therapy such as ofatumumab because anti-CD20 therapy selectively targets B-lymphocytes, the immune cells that secrete immunoglobulins. Further, there is an established direct relationship between CD20 inhibition using monoclonal antibodies and a relatively acute downregulation of IgM release from B-cells. Dr. Rodichok notes in his review of laboratory findings that the median serum reduction in serum IgM of 28% (versus 17% noted with teriflunomide treatment) occurs early in treatment (within 90 days of therapy initiation) with Kesimpta. The IgM reduction appears

relatively selective for IgM and was not noted as consistently with IgG. In patients who completed 96 weeks of treatment, the mean decrease in IgM was approximately 40% vs. 20% for teriflunomide treated patients at the same time point. Given the observation that IgM reduction appears to increase over longer durations of treatment, there is concern that the longest observation duration for patients in the MS development program, approximately 30 months, is not sufficient to determine the nadir of this IgM reduction. Published data from similar B-cell precursor depleting therapies (i.e., rituximab, ocrelizumab) suggest that chronic administration of anti-CD20 B-cell depleting monoclonal antibodies causes serial B-cell precursor depletion that eventually impacts the pool of mature plasma cells that maintain the serum IgM and IgG pools necessary to prevent recurrent or serious infections. Based on the controlled trial findings for Kesimpta, low IgM was the most common cause of discontinuation of treatment within 2 years of therapy, and if the IgM or IgG continued to worsen over years of further treatment, hypogammaglobulinemia could yield clinically significant immune suppression and recurrent or serious infections that may limit longitudinal therapy in some patients. Since ofatumumab is administered as a short-term therapy to treat CLL, there are no comparable longitudinal data from previous ofatumumab experience to inform this potential safety risk. Therefore, labeling needs to warn of the observed IgM reduction, advise of a need for immunoglobulin screening, and that a postmarketing study to evaluate IgM and IgG in patients with MS receiving chronic Kesimpta is needed to clarify the consequences of B-cell depletion associated with ofatumumab. The goal of this postmarketing requirement would be to identify whether the immunoglobulin levels in patients reach a consistent nadir, to identify whether there are more patients who may require exogenous immunoglobulins to treat hypogammaglobulinemia and recurrent opportunistic infections, and to identify the timetable for recovery of immunoglobulins in patients who discontinue therapy.

Treatment-Emergent Adverse Events

The following tables, adapted from Dr. Rodichok's safety review, summarize the most common treatment-emergent adverse events that occurred in clinical trial subjects in Studies G2301 and G2302:

Table 15: Treatment Emergent Adverse Events by Preferred Term, End of Study+100 days, Occurring in 5% or More in Either Treatment Group, Study G2301

Adverse Event Preferred Term	Kesimpta 20 mg (n=465)	Teriflunomide 14 mg (n=462)
Nasopharyngitis	82 (17.6%)	69 (14.9%)
Injection related reaction	76 (16.3%)	77 (16.7%)
Headache	57 (12.3%)	51 (11.0%)
Upper respiratory tract infection	48 (10.3%)	73 (15.8%)
Fatigue	46 (9.9%)	40 (8.7%)
Urinary tract infection	42 (9.0%)	41 (8.9%)
Injection site reaction	42 (9.0%)	26 (5.6%)
Back pain	37 (8.0%)	34 (7.4%)
Influenza	32 (6.9%)	29 (6.3%)
Nausea	31 (6.7%)	32 (6.9%)
Alopecia	27 (5.8%)	64 (13.9%)
Blood immunoglobulin M decreased	26 (5.6%)	13 (2.8%)
Arthralgia	25 (5.4%)	23 (5.0%)
Diarrhea	21 (4.5%)	62 (13.4%)
Pain in extremity	23 (4.9%)	36 (7.8%)
Paresthesia	16 (3.4%)	31 (6.7%)
Hypertension	15 (3.2%)	24 (5.2%)

Source: Clinical Safety Review, Table 71

Table 16: Treatment Emergent Adverse Events by Preferred Term, End of Study+100 days, Occurring in 5% or More in Either Treatment Group, Study G2302

Adverse Event Preferred Term	Kesimpta 20 mg (n=481)	Teriflunomide 14 mg (n=474)
Injection related reaction	119 (24.7%)	66 (13.9%)
Nasopharyngitis	88 (18.3%)	87 (18.4%)
Headache	69 (14.3%)	65 (13.7%)
Injection site reaction	61 (12.7%)	26 (5.5%)
Urinary tract infection	55 (11.4%)	37 (7.8%)
Upper respiratory tract infection	49 (10.2%)	47 (9.9%)
Back pain	35 (7.3%)	24 (5.1%)
Blood immunoglobulin M decreased	30 (6.2%)	8 (1.7%)
Influenza	30 (6.2%)	30 (6.3%)
Nausea	30 (6.2%)	32 (6.8%)
Diarrhea	28 (5.8%)	49 (10.3%)
Anxiety	28 (5.8%)	18 (3.8%)
Alopecia	27 (5.6%)	74 (15.6%)
Fatigue	25 (5.2%)	32 (6.8%)
Insomnia	24 (5.0%)	19 (4.0%)
Depression	24 (5.0%)	24 (5.1%)
Arthralgia	24 (5.0%)	21 (4.4%)
Pain in extremity	23 (4.8%)	30 (6.3%)
Hypertension	20 (4.2%)	31 (6.5%)

Source: Clinical Safety Review, Table 73

Adverse Events of Special Interest and Special Safety Concerns

Serious Infections

As noted above, infections were among the most common adverse events in the two controlled clinical trials in patients with MS. Ofatumumab is an immune suppressant; ofatumumab treatment is expected to confer an increased risk of infection. Labeling can advise prescribers and patients of this potential adverse event as it does for Arzerra. Enhanced pharmacovigilance for serious infections will provide expedited reporting to identify risks in postmarketing that were not noted in the clinical trials.

The risk of progressive multifocal leukoencephalopathy (PML), identified with Arzerra, should be included among the labeling risks for Kesimpta. PML is a serious potentially serious, potentially fatal, opportunistic infection. PML occurred with ofatumumab given for a shorter duration (but at a higher dose) in patients with CLL, but PML is an identified risk associated with other MS therapies, including the anti-CD20 treatment ocrelizumab, and therefore a significant potential exists for PML occurring with chronic use of Kesimpta.

Dr. Rodichok notes that Arzerra has a boxed warning for reactivation of hepatitis B infection. In patients with refractory CLL, hepatitis B virus reactivation would represent a severe and life-threatening event in a patient being treated with multiple concurrent immune suppressants and merits a boxed warning in that setting (medically fragile patients with an ablated immune system). However, there were no hepatitis reactivation cases in the Kesimpta development program. Ocrelizumab (an anti-CD20 therapy like ofatumumab) with a labeled risk of hepatitis B reactivation based on observed cases does not convey that risk in a boxed warning because the severity of cases with reactivated hepatitis B did not merit such a significant elevation in the warning. Because of the lack of observed hepatitis reaction in patients with MS treated in this development program, and the relative immune competence in typical MS patients as compared to patients with CLL, there is insufficient basis for a boxed warning for hepatitis reactivation in the Kesimpta labeling as there is in the Arzerra labeling. Even without hepatitis B cases occurring in the MS program, based on the CLL development program safety database and the postmarketing experience of other anti-CD20 mAbs, there exists a potential for reactivation of hepatitis B in patients with MS treated with Kesimpta that merits a labeling warning and a contraindication for use in

patients with active hepatitis B infection. Finally, hepatitis B infection status should be assessed before beginning Kesimpta treatment.

The observed, and expected, risks of serious and opportunistic infections associated with Kesimpta appear similar to other approved therapies for relapsing forms of MS and do not preclude approval.

Injection-related Reactions

Arzerra's labeling lists a warning and precaution for infusion-related reactions, advises a premedication regimen, and states that 67% of patients experienced any infusion-related reaction, with 10% of those reactions being Grade 3 or higher in severity. However, Arzerra is infused via the intravenous route at a higher administered dose than Kesimpta, which is administered subcutaneously. According to Dr. Rodichok's review, a treatment-emergent adverse event with the preferred term of "injection-related reaction" occurred in 20.6% of subjects treated with Kesimpta as compared to 15.2% of those who received a placebo dummy injection. Most patients treated with Kesimpta who experienced a reaction reported this adverse event on the first day (84%) or second day (13%) of administration. There were two patients treated with Kesimpta who experienced a serious injection-related event; neither of these events was life-threatening and both events responded to treatment without a need for hospitalization. One patient each in the Kesimpta and dummy treatment groups discontinued treatment due to injection-related reactions in the Phase 3 trials. According to Dr. Rodichok's analysis, premedication with steroids (6.9% vs. 6.9%) or with non-steroidal anti-inflammatory treatments (4.5% vs. 4.4%) reduced injection-related reactions to the same extent in both the Kesimpta and placebo-treated patients. Based on these findings, it appears ofatumumab administered via the subcutaneous route as Kesimpta yields an overall lower rate of reactions and a much lower risk of serious adverse events than ofatumumab administered intravenously as Arzerra. The rate of systemic reactions for Kesimpta is overall quite low in comparison to those reported for the other chimeric anti-CD20 therapies approved for autoimmune diseases, which is consistent with ofatumumab being a fully human antibody with less antigenic potential than murine hybrid chimeric antibodies. Premedication appears to have no significant differential impact on injection-related reactions for Kesimpta and will not be recommended as a universal measure before administration. The usually mild nature of injection-related reactions reported in these trials do not appear to pose a significant safety risk for Kesimpta's use in a home setting without medical supervision.

Safety Conclusions

Kesimpta is associated with adverse reactions, some serious, but the risks of most treatment-emergent events identified in the clinical trials undertaken in patients with MS can be reduced through minimally invasive screening, monitoring, and mitigated by discontinuation of therapy. The most common treatment-emergent adverse events, injection reactions, mild upper respiratory infection, and headache, were similar to the active comparator treatment arm, were not serious, and were not the most frequent reasons for discontinuing use of Kesimpta. Overall, the identified risks are consistent with those identified for ofatumumab in patients with refractory CLL. There were no deaths in the MS development program, and the most serious adverse events associated with Arzerra, such as hepatitis B reactivation and PML, were not reported in MS patients. There are several possible explanations for why the safety profile for Arzerra is appears to have greater risk of more serious outcomes than for Kesimpta. Patients with CLL have a serious, life-threatening illness that is considerably more acute and likely to be fatal than MS. Second, the degree of immune suppression in CLL patients is much greater than would be necessary to treat MS. The goal of the combined immunosuppressive treatment regimen for patients with CLL is total eradication of lymphocytes, as opposed to a reduction of serum B-cells below the lower limit of normal range as would be the goal with MS therapy. Aggressive rapid immune ablation using multiple agents would confer a much greater risk of serious, potentially fatal opportunistic infections than Kesimpta would. Finally, Arzerra is administered at a higher dose (albeit for a shorter duration of treatment) than Kesimpta and thus potentiates serious risks within a shorter exposure duration. This final point regarding duration of therapy is noteworthy because, while Kesimpta may be administered at a lower per administration dose than Arzerra, there is an expectation that patients will continue treatment with Kesimpta on a chronic basis for years, perhaps lifelong, which differs significantly from Arzerra's use as a short-term chemotherapy agent. It is expected that, given sufficient chronicity in a larger population of patients with MS, some safety issues associated with Kesimpta that were not apparent in the relatively short-term use in these pivotal trials will emerge. The labeling of Kesimpta therefore justifiably includes risks of PML and hepatitis B reactivation both because Arzerra has an association with these outcomes and because reactivated hepatitis B and PML have occurred in the postmarketing setting in patients treated with another anti-CD20 mAb therapy (ocrelizumab) approved to treat patients with MS. The inclusion in labeling of a need to monitor immunoglobulins is also a recognition that there is emerging evidence that chronic long-term use of mAb anti-CD20 therapies is associated with, eventually, a clinically significant depletion of immunoglobulin pools in serum, with a concurrent potential increased risk of serious infection. A postmarketing requirement to study immunoglobulins during long-term Kesimpta therapy is being imposed to allow for

further understanding of this emerging, potentially fatal, safety issue. Pregnancy registry and outcomes studies are needed because Kesimpta will be used in the MS population which is predominantly women of childbearing potential and data regarding pregnancy outcomes are limited. Furthermore, animal studies suggest *in utero* ofatumumab exposure is associated with B-cell depletion and reduced immune responses in offspring so women using Kesimpta need to use effective contraception and labeling will provide a warning to this effect. Even with these potentially serious concerns, relapsing forms of MS have serious, potentially fatal sequelae. Kesimpta is a highly effective therapy and therefore can be approved even with proven or strongly suspected serious safety risks because the disease that Kesimpta is proposed to treat, MS, remains incurable, disabling, and possibly fatal.

7. Advisory Committee Meeting

This application was not referred to an Advisory Committee for review because this biologic is not the first in its class, the safety profile is known because of its previous pre- and post-marketing experience in other indications, and is similar to that of the other biologic in this class approved for this indication, the clinical trial designs were acceptable, the efficacy findings were clear, and the safety profile was acceptable in light of the serious nature of the disease being treated. Labeling specific to the MS indication will make prescribers fully aware of the risks associated with Kesimpta treatment for MS.

8. Pediatrics

No clinical pediatric data are provided. An initial Pediatric Study Plan to study Kesimpta in patients ages 10-17 years with relapsing forms of MS that was submitted by the applicant on August 30, 2018, as required by the Pediatric Research Equity Act (PREA), was deemed acceptable. The PMR for a pediatric study is described in Section 11.

9. Other Relevant Regulatory Issues

This section may include discussion on other issues (if not addressed in previous sections):

- The Division of Medication Error Prevention and Analysis (DMEPA) provided a review of the proprietary name, "Kesimpta." Dr. Denise Baugh was the primary evaluator and Dr. Briana Rider was the team leader. The DMEPA team did not identify any potential risks with there being two proprietary names (Arzerra and Kesimpta) for ofatumumab. After a standard battery of assessments, the DMEPA team concluded that the name Kesimpta, and the name proposed for the subcutaneous delivery device ("Kesimpta Sensoready Pen") were acceptable for use.

- DMEPA provided a review of the human factors validation studies submitted with the sNDA. The applicant provided human factor validation studies of the two proposed presentations of Kesimpta, the prefilled syringe and the prefilled pen. Review of these studies identified errors and difficulties of use for which the applicant provided acceptable remedies. DMEPA provided additional recommendations to the labeling instructions for use for both presentations, with subsequent agreement by the applicant, and concluded no additional mitigation strategies were necessary to ensure safe, effective use.

- The Office of Scientific Investigations (OSI) conducted an inspection of one clinical site (Dr. Sundaram). The OSI review noted minor discrepancies associated with transcription of EDSS scores recorded at scheduled visits from paper to electronic format but concluded all but one of these discrepancies would not impact the secondary disability outcome measure which largely relied on EDSS scores obtained at baseline and unscheduled visits. In the one instance of a discrepancy that impacted a baseline EDSS score which could affect the disability outcome assessment, an information request to the applicant confirmed the change of the score in the applicant's database, and a new analysis with this corrected baseline score yielded the same overall statistical outcomes for confirmed disability worsening. The COVID-19 global pandemic precluded inspection of additional study sites as originally planned, but OSI provided a consult dated January 21, 2020, summarizing recent Good Clinical Practice (GCP) inspections for three other clinical sites (Drs. Selmaj, Maciejowski, and Bosnjak-Pasic) used in Studies G2301 and G2302. These sites were noted to be in compliance with GCP at the time of their most recent inspections.

10. Labeling

See the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

11. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A REMS is not necessary for Kesimpta (ofatumumab). A REMS was not necessary after approval of Arzerra (ofatumumab).

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following are postmarketing requirements:

1. A two-part study of Kesimpta (ofatumumab) in pediatric patients with relapsing forms of multiple sclerosis (RMS) at least 10 years and less than 18 years of age. Part A is an open-label study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of Kesimpta (ofatumumab) in pediatric patients. Part A will include two cohorts, one with body weights less than 40 kg and the other with body weights 40 kg or more. The objective of Part A is to determine maintenance doses of Kesimpta (ofatumumab) that will result in PK and PD effects that are comparable to those of the dose administered to adult patients. Part B is a randomized, blinded, non-inferiority trial with Gilenya (fingolimod) as a comparator.

Draft Protocol Submission:	09/2020
Final Protocol Submission:	01/2021
Study Completion:	09/2025
Final Report Submission:	03/2026

2. Prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Kesimpta (ofatumumab) during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to Kesimpta (ofatumumab) before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Draft Protocol Submission:	06/2021
Final Protocol Submission:	02/2022
Annual Interim Report Submissions:	08/2023
	08/2024
	08/2025
	08/2026
	08/2027
	08/2028
	08/2029
	08/2030
	08/2031
	08/2032
Study Completion:	02/2033
Final Report Submission:	02/2034

3. A pregnancy outcomes study using a different study design than provided for in PMR 3901-2 (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control

study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Kesimpta (ofatumumab) during pregnancy compared to an unexposed control population.

Draft Protocol Submission:	06/2021
Final Protocol Submission:	02/2022
Annual Interim Report Submissions:	08/2023
	08/2024
	08/2025
	08/2026
	08/2027
	08/2028
	08/2029
	08/2030
	08/2031
	08/2032
Study Completion:	02/2033
Final Report Submission:	02/2034

4. A safety trial to monitor serum immunoglobulin G and M levels in patients with relapsing forms of multiple sclerosis during treatment with Kesimpta (ofatumumab) to establish the nadir in circulating immunoglobulins during chronic treatment, and to monitor patients after discontinuation of treatment with Kesimpta (ofatumumab) in order to ascertain the time needed to ensure restoration of pre-treatment baseline circulating serum levels of immunoglobulins G and M. This trial also should be designed to capture rates of infections, especially opportunistic and recurrent infections associated with immune suppression, and there should be monitoring of B-cell counts throughout treatment and after discontinuation until repletion of immunoglobulin levels.

Draft Protocol Submission:	05/2021

Final Protocol Submission:	01/2022
Trial Completion:	05/2028
Final Report Submission:	05/2029

The following is a postmarketing commitment:

1. Conduct a study to evaluate the presence of leachables in pre-filled syringe drug product material that is representative of the commercial process and stored in the intended pre-filled syringe at long-term storage conditions (5±3°C) up to the proposed expiry date (b) (4)

Trial Completion:	10/31/2021
Final Report Submission:	12/31/2021

2. Recommended Comments to the Applicant

There are no additional recommended comments to the applicant.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAUL R LEE
08/19/2020 04:21:10 PM

NICHOLAS A KOZAUER
08/19/2020 04:53:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326Orig1s070

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125326 SUPPL-70 (Efficacy)
Priority or Standard	Priority
Submit Date(s)	12/20/2019
Received Date(s)	12/20/2019
PDUFA Goal Date	6/20/2020
Division/Office	DN2/Office of Neuroscience
Reviewer Name(s)	Lawrence Rodichok MD
Review Completion Date	6/17/2020
Established/Proper Name	ofatumumab
(Proposed) Trade Name	Arzerra
Applicant	Novartis Pharmaceuticals Corporation
Dosage Form(s)	20 mg/4mL for injection
Applicant Proposed Dosing Regimen(s)	Initial dose: 20 mg SC at Weeks 0, 1, and 2 20 mg SC monthly starting at Week 4
Applicant Proposed Indication(s)/Population(s)	Adults with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adults with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

Table of Contents

APPEARS THIS WAY ON ORIGINAL

Table of Tables

Table of Figures

Glossary

AC	advisory committee
ADA	anti-drug antibodies
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AR	adverse reaction
ARR	annualized relapse rate
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BUN	blood urea nitrogen
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CIS	clinically isolated syndrome
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia suicide severity rating scale
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	common terminology criteria for adverse events
DBP	diastolic blood pressure
DMC	data monitoring committee
DMT	disease modifying treatment
ECG	electrocardiogram
EDSS	expanded disability status scale
eCTD	electronic common technical document
EOS	end of study
EOT	end of treatment
ETASU	elements to assure safe use

FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
Gd	gadolinium
GRMP	good review management practice
HBV	hepatitis B virus
HDL	high density lipoprotein
HIV	human immunodeficiency virus
ICH	International Council for Harmonization
IgG	immunoglobulin G
IgM	immunoglobulin M
IND	Investigational New Drug Application
IRR	injection related reaction
ISE	integrated summary of effectiveness
ISR	injection site reaction
ISS	integrated summary of safety
ITT	intent to treat
LDL	low density lipoprotein
LLN	lower limit of normal
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRI	magnetic resonance imaging
MS	multiple sclerosis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NEDA	no evidence of disease activity
NME	new molecular entity
OCS	Office of Computational Science
OMB	ofatumumab
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PML	progressive multifocal leukoencephalopathy
PMR	postmarketing requirement

PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RMS	relapsing forms of MS
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SGE	special government employee
SOC	system organ class
TEAE	treatment emergent adverse event
TER	teriflunomide
US	United States of America

1. Executive Summary

1.1. Product Introduction

Ofatumumab is a fully human anti-CD20 monoclonal antibody (mAb) that targets an epitope of the CD20 molecule on the cell membrane. It is approved for the treatment of patients with chronic lymphocytic leukemia (Arzerra®). Other mAbs that target the CD20 molecule are rituximab, commonly used off-label for the treatment of relapsing forms of multiple sclerosis (RMS), and ocrelizumab, approved for the treatment of relapsing and progressive forms of MS (Ocrevus®). Ofatumumab induces B-cell lysis primarily by complement-dependent cytotoxicity (CDC) and by antibody-dependent cell-mediated cytotoxicity (ADCC). The link to the Arzerra® is below.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125326s063lbl.pdf

1.2. Conclusions on the Substantial Evidence of Effectiveness

Two adequate and well-controlled trials provide substantial evidence that treatment with ofatumumab 20 mg administered subcutaneously (SC) at an initial dose: 20 mg SC at Weeks 0, 1, and 2 and then 20 mg SC monthly starting at Week 4 reduces the frequency of relapses in comparison to treatment with teriflunomide in patients with relapsing forms of MS. A reduction in the proportion of RMS patients with 3-month confirmed progression of disability was demonstrated in the pooled population from the two pivotal trials. Treatment with ofatumumab significantly reduced MRI evidence of MS disease activity in comparison to teriflunomide.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Two adequate and well controlled trials in adult patients with RMS have provided substantial evidence that treatment with ofatumumab reduces the annualized relapse rate, reduces periods of disability lasting 12 weeks, and reduces evidence of disease activity on magnetic resonance imaging in comparison to teriflunomide. There is evidence of a benefit on the acute loss of function due to a relapse (defined in part by an increase in disability) as well as for the longer 3-month periods of disability that are generally not related to relapses. These are all clinically relevant benefits that would justify a low to moderate safety risk. The risks of ofatumumab treatment of RMS are those expected with suppression of B-cells and decreased levels of immunoglobulin M, most notably an increased risk of infections. Serious or opportunistic infections do not appear to be a major safety issue although longer term experience is needed to further assess these risks. The risk can be mitigated to some extent with ongoing surveillance and continued monitoring of immunoglobulin M levels. Infusion reactions were not a serious safety concern, even without the use of pre-medications. Therefore, based on the available data, the manageable risk justifies the benefit of treatment with ofatumumab in patients with RMS.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• RMS is a condition associated periods of short-term neurologic signs and symptoms due to relapses. It is also associated with periods of disability due in part to incomplete recovery from relapses. These periods of disability typically last about 3 to 6 months but commonly resolve after that. These features of RMS are generally thought to be due to acute inflammatory events that are disseminated over time and occur in most myelinated areas of the CNS and to a lesser extent within neuronal aggregates and even within the meninges. However longer term and irreversible disability may also develop due to neurodegenerative changes that are largely independent of the occurrence of relapses. These may not be due to acute inflammation but rather to a different but	Treatment with ofatumumab results in a statistically significant and clinically meaningful reduction in relapses and in the occurrence of short-term periods of disability largely unrelated to relapses. Two adequate and well-controlled studies have demonstrated a reduction in the annualized relapse rate and the proportion of patients experiencing 12-week confirmed progression of disability, endpoints considered valid-measures of function in MS patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	perhaps related type of pathophysiology. There is uncertainty as to whether current therapies have a beneficial effect on the latter process and therefore there is uncertainty as to whether current therapies reduce long-term (5 to 20 years) disability	
Current Treatment Options	• There are currently multiple treatment options all of which have been demonstrated to reduce the frequency of relapses and many of which have been shown to have some effect on short term but still largely reversible disability. All target some aspect of the immune system. In general, those that have demonstrated a greater benefit also are associated with greater risk. The primary risk is an increased risk of infection. Many are also associated with an increased risk of autoimmune disorders. Some with an increased risk of neoplasms.	Current treatment options offer a spectrum of benefit to risk balance. Nevertheless, there remains a significant population of patients with RMS with a need for a more effective therapy.
Benefit	• Two adequate and well-controlled trials provide substantial evidence that treatment with ofatumumab will reduce the occurrence of disabling relapses in a statistically significant and clinically relevant proportion of the RMS population. The two pivotal trials also demonstrate a statistically significant reduction in the relatively small proportion of patients with RMS who experience periods of disability not attributable to relapses over a 1- to 2-year period. The trial results leave minimal uncertainty regarding these benefits.	There is substantial evidence that treatment of RMS with ofatumumab provides a clinically meaningful benefit
Risk and Risk Management	• The primary risk of treatment of RMS with ofatumumab is the risk of infection. The trial data suggest that this is not a major risk and primarily involves viral upper respiratory infections. Ongoing clinical surveillance and monitoring of IgM levels may be able to mitigate the risk of more serious infections.	The risk of treatment of RMS with ofatumumab appears to be relatively modest. The demonstrated benefit justifies the risks.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		X	Patient reported outcome (PRO)	6.1.2, 6.2.2
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	6.1.2, 6.2.2
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Multiple Sclerosis is a chronic disorder of the CNS characterized by recurrent episodes (relapses) of neurologic deficits that are due to one or more areas of acute injury to myelin, oligodendrocytes, and to a lesser extent axons and neurons. Areas of acute inflammatory injury may involve subcortical white matter, brainstem, optic nerve and /or spinal cord. The diagnostic criteria for MS essentially require clinical and/or imaging evidence of a dissemination of these events "in space and time" [1]. Although early relapses may be followed by complete recovery, over time the recurrent relapses are associated with an accumulation of residual deficits and increasing disability[2]. Over time a slow progression of disability independent of the occurrence of relapses is seen in most patients with MS[3,4]. This "relapsing and remitting" pattern with or without the slow progression of disability, occurs in approximately 85% of patients with MS. Of those with a typical relapsing onset, approximately one-third will enter a slowly progressive phase with or without superimposed relapses[5]. Although disability can result from residual deficits following relapses[6], relapses may not be the dominant factor resulting in severe and permanent disability[7]. Therefore, a reduction in the relapse rate does not necessarily correlate with a significant reduction in long term disability. However, the early frequency and severity of relapses and incomplete recovery from early relapses all tend to predict a more rapid progression of irreversible disability[3,8]. Relapses are associated with a mean increase of 0.75 on the EDSS scale[6]. For most patients, the disability incurred at a relapse improves significantly within 2 to three months[6]. Increases on the EDSS that meet generally accepted criteria for confirmed progression of disability for 3 or 6 months are usually not sustained to one or two years[9].

2.2. Analysis of Current Treatment Options

Relapsing forms of MS

The currently approved therapies for RMS are shown in **Table 1** below. Available therapies reduce the relapse rate by 30 to 50%. While a reduction in the number of relapses is desirable, it is unclear that this alone will result in a significant reduction in long term disability. Differences in methodology and the populations studied limit interpretation of the effect of these therapies on long-term disability. Several have shown a numeric reduction in some measure of disability that was confirmed 12 and/or 24 weeks after an initial significant increase in EDSS score. However, if a statistically significant reduction was seen in one trial, the result was often not replicated in a second trial. However, ocrelizumab has recently been approved for the treatment of primary progressive MS in part because a reduction of confirmed disability progression was demonstrated, and which could not be attributed to the reduction in relapses. Although most therapies approved for the treatment of RMS show a reduction in various MRI findings in RMS, there is no evidence at this time to support the use of any of these MRI measures as the primary criterion for the choice of therapy.

Because they were the earliest approved therapies and because there have been relatively few major safety concerns, either a β -interferon or glatiramer acetate are often the initial choice for treatment for new onset typical RMS. Because the interferons share the same presumed mechanism of action and have similar efficacy, if the response is not adequate to one interferon then the choice of next therapy is usually not a different interferon and usually not glatiramer acetate. There are now several approved alternative therapies with efficacy at least comparable and in some cases demonstrated in controlled trials to be superior to the interferons and glatiramer acetate. Each of the approved therapies has somewhat unique benefits and risks. The choice of first line therapy and any subsequent therapies due to lack of efficacy or safety concerns is determined based on the risk compared to the potential benefit for an individual patient.

Table 1: Current approved treatments for relapsing forms of MS

Approved Drug	Name	Sponsor	Approved	Dose	Frequency	Major Safety Concerns
Beta interferon 1b	Betaseron (Betaferon in the EU)	Bayer	1993	0.25 mg – (initial dose 0.0625 mg - gradually increase over 6 weeks)	SC qod	None
Beta interferon 1a	Avonex	Biogen Idec	1996	30 µg (may start at 7.5µg & increase by 7.5 µg weekly for 3 weeks)	IM q week	None
Glatiramer acetate	Copaxone	Teva	1996	20 mg/day	SQ qd	None
Mitoxantrone	Novantrone	EMD Serono	2000	12mg/m^2 IV over 5 to 15 min	IV q 3 mo	Cardiotoxicity
Beta interferon 1a	Rebif	EMD Serono Pfizer Inc.	2002	22µg or 44µg (start at 20% of target; increase over 4 weeks)	SQ tiw	None
Natalizumab	Tysabri	Elan	2004	300mg IV over 1 hour	every 4 weeks	PML
Beta interferon 1b	Extavia	Novartis	2009 (1993)	0.25 mg – (initial dose 0.0625 mg - gradually increase over 6 weeks)	SQ qod	None
Fingolimod	Gilenya	Novartis	2010	0.5 mg	orally once daily	First dose bradycardia CI for recent MI, unstable angina, TIA, CHF Macular edema Impaired PFTs Fetal risk
Teriflunomide	Aubagio	Sanofi	2012	7 mg or 14 mg	orally once daily	Black box warning for hepatotoxicity and teratogenicity; additional concerns

Approved Drug	Name	Sponsor	Approved	Dose	Frequency	Major Safety Concerns
						for WBC decrease, renal failure, skin reactions; peripheral neuropathy
Dimethyl fumarate	Tecfidera	Biogen-Idec	2013	120 mg for 7 days, then 240 mg	twice daily	Lymphopenia
PEGylated interferon β	Plegridy	Biogen	2014	125 µg (63 µg on day 1, 94 µg on day 15, the full dose starting on day 29)	Q2 weeks	None
Alemtuzumab	Lemtrada	Genzyme	2015	1st course: 12 mg/dy X5 2nd course: 12 mg/dy X3	2 courses 12 months apart	Black box warning for serious/fatal autoimmune conditions including thrombocytopenia and anti-glomerular basement membrane disease; serious and life-threatening infusion reactions; special facilities required for infusion; increased risk of malignancies; REMS
Ocrelizumab	Ocrevus	Genentech	2017	Initial dose of 300 mg IV followed by second dose of 300 mg IV 2 weeks later Subsequent doses of 600 mg IV every 6 months		Infusion reactions Infections Increased risk of malignancies
Siponimod	Mayzent	Novartis	2019	2 mg after titration	Daily	CI for recent myocardial infarction unstable angina, stroke, TIA, decompensated CHF, Mobitz II second-degree, third-degree AV block, sick sinus syndrome Infections, bradyarrhythmias and AV conduction delays, liver injury, fetal risk, increased blood pressure, decline in respiratory function, macular edema
Cladribine	Mavenclad	EMD Serono	2019	Cumulative dosage of 3.5 mg/kg administered orally and divided into 2	2 courses one year apart	Black Box Warning for malignancies and teratogenicity

Approved Drug	Name	Sponsor	Approved	Dose	Frequency	Major Safety Concerns
				treatment courses (1.75 mg/kg per treatment course). Each treatment course is divided into 2 treatment cycles		Lymphopenia, infections, liver injury, graft vs. host reaction with blood transfusion, hematologic toxicity
Diroximel Fumarate	Vumerity	Biogen	2019	462 mg after titration	Daily	Same as for Dimethly fumarate (Tecfidera)
Ozanimod	Zeposia	Celgene	2020	0.92 mg after titration	Daily	CI for recent myocardial infarction unstable angina, stroke, TIA, decompensated CHF Infections, bradyarrhythmias and AV conduction delays, liver injury, fetal risk, increased blood pressure, decline in respiratory function, macular edema
Monomethyl fumarate	Bafiertam	Banner	2020	190 mg after titration	Daily	Same as for Dimethly fumarate (Tecfidera)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ofatumumab is currently marketed as Arzerra®. It was granted accelerated approval on October 26, 2009, for treatment of chronic lymphocytic leukemia (CLL) refractory to alemtuzumab and fludarabine. The submission for the treatment of RMS is a supplemental BLA with a different proposed trade name (Kesimpta) to differentiate the therapy's indicated use and because of a different route of administration.

3.2. Summary of Presubmission/Submission Regulatory Activity

Original IND 111116: 4/29/2011
EOP2 meeting: 3/25/14
Agreed iPSP: 8/30/18
Pre-BLA meeting: 10/2/19
Priority review voucher notification (PRV 208711): 9/17/19

3.3. Foreign Regulatory Actions and Marketing History

Arzerra® was first approved in the EU on 4/19/2010 for the treatment of the treatment of CLL refractory to alemtuzumab and fludarabine.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Clinical Inspection Summary has been submitted. Because of the COVID-19 pandemic, one of 4 planned inspections was completed and there were no significant findings at that site. Based on an early assessment of the quality of the data submitted, and the risk to FDA personnel, the 3 inspections of sites outside the US were deemed unnecessary.

4.2. Product Quality

See the review by the CMC reviewer. At this time, there do not appear to be major product quality issues.

4.3. Clinical Microbiology

See the review by the microbiology reviewer.

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical review is not complete at this time

4.5. Clinical Pharmacology

The Clinical Pharmacology review is not complete at this time.

4.6. Devices and Companion Diagnostic Issues

There do not appear to be any device issues at this time. There is no companion diagnostic.

4.7. Consumer Study Reviews

There are no consumer studies.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Table of Clinical Studies

Trial Identifier	NCT no.	Design	Dose regimen	Endpoints	Treatment duration	Number treated	Population
Controlled Clinical Studies							
COMB157G2301	NCT02792218	Active comparator-controlled RCT	OMB: 20 mg SC on days 1, 7, 14 then 20 mg SC q4W TERI: 14 mg qd	Primary	Variable; Max of 30 months	OMB: 465 TERI: 462	Relapsing forms of MS
COMB157G2302	NCT02792231	Active comparator-controlled RCT	Same as Study 2301	Same as Study 2301	Same as Study 2301	OMB: 481 TERI: 474	Relapsing forms of MS
Studies to Support Safety							
COMB157G2102		Open label; BE study of PFS vs. autoinjector	20 mg SC weekly X 3 doses then 20 mg q4W	BE	12 weeks	284	Relapsing forms of MS
OMS112831		Placebo-controlled RCT	OMB 3mg, 30mg, 60 mg SC q12W, 60mg SC q4W	Safety and MRI measures of MS activity	24 weeks	PBO for 12 weeks then OMB 3mg q12W: 67 OMB: 3mg q12W: 34 OMB 30 mg q12W: 32 OMB 60 mg q12W: 34 OMB 60mg q4W: 64	Relapsing forms of MS
OMS115102		Placebo-controlled double-blind dose ranging cross-over	OMB 100mg, 300mg, 700 mg IV	PK and safety	24 weeks	OMB 100mg: 12 OMB 300mg: 15 OMB 700mg: 11	Relapsing forms of MS
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
	No other clinical studies						

5.2. Review Strategy

The two large randomized-controlled clinical trials, studies COMB157G2301 and COMB157G2302, are the primary focus of the review of both efficacy and safety. The phase 2, dose-finding study OMS112831 provides limited efficacy and safety data. Additional safety data are available from a small number of additional studies.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study COMB157G2301: A Randomized, double-blind, double dummy, parallel group study comparing the efficacy and safety of ofatumumab vs. teriflunomide in patients with relapsing multiple sclerosis

6.1.1. Study Design

Overview and Objective

The primary objective of this study was to demonstrate that ofatumumab 20 mg administered subcutaneously (SC) once every 4 weeks (q4W) is superior to teriflunomide 14 mg administered orally (po) once daily in reducing the frequency of confirmed relapses as evaluated by the annualized relapse rate (ARR) in patients with relapsing Multiple Sclerosis (MS).

Trial Design

The study had a randomized, double-blind, double-dummy, active comparator, parallel group design. The comparator was teriflunomide which is approved for the treatment of relapsing forms of MS. Treatment duration was variable because the study was to continue until the End of Study (EOS) criteria were met. The maximum duration of randomized treatment was limited to 30 months. Eligible patients were randomized 1:1 to either ofatumumab 20 mg SC weekly for 3 doses followed by 20 mg SC every 4 weeks, or teriflunomide 14 mg orally once daily. Patients assigned to ofatumumab received a daily teriflunomide placebo and those assigned to teriflunomide received an ofatumumab placebo SC injection on the same dosing schedule as the active ofatumumab patients.

Each of the following end of study criteria had to be met for enrollment to cease:

1. Each of the two confirmatory studies had to have collected sufficient data to provide 90% power for the primary endpoint (Annualized Relapse Rate (ARR)).

2. The number of 3-month confirmed disability worsening (3mCDW) events in the pooled 2 confirmatory studies had to be sufficient to provide 90% power for that endpoint
3. The number of 6-month CDW (6mCDW) events in the pooled 2 confirmatory studies had to be sufficient to provide 80% power for that endpoint.

The Screening period could last up to 45 days and "baseline period" was defined as Study Day minus 7 to Day 1. Eligibility was based on assessment results from the screening and baseline periods.

Study Day 1 was the beginning of the Randomized Treatment Phase (RTP). The first injection was administered by the study staff on Day 1. Subjects returned to the site at Day 7, Day 14 and Day 28 to administer injections under supervision of the study staff. Subjects then returned to the site at month 3 and every 3 months thereafter. An EOS assessment was conducted when subjects reached 30 months of treatment or when EOS was declared.

Subjects who completed the treatment phase were eligible to enter an open-label treatment study (OLP). Those who completed the treatment phase but chose to not enter the open-label study were to be followed for a minimum of 9 months in a Safety Follow-up phase (SFP).

Subjects were to enter the SFP phase if:

1. The subject completed the RTP but did not agree to enter the OLP
2. The subject discontinued the study treatment prematurely and did not agree continued follow-up in the RTP
3. The subjects discontinued treatment prematurely but did agree to be followed in the RTP but had less than 9 months of follow-up at EOS

All subjects were to be followed for a minimum of 9 months after discontinuation of study treatment, either in the RTP or the SFP. Follow-up continued beyond 9 months, if necessary, until the B-cell count returned to baseline or to the lower limit of normal. Follow-up also continued if the teriflunomide level was above 0.02 mg/L at 9 months. If a new disease modifying or immunosuppressant drug was started before the end of this 9-month follow-up period, then there was no further follow-up assessment.

A phase 2 study in MS patients (OMS112831) of multiple SC and IV regimens was conducted and assessed PK, PD, MRI and clinical outcomes. The dosing regimen is based on data from that study plus PK/PD modelling that support the use of a loading dose of 20 mg SC weekly for three doses in order to attain "high level" depletion of CD19+ cells, i.e. ≤ 8 cells/ µL in ≥95% of patients. The dose resulted in a significant reduction in disease activity on imaging studies. Higher doses were associated with more adverse events.

Reviewer Comment: The comparator, teriflunomide, is approved for the treatment of relapsing forms of MS. In the two large confirmatory trials, a statistically significant reduction in ARR and time to confirmed disability progression was demonstrated. Aubagio is contraindicated in patients with severe hepatic impairment and in pregnant women and females of reproductive potential not using effective contraception. It may cause fetal harm. The link to the Aubagio label is below.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202992s008lbl.pdf

Eligibility Criteria

Key inclusion criteria

- Male or female patients aged 18 to 55 years (inclusive) at Screening
- Diagnosis of MS according to the 2010 Revised McDonald criteria (Polman et al. 2011)[1]
- Relapsing MS: relapsing-remitting course (RRMS), or secondary progressive (SPMS) course with disease activity, as defined by Lublin et al 2014[10]
- Disability status at Screening with an EDSS score of 0 to 5.5 (inclusive)
- 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 gadolinium-enhancing (GdE) MRI scan during the year prior to randomization. Note: Screening MRI scan could be used if no positive GdE scan existed from prior year.
- Neurologically stable within 1 month prior to randomization

Key exclusion criteria

- Patients with primary progressive MS (Polman et al. 2011[1]) or SPMS without disease activity (Lublin et al. 2014)[10]
- Patients meeting criteria for neuromyelitis optica (Wingerchuk et al. 2006)[11]
- Disease duration of more than 10 years in patients with EDSS score of 2 or less
- Patients with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g. rheumatoid arthritis, scleroderma, Sjögren's syndrome, Crohn's disease, ulcerative colitis, etc.) or with immunodeficiency syndrome (hereditary immune deficiency, drug-induced immune deficiency)
- Patients with active systemic bacterial, viral or fungal infections, or known to have AIDS or to test positive for HIV antibody at Screening
- Patients with neurological findings consistent with PML or confirmed PML
- Patients at risk of developing or having reactivation of syphilis or tuberculosis
- Patients at risk of developing or having reactivation of hepatitis

- Have received any live or live-attenuated vaccines (including for varicella-zoster virus or measles) within 2 months prior to randomization
- History of malignancy of any organ system (other than basal cell carcinoma, in situ squamous cell carcinoma of skin, or in situ carcinoma of cervix of the uterus that have been radically treated e.g. completely excised with clear margins), within the past 5 years, regardless of whether or not there is evidence of local recurrence or metastases
- Any of the following abnormal laboratory values prior to randomization
    - White blood cell (WBC) count < 3,500/mm^3 (< 3.5 x 10^9/L)
    - Lymphocyte count < 800/mm3 (< 0.8 x 10^9/L)
    - Serum IgG and IgM < lower limit of normal (according to central laboratory range)

Reviewer Comment: See 13.3 for the complete list of eligibility criteria which include criteria related to male and female contraception, the use of immune modulators and immunosuppressants prior to randomization, and excluded neurologic and medical illnesses.

Eligible patients were randomized 1:1 to either:

- Ofatumumab 20 mg SC injections on Day 1, 7, 14, Week 4 (Study Month 1) and every 4 weeks thereafter + teriflunomide-matching placebo capsule orally once daily.

Or

- Teriflunomide 14 mg capsule orally once daily + ofatumumab-matching placebo injections on Day 1, 7, 14, Week 4 (Study Month 1) and every 4 weeks thereafter.

Randomization was stratified by geographic region, MS subtype (RRMS, Active SPMS)

Blinding to treatment assignment

Only the Data Monitoring Committee (DMC) members, Independent Statisticians and Programmers had access to treatment assignment

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

For those subjects requiring safety follow-up beyond 9 months because B-cells had not yet been repleted, or whose teriflunomide level remained above 0.2 mg/L, B-cell counts and teriflunomide, the assessment of B-cell counts and teriflunomide plasma levels every 3 months

was performed centrally and the Investigators and Sponsor study team were only informed of whether or not continued follow up was necessary.

The following measures were taken to facilitate blinding of the Independent EDSS 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.

Treatment

Premedication with acetaminophen and/or antihistamines (or equivalent) was recommended but not required. For the first injection only, the addition of premedication with corticosteroids (methylprednisolone 100 mg IV or the equivalent) was recommended. It was recommended that any premedication should be administered 30 to 60 minutes prior to study drug injection

Subjects were monitored at the site for at least 5 hours after the first dose of investigational product (IP). Dose adjustment was not permitted. Dose delay was permitted if clinically indicated, e.g. for a Serious Adverse Event (SAE), a medical condition, or an abnormal laboratory value of examination result.

The recommended treatment for an MS relapse was methylprednisolone up to 1000 mg per day (or equivalent corticosteroid and dose) for 3 to 5 days. A taper with oral corticosteroids was not permitted.

Prohibited medications

Medication	Additional action
Immunosuppressive/chemotherapeutic medications (including herbal) or procedures, including but not limited to cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, lymphoid irradiation and hematopoietic stem cell transplantation	Discontinue study treatment, increase vigilance regarding infections. NOTE: Restarting study treatment in patients exposed to these medications is not permitted.
Monoclonal antibodies targeting the immune system, including but not limited to natalizumab, alemtuzumab, and B-cell depleting agents such as but not limited to rituximab, ocrelizumab and obinutuzumab	Discontinue study treatment, increase vigilance regarding infections. NOTE: Restarting study treatment after exposure to B-cell depleting agents is not permitted. For others only after consultation with the Sponsor Medical Advisor.
Any other immunomodulatory or disease-modifying MS treatment, including but not limited to fingolimod, interferon	Interrupt or discontinue study treatment, increase vigilance regarding infections.

Medication	Additional action
beta, glatiramer acetate, dimethyl fumarate or systemic corticosteroids (except for when given for MS relapse treatment	
Leflunomide	Discontinue study treatment
Administration of any live or live-attenuated vaccine (including for measles) is prohibited while patients are exposed to study drug (long-lasting effects of the study drugs should be taken into consideration)	They may be administered when patients are no longer exposed to study drug. Consider risk/benefit and follow local labels

Required discontinuation of study treatment

In addition to the more standard criteria for discontinuation of study treatment, the following specific criteria were added:

- Patient with active serious infections or reactivation (e.g. tuberculosis, hepatitis B or C)
- Skin and /or mucosal reactions which raise the suspicion of severe generalized major skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome)
- Hypersensitivity to the study medication
- Severe hypoproteinemia
- Interstitial lung disease or new onset or worsening of pulmonary symptoms, such as persistent cough and dyspnea, with or without associated fever, suspicious of interstitial lung disease

The Investigator was responsible for the routine care of subjects, determination of eligibility for the trial, referral to the Independent EDSS rater at the time of a potential relapse, and management of relapses.

The Independent EDSS rater was responsible for determining the EDSS score at routine visits and at the time of a potential relapse on referral from the investigator. The independent rater also administered the Timed 25-foot Walk (T25FW), the 9-hole peg test (9HPT), and the Single Digit Modalities Test (SDMT). The communication of new neurological findings on the neurological examination, including the EDSS score, from the Independent EDSS Rater to the Investigator was not permitted. The Independent EDSS Rater remained blinded to adverse events, concomitant medications, laboratory data and any other data that have the potential of revealing the treatment assignment.

Assessments

During the Screening period subjects had an initial screening visit that occurred 8 to 45 days

prior to the Day 1 visit when the first dose of IP was given. The 7 days prior to the Day 1 visit were considered the baseline period. Subjects returned on Days 7 and 14 for the next doses of IP and selected clinical laboratory assessments. Beginning with the visit at month 1, subjects returned every 3 months to end of study or end of treatment. Adverse events were collected at every visit after the start of investigational treatment. The key assessments are listed in **Table 3**.

APPEARS THIS WAY ON ORIGINAL

Table 3: Schedule of key assessments during the RCP

EPOCH	Screening		Treatment											
Visit	SCR Dy -45 to D -8	BL Dy -7 to D 1	D1[1]	D7	D14	M1	M3	M6	M9	M12/24	M15/21/275	M18	EOT	EOS
Visit No.	1	2	101	102	103	104	105	106	107	108/112	109/111/113	110	198	199
Phone Interview				X	X	Monthly between scheduled visits								
Physical exam	X[2a]													
Routine labs	X[3]	X				X	X	X	X	X	X	X	X	X
B-cell count	X	X		X	X	X	X	X	X	X	X	X	X	X
TERI level														X6
IgG, IgM	X	X				X	X	X	X	X	X	X	X	X
ECG	X	X											X	X
MRI	X									X				X
eSSRS	X[6]	X4	X	X	X	X	X	X	X	X	X	X	X	X
MS relapse			X	X	X	X	X	X	X	X	X	X	X	X
EDSS	X	X[2b]	X[2b]				X	X	X	X	X	X	X	X
T25FW	X[2a]	X[2a]					X	X	X	X	X	X	X	X
9HPT	X[2a]	X[2a]						X		X		X	X	X
SDMT	X[2a]	X[2a]						X		X		X	X	X

1. Randomization and first dose (usually expected on the same day). If first dose occurs on a different day after randomization, the day of first dose should be considered to be Day 1
2. a) Assessment can be conducted either at Screening OR Baseline visit b) Assessment can be conducted at either the Baseline OR the Day 1 visit (they must be conducted before the first dose of investigational treatment).
3. Serology testing to check patient eligibility conducted at Screening only
4. The eCSSRS must be assessed once before randomization, either at the Screening (recommended) or the Baseline visit.
5. For patients who reach Month 27 visit, the next (and last) 3-monthy scheduled visit is the EOS Visit; EOS assessments will be done for all patients; End of treatment (EOT) assessments are done only for patients who prematurely discontinue study drug (at the time of study drug discontinuation) and who continue to stay in the Treatment epoch
6. Only for patients who had EOT ≥ 9 months earlier

Subjects were instructed to complete a diary to recorded administration of study drug and home pregnancy tests where applicable. Beginning at Month 2, subjects were contacted by telephone for a structured interview to identify any new or worsening symptoms that might merit an unscheduled visit, to collect information on any reactions to injections, and to assess adherence to contraception requirements

The assessments during the Safety Follow-up Phase are listed in Table 4.

Table 4: Assessments during Safety Follow-up

Visit Month[1] (relative to EOS)	+M3	+M6	+M9	Every 3 months[5]	End of Safety-FU[2]
Visit Number	201	202	203	204/20X	299
Visit window (days)	±14	±14	±14	±14	
AEs	X	X	X	X	X
Concomitant Meds*	X	X	X	X	X
Vital Signs	X	X	X	X	X
eCSSRS	X	X	X	X	X
Urine pregnancy test[3]	X	X	X	X	X
Contraception status	X	X	X	X	X
B-cells	X	X	X	X	X
TERI plasma level[6]	X	X	X	X	X
MS Relapse	X	X	X	X	X
EDSS	X	X	X	X	X
AEP	X[4]				

1. Time measured from the EOS Visit. M=month.
2. If scheduled visit and End of Safety-FU occur at the same time only End of Safety-FU visit should be done. If patient is prematurely withdrawn from the Safety-FU epoch, the End of Safety-FU assessments should be done at time of withdrawal.
3. Female patients only: monthly urine home pregnancy testing will be conducted between clinic visits. The patient must contact the Investigator immediately in the case of a positive test for confirmatory testing at the Investigator's discretion.
4. AEP. Patients may undergo an accelerated elimination process at Investigator's discretion
5. As needed for patients requiring prolonged B-cell/teriflunomide plasma level monitoring (Section 3.1)
6. As needed (teriflunomide level assessed only when patient has had a total of at least 9 months of follow up and then 3-monthly as needed after study drug discontinuation)

*including steroids for MS relapse and newly started DMT as applicable

Relapse Assessment

Subjects were instructed to make an appointment for an unscheduled visit if any or worsening of old symptoms occurred. There was no requirement that such a visit occur within a specific time interval from the onset. A relapse was defined as the 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 or known infection. If the investigator determined that the symptoms were consistent with a relapse, the subject was to be referred to the Independent EDSS assessor. No specific time interval was required to complete that assessment. A confirmed MS relapse required an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two functional scores (FS) 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). Confirmation of MS relapse was be done centrally. All MS relapses, regardless if they met the definition for confirmation or not, were reported on the MS relapse CRF. MS relapses were not reported as an AE/SAE.

MRI scans were read at a single central imaging center blinded to treatment assignment. MRI scans were not to be performed within 30 days after treatment with corticosteroids.

Laboratory studies

Hematology: red blood cell (RBC) count, hemoglobin, hematocrit, platelets, total white blood cell (WBC) count, WBC differential counts (neutrophils, lymphocytes, basophils, eosinophils, monocytes) and CD19+ B-cell counts.

Chemistry: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, P), random glucose, total protein, blood urea nitrogen (BUN), albumin (Alb), alkaline phosphatase, ALT, AST, GGT, total bilirubin (TBIL), conjugated bilirubin, creatinine, amylase, total cholesterol, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL), C-Reactive protein (CRP).

Routine urinalysis

Immunology: Total IgM and IgG levels.

Teriflunomide levels

Serum pregnancy tests were conducted for all women who of child bearing potential at the Screening, EOT and EOS Visits. Urinary pregnancy tests were conducted for all women who were of child bearing potential at all other scheduled clinic visits. In addition, the women will be provided with urinary pregnancy test kits for monthly home pregnancy testing required between the scheduled 3-monthly clinic visits.

Patient Reported Outcomes

The Multiple Sclerosis Impact Scale-29 (MSIS-29), European Quality of Life – 5 Dimensions (EQ-5D), and the Work Productivity and Activity Impairment for Multiple Sclerosis (WPAI-MS) were collected at 6 to 12-month intervals throughout the trial period.

Safety Assessments

Assessment of adverse events adhered to the standard of Good Clinical Practice. Severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) severity scale. An MS relapse or worsening of disability were not reported as an AE or SAE unless the investigator considered the event unexpected or unusually severe. There were protocol-defined criteria for laboratory and clinical events indicative of potential hepatotoxicity that required enhanced follow-up laboratory studies and possible discontinuation of study treatment. There were comparable criteria for potential renal toxicity. Guidance was provided for the assessment of new clinical or MRI findings that were not compatible with MS, especially possible PML. Guidance was also provided for the accelerated elimination procedure for teriflunomide if that was necessary.

A Data Monitoring Committee was responsible for ongoing review of safety and, if requested, efficacy data.

Study Endpoints

The primary endpoint is the Annualized Relapse Rate

The Secondary Endpoints were:

3-month confirmed disability worsening (pooled studies 2301 and 2302)
The number of GdE lesions
The number of new or enlarging T2 lesions
6-month confirmed disability worsening (pooled studies 2301 and 2302)
Brain volume loss
6-month confirmed disability improvement

Secondary endpoints were analyzed in a closed sequential hierarchy as listed above.

Statistical Analysis Plan

The Full Analysis dataset (FAS) was defined as all randomized subjects who had received a treatment assignment. The FAS was used for all efficacy analyses which were based on the intended treatment.

The Safety analysis dataset (SAF) was defined as all subjects who had received at least one dose of investigational product. Safety analyses were based on the actual treatment received.

The sample size was based on an estimated ARR in the teriflunomide group of 0.28, based on

several previous studies of teriflunomide. An ARR reduction of 40% was assumed, based in part on the reduction seen with ocrelizumab, a comparable anti-CD20 monoclonal antibody (mAb), and on the results of phase 2 studies of ofatumumab. A 20% drop-out rate was assumed. This yielded a total sample size of 805 was required to demonstrate superiority of ofatumumab at 90% power and one-sided alpha of 0.025. At 900 subjects for each of the two trials, there would be adequate power to demonstrate superiority on the 3mCDW endpoint.

A sample size reassessment was planned based on a blinded data review prior to completion of enrollment. The reassessment was to address the sample size needed for the primary endpoint and for the secondary endpoint Confirmed Disability Worsening confirmed over 3 months (3mCDW). The 3mCDW endpoint was to be analyzed for the pooled population from studies OMB157G2301 and OMB157G2302, which were identical in design. The maximum enrollment was 1250 patients.

Blinded data were also reviewed to determine the end of study date.

Analysis of the ARR used a negative binomial model with the individual confirmed relapse count as the response variable and the time in study as the offset variable. Treatment and region were used as factors, and the number of relapses in the previous year, baseline EDSS, baseline number of GdE lesions at baseline and the subject's age as covariates. This analysis was repeated based on all reported (as opposed to confirmed) relapses. The analysis was also repeated based on time on study drug as opposed to time on study. Time to the first relapse was also calculated using a Cox proportional hazards model.

A 3-month and 6-month confirmed disability worsening (3mCDW, 6mCDW) were defined as an increase from baseline in EDSS sustained for at least 3 and 6 months, respectively. After a scheduled or unscheduled visit at which the patient fulfills the disability worsening criterion, all EDSS assessments (scheduled or unscheduled) were required fulfill the worsening criteria until the worsening was confirmed at the first scheduled visit that occurred 3-months or 6 months after the onset of the worsening, or later. All patients who did not experience a 3mCDW (or 6mCDW) event in the Study were censored at the time of the last available EDSS assessment. Subjects who had a "tentative" disability worsening that could not be confirmed due to an early discontinuation or any another reason were also censored at the time from the first dose to the last available EDSS assessment. The worsening criteria were as follows:

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

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

A 3-month confirmed disability worsening (3mCDW) could have an onset at any scheduled or unscheduled visit if the disability worsening criterion was met. A disability worsening could only be confirmed at a scheduled visit if, over a period of 3 months (≥90 days), all assessments met the worsening criterion.

A 6-month confirmed disability worsening (6-mCDW) could have an onset at any scheduled or unscheduled visit if the disability worsening criterion was met. A disability worsening event could only be confirmed at a scheduled visit if, over a period of 6 months (≥166 days), all assessments meet the worsening criterion.

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

> ***Reviewer Comment:*** ***It appears from the above criteria that a period of confirmed worsening of disability could start with a relapse. Since the period of recovery from a relapse may extend over 3 to 6 months, some of these periods of confirmed disability progression may simply represent relapses and, therefore, be a partial replication of any reduction in relapses. In sequence 0264, the sponsor responded to a request for additional information regarding this endpoint and provided an analysis of confirmed progression (as opposed to worsening) using standard DN2 criteria for that endpoint.***

6 month confirmed disability improvement was defined as for 6 month confirmed disability worsening with the following criteria for improvement:

Total EDSS at baseline*	"Disability improvement" criterion
0 to 1.5	No improvement possible
≥2 to 6	≤ -1
≥6.5 to 9.5	≤ -0.5

6mCDI: A disability improvement could have an onset at any scheduled or unscheduled visit if the disability improvement criterion was met. A disability improvement could only be "confirmed" at a scheduled visit if, over a period of 6 months (≥166 days) time interval, all assessments met the improvement criterion. A 6mCDI sustained until the End of Study is defined as a 6mCDI after which all EDSS assessments met the disability improvement criterion through End of Study.

The analysis of the number of GdE lesions per scan used a negative binomial regression model

with the cumulative number of GdE across all MRI scans per subject as the response variable and natural logarithm of the number of MRI scans as the offset variable.

The analysis of the annualized rate of new or enlarging T2 lesions also used a negative binomial regression model with the number of new or enlarging T2 lesions on the last available MRI scan relative to baseline as the response variable with the natural logarithm of the time in years from baseline to the last MRI scan as the offset variable.

Protocol Amendments

Amendment 1: January 19, 2017

Amendment 1 was created at the request of several Health Authorities to provide additional guidance to the Investigators in regard to:

- switching to alternative disease modifying therapy for patients that have discontinued study drug
- re-evaluation of benefit/risk of continuing study treatment in patients, who experience relevant progression of their disease (have met criterion for 6-month confirmed disease worsening) while on study medication.

Amendment 2: August 6, 2018

Amendment 2 was created to update the secondary objectives of the study and to provide clarification of the rescreening of patients.
Modifications to the secondary objectives include:

- Addition of endpoints related to neurofilament light chain (NfL) as secondary objectives
- Additional endpoint related to cognitive decline as measured on the Symbol Digit Modalities Test (SDMT)
- Addition of composite endpoint related to physical disability and cognition, as measured by disability worsening on Expanded Disability Status Scale (EDSS) and cognitive decline on SDMT

6.1.2. Study Results

Compliance with Good Clinical Practices

The sponsor reports that "All studies were conducted in full compliance with current Good Clinical Practices. Studies G2301, G2302 and G2102 were closely monitored by Novartis personnel or a contract organization for compliance to the protocol, Novartis standard

operating procedures, and applicable regulatory guidance. Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. The subject was provided as much time as necessary to review the document, to inquire about details of the study, and to decide whether or not to participate in the study. The informed consent was signed and dated by the study subject and by the person who conducted the informed consent discussion."

Financial Disclosure

No clinical investigators were full or part-time employees of Novartis Pharmaceuticals Corporation. There were 7 investigators who participated in study 2301 who had a disclosable financial interest. Dr. (b) (6) at site (b) (6) held Novartis stock shares valued at over $50,000. The (b) (6) of Dr. (b) (6) at site (b) (6) held Novartis stock options. The other investigators had financial interests of other sorts, typically research grants or speaking honoraria.

Patient Disposition

Nine-hundred and twenty-seven (927) patients were randomized, 465 to ofatumumab 20mg and 462 to teriflunomide 14 mg. Eighty-six percent of the ofatumumab group and 78.8% of the teriflunomide group completed the study on treatment (Table 5). The reasons for discontinuation from treatment are listed in Table 6.

Table 5: Disposition by End of Treatment status, FAS, Study 2301

End of Treatment Status (EOTSTT)	Total		OMB 20 mg		TERI 14 mg	
	N	%	N	%	N	%
COMPLETED	764	82.4%	400	86.0%	364	78.8%
DISCONTINUED	163	17.6%	65	14.0%	98	21.2%
TOTAL	927	100.0%	465	100.0%	462	100.0%

Source: FASFL_Y Subset of ADSL 2301 TRT01P By (EOTSTT)

Table 6: Reason for early discontinuation from treatment, FAS, Study 2301

Reason for Discontinuation from Treatment (DCTREAS)	Total		OMB 20 mg		TERI 14 mg	
	N	%	N	%	N	%
SUBJECT/GUARDIAN DECISION	61	6.6%	23	4.9%	38	8.2%
ADVERSE EVENT	47	5.1%	24	5.2%	23	5.0%
PHYSICIAN DECISION	40	4.3%	10	2.2%	30	6.5%
LOST TO FOLLOW-UP	9	1.0%	4	0.9%	5	1.1%
PREGNANCY	2	0.2%	2	0.4%	0	0.0%

Reason for Discontinuation from Treatment (DCTREAS)	Total		OMB 20 mg		TERI 14 mg	
	N	%	N	%	N	%
TECHNICAL PROBLEMS	4	0.4%	2	0.4%	2	0.4%
Total	163	17.6%	65	14.0%	98	21.2%

Source: EOTSTT_DISC Subset of FASFL_Y Subset of ADSL 2301 TRT01P by (DCTREAS)

Reviewer Comment: The number of subjects who were discontinued from treatment due to "Subject/Guardian decision" and "Physician decision" was much higher in the teriflunomide group (14.7%) compared to the ofatumumab group (7.1%). The imbalance is not likely to affect interpretation of efficacy or safety results. Review of the CRFs did not reveal any additional details.

Study completion status is listed in Table 7. There were 16 subjects in the ofatumumab group who discontinued treatment but completed the study period and one ofatumumab subject who discontinued treatment and was considered ongoing at the time of data cutoff; that subject completed the study after the cutoff date of July 5, 2019. Seventeen subjects in the teriflunomide group discontinued treatment early but completed the study period and 5 were considered ongoing at the time of data cutoff; 4 of those 5 completed the study after the cutoff date and one discontinued the study early. The reasons for premature study discontinuation are listed in Table 8.

Table 7: Disposition by End of Study status, FAS, Study 2301

End of Study Status (EOSSTT)	Total		OMB 20 mg		TERI 14 mg	
	N	%	N	%	N	%
COMPLETED	792	85.4%	416	89.5%	376	81.4%
DISCONTINUED	129	13.9%	48	10.3%	81	17.5%
ONGOING	6*	0.6%	1*	0.2%	5*	1.1%
TOTAL	927	100.0%	465	100.0%	462	100.0%

Source: FASFL_Y Subset of ADSL 2301 TRT01P by (EOSSTT)

Table 8: Reasons for early study discontinuation, FAS, Study 2301

Reasons for Discontinuation from Study (DCSREAS)	Total		OMB 20 mg		TERI 14 mg	
	N	%	N	%	N	%
SUBJECT/GUARDIAN DECISION	58	6.3%	16	3.4%	42	9.1%
ADVERSE EVENT	28	3.0%	14	3.0%	14	3.0%
LOST TO FOLLOW-UP	15	1.6%	10	2.2%	5	1.1%
PHYSICIAN DECISION	7	0.8%	3	0.6%	4	0.9%
PROTOCOL DEVIATION	5	0.5%	3	0.6%	2	0.4%

Reasons for Discontinuation from Study (DCSREAS)	Total		OMB 20 mg		TERI 14 mg	
	N	%	N	%	N	%
LACK OF EFFICACY	13	1.4%	1	0.2%	12	2.6%
PREGNANCY	1	0.1%	1	0.2%	0	0.0%
NEW THERAPY FOR STUDY INDICATION	1	0.1%	0	0.0%	1	0.2%
NON-COMPLIANCE WITH STUDY TREATMENT	1	0.1%	0	0.0%	1	0.2%
TOTAL	129	13.9%	48	10.3%	81	17.5%

Source: EOSSTT_DISC Subset of FASFL_Y Subset of ADSL 2301 TRT01P by (DCSREAS)

Reviewer Comment: The number of subjects discontinued from the study for "Subject/guardian decision" and "Physician Decision" was higher in the group treated with teriflunomide (10%) compared to ofatumumab (4%). The CRFs for those subjects who discontinued due to "Subject/Guardian decision" and due to "physician decision" were generally not included in the submission (and were not specifically requested. Of those that were available, there was usually no additional comment or the comments from the investigator were consistent with the recorded reason for discontinuation.

The most common adverse event that resulted in discontinuation of treatment (DAE) with ofatumumab was decreased blood IgM; for the teriflunomide group the most common DAE was alopecia (Table 66).

The number of patients randomized was balanced by major region. Slightly over one-half of the subjects randomized were from either Eastern Europe or North America and Australia (Table 9).

Table 9: Randomization by Region, FAS, Study 2301

REGION	Total N=927		OMB 20 mg N=465		TERI 14 mg N=462	
	N*	%	N*	%	N*	%
Asia Pacific	30	3.24	15	3.23	15	3.25
Eastern Europe	325	35.1	163	35.1	162	35.1
Latin America	26	2.8	13	2.8	13	2.81
North America and AUS	212	22.9	106	22.8	106	22.9
Others	164	17.7	82	17.6	82	17.7
Western Europe	170	18.3	86	18.5	84	18.2

Source: FASFL_Y Subset of ADSL 2301 TRT0P By (REGION2).jmp

Reviewer Comment: One site randomized 73 patients, 7.9% of the total. The 10 highest enrolling sites randomized 33.6% of the patients. Nine of these sites were from Poland or Russia. Randomization was more evenly distributed in study 2302 (see Table 33).

Protocol Violations/Deviations

The number of subjects with at least one protocol deviation was 88 (18.9%) in the ofatumumab treatment group and 92 (19.9%) in the teriflunomide group (Table 10).

Table 10: Protocol deviations, FAS population, study 2301

Protocol Deviation Coded Term	Protocol Deviation Term	Ofatumumab 20 mg	Teriflunomide 14 mg
Other Deviation	EDSS rater acted as a treating physician or treating physician acted as EDSS rater	3 (0.6%)	0 (0.0%)
	Investigator reviewing EDSS results or Independent EDSS Rater reviewing patient's medical records other than EDSS assessment-related records	19 (4.1%)	11 (2.4%)
	Investigator reviewing MRI and/or MRI report	17 (3.7%)	14 (3.0%)
	Not following per protocol blinding procedures such that the integrity of the study is compromised	3 (0.6%)	5 (1.1%)
Prohibited Concomitant Medication	Any other immunomodulatory or disease-modifying MS treatment such as fingolimod, interferon beta, glatiramer acetate, dimethyl fumarate or systemic corticosteroids while taking double-blind treatment	3 (0.6%)	1 (0.2%)
Selection Criteria Not Met	AST (SGOT) or ALT (SGPT) greater than 1.5 times the ULN range prior to randomization or missing	2 (0.4%)	3 (0.6%)
	Disease duration of more than 10 years in patients with EDSS score of 2 or less	8 (1.7%)	17 (3.7%)
	DNA sample taken prior to signing pharmacogenetic informed consent or pharmacogenetic informed consent is No or missing	1 (0.2%)	0 (0.0%)
	EDSS score at screening 0 to 5.5 and not missing	4 (0.9%)	4 (0.9%)
	Gamma-glutamyl-transferase (GGT) greater than 2 times the ULN range prior to randomization or missing	1 (0.2%)	0 (0.0%)
	Lymphocyte count < 800/mm3 (< 0.8 10E9/L) prior to randomization or missing data	1 (0.2%)	1 (0.2%)
	Missing serum pregnancy test at screening	4 (0.9%)	6 (1.3%)
	Patient age at screening <18 or 55< or missing data	1 (0.2%)	0 (0.0%)
	Patients at risk of developing or having reactivation of syphilis or tuberculosis	29 (6.2%)	23 (5.0%)
	Patients currently treated with or needing treatment with cholestyramine (unless for accelerated teriflunomide elimination) during the study	0 (0.0%)	1 (0.2%)

Protocol Deviation Coded Term	Protocol Deviation Term	Ofatumumab 20 mg	Teriflunomide 14 mg
	Patients with suicidal ideation in the past 6 months or suicidal behavior in the past 2 years prior to randomization	3 (0.6%)	2 (0.4%)
	Positive results of screening period testing for serological markers for hepatitis A, B, C, and E indicating acute or chronic infection or missing data	0 (0.0%)	2 (0.4%)
	Serum IgG or IgM < Lower limit of normal	3 (0.6%)	5 (1.1%)
	Systemic steroid or adrenocorticotropic hormone treatment within 30 days prior to Screening MRI	3 (0.6%)	3 (0.6%)
	White blood cell (WBC) count < 3,500/mm³ (< 3.5 x 10E⁹/L) prior to randomization or missing data	1 (0.2%)	0 (0.0%)
	Women of child-bearing potential not using highly effective contraception	4 (0.9%)	5 (1.1%)
Subject Not Withdrawn as Per Protocol	Emergence of certain adverse events, such as malignancy, liver failure or serious chronic infection and treatment was not discontinued	0 (0.0%)	1 (0.2%)
	Protocol violation that results in a significant risk to the patient's safety, but treatment was not discontinued	0 (0.0%)	1 (0.2%)
Treatment Deviation	Patient received damaged or expired study drug	1 (0.2%)	5 (1.1%)
	Patient received incorrect study drug	2 (0.4%)	2 (0.4%)
	Site or global team unintentionally unblinded to the treatment allocation of an individual patient by vendor (including drug supply)	0 (0.0%)	1 (0.2%)
Total	Subjects(filtered)	465 (100.0%)	462 (100.0%)
Total	1stCollItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevSelADSL2301FASFL_Y EPOCHbyDVDECODbyDVTERM

Reviewer Comment: The number and types of protocol deviations are not likely to affect interpretation of efficacy, given the relatively large effect size seen in both pivotal studies. The number and types of deviations are not likely to affect interpretation of safety.

Table of Demographic Characteristics

Table 11

Table 11: Baseline demographic characteristics, study 2301

Subgroup	Ofatumumab 20 mg (N = 465) n (%)	Teriflunomide 14 mg (N = 462) n (%)	Total (N = 927) n (%)
Sex			
Female	318 (68.4)	317 (68.6)	635 (68.5)
Male	147 (31.6)	145 (31.4)	292 (31.5)
Age			
Mean	38.84	37.75	38.3
Standard Deviation	8.77	8.94	8.87
Minimum	19	18	18
Median	40	38	39
Maximum	56	55	56
Age Group			
Age Group 1 (AGE < 40)	230 (49.5)	269 (58.2)	499 (53.8)
Age Group 2 (40 <= AGE)	235 (50.5)	193 (41.8)	428 (46.2)
AGEGR1			
> 55 Years	1 (0.2)	0 (0.0)	1 (0.1)
18 to 30 Years	94 (20.2)	104 (22.5)	198 (21.4)
31 to 40 Years	152 (32.7)	178 (38.5)	330 (35.6)
41 to 55 Years	218 (46.9)	180 (39.0)	398 (42.9)
Race			
Asian	15 (3.2)	16 (3.5)	31 (3.3)
Black or African American	15 (3.2)	20 (4.3)	35 (3.8)
Missing	2 (0.4)	0 (0.0)	2 (0.2)
Other	22 (4.7)	14 (3.0)	36 (3.9)
White	411 (88.4)	412 (89.2)	823 (88.8)
Ethnicity			
Hispanic or Latino	37 (8.0)	36 (7.8)	73 (7.9)
Missing	68 (14.6)	71 (15.4)	139 (15.0)
Not Hispanic or Latino	360 (77.4)	355 (76.8)	715 (77.1)
Region			
Asia	27 (5.8)	27 (5.8)	54 (5.8)

Subgroup	Ofatumumab 20 mg (N = 465) n (%)	Teriflunomide 14 mg (N = 462) n (%)	Total (N = 927) n (%)
Canada	6 (1.3)	9 (1.9)	15 (1.6)
Europe	319 (68.6)	316 (68.4)	635 (68.5)
Other	3 (0.6)	1 (0.2)	4 (0.4)
South America	13 (2.8)	13 (2.8)	26 (2.8)
United States	97 (20.9)	96 (20.8)	193 (20.8)

Source: DM_TOOL Study 2301

Medical History

Medical conditions that ended prior to the start of the study were most commonly previous surgical procedures such as a tonsillectomy, cholecystectomy, and appendectomy. The remaining conditions were relatively infrequent and are generally not relevant to the study results.

The most common medical conditions that were concurrent during the study are listed by Body System in Table 12 and by Body System and preferred term in Table 14. Depression was the single most common individual medical history term (Table 13). Of the psychiatric disorders, terms that included depression were the most common preferred medical history terms and occurred in 17.9% of the ofatumumab group and in 15.6% of the teriflunomide group. Headache and migraine were the most common nervous system disorders, each occurring in approximately 8% of subjects.

Table 12: Concurrent medical disorders by MHSOC, 10% or more of OMB group, study 2301

Body System or Organ Class	Ofatumumab 20 mg	Teriflunomide 14 mg
Psychiatric disorders	124 (26.7%)	101 (21.9%)
Nervous system disorders	119 (25.6%)	119 (25.8%)
Musculoskeletal and connective tissue disorders	106 (22.8%)	108 (23.4%)
Metabolism and nutrition disorders	76 (16.3%)	72 (15.6%)
Gastrointestinal disorders	65 (14.0%)	52 (11.3%)
Immune system disorders	62 (13.3%)	58 (12.6%)
Vascular disorders	57 (12.3%)	49 (10.6%)
Subjects(filtered)	331 (71.2%)	318 (68.8%)
1stCollItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevSelADSLFASFL_Y MHSOCbyTRT01PfiltMHCAT_GEN MHENRF_DURING AFTER

Table 13: Concurrent medical disorders by MHDECOD, 5% for more of OMB group, study 2301

Dictionary Derived Term	Ofatumumab 20 mg	Teriflunomide 14 mg
Depression	78 (16.8%)	69 (14.9%)
Hypertension	49 (10.5%)	37 (8.0%)
Migraine	41 (8.8%)	37 (8.0%)
Anxiety	41 (8.8%)	34 (7.4%)
Headache	39 (8.4%)	35 (7.6%)
Drug hypersensitivity	31 (6.7%)	32 (6.9%)
Seasonal allergy	30 (6.5%)	28 (6.1%)
Back pain	27 (5.8%)	27 (5.8%)
Hypothyroidism	27 (5.8%)	26 (5.6%)
Insomnia	26 (5.6%)	26 (5.6%)
Subjects(filtered)	331 (71.2%)	318 (68.8%)
1stColItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevSelADSLFASFL_Y MHDECODbyTRT01PfiltMHCAT_GEN MHENRF_DURING AFTER

Table 14: Selected concurrent medical disorders by MHSOC and preferred term, study 2301

Body System or Organ Class	Dictionary Derived Term	OMB 20 mg	TERI 14 mg
Blood and lymphatic system disorders	Anaemia	13 (2.8%)	6 (1.3%)
	Anaemia megaloblastic	0 (0.0%)	1 (0.2%)
	Anaemia of pregnancy	0 (0.0%)	1 (0.2%)
	Hypochromic anaemia	1 (0.2%)	0 (0.0%)
	Iron deficiency anaemia	1 (0.2%)	5 (1.1%)
	Normocytic anaemia	1 (0.2%)	0 (0.0%)
Endocrine disorders	Autoimmune thyroiditis	5 (1.1%)	8 (1.7%)
	Basedow's disease	2 (0.4%)	0 (0.0%)
	Goitre	3 (0.6%)	1 (0.2%)
	Hyperthyroidism	3 (0.6%)	0 (0.0%)
	Hypothyroidism	27 (5.8%)	26 (5.6%)
	Thyroiditis	1 (0.2%)	1 (0.2%)
Gastrointestinal disorders	Chronic gastritis	6 (1.3%)	5 (1.1%)
	Gastritis	3 (0.6%)	4 (0.9%)
	Gastrooesophageal reflux disease	22 (4.7%)	7 (1.5%)
General disorders and administration site conditions	Chronic fatigue syndrome	0 (0.0%)	1 (0.2%)
	Fatigue	23 (4.9%)	23 (5.0%)
Immune system disorders	Drug hypersensitivity	31 (6.7%)	32 (6.9%)
Infections and infestations	Genital herpes simplex	0 (0.0%)	1 (0.2%)
	Gingivitis	1 (0.2%)	0 (0.0%)
	Herpes simplex	2 (0.4%)	2 (0.4%)
	Herpes zoster	1 (0.2%)	1 (0.2%)
	Oral herpes	9 (1.9%)	4 (0.9%)
	Proctitis herpes	0 (0.0%)	1 (0.2%)
Investigations	JC polyomavirus test positive	3 (0.6%)	3 (0.6%)

Body System or Organ Class	Dictionary Derived Term	OMB 20 mg	TERI 14 mg
	Vitamin D decreased	5 (1.1%)	5 (1.1%)
Metabolism and nutrition disorders	Vitamin D deficiency	22 (4.7%)	22 (4.8%)
Musculoskeletal and connective tissue disorders	Arthralgia	8 (1.7%)	10 (2.2%)
Nervous system disorders	Headache	39 (8.4%)	35 (7.6%)
	Migraine	41 (8.8%)	37 (8.0%)
	Migraine with aura	1 (0.2%)	3 (0.6%)
	Migraine without aura	1 (0.2%)	1 (0.2%)
	Muscle spasticity	19 (4.1%)	12 (2.6%)
	Neuralgia	13 (2.8%)	10 (2.2%)
	Optic neuritis	6 (1.3%)	9 (1.9%)
	Restless legs syndrome	3 (0.6%)	7 (1.5%)
	Seizure	3 (0.6%)	1 (0.2%)
	Temporal lobe epilepsy	1 (0.2%)	0 (0.0%)
Psychiatric disorders	Anxiety	41 (8.8%)	34 (7.4%)
	Anxiety disorder	6 (1.3%)	2 (0.4%)
	Bipolar disorder	3 (0.6%)	5 (1.1%)
	Depression	78 (16.8%)	69 (14.9%)
	Depressive symptom	1 (0.2%)	0 (0.0%)
	Insomnia	26 (5.6%)	26 (5.6%)
	Major depression	2 (0.4%)	1 (0.2%)
	Mixed anxiety and depressive disorder	1 (0.2%)	0 (0.0%)
	Persistent depressive disorder	2 (0.4%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Asthma	16 (3.4%)	15 (3.2%)
	Sleep apnoea syndrome	8 (1.7%)	3 (0.6%)
Vascular disorders	Essential hypertension	3 (0.6%)	3 (0.6%)
	Hypertension	49 (10.5%)	37 (8.0%)
Subtotal	Subjects(filtered)	331 (71.2%)	318 (68.8%)
Total	1stCollItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevSelADSLFASFL_Y MHSOCbyMHDECODbyTRT01PfiltMHCAT_GEN MHENRF_DURING AFTER

Other Baseline Characteristics (disease characteristics, important concomitant drugs)

Previous treatment for MS

Interferons and glatiramer acetate were the most common previous treatment for MS (Table 15). Treatment-naïve patients accounted for 41.1% of the ofatumumab treatment group and for 39.4% of the teriflunomide treatment group. The most recent treatments for MS are listed in Table 16.

Table 15: All previous treatments for MS, FAS, study 2301

Standardized Medication Name	OMB 20 mg	TERI 14 mg
INTERFERON BETA-1A	121 (26.0%)	117 (25.3%)
GLATIRAMER ACETATE	124 (26.7%)	106 (22.9%)
INTERFERON BETA-1B	62 (13.3%)	66 (14.3%)
DIMETHYL FUMARATE	36 (7.7%)	37 (8.0%)
NATALIZUMAB	31 (6.7%)	36 (7.8%)
FINGOLIMOD HYDROCHLORIDE	17 (3.7%)	29 (6.3%)
FINGOLIMOD	10 (2.2%)	15 (3.2%)
DACLIZUMAB	5 (1.1%)	12 (2.6%)
INTERFERON BETA	6 (1.3%)	10 (2.2%)
PEGINTERFERON BETA-1A	6 (1.3%)	9 (1.9%)
INTERFERONS	6 (1.3%)	8 (1.7%)
TERIFLUNOMIDE	8 (1.7%)	6 (1.3%)
AZATHIOPRINE	7 (1.5%)	5 (1.1%)
LAQUINIMOD	5 (1.1%)	4 (0.9%)
INVESTIGATIONAL DRUG	5 (1.1%)	2 (0.4%)
MITOXANTRONE	2 (0.4%)	4 (0.9%)
INTERFERON	3 (0.6%)	2 (0.4%)
OCRELIZUMAB	2 (0.4%)	2 (0.4%)
CLADRIBINE	3 (0.6%)	1 (0.2%)
METHOTREXATE	1 (0.2%)	2 (0.4%)
CYCLOPHOSPHAMIDE	0 (0.0%)	2 (0.4%)
MYCOPHENOLATE MOFETIL	2 (0.4%)	0 (0.0%)
RITUXIMAB	0 (0.0%)	1 (0.2%)
MITOXANTRONE HYDROCHLORIDE	0 (0.0%)	1 (0.2%)
Subjects(filtered)	274 (58.9%)	280 (60.6%)
1stCollItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevSelADSLFASFL_Y CMDECODbyTRT01PfiltANL01FL_Y

Table 16: Most recent treatment for MS, FAS, study 2301

Standardized Medication Name	Ofatumumab 20 mg	Teriflunomide 14 mg
GLATIRAMER ACETATE	82 (17.6%)	64 (13.9%)
INTERFERON BETA-1A	62 (13.3%)	63 (13.6%)
INTERFERON BETA-1B	32 (6.9%)	30 (6.5%)

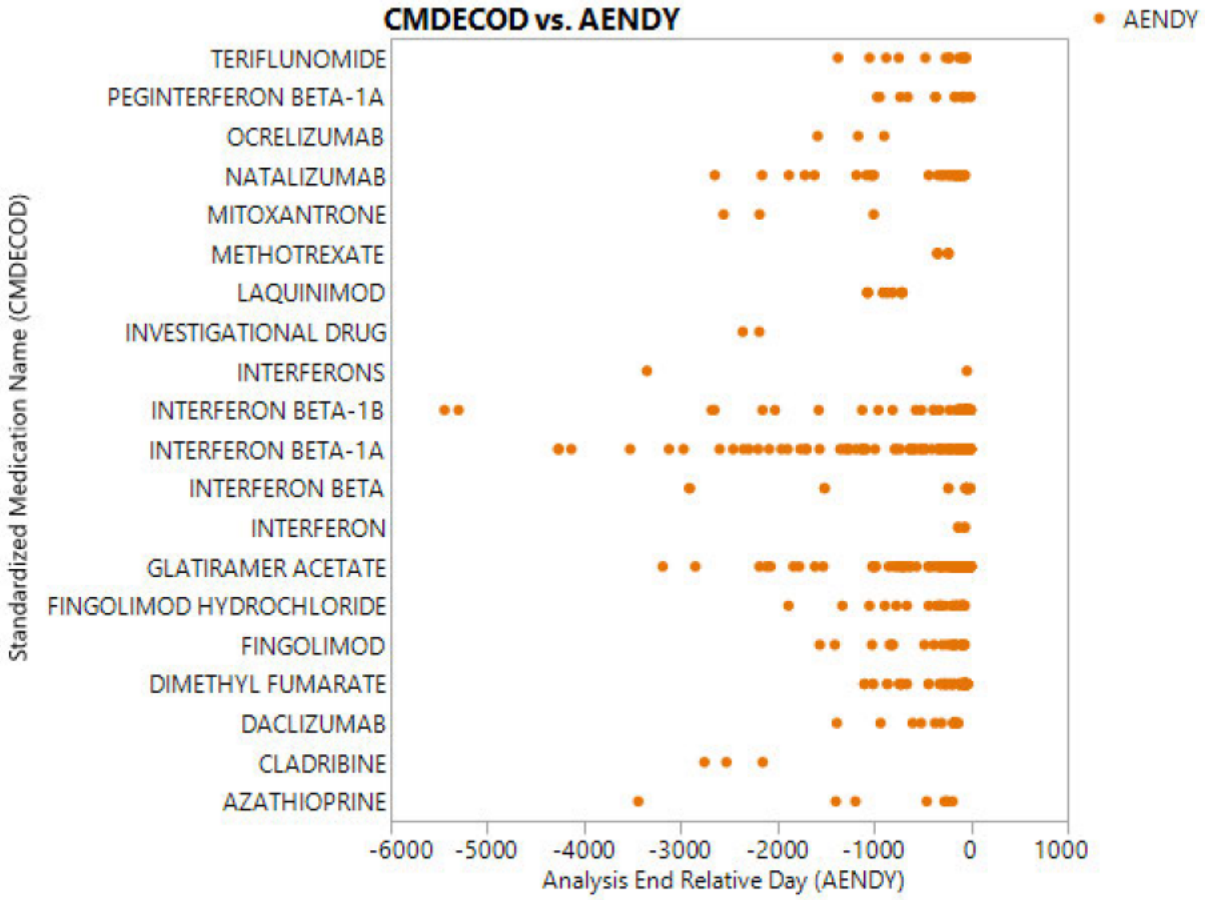
Standardized Medication Name	Ofatumumab 20 mg	Teriflunomide 14 mg
DIMETHYL FUMARATE	26 (5.6%)	29 (6.3%)
NATALIZUMAB	17 (3.7%)	17 (3.7%)
FINGOLIMOD HYDROCHLORIDE	10 (2.2%)	18 (3.9%)
FINGOLIMOD	7 (1.5%)	14 (3.0%)
DACLIZUMAB	3 (0.6%)	11 (2.4%)
PEGINTERFERON BETA-1A	6 (1.3%)	7 (1.5%)
TERIFLUNOMIDE	7 (1.5%)	5 (1.1%)
INTERFERON BETA	5 (1.1%)	6 (1.3%)
AZATHIOPRINE	4 (0.9%)	4 (0.9%)
LAQUINIMOD	5 (1.1%)	3 (0.6%)
CLADRIBINE	2 (0.4%)	1 (0.2%)
OCRELIZUMAB	2 (0.4%)	1 (0.2%)
MITOXANTRONE	0 (0.0%)	3 (0.6%)
INTERFERON	1 (0.2%)	1 (0.2%)
METHOTREXATE	0 (0.0%)	2 (0.4%)
INTERFERONS	1 (0.2%)	1 (0.2%)
INVESTIGATIONAL DRUG	2 (0.4%)	0 (0.0%)
Subjects(filtered)	274 (58.9%)	280 (60.6%)
1stCollItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevSelADSLFASFL_Y CMDECODbyTRT01PfiltANL02FL_Y

The distribution of the relative study day that the last dose of the most recent treatment for MS was given is shown in **Figure 1** . The most recent end date by therapy is shown in **Table 17** which also includes a column for the protocol-defined limit for the most recent dose of the medication.

> *Reviewer Comment: The last date of treatment with previous MS therapies appear to be within the protocol requirements for the individual drugs.*

Figure 1: Distribution of end date for most recent MS treatment, study 2301



Source: AENDYbyCMDECOD ANL02FL_Y subset ADCM 2301.jrp

Table 17: Most recent end date of previous MS treatment, study 2301

CMDECOD	Last day limit for eligibility	Total subjects	Max(AENDY)	
			OMB 20 mg	TERI 14 mg
AZATHIOPRINE	180	8	-252	-187
CLADRIBINE	730	3	-2151	-2526
DACLIZUMAB	60	14	-128	-136
DIMETHYL FUMARATE	30	110	-33	-36
FINGOLIMOD	60	22	-68	-63
FINGOLIMOD HYDROCHLORIDE	60	29	-62	-68
GLATIRAMER ACETATE	0	151	-1	-1
INTERFERON	0	4	-129	-62
INTERFERON BETA	0	22	-37	-6
INTERFERON BETA-1A	0	131	-2	-1
INTERFERON BETA-1B	0	63	-1	-1
INTERFERONS	0	2	-39	-3349

CMDECOD	Last day limit for eligibility	Total subjects	Max(AENDY)	
			OMB 20 mg	TERI 14 mg
INVESTIGATIONAL DRUG		2	-2186	
LAQUINIMOD	730	16	-708	-708
METHOTREXATE	180	6		-230
MITOXANTRONE	730	3		-1003
NATALIZUMAB	60	35	-61	-96
OCRELIZUMAB	730	3	-1165	-895
PEGINTERFERON BETA-1A	0	14	-1	-14
TERIFLUNOMIDE	105 (30 with AEP)	13	-58	-48

Source: ANL02FL_Y Subset of ADCM 2301 By (CMDECOD) 2.jmp

The baseline disease characteristics are listed in Table 18. The clinical and MRI characteristics were generally well balanced between the treatment groups. One notable exception is the number of baseline gadolinium-enhancing lesions. There were many more such lesions in the group treated with ofatumumab compared to teriflunomide. The difference in the mean is nominally statistically significant but the median is zero for both groups. The difference appears attributable to a small number of subjects in the ofatumumab group with an unusually large number of lesions (Figure 2).

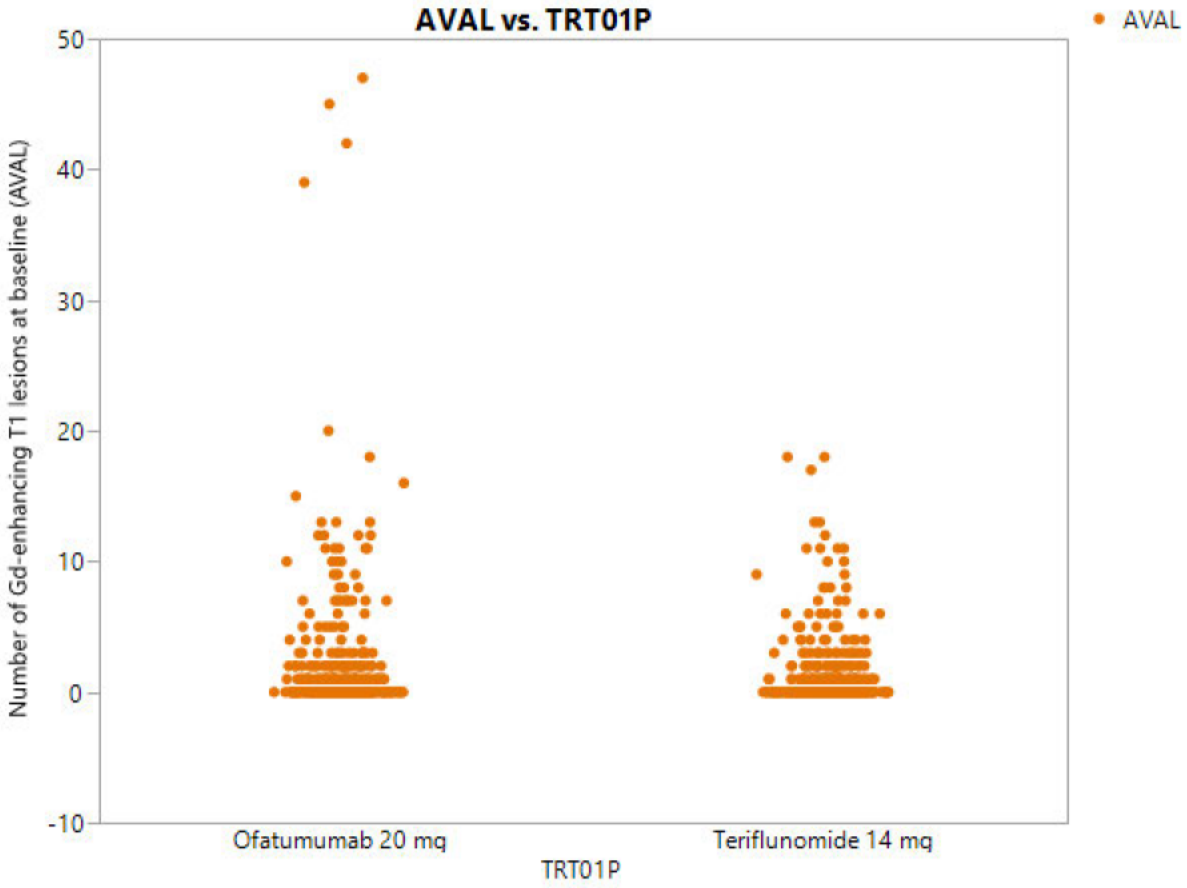
Table 18: Baseline disease characteristics, FAS, study 2301

TRT01P	N	Mean	Std Dev	Min	Max	Median
EDSS						
Ofatumumab 20 mg	465	2.97	1.36	0	6	3
Teriflunomide 14 mg	462	2.94	1.36	0	6.5	3
25FWT						
Ofatumumab 20 mg	465	7.47	7.11	3.15	101	5.75
Teriflunomide 14 mg	462	7.99	9.76	2.5	140	5.65
Duration of MS since diagnosis (years)						
Ofatumumab 20 mg	465	5.77	6.05	0.1	29	3.94
Teriflunomide 14 mg	462	5.64	6.2	0.07	35.8	3.49
Duration of MS since first symptom (years)						
Ofatumumab 20 mg	465	8.36	6.84	0.14	38.7	6.41
Teriflunomide 14 mg	462	8.18	7.21	0.24	35.8	6.69
Number of relapses in the 12 to 24 months prior to screening						
Ofatumumab 20 mg	465	0.89	0.95	0	5	1
Teriflunomide 14 mg	462	0.95	1.21	0	12	1
Number of relapses in the last year prior to screening						
Ofatumumab 20 mg	465	1.22	0.63	0	4	1
Teriflunomide 14 mg	462	1.27	0.69	0	5	1
Time since the onset of the most recent relapse (months)						
Ofatumumab 20 mg	465	7.13	10.5	1.25	119	4.86
Teriflunomide 14 mg	462	7.94	16.1	1.22	265	5.34
Number of Gd-enhancing T1 lesions at baseline						
Ofatumumab 20 mg	465	1.74*	4.93	0	47	0
Teriflunomide 14 mg	462	1.17	2.58	0	18	0
Volume of T2 lesions (cc) at baseline						
Ofatumumab 20 mg	465	13.2	13.3	0.08	85.9	8.78

TRT01P	N	Mean	Std Dev	Min	Max	Median
Teriflunomide 14 mg	462	13.1	14.6	0.05	93.5	7.67

*: p=0.0278, unpaired t-test, two sided

Figure 2: Number of GdE lesions at baseline, study 2301



Source: PARAM_BLT1GDN Subset of ADBS 2301 TRT01P By (AVAL).jmp

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Compliance for each treatment group is shown in Table 19. Compliance was close to 100% for both treatment groups.

Table 19: Percent compliance by treatment group, study 2301

TRT01P	Total	AVAL				
		Mean	Std Dev	Min	Max	Median
Ofatumumab 20 mg	465	98.2	3.99	73.7	100	99.8
Teriflunomide 14 mg	462	98.7	4.91	57.9	100	100

Source: PARAM_COMPLIANCE Subset of ADEX 2301 AVAL By (TRT01P).jmp

Concomitant medications during the RCP

The most common concurrent medications not being used to treat MS or an MS relapse are listed in Table 20.These drugs primarily represent drugs used to treat common general medical conditions or medications used prior to administration of the study drugs.

Table 20: Concurrent medications, not MS-related, RCP, 10% or more of OMB treatment group, study 2301

WHODrug ATC 3	OMB 20 mg	TERI 14 mg
OTHER ANALGESICS AND ANTIPYRETICS	320 (68.8%)	297 (64.3%)
ANTIHISTAMINES FOR SYSTEMIC USE	293 (63.0%)	287 (62.1%)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	156 (33.5%)	157 (34.0%)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	152 (32.7%)	144 (31.2%)
VITAMIN A AND D, INCL. COMBINATIONS OF THE TWO	133 (28.6%)	108 (23.4%)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	132 (28.4%)	123 (26.6%)
HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE	131 (28.2%)	143 (31.0%)
THROAT PREPARATIONS	127 (27.3%)	122 (26.4%)
ANTIDEPRESSANTS	120 (25.8%)	109 (23.6%)
STOMATOLOGICAL PREPARATIONS	108 (23.2%)	106 (22.9%)
OTHER GYNECOLOGICALS	108 (23.2%)	115 (24.9%)
ANTIEPILEPTICS	96 (20.6%)	97 (21.0%)
(missing)	95 (20.4%)	89 (19.3%)
OTHER CARDIAC PREPARATIONS	92 (19.8%)	100 (21.6%)
ANTIINFECTIVES	83 (17.8%)	87 (18.8%)
HYPNOTICS AND SEDATIVES	82 (17.6%)	86 (18.6%)
ANXIOLYTICS	81 (17.4%)	74 (16.0%)
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	76 (16.3%)	93 (20.1%)
MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS	74 (15.9%)	68 (14.7%)
OTHER DERMATOLOGICAL PREPARATIONS	72 (15.5%)	48 (10.4%)
ANTIINFECTIVES AND ANTISEPTICS, EXCL. COMBINATIONS WITH CORTICOSTEROIDS	70 (15.1%)	65 (14.1%)
ANTIINFLAMMATORY AGENTS	66 (14.2%)	56 (12.1%)
UROLOGICALS	63 (13.5%)	65 (14.1%)

WHODrug ATC 3	OMB 20 mg	TERI 14 mg
BETA-LACTAM ANTIBACTERIALS, PENICILLINS	63 (13.5%)	56 (12.1%)
CONTRACEPTIVES FOR TOPICAL USE	60 (12.9%)	62 (13.4%)
OTHER OPHTHALMOLOGICALS	59 (12.7%)	71 (15.4%)
DIRECT ACTING ANTIVIRALS	57 (12.3%)	56 (12.1%)
OPIOIDS	48 (10.3%)	54 (11.7%)

Source: JRevSelADSLFASFL_Y CMCAT3byTRT01PfiltCMCAT_GEN ACAT01_CONMED

Rescue medication

The proportion of subjects with at least one dose of systemic corticosteroids for the treatment of a relapse is shown in Table 21. More frequent use in the teriflunomide group reflects the higher relapse rate in that treatment group.

Table 21: Proportion of subjects with at least one dose of systemic corticosteroids for relapse treatment during the RCP, FAS, study 2301

Planned treatment (TRT01P)	N Rows	N(USUBJID)	% of FAS
Ofatumumab 20 mg	85	85	18.3%
Teriflunomide 14 mg	143	143	31.0%

Source: ACAT01_CONMED Subset of CMCAT2_SYSTEMIC CS Subset of CMSCAT_MSRL Subset EPOCH_TRT Subset ADCM 2301 By (USUBJID, TRT01P) NUSUBJID By (TRT01P).jmp

Efficacy Results – Primary Endpoint

The proportion of subjects who did not have a confirmed relapse was 83.0% for those treated with ofatumumab and 71.4% for those treated with teriflunomide. Seventy-nine subjects treated with ofatumumab had a total of 90 confirmed relapses during the RCP and 132 subjects treated with teriflunomide had a total of 177 relapses (Table 22).

Table 22: Confirmed relapses, FAS, study 2301

Num RLP (AVAL)	Ofatumumab 20 mg			Teriflunomide 14 mg		
	N, Subjects	% of N	RL total	Num subjects	% of N	RL total
0	386	83.0%		330	71.4%	
1	68	14.6%	68	99	21.4%	99
2	11	2.4%	22	23	5.0%	46
3	0	0.0%	0	8	1.7%	24
4	0	0.0%	0	2	0.4%	8
Total	465	100.0%	90	462	100.0%	177

Source: PARAM_NCFRLSTY Subset of ADARR 2301 TRT01P by (AVAL)

The mean and median period of observation for relapses was very similar for the two treatment groups (Table 23).

Table 23: Time in study, years, FAS, study 2301

TRT01P	N	Time in study - Overall (Years)- FAS (AVAL)				
		Mean	Std Dev	Min	Max	Median
Ofatumumab 20 mg	465	1.65	0.41	0.1	2.57	1.63
Teriflunomide 14 mg	462	1.6	0.43	0.04	2.56	1.61

Source: PARAM_TIMESYRS Subset of ADARR 2301 AVAL By (TRT01P).jmp

Unadjusted Annualized Relapse Rate, confirmed relapses

Ofatumumab: 90/769.131 sum of years in study = 0.117
Teriflunomide: 177/741.065 sum of years in study = 0.239
ARR ratio: 0.49

> ***Reviewer Comment:*** *The sponsor's analysis of ARR used a negative binomial model and did adjust for the number of baseline gadolinium-enhancing lesions as well as for region, number of relapses in the preceding year, baseline EDSS, and baseline age. The adjusted ARR using these methods was 0.11 (0.09, 0.14) for the ofatumumab group and 0.22 (0.18, 0.26), yielding a rate ratio of 0.495 (0.374, 0.654), p<0.001.*

The proportion of subjects who did not have a confirmed or unconfirmed relapse was 79.4% for those treated with ofatumumab and 64.1% for those treated with teriflunomide. Ninety-six subjects treated with ofatumumab had a total of 122 confirmed or unconfirmed relapses and 166 subjects treated with teriflunomide had a total of 234 confirmed or unconfirmed relapses (Table 24).

Table 24: All reported relapses, FAS, study 2301

Num RLP (AVAL)	Ofatumumab 20 mg			Teriflunomide 14 mg		
	Num subjects	% of N	RL total	Num subjects	% of N	RL total
0	369	79.4%		296	64.1%	
1	77	16.6%	77	116	25.1%	116
2	15	3.2%	30	35	7.6%	70
3	2	0.4%	6	12	2.6%	36
4	1	0.2%	4	3	0.6%	12
5	1	0.2%	5	0	0.0%	0
Total	465	100.0%	122	462	100.0%	234

Source: PARAM_NRLSTY Subset of ADARR 2301 TRT01P By (AVAL)

Unadjusted Annualized Relapse Rate, all relapses

Ofatumumab: 122/769.131 sum of years in study = 0.159
Teriflunomide: 234/741.065 sum of years in study = 0.316
ARR ratio: 0.503

> *Reviewer Comment: The sponsor reports an ARR of 0.15 for the ofatumumab group and 0.30 for the teriflunomide group using the negative binomial model with the same adjustments.*

The proportion of reported relapses that were confirmed was similar by treatment group (Table 25). This supports a lack of bias in that phase of the relapse identification process.

Table 25: Rate of confirmation of relapses by assigned treatment, FAS

	Ofatumumab	Teriflunomide
All relapses	122	234
Confirmed	90	177
% confirmed	73.8%	75.6%

The ARR was also analyzed for the first 8 weeks of treatment and compared to rates after the first 8 weeks on the assumption that treatment with ofatumumab may require that period of time for full benefit. This is included in Table 27 which also includes a comparison of the unadjusted ARR as calculated by the reviewer and the adjusted rate calculated by the sponsor.

The severity of the relapses, confirmed and unconfirmed, is shown in Table 26. The severity rating criteria are listed in Appendix 13.4. Relapses that were not confirmed tended to be much milder that those that were confirmed. The severity of those that were confirmed as well as those that were not confirmed did not differ greatly by treatment group.

Table 26: Relapse severity rating, confirmed and unconfirmed relapses, FAS, study 2301

AVAL**	Total	Ofatumumab 20 mg				Teriflunomide 14 mg			
		CRIT1FL*							
		N		Y		N		Y	
	N	N	%	N	%	N	%	N	%
0	38	16	50.0%	0	0.0%	22	38.6%	0	0.0%
1	98	8	25.0%	29	31.5%	20	35.1%	41	22.7%
2	154	0	0.0%	46	50.0%	1	1.8%	107	59.1%
3	50	0	0.0%	17	18.5%	0	0.0%	33	18.2%
99	22	8	25.0%	0	0.0%	14	24.6%	0	0.0%
Total	362	32	100.0%	92	100.0%	57	100.0%	181	100.0%

Source: ANL01FL_Y Subset of ADMSREL 2301 TRT01P by CRIR1FL By (AVAL)
*: "Y" = confirmed relapse

**: 0: No worsening; 1: MILD; 2: MODERATE; 3: SEVERE; 99: Missing EDSS

Table 27: ARR calculations, unadjusted vs. adjusted, FAS, study 2301

	OMB	TERI
Confirmed Relapses		
Unadjusted ARR /Adjusted ARR (sponsor)	0.117/0.11	0.239/0.22
Rate ratio reviewer/sponsor	0.49/0.495	
All relapses		
Unadjusted ARR /Adjusted ARR (sponsor)	0.159/0.15	0.316/0.30
Rate ratio reviewer/sponsor	0.50/0.50	
Relapses within 8 weeks or less		
Unadjusted ARR /Adjusted ARR (sponsor)	0.365/0.391	0.326/0.328
Rate ratio reviewer/sponsor	1.12/1.19	
Relapses after 8 weeks		
Unadjusted ARR /Adjusted ARR (sponsor)	0.092/0.095	0.230/0.240
Rate ratio reviewer/sponsor	0.40/0.397	
ARR based on mean of individual subject rates – confirmed relapses		
ARR	0.12	0.29
Rate ratio	0.41	
ARR based on mean of individual subject rates		
ARR	0.17	0.38
Rate ratio	0.45	

Reviewer Comment: The reduction of the ARR attributable to ofatumumab treatment appears to occur predominantly after 8 weeks of treatment.

Data Quality and Integrity

There were no issues regarding the quality or integrity of the data submitted.

Efficacy Results – Secondary and other relevant endpoints

3-month confirmed disability worsening (3MCDW)

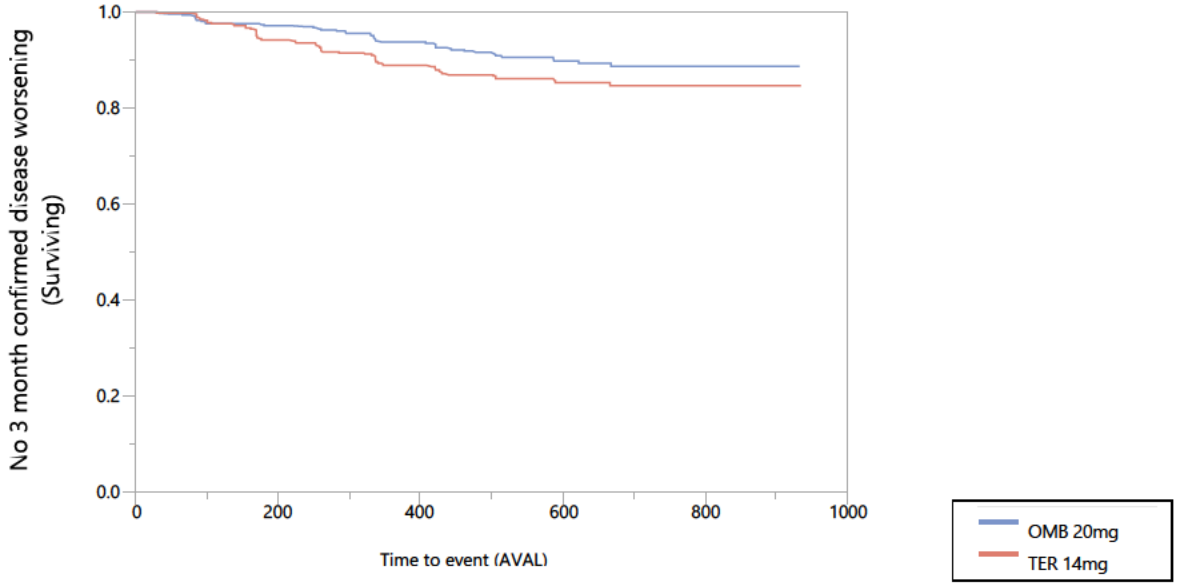
The population for the primary analysis for confirmed disability worsening is the combined population from studies 2301 and 2302 – see Section 7.1.2. The analysis of 3MCDW for the study 2301 population as defined by the sponsor is shown in Figure 3. The analysis of the time to 3-month confirmed disability (T3MCDW) does not clearly exclude periods that started with a relapse, does not exclude the possibility of a relapse during the period of disability, but does exclude confirmation at a relapse. To address the concern that relapses may have influenced

the analysis of T3MCDW, an analysis of the subpopulation from study 2301 that had no relapses at any time during the trial is shown in Figure 4.

Figure 3: Time to 3-month confirmed disability worsening, FAS, study 2301

Product-Limit Survival Fit

Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	45	420	0.672	0.652 (0.445, 0.957) P=0.029
TER 14mg	63	396		
Combined	108	816		

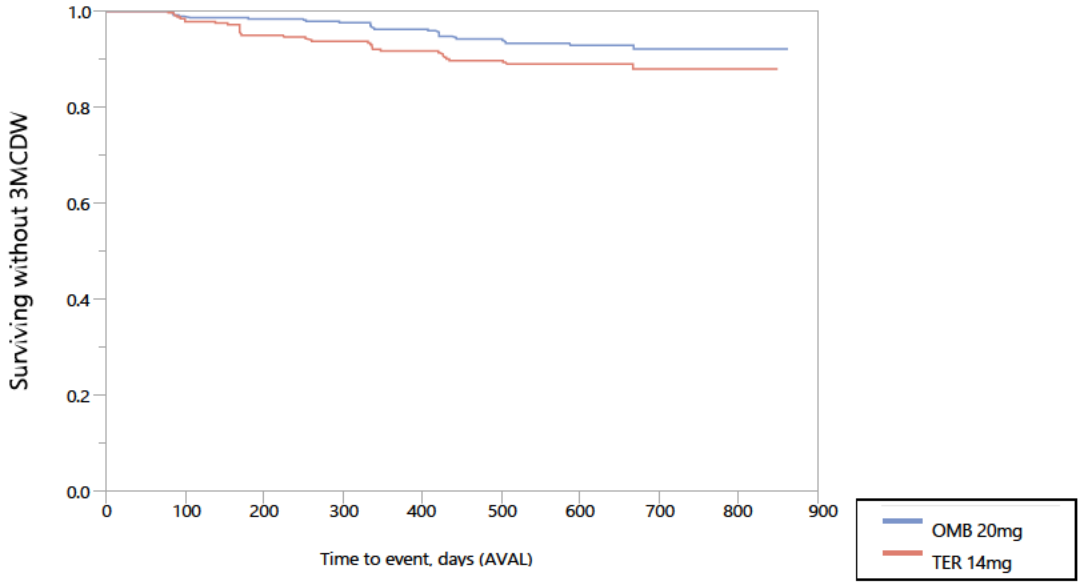
Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.1180	1	0.0424*
Wilcoxon	4.8160	1	0.0282*

Source: PARAM_T3MCDW Subset of STUDYID_COMB157G2301Subset of ADTTCD ISE.jmp

Figure 4: Time to 3-month confirmed disability worsening, no relapses during trial, FAS, study 2301

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL of STUDYID_COMB157G2301Subset of ADTTCD ISE
Censored by CNSR
Censor Code 1
Grouped by TRT01P of STUDYID_COMB157G2301Subset of ADTTCD ISE

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	26	360	0.603	0.564 (0.339, 0.937) p=0.027)
TER 14mg	35	292		
Combined	61	652		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.8364	1	0.0502
Wilcoxon	4.3934	1	0.0361*

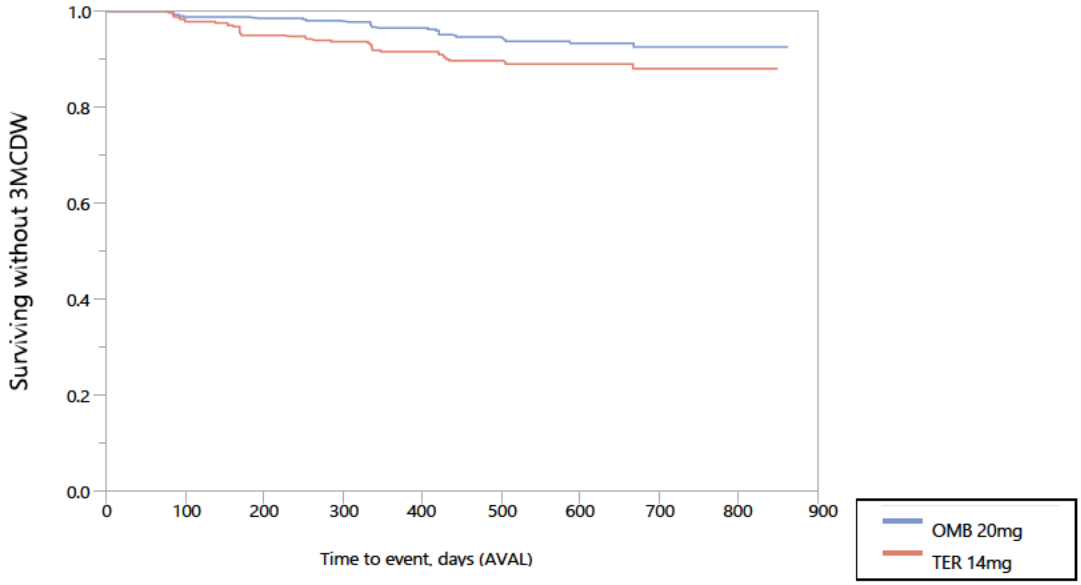
Source: T3MCDW Relapse Free Study 2301 Survival.jrp; PARAM_T3MCDW Subset of Join AVAL_0 of PARAM_NCFRLSTY ADARR 2301 c 2301 subset of ADTTCD ISE.jmp

Reviewer Comment: The above is in agreement with the sponsor's analysis of the relapse-free population provided in Table C2 1.3.6-1a - page 329 of SCE Appendix 1.

An analysis similar to the above analysis but including subjects in the analysis who did have a relapse prior to the start of an otherwise confirmed period of disability worsening, but censoring those subjects at the day of the progression event is shown in **Figure 5.**

Figure 5: Time to 3-month confirmed disability worsening, censor at any preceding relapse, FAS, study 2301

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	26	439	0.604	0.536 (0.344, 0.837) p= 0.006
TER 14mg	41	418		
Combined	67	857		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.6834	1	0.0171*
Wilcoxon	6.7961	1	0.0091*

Source: T3MIPCW Study 2301 Survival.jrp; PARAM_T3MIPCW Subset of STUDYID_COMB157G2301Subset of ADTTCD ISE.jmp

Reviewer Comment: The results for study 2301 are supportive of the analyses of disability worsening in the pooled population. Analyses that at least minimize

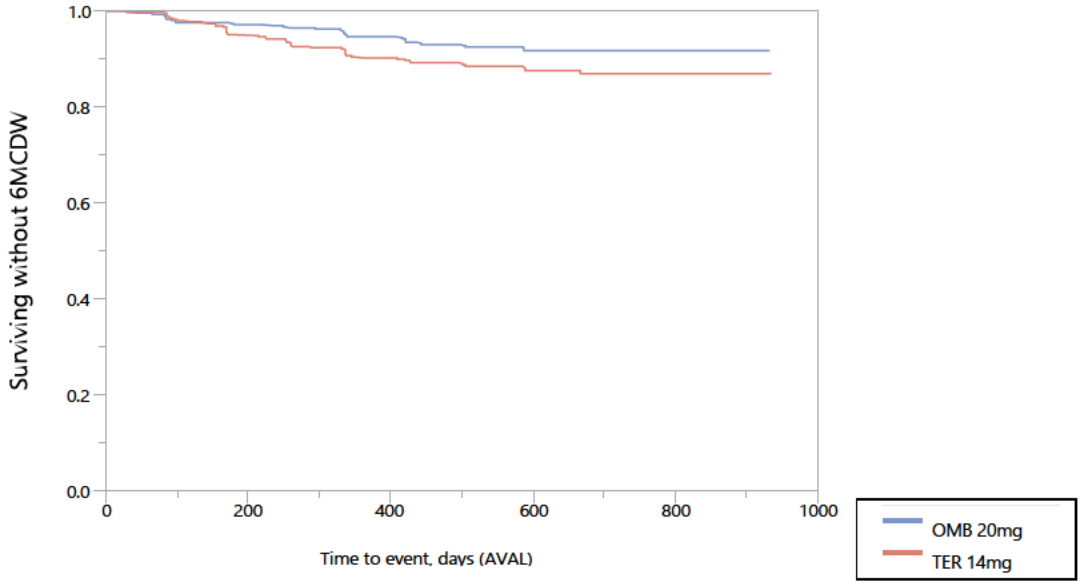
any effect of relapses on the period of disability are more comparable to those typically considered confirmed disability progression.

6-month confirmed disability worsening (6MCDW)

The analysis of time to 6-month confirmed disability worsening for study 2301 alone is shown in Figure 6. Because this analysis did not exclude relapses that may have occurred just before or during the period of worsened disability, an analysis of the population that did not experience a relapse at any time during the trial was conducted and is shown in Figure 7.

Figure 6: Time to 6-month confirmed disability worsening, FAS, study 2301

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	35	430	0.624	0.607 (0.396, 0.390) p=0.022
TER 14mg	53	406		
Combined	88	836		

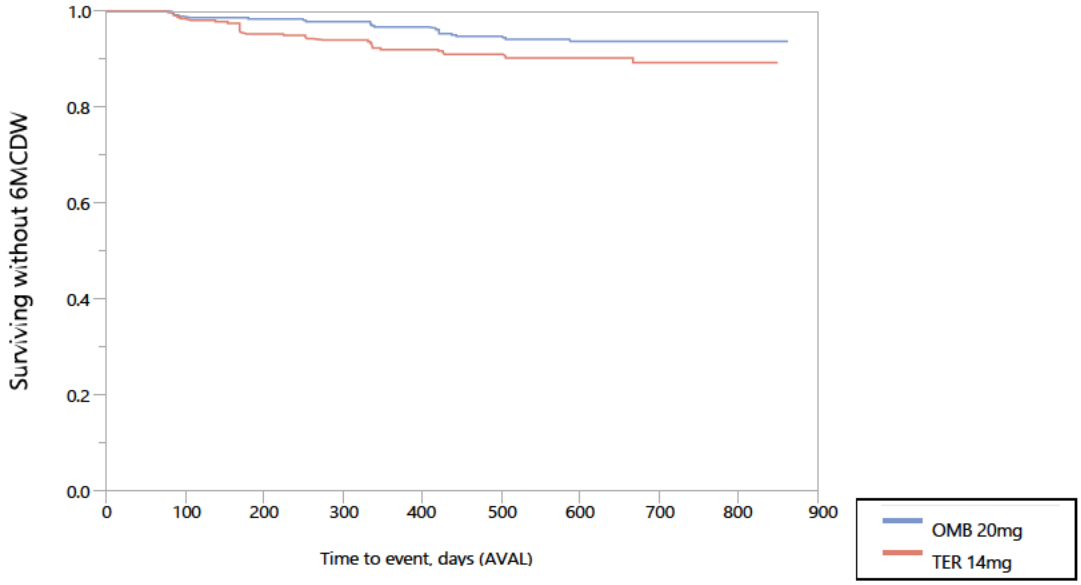
Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.6284	1	0.0314*
Wilcoxon	4.5062	1	0.0338*

Source: T6MCDW Study 2301.jrp

Figure 7: Time to 6-month confirmed disability worsening, subjects with no relapses at any time, FAS, study 2301

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL of STUDYID_COMB157G2301Subset of ADTTCD ISE
Censored by CNSR
Censor Code 1
Grouped by TRT01P of STUDYID_COMB157G2301Subset of ADTTCD ISE

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	22	364	0.577	0.546 (0.315, 0.944) P=0.30
TER 14mg	31	296		
Combined	53	660		

Tests Between Groups

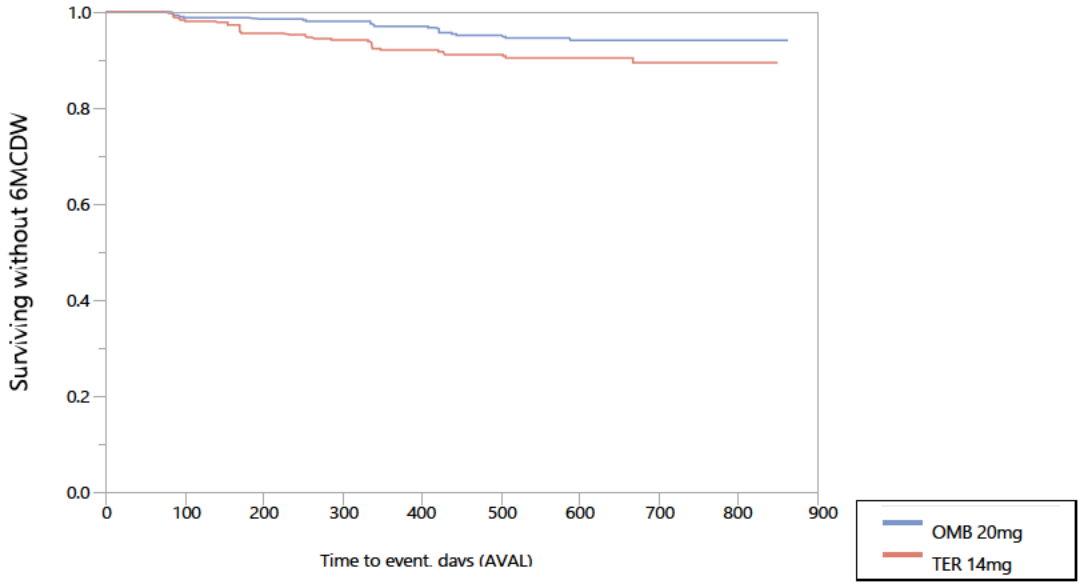
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.8961	1	0.0484*
Wilcoxon	4.0767	1	0.0435*

Source: T6MCDW AVAL_0 NCFRLSTY ADARR 2301 Survival.jrp; T6MCDW Subset of Join AVAL_0 of PARAM_NCFRLSTY ADARR 2301 c 2301 subset of ADTTCD ISE.jmp

An analysis that is similar to the above analysis but including subjects in the analysis who did have a relapse prior to the start of an otherwise confirmed period of disability worsening, but censoring those subjects at the day of the progression event is shown in **Figure 8**.

Figure 8: Time to 6-month confirmed disability worsening, censor at any preceding relapse, FAS, study 2301

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	22	443	0.584	0.525 (0.325, 0.848) P=0.008
TER 14mg	36	423		
Combined	58	866		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.3953	1	0.0202*
Wilcoxon	5.9542	1	0.0147*

Source: T6MIPCW study 2301 Survival.jrp; PARAM_T6MIPCW Subset of STUDYID_COMB157G2301Subset of ADTTCD ISE.jmp

Reviewer Comment: Although the odds ratio and hazard ratio are slightly higher when subjects with relapses are excluded or censored if they occurred prior to a period of disability worsening, the results clearly favor ofatumumab treatment compared to teriflunomide which itself has shown a benefit on disability in other studies.

MRI lesions

Number of gadolinium-enhancing lesions per scan

For the treatment period there were 0.018 lesions per scan for those treated with ofatumumab and 0.645 per scan for those treated with teriflunomide. The percent reduction was 93.8%. The sponsor's analysis using a negative binomial model and adjusting for region, age and the number of GdE lesions at baseline yielded adjusted means of 0.0317 lesions per scan for ofatumumab and 0.514 lesions per scan for teriflunomide for a 93.8% reduction.

Annualized rate of new T2 lesions

For the treatment period, the annual rate of new T2 lesions was 1.11 for the ofatumumab group and 5.16 for the teriflunomide group. The percent reduction was 78.5%. The sponsor's analysis using a negative binomial model and adjusting for region, age and the baseline volume of T2 lesions yielded an adjusted mean annual rate of 0.72 for the ofatumumab group and 4.00 for the teriflunomide group (to the end of study visit). The percent reduction was 82.0%.

Patient-reported outcome measure – Multiple Sclerosis Impact scale (MSIS-29)

The sponsor reports a reduction (reduced impact) of physical impact score in the MSIS-29 with ofatumumab treatment. As this was an exploratory endpoint, it will not be analyzed further in this review.

Dose/Dose Response

A single dose was studied in studies 2301 and 2302.

Durability of Response

The durability of the response was not studied.

Persistence of Effect

The persistence of the response was not studied.

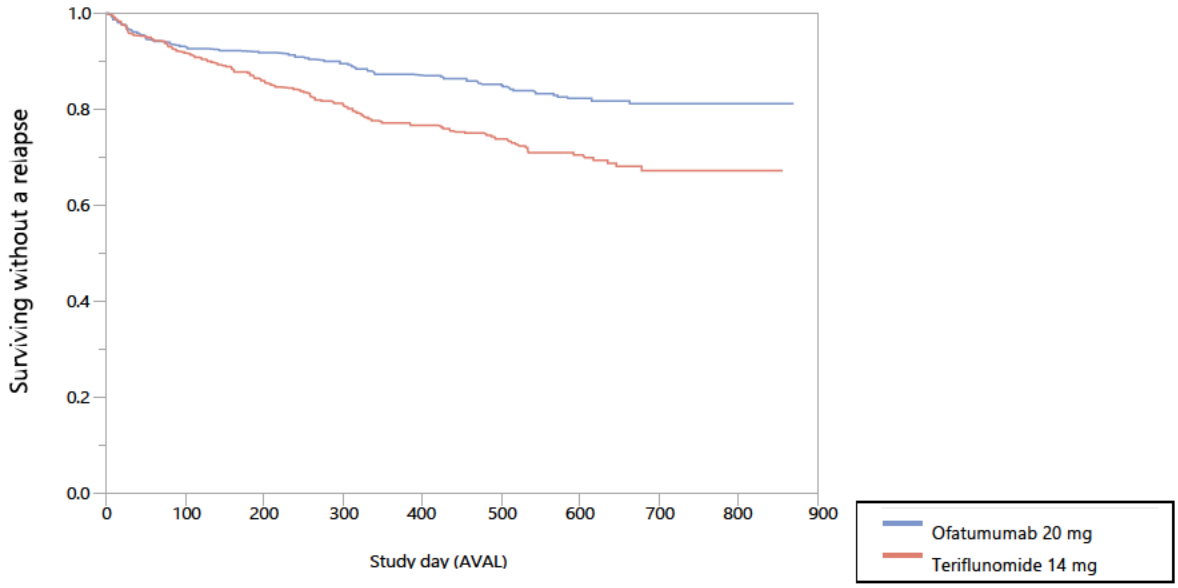
Additional Analyses Conducted on the Individual Trial

Time to first confirmed relapse

The time to the first confirmed relapse was significantly prolonged with ofatumumab treatment (Figure 9). If all relapses are included, the odds ratio is 0.464, p <0.0001.

Figure 9: Time to first confirmed relapse, study 2301

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR
Ofatumumab 20 mg	79	386	0.512
Teriflunomide 14 mg	132	330	
Combined	211	716	

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	18.3612	1	<.0001*
Wilcoxon	16.4552	1	<.0001*

Source: Time to first confirmed relapse study 2301.jrp

6.2. Study COMB157G2302: A Randomized, double-blind, double dummy, parallel group study comparing the efficacy and safety of ofatumumab vs. teriflunomide in patients with relapsing multiple sclerosis

6.2.1. Study Design

Overview and Objective

Trial Design

The design of study 2302 is identical to that of study 2301.

Study Endpoints

The endpoints for study 2302 are the same as those for study 2301.

Statistical Analysis Plan

The plan for statistical analysis of study 2302 is the same as for study 2301.

Protocol Amendments

The amendments for study 2302 are the same as those for study 2301.

6.2.2. Study Results

Compliance with Good Clinical Practices

The sponsor reports that "All studies were conducted in full compliance with current Good Clinical Practices. Studies G2301, G2302 and G2102 were closely monitored by Novartis personnel or a contract organization for compliance to the protocol, Novartis standard operating procedures, and applicable regulatory guidance. Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. The subject was provided as much time as necessary to review the document, to inquire about details of the study, and to decide whether or not to participate in the study. The informed consent was signed and dated by the study subject and by the person who conducted the informed consent discussion."

Financial Disclosure

Six investigators who participated in study 2302 had reportable financial interests. Two held stock in Novartis and 4 had financial interests of other sorts, primary research grants to their institutions. The number of investigators with such interests are not likely to have influenced the trial results.

Patient Disposition

Nine hundred and fifty-five (955) patients were randomized, 481 to treatment with ofatumumab and 474 to treatment with teriflunomide. The proportion of subjects who completed the study on treatment was 80% for the ofatumumab group and 78.5% for the teriflunomide group (Table 28). The reasons for discontinuation of treatment are listed in Table 29. The reasons for discontinuation of treatment were reasonably balanced by treatment group.

Table 28: Disposition of subjects by treatment status, ITT, study 2302

End of Treatment Status (EOTSTT)	Total		OMB 20 mg		TERI 14 mg	
	N	%	N	%	N	%
COMPLETED	757	79.3%	385	80.0%	372	78.5%
DISCONTINUED	198	20.7%	96	20.0%	102	21.5%
Total	955	100.0%	481	100.0%	474	100.0%

Source: FASFL_Y subset of ADSL 2302 TRT01P By (EOTSTT)

Table 29: Reasons for discontinuation of treatment, ITT, study 2302

Reason for Discontinuation of Treatment (DCTREAS)	Total		OMB 20 mg		TERI 14 mg	
	N	%	N	%	N	%
SUBJECT/GUARDIAN DECISION	72	7.5%	35	7.3%	37	7.8%
PHYSICIAN DECISION	57	6.0%	25	5.2%	32	6.8%
ADVERSE EVENT	50	5.2%	27	5.6%	23	4.9%
LOST TO FOLLOW-UP	12	1.3%	8	1.7%	4	0.8%
PREGNANCY	5	0.5%	1	0.2%	4	0.8%
TECHNICAL PROBLEMS	2	0.2%	0	0.0%	2	0.4%
Total	198	20.7%	96	20.0%	102	21.5%

EOTSTT_DISC Subset of FASFL_Y subset of ADSL 2302 TRT01P By (DCTREAS)

Reviewer Comment: Although more balanced by treatment group compared to study 2301, the number of subjects discontinued from treatment due to "Subject/guardian decision" and "Physician decision" seems unusually large at a total of 12.5% for the ofatumumab group and 14.6% for the teriflunomide

group. Relatively few CRFs are submitted from these subjects. Of those that were available, there was usually no additional comment or the comments from the investigator were consistent with the recorded reason for discontinuation.

Of the 96 subjects in the ofatumumab group who discontinued treatment prematurely, 11 completed the RCP off medication and one (subject [redacted] (b) (6)) was considered "ongoing" at the end of the RCP. Of the 102 subjects in the teriflunomide group who discontinued treatment prematurely, 17 completed the study off treatment and one (subject [redacted] (b) (6)) was considered ongoing at the end of the RCP.

Table 30: End of Study status, ITT, study 2302

End of Study Status (EOSSTT)	Total		OMB 20 mg		TERI 14 mg	
	N	%	N	%	N	%
COMPLETED	786	82.3%	397	82.5%	389	82.1%
DISCONTINUED	167	17.5%	83	17.3%	84	17.7%
ONGOING	2	0.2%	1	0.2%	1	0.2%
Total	955	100.0%	481	100.0%	474	100.0%

Source: FASFL_Y subset of ADSL 2302 TRT01P by (EOSSTT)

Table 31: Reasons for Discontinuation from study, ITT, study 2302

Reason for Discontinuation from Study (DCSREAS)	Total		OMB 20 mg		TERI 14 mg	
	N	%	N	%	N	%
ADVERSE EVENT	29	3.0%	16	3.3%	13	2.7%
LACK OF EFFICACY	16	1.7%	7	1.5%	9	1.9%
LOST TO FOLLOW-UP	14	1.5%	9	1.9%	5	1.1%
NON-COMPLIANCE WITH STUDY TREATMENT	3	0.3%	2	0.4%	1	0.2%
PHYSICIAN DECISION	25	2.6%	14	2.9%	11	2.3%
PREGNANCY	4	0.4%	1	0.2%	3	0.6%
PROTOCOL DEVIATION	2	0.2%	2	0.4%	0	0.0%
SUBJECT/GUARDIAN DECISION	73	7.6%	32	6.7%	41	8.6%
TECHNICAL PROBLEMS	1	0.1%	0	0.0%	1	0.2%
	167	17.5%	83	17.3%	84	17.7%

Source: EOSTT_DISC Subset of FASFL_Y subset of ADSL 2302 TRT01P By (DCSREAS)

The most common TEAE that resulted in discontinuation of treatment in the ofatumumab group was a reduction in IgM or IgG or both (see Table 68 and Table 69). The most common TEAE that resulted in discontinuation of treatment in the teriflunomide group was related to elevation of liver transaminases (see Table 68).

Randomization evenly distributed by the major regions with approximately 25% coming from the US, Canada and Australia (Table 32). Approximately 20% of those randomized were from the US, and 20% from Russia. No other country randomized more than 10% of the patients. No single site randomized more than 5% of the patients.

Table 32: Randomization by region, FAS, study 2302

REGION1	OMB 20 mg		TER 14 mg	
	N	%	N	%
Eastern Europe	117	24.3	116	24.5
North America and AUS	107	22.2	107	22.6
Others	132	27.4	130	27.4
Western Europe	125	26	121	25.5

Source: FASFL_Y subset of ADSL 2302 TRT01P By (REGION1).jmp

Protocol Violations/Deviations

One or more protocol deviations occurred in 111 (23.1%) of subjects in the ofatumumab group and in112 (23.6%) of the teriflunomide group (Table 33).

Reviewer Comment: Protocol deviations were less frequent in study 2302 compared to study 2301. They are unlikely to affect the trial results.

Table 33: Protocol deviations, FAS population, study 2302

Protocol Deviation Coded Term	Protocol Deviation Term	Ofatumumab 20 mg	Teriflunomide 14 mg
OTHER DEVIATION	EDSS rater acted as a treating physician or treating physician acted as EDSS rater	4 (0.8%)	3 (0.6%)
	Investigator reviewing EDSS results or Independent EDSS Rater reviewing patient's medical records other than EDSS assessment-related records	9 (1.9%)	4 (0.8%)
	Investigator reviewing MRI and/or MRI report	20 (4.2%)	20 (4.2%)
	Not following per protocol blinding procedures such that the integrity of the study is compromised	7 (1.5%)	5 (1.1%)
PROHIBITED CONCOMITANT MEDICATION	Any other immunomodulatory or disease-modifying MS treatment such as fingolimod, interferon beta, glatiramer acetate, dimethyl fumarate or systemic corticosteroids while taking double-blind treatment	3 (0.6%)	0 (0.0%)
	Oral activated charcoal or cholestyramine while taking double-blind treatment	0 (0.0%)	1 (0.2%)
SELECTION CRITERIA NOT MET	(missing)	0 (0.0%)	0 (0.0%)
	Alkaline phosphatase (AP) greater than 1.5 times the ULN range prior to randomization or missing	1 (0.2%)	0 (0.0%)
	Any other clinically significant laboratory assessment as determined by the Investigator (e.g. significant anemia, neutropenia, thrombocytopenia, signs of impaired bone marrow function)	0 (0.0%)	1 (0.2%)
	AST (SGOT) or ALT (SGPT) greater than 1.5 times the ULN range prior to randomization or missing	2 (0.4%)	0 (0.0%)
	Dimethyl fumarate within 1 month prior to randomization	1 (0.2%)	0 (0.0%)
	Disease duration of more than 10 years in patients with EDSS score of 2 or less	7 (1.5%)	10 (2.1%)

Protocol Deviation Coded Term	Protocol Deviation Term	Ofatumumab 20 mg	Teriflunomide 14 mg
	DNA sample taken prior to signing pharmacogenetic informed consent or pharmacogenetic informed consent is No or missing	1 (0.2%)	0 (0.0%)
	EDSS score at screening 0 to 5.5 and not missing	1 (0.2%)	5 (1.1%)
	Gamma-glutamyl-transferase (GGT) greater than 2 times the ULN range prior to randomization or missing	1 (0.2%)	0 (0.0%)
	History of malignancy of any organ system within the past 5 years, regardless of evidence of local recurrence or metastases.	1 (0.2%)	0 (0.0%)
	Lymphocyte count < 800/mm3 (< 0.8 10E9/L) prior to randomization or missing data	2 (0.4%)	4 (0.8%)
	Missing serum pregnancy test at screening	6 (1.2%)	4 (0.8%)
	One or more relapse in the 1 year prior to screening OR 2 or more relapses in the 2 years prior to screening OR a positive GDE MRI scan in the year prior to randomization	1 (0.2%)	0 (0.0%)
	Patients at risk of developing or having reactivation of syphilis or tuberculosis	47 (9.8%)	43 (9.1%)
	Patients currently treated with or needing treatment with cholestyramine (unless for accelerated teriflunomide elimination) during the study	1 (0.2%)	3 (0.6%)
	Patients with an active chronic disease (or stable but treated) of the immune system other than MS or with a known immunodeficiency syndrome	0 (0.0%)	1 (0.2%)
	Patients with suicidal ideation in the past 6 months or suicidal behavior in the past 2 years prior to randomization	2 (0.4%)	2 (0.4%)
	Positive results of screening period testing for serological markers for hepatitis A, B, C, and E indicating acute or chronic infection or missing data	1 (0.2%)	0 (0.0%)
	Serum IgG or IgM < Lower limit of normal	3 (0.6%)	4 (0.8%)
	Systemic steroid or adrenocorticotropic hormone treatment within 30 days prior to Screening MRI	1 (0.2%)	1 (0.2%)
	Teriflunomide within 3.5 months prior to randomization or 1 month prior to randomization following accelerated elimination procedure and documented teriflunomide plasma level below 0.02 mg/L	0 (0.0%)	1 (0.2%)
	White blood cell (WBC) count < 3,500/mm3 (< 3.5 x 10E9/L) prior to randomization or missing data	3 (0.6%)	3 (0.6%)
	Women of child-bearing potential not using highly effective contraception	2 (0.4%)	3 (0.6%)
TREATMENT DEVIATION	Patient received damaged or expired study drug	3 (0.6%)	5 (1.1%)
	Patient received incorrect study drug	5 (1.0%)	2 (0.4%)
	Site or global team unintentionally unblinded to the treatment allocation of an individual patient by vendor (including drug supply)	0 (0.0%)	2 (0.4%)
	Subjects(filtered)	481 (100.0%)	474 (100.0%)

Protocol Deviation Coded Term	Protocol Deviation Term	Ofatumumab 20 mg	Teriflunomide 14 mg
	1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRevSelADSL2302FASFL_Y DVDECODbyDVTERMbyTRT01P

APPEARS THIS WAY ON ORIGINAL

Table of Demographic Characteristics

The demographic characteristics of the population in study 2302 are generally similar to those of study 2301 (Table 34). There are no major differences between the treatment group. The population is reasonably typical of patients with relapsing forms of MS.

Table 34: Baseline demographic characteristics, study 2302

Subgroup	Ofatumumab 20 mg (N = 481) n (%)	Teriflunomide 14 mg (N = 474) n (%)	Total (N = 955) n (%)
Sex			
Female	319 (66.3)	319 (67.3)	638 (66.8)
Male	162 (33.7)	155 (32.7)	317 (33.2)
Age			
Mean	37.89	38.16	38.02
Standard Deviation	9.28	9.48	9.38
Minimum	18	18	18
Median	38	38	38
Maximum	56	56	56
Age Group			
Age Group 1 (AGE < 40)	266 (55.3)	270 (57.0)	536 (56.1)
Age Group 2 (40 <= AGE)	215 (44.7)	204 (43.0)	419 (43.9)
AGE Group 1			
> 55 Years	2 (0.4)	1 (0.2)	3 (0.3)
18 to 30 Years	129 (26.8)	115 (24.3)	244 (25.5)
31 to 40 Years	154 (32.0)	167 (35.2)	321 (33.6)
41 to 55 Years	196 (40.7)	191 (40.3)	387 (40.5)
Race			
Asian	21 (4.4)	19 (4.0)	40 (4.2)
Black or African American	13 (2.7)	18 (3.8)	31 (3.2)
Missing	9 (1.9)	6 (1.3)	15 (1.6)
Other	20 (4.2)	14 (3.0)	34 (3.6)
White	418 (86.9)	417 (88.0)	835 (87.4)
Ethnicity			
Hispanic or Latino	39 (8.1)	35 (7.4)	74 (7.7)
Missing	91 (18.9)	75 (15.8)	166 (17.4)

Subgroup	Ofatumumab 20 mg (N = 481) n (%)	Teriflunomide 14 mg (N = 474) n (%)	Total (N = 955) n (%)
Not Hispanic or Latino	351 (73.0)	364 (76.8)	715 (74.9)
Region			
Africa	5 (1.0)	6 (1.3)	11 (1.2)
Asia	23 (4.8)	20 (4.2)	43 (4.5)
Canada	10 (2.1)	3 (0.6)	13 (1.4)
Europe	336 (69.9)	332 (70.0)	668 (69.9)
Other	0 (0.0)	1 (0.2)	1 (0.1)
South America	10 (2.1)	9 (1.9)	19 (2.0)
United States	97 (20.2)	103 (21.7)	200 (20.9)

Source: DM_TOOL 2302

General Medical Conditions

Medical conditions that ended prior to the start of the study were most commonly previous surgical procedures such as a tonsillectomy, cholecystectomy, and appendectomy. The remaining conditions were relatively infrequent and are generally not relevant to the study results.

The most common medical conditions that were concurrent during the trial are listed by Body System in (Table 35). Depression was the single most common individual term (Table 36). Of the psychiatric disorders, terms that included depression were the most common preferred terms and occurred in 13.5% of the ofatumumab group and in 13.7% of the teriflunomide group. Headache was the most common nervous system disorder, occurring in 7.7% of ofatumumab subjects and in 9.5% of teriflunomide subjects. Migraine occurred in 5.4% of ofatumumab subjects and in 10.5% of teriflunomide subjects. Vitamin D deficiency was a concurrent condition in 7.5%. Other selected concurrent medical disorders of interest are listed by SOC in Table 37.

Table 35: Concurrent medical disorders by MHSOC, 10% or more of OMB group, study 2302

Body System or Organ Class	Ofatumumab 20 mg	Teriflunomide 14 mg
Nervous system disorders	120 (24.9%)	136 (28.7%)
Psychiatric disorders	114 (23.7%)	103 (21.7%)
Musculoskeletal and connective tissue disorders	99 (20.6%)	91 (19.2%)
Metabolism and nutrition disorders	78 (16.2%)	84 (17.7%)
Gastrointestinal disorders	82 (17.0%)	78 (16.5%)
Immune system disorders	68 (14.1%)	71 (15.0%)
Vascular disorders	56 (11.6%)	57 (12.0%)

Body System or Organ Class	Ofatumumab 20 mg	Teriflunomide 14 mg
Subjects(filtered)	329 (68.4%)	322 (67.9%)
1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRevSelADSLFASFL_Y MHSOCbyTRT01PfiltMHCAT_GEN MHENRF_DURING AFTER

Table 36: Concurrent medical disorders by MHDECOD, 5% or more of OMB population, study 2302

Dictionary Derived Term	Ofatumumab 20 mg	Teriflunomide 14 mg
Depression	63 (13.1%)	64 (13.5%)
Hypertension	46 (9.6%)	48 (10.1%)
Anxiety	47 (9.8%)	41 (8.6%)
Headache	37 (7.7%)	45 (9.5%)
Vitamin D deficiency	36 (7.5%)	40 (8.4%)
Migraine	26 (5.4%)	50 (10.5%)
Insomnia	34 (7.1%)	37 (7.8%)
Seasonal allergy	34 (7.1%)	36 (7.6%)
Drug hypersensitivity	29 (6.0%)	27 (5.7%)
Fatigue	24 (5.0%)	31 (6.5%)
Back pain	25 (5.2%)	27 (5.7%)
Hypothyroidism	25 (5.2%)	21 (4.4%)
Subjects(filtered)	329 (68.4%)	322 (67.9%)
1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRevSelADSLFASFL_Y MHDECODbyTRT01PfiltMHCAT_GEN MHENRF_DURING AFTER

Table 37: Selected concurrent medical disorders, by MHSOC, study 2302

Body System or Organ Class	Dictionary Derived Term	OMB 20 mg	TERI 14 mg
Blood and lymphatic system disorders	Anaemia	6 (1.2%)	6 (1.3%)
	Hypochromic anaemia	1 (0.2%)	0 (0.0%)
	Iron deficiency anaemia	9 (1.9%)	4 (0.8%)
Endocrine disorders	Autoimmune hypothyroidism	0 (0.0%)	1 (0.2%)
	Autoimmune thyroiditis	3 (0.6%)	5 (1.1%)
	Basedow's disease	1 (0.2%)	1 (0.2%)
	Goitre	1 (0.2%)	5 (1.1%)
	Hyperthyroidism	1 (0.2%)	2 (0.4%)
	Hypothyroidism	25 (5.2%)	21 (4.4%)
	Thyroiditis	1 (0.2%)	0 (0.0%)
	Thyroiditis chronic	1 (0.2%)	0 (0.0%)
Gastrointestinal disorders	Chronic gastritis	17 (3.5%)	11 (2.3%)
	Constipation	13 (2.7%)	15 (3.2%)
	Gastritis	6 (1.2%)	6 (1.3%)
	Gastritis erosive	0 (0.0%)	1 (0.2%)
	Gastrooesophageal reflux disease	17 (3.5%)	25 (5.3%)
	Irritable bowel syndrome	5 (1.0%)	7 (1.5%)

Body System or Organ Class	Dictionary Derived Term	OMB 20 mg	TERI 14 mg
General disorders and administration site conditions	Fatigue	24 (5.0%)	31 (6.5%)
	Gait disturbance	6 (1.2%)	5 (1.1%)
Immune system disorders	Drug hypersensitivity	29 (6.0%)	27 (5.7%)
	Immunodeficiency	1 (0.2%)	0 (0.0%)
Infections and infestations	Genital herpes	2 (0.4%)	0 (0.0%)
	Genital herpes simplex	0 (0.0%)	1 (0.2%)
	Herpes ophthalmic	0 (0.0%)	1 (0.2%)
	Herpes simplex	4 (0.8%)	8 (1.7%)
	Herpes virus infection	0 (0.0%)	1 (0.2%)
	Oral herpes	6 (1.2%)	12 (2.5%)
Investigations	JC polyomavirus test positive	4 (0.8%)	4 (0.8%)
	Vitamin D decreased	1 (0.2%)	2 (0.4%)
Metabolism and nutrition disorders	Vitamin D deficiency	36 (7.5%)	40 (8.4%)
Nervous system disorders	Epilepsy	4 (0.8%)	2 (0.4%)
	Headache	37 (7.7%)	45 (9.5%)
	Migraine	26 (5.4%)	50 (10.5%)
	Migraine with aura	2 (0.4%)	1 (0.2%)
	Migraine without aura	3 (0.6%)	4 (0.8%)
	Neuralgia	10 (2.1%)	13 (2.7%)
	Neuropathy peripheral	6 (1.2%)	8 (1.7%)
	Optic neuritis	1 (0.2%)	8 (1.7%)
	Restless legs syndrome	4 (0.8%)	6 (1.3%)
	Seizure	4 (0.8%)	2 (0.4%)
	Tension headache	10 (2.1%)	2 (0.4%)
	Trigeminal neuralgia	4 (0.8%)	4 (0.8%)
Psychiatric disorders	Anxiety	47 (9.8%)	41 (8.6%)
	Anxiety disorder	3 (0.6%)	1 (0.2%)
	Depressed mood	2 (0.4%)	1 (0.2%)
	Depression	63 (13.1%)	64 (13.5%)
	Generalised anxiety disorder	2 (0.4%)	0 (0.0%)
	Insomnia	34 (7.1%)	37 (7.8%)
Respiratory, thoracic and mediastinal disorders	Asthma	19 (4.0%)	17 (3.6%)
	Sleep apnoea syndrome	7 (1.5%)	5 (1.1%)
Vascular disorders	Essential hypertension	1 (0.2%)	3 (0.6%)
	Hypertension	46 (9.6%)	48 (10.1%)
	Labile hypertension	1 (0.2%)	0 (0.0%)
Subtotal	Subjects(filtered)	329 (68.4%)	322 (67.9%)
Total	1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRevSelADSLFASFL_Y MHSOCbyTRT01PfiltMHCAT_GEN MHENRF_DURING AFTER

Other Baseline Characteristics (disease characteristics, important concomitant drugs)

Previous treatment for MS

Interferons and glatiramer acetate were the most common previous MS treatments (Table 38). Treatment naïve patients accounted for 40.5% of the ofatumumab treatment group and for 38.2% of the teriflunomide treatment group. The most recent treatment for MS is listed in Table 39.

Table 38: All previous treatments for MS, FAS, study 2302

Standardized Medication Name	OMB 20 mg	TERI 14 mg
INTERFERON BETA-1A	126 (26.2%)	131 (27.6%)
GLATIRAMER ACETATE	118 (24.5%)	149 (31.4%)
INTERFERON BETA-1B	61 (12.7%)	53 (11.2%)
DIMETHYL FUMARATE	36 (7.5%)	44 (9.3%)
FINGOLIMOD HYDROCHLORIDE	26 (5.4%)	33 (7.0%)
NATALIZUMAB	26 (5.4%)	20 (4.2%)
FINGOLIMOD	13 (2.7%)	10 (2.1%)
TERIFLUNOMIDE	13 (2.7%)	9 (1.9%)
PEGINTERFERON BETA-1A	10 (2.1%)	12 (2.5%)
INTERFERONS	10 (2.1%)	14 (3.0%)
INTERFERON BETA	10 (2.1%)	9 (1.9%)
DACLIZUMAB	8 (1.7%)	7 (1.5%)
MITOXANTRONE	6 (1.2%)	2 (0.4%)
INVESTIGATIONAL DRUG	6 (1.2%)	10 (2.1%)
AZATHIOPRINE	6 (1.2%)	4 (0.8%)
LAQUINIMOD	2 (0.4%)	7 (1.5%)
METHOTREXATE	1 (0.2%)	0 (0.0%)
SIPONIMOD	1 (0.2%)	1 (0.2%)
INTERFERON	1 (0.2%)	0 (0.0%)
MITOXANTRONE HYDROCHLORIDE	1 (0.2%)	1 (0.2%)
CYCLOPHOSPHAMIDE	0 (0.0%)	1 (0.2%)
OZANIMOD	0 (0.0%)	1 (0.2%)
PEGINTERFERON	0 (0.0%)	1 (0.2%)
CLADRIBINE	0 (0.0%)	1 (0.2%)
Subjects(filtered)	286 (59.5%)	293 (61.8%)
1stColItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRevSelADSLFASFL_Y CMDECODbyTRT01PfiltANL01FL_Y

Table 39: Most recent MS treatment, FAS, study 2302

Standardized Medication Name	OMB 20 mg	TERI 14 mg
GLATIRAMER ACETATE	74 (15.4%)	82 (17.3%)
INTERFERON BETA-1A	66 (13.7%)	68 (14.3%)
INTERFERON BETA-1B	41 (8.5%)	31 (6.5%)
DIMETHYL FUMARATE	30 (6.2%)	31 (6.5%)
FINGOLIMOD HYDROCHLORIDE	15 (3.1%)	21 (4.4%)
NATALIZUMAB	13 (2.7%)	5 (1.1%)
TERIFLUNOMIDE	10 (2.1%)	8 (1.7%)
PEGINTERFERON BETA-1A	8 (1.7%)	9 (1.9%)

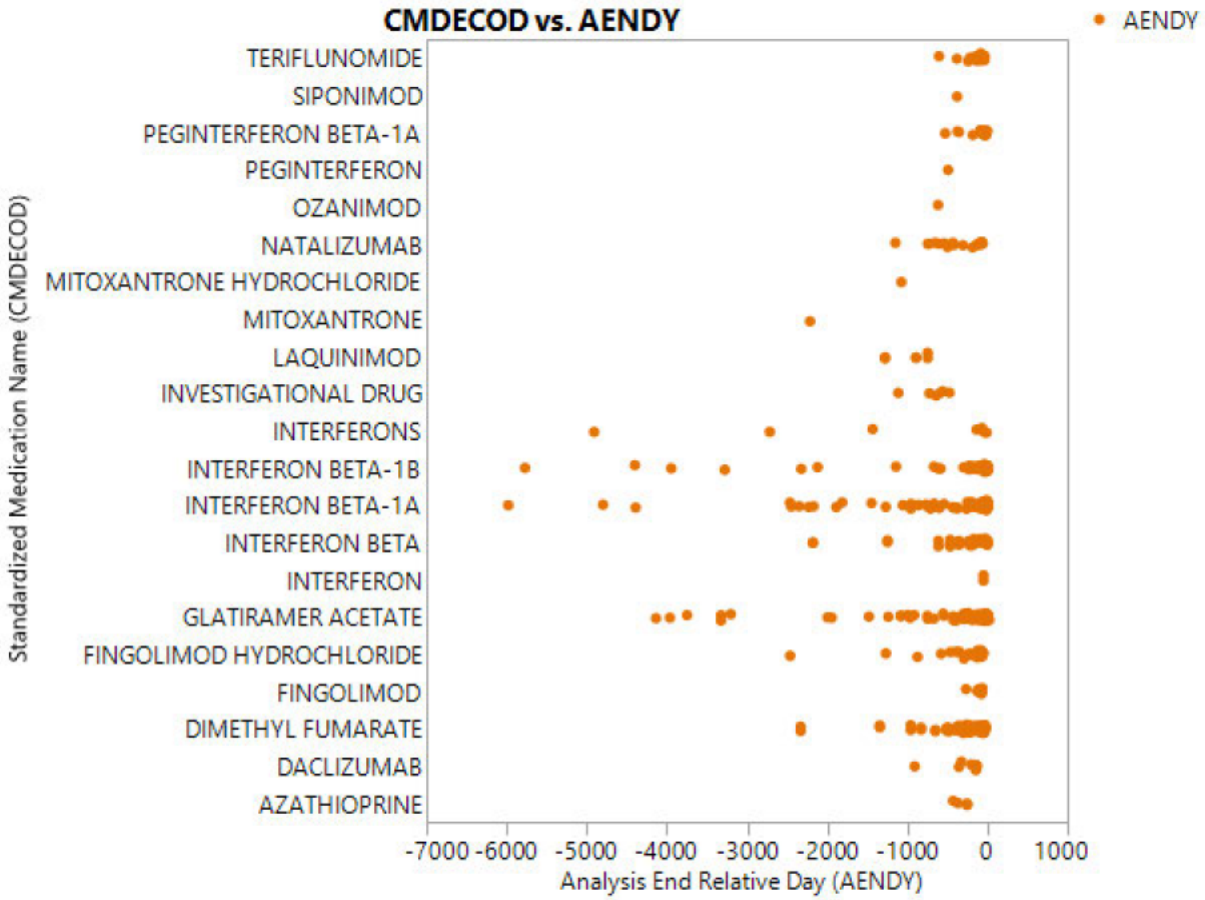
Standardized Medication Name	OMB 20 mg	TERI 14 mg
DACLIZUMAB	8 (1.7%)	5 (1.1%)
FINGOLIMOD	7 (1.5%)	6 (1.3%)
INTERFERON BETA	7 (1.5%)	8 (1.7%)
INVESTIGATIONAL DRUG	2 (0.4%)	4 (0.8%)
INTERFERONS	2 (0.4%)	5 (1.1%)
SIPONIMOD	1 (0.2%)	0 (0.0%)
INTERFERON	1 (0.2%)	0 (0.0%)
AZATHIOPRINE	1 (0.2%)	3 (0.6%)
MITOXANTRONE	0 (0.0%)	1 (0.2%)
MITOXANTRONE HYDROCHLORIDE	0 (0.0%)	1 (0.2%)
OZANIMOD	0 (0.0%)	1 (0.2%)
PEGINTERFERON	0 (0.0%)	1 (0.2%)
LAQUINIMOD	0 (0.0%)	3 (0.6%)
Subjects(filtered)	286 (59.5%)	293 (61.8%)
1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRevSelADSLFASFL_Y CMDECODbyTRT01PfiltANL02FL_Y

The distribution of the relative study day that the last dose of the most recent treatment for MS was given is shown in Figure 10. The most recent relative study day of previous treatment for MS is listed in Table 40 which also includes a column for the protocol required interval from last day of treatment to randomization (relative study day 1).

Reviewer Comment: Discontinuation of previous treatment is within the interval required by protocol for each drug.

Figure 10: Distribution of the last date of most recent MS treatment, FAS, study 2302



Source: AENDY by CMDECOD ANL02FL_Y subset ADCM 2302.jrp

Table 40: The last relative study day of previous treatment for MS, by CMDECOD, FAS, study 2302

CMDECOD	Last day limit	Total N	Max(AENDY)	
			OMB 20 mg	TERI 14 mg
AZATHIOPRINE	180	4	-251	-253
DACLIZUMAB	60	13	-129	-142
DIMETHYL FUMARATE	30	122	-28	-34
FINGOLIMOD	60	13	-66	-61
FINGOLIMOD HYDROCHLORIDE	60	36	-62	-49
GLATIRAMER ACETATE	0	158	24	-1
INTERFERON	0	2	-48	
INTERFERON BETA	0	36	-2	-1
INTERFERON BETA-1A	0	137	-2	-1

CMDECOD	Last day limit	Total N	Max(AENDY)	
			OMB 20 mg	TERI 14 mg
INTERFERON BETA-1B	0	72	-1	-1
INTERFERONS	0	7	-38	-8
INVESTIGATIONAL DRUG		6	-473	-554
LAQUINIMOD	730	6		-744
MITOXANTRONE	730	1		-2213
MITOXANTRONE HYDROCHLORIDE	730	1		-1073
NATALIZUMAB	60	18	-57	-77
OZANIMOD	60	1		-615
PEGINTERFERON	0	1		-489
PEGINTERFERON BETA-1A	0	18	-14	-2
SIPONIMOD	60	1	-377	
TERIFLUNOMIDE	105 (30 with AEP)	23	-35	-38

ANL02FL_Y Subset of ADCM 2302 MAX(AENDY)byTRT01P By (CMDECOD).jmp

Other baseline disease characteristics

The baseline characteristics of MS were generally well-balanced by treatment groups (Table 41). The number of gadolinium-enhancing lesions was higher in the group treated with ofatumumab, but the difference was not statistically significant as it was for study 2301 (Table 18).

Table 41: Baseline disease characteristics, study 2302

TRT01P	N	Mean	Std Dev	Min	Max	Median
EDSS						
Ofatumumab 20 mg	481	2.9	1.34	0	6	3
Teriflunomide 14 mg	474	2.86	1.37	0	6	2.5
25FWT						
Ofatumumab 20 mg	481	7.41	7.75	2.8	99	5.5
Teriflunomide 14 mg	474	7.19	6.88	2.85	88.5	5.5
Duration of MS since diagnosis (years)						
Ofatumumab 20 mg	481	5.59	6.38	0.06	31.8	3.15
Teriflunomide 14 mg	474	5.48	6.0	0.1	33.5	3.1
Duration of MS since first symptom (years)						
Ofatumumab 20 mg	481	8.2	7.4	0.12	34.5	5.7
Teriflunomide 14 mg	474	8.19	7.38	0.17	36.1	6.3
Number of relapses in the 12 to 24 months prior to screening						
Ofatumumab 20 mg	481	0.7	0.95	0	5	0
Teriflunomide 14 mg	474	0.78	1.02	0	6	0
Number of relapses in the last year prior to screening						
Ofatumumab 20 mg	481	1.28	0.74	0	7	1
Teriflunomide 14 mg	474	1.26	0.73	0	6	1
Time since the onset of the most recent relapse (months)						
Ofatumumab 20 mg	481	7.79	15	1.28	262	5.17
Teriflunomide 14 mg	474	7.66	11.1	1.18	150	5.22
Number of Gd-enhancing T1 lesions at baseline						

TRT01P	N	Mean	Std Dev	Min	Max	Median
Ofatumumab 20 mg	481	1.61*	4.07	0	58	0
Teriflunomide 14 mg	474	1.49	4.07	0	63	0
Volume of T2 lesions (cc) at baseline						
Ofatumumab 20 mg	481	14.3	14.2	0.08	81.9	9.01
Teriflunomide 14 mg	474	12	13	0.04	112	7.66

*: p=0.6488

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Compliance with treatment for the RCP was close to 100% for both treatment groups (Table 42).

Table 42: Percent compliance, study 2302

TRT01P	N Rows	(AVAL)				
		Mean	Std Dev	Min	Max	Median
Ofatumumab 20 mg	481	98.5	4.96	24.2	100	100
Teriflunomide 14 mg	474	98.8	4.13	38.7	100	100

Source: PARAM_COMPL Subset of ADEX 2302 AVAL By (TRT01P).jmp

Concomitant Medications during the trial

The most common concomitant medications during the trial are listed in Table 43. The most common concomitant medications most likely represent symptomatic treatment for common medical conditions and medications given prior to administration of study drug.

Table 43: Concurrent non-MS drugs during the trial. 10% or more in OMB group, study 2302

WHODrug ATC 3	OMB 20 mg	TERI 14 mg
OTHER ANALGESICS AND ANTIPYRETICS	345 (71.7%)	344 (72.6%)
ANTIHISTAMINES FOR SYSTEMIC USE	293 (60.9%)	289 (61.0%)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	203 (42.2%)	175 (36.9%)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	183 (38.0%)	161 (34.0%)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	180 (37.4%)	179 (37.8%)
THROAT PREPARATIONS	172 (35.8%)	133 (28.1%)
VITAMIN A AND D, INCL. COMBINATIONS OF THE TWO	165 (34.3%)	185 (39.0%)
HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE	145 (30.1%)	148 (31.2%)
OTHER CARDIAC PREPARATIONS	141 (29.3%)	113 (23.8%)
OTHER GYNECOLOGICALS	140 (29.1%)	123 (25.9%)
ANTIDEPRESSANTS	118 (24.5%)	128 (27.0%)
(missing)	117 (24.3%)	123 (25.9%)
STOMATOLOGICAL PREPARATIONS	115 (23.9%)	146 (30.8%)

WHODrug ATC 3	OMB 20 mg	TERI 14 mg
ANXIOLYTICS	103 (21.4%)	100 (21.1%)
ANTIINFECTIVES	100 (20.8%)	98 (20.7%)
ANTIEPILEPTICS	100 (20.8%)	108 (22.8%)
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	98 (20.4%)	135 (28.5%)
HYPNOTICS AND SEDATIVES	96 (20.0%)	101 (21.3%)
MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS	85 (17.7%)	69 (14.6%)
BETA-LACTAM ANTIBACTERIALS, PENICILLINS	75 (15.6%)	73 (15.4%)
DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE	65 (13.5%)	62 (13.1%)
ANTIINFECTIVES AND ANTISEPTICS, EXCL. COMBINATIONS WITH CORTICOSTEROIDS	64 (13.3%)	73 (15.4%)
OTHER OPHTHALMOLOGICALS	63 (13.1%)	81 (17.1%)
UROLOGICALS	60 (12.5%)	67 (14.1%)
CONTRACEPTIVES FOR TOPICAL USE	57 (11.9%)	61 (12.9%)
ANTIINFLAMMATORY AGENTS	53 (11.0%)	65 (13.7%)
DRUGS FOR CONSTIPATION	52 (10.8%)	38 (8.0%)
OTHER DERMATOLOGICAL PREPARATIONS	51 (10.6%)	65 (13.7%)
PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS	51 (10.6%)	55 (11.6%)
OPIOIDS	48 (10.0%)	59 (12.4%)
Subjects(filtered)	459 (95.4%)	457 (96.4%)
1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRevSelADSLFASFL_Y CMCAT3byTRT01PfiltCMCAT_GEN ACAT01_CONMED

Rescue Medication

The proportion of subjects treated for one or more relapses with systemic corticosteroids is shown in Table 44. Subjects may have been treated on more than one occasion.

Table 44: Proportion of subjects with one or more courses of systemic corticosteroids for relapse treatment during the RCP, FAS, study 2302

TRT01P	N(USUBJID)	% of FAS
Ofatumumab 20 mg	67	13.9%
Teriflunomide 14 mg	140	29.5%

Source: ACAT01_CONMED Subset CMCAT2_SYSTEMIC CS Subset CMSCAT_MSRLP Subset of EPOCH_TRT Subset ADCM 2302 By (USUBJID, TRT01P) NUSUBJID By (TRT01P).jmp

Efficacy Results – Primary Endpoint

The proportion of subjects who did not have a confirmed relapse was 85.0% for those treated with ofatumumab and 70.9% for those treated with teriflunomide. Seventy-two subjects treated with ofatumumab had a total of 95 confirmed relapses during the RCP and 138 subjects treated with teriflunomide had a total of 198 confirmed relapses (Table 45).

Table 45: Confirmed relapses, FAS, study 2302

Num RLP (AVAL)	Ofatumumab 20 mg			Teriflunomide 14 mg		
	Num subjects	% of N	RL total	Num subjects	% of N	RL total
0	409	85.0%		336	70.9%	
1	54	11.2%	54	104	21.9%	104
2	15	3.1%	30	18	3.8%	36
3	1	0.2%	3	9	1.9%	27
4	2	0.4%	8	6	1.3%	24
7	0	0.0%	0	1	0.2%	7
Total	481	100.0%	95	474	100.0%	198

Source: PARAM_NCFRLSTY Subset of ADARR 2302 TRT01P By (AVAL)

The mean and median period of observation for relapses was very similar for the two treatment groups (Table 46).

Table 46: Time in study, years, FAS, study 2302

TRT01P	N	Time in study - Overall (Years)- FAS (AVAL)				
		Mean	Std Dev	Min	Max	Median
Ofatumumab 20 mg	481	1.6	0.45	0.003	2.37	1.61
Teriflunomide 14 mg	474	1.58	0.44	0.04	2.65	1.61

Source: PARAM_TIMESYRS Subset of ADARR 2302 TIMESYRS By (TRT01P).jmp

Unadjusted Annualized Relapse Rate, confirmed relapses

Ofatumumab: 95/767.781 sum of years in study = 0.124
Teriflunomide: 198/749.771 sum of years in study = 0.264
ARR ratio: 0.470

> *Reviewer Comment: The sponsor's analysis of ARR used a negative binomial model and did adjust for the number of baseline gadolinium-enhancing lesions as well as for region, number of relapses in the preceding year, baseline EDSS, and baseline age. The adjusted ARR using these methods was 0.10 (0.08, 0.13) for the ofatumumab group and 0.25 (0.21, 0.30), yielding a rate ratio of 0.415 (0.308, 0.559), p<0.001.*

The proportion of subjects who did not have a confirmed or unconfirmed relapse was 80.9% for those treated with ofatumumab and 65.8% for those treated with teriflunomide. Ninety-two subjects treated with ofatumumab had a total of 131 confirmed or unconfirmed relapses and 162 subjects treated with teriflunomide had a total of 250 confirmed or unconfirmed relapses (Table 47).

Table 47: All reported relapses, FAS, study 2302

Num RLP (AVAL)	Total			Ofatumumab 20 mg			Teriflunomide 14 mg		
	Num subjects	% of N	RL total	Num subjects	% of N	RL total	Num subjects	% of N	RL total
0	701	73.4%		389	80.9%		312	65.8%	
1	179	18.7%	179	67	13.9%	67	112	23.6%	112
2	49	5.1%	98	17	3.5%	34	32	6.8%	64
3	11	1.2%	33	4	0.8%	12	7	1.5%	21
4	11	1.2%	44	2	0.4%	8	9	1.9%	36
5	2	0.2%	10	2	0.4%	10	0	0.0%	0
7	1	0.1%	7	0	0.0%	0	1	0.2%	7
10	1	0.1%	10	0	0.0%	0	1	0.2%	10
Total	955	100.0%	381	481	100.0%	131	474	100.0%	250

Source: PARAM_NRLSTY Subset of ADARR 2302 TRT01P By (AVAL)

Unadjusted Annualized Relapse Rate, all relapses

Ofatumumab: 131/767.781 sum of years in study = 0.171
Teriflunomide: 250/749.771 sum of years in study = 0.333
ARR ratio: 0.514

Reviewer Comment: For all relapses, the sponsor reports an ARR of 0.14 for the ofatumumab group and 0.32 for the teriflunomide group using the negative binomial model with the same adjustments.

The proportion of reported relapses that were confirmed was similar by treatment group (Table 48).

Reviewer Comment: The comparable rate of confirmation supports a relative lack of bias in the confirmation process, as was the case for study 2301.

Table 48: Rate of confirmation of relapses by assigned treatment, FAS, study 2302

	Ofatumumab	Teriflunomide
All relapses	131	250
Confirmed	95	198
% confirmed	72.5%	79.2%

The ARR was also analyzed for the first 8 weeks of treatment and compared to rates after the first 8 weeks on the assumption that treatment with ofatumumab may require that period of

time for full benefit. This is included in (Table 49) which also includes a comparison of the unadjusted ARR as calculated by this reviewer and the adjusted rate calculated by the sponsor.

Table 49: ARR calculations, unadjusted vs. adjusted, FAS, study 2302

	OMB	TERI
Confirmed Relapses		
Unadjusted ARR /Adjusted ARR (sponsor)	0.124/0.10	0.264/0.25
Rate ratio reviewer/sponsor	0.470/0.415	
All relapses		
Unadjusted ARR /Adjusted ARR (sponsor)	0.171/0.14	0.333/0.32
Rate ratio reviewer/sponsor	0.514/0.454	
Relapses within 8 weeks or less		
Unadjusted ARR /Adjusted ARR (sponsor)	0.219/0.197	0.400/0.378
Rate ratio reviewer/sponsor	0.548/0.52	
Relapses after 8 weeks		
Unadjusted ARR /Adjusted ARR (sponsor)	0.114/0.097	0.250/0.242
Rate ratio reviewer/sponsor	0.456/0.399	
ARR based on mean of individual subject rates – confirmed relapses		
ARR	0.13	0.32
Rate ratio	0.406	
ARR based on mean of individual subject rates – all relapses		
ARR	0.18	0.39
Rate ratio	0.462	

Reviewer Comment: The unadjusted and adjusted ARRs and rate ratios are very similar and support the validity of the sponsor's results and methods. Unlike the results for study 2301 in which the benefit was seen only after the first 8 weeks (Table 27) the treatment effect over the full treatment period and after 8 weeks of treatment was similar.

Data Quality and Integrity

There were no issues regarding the quality or integrity of the data submitted.

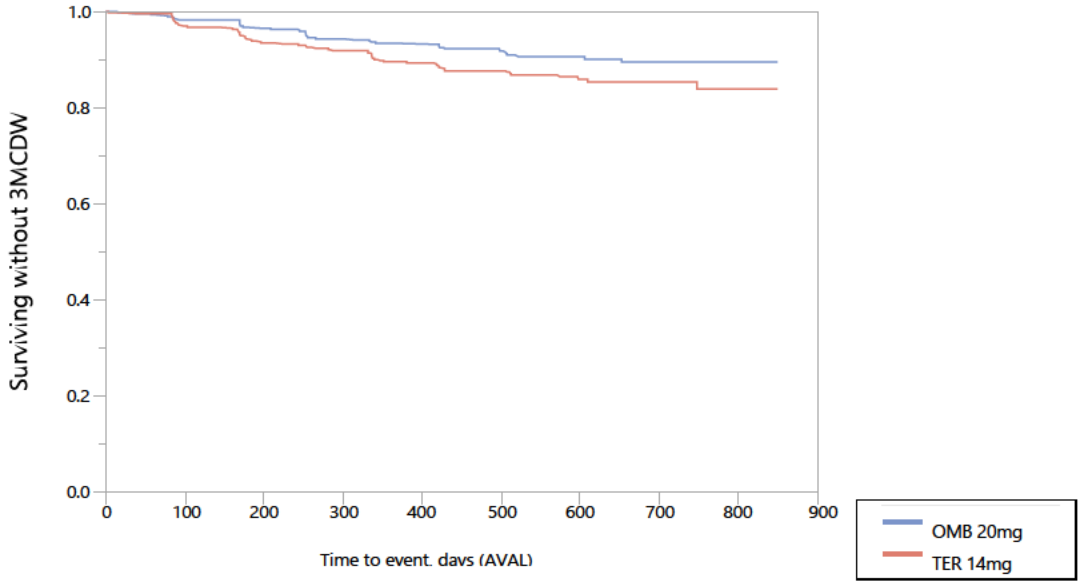
Efficacy Results – Secondary and other relevant endpoints

Time to 3-month confirmed disability worsening (3MCDW)

The population for the primary analysis for confirmed disability worsening is the combined population from studies 2301 and 2302 – see Section **7.1.2**. The analysis of 3MCDW for the study 2302 population is shown in **Figure 11**. The analysis of the time to 3-month confirmed disability worsening (T3MCDW) does not exclude periods that started with a relapse, does not exclude the possibility of a relapse during the period of disability, but does exclude confirmation at a relapse. To address the concern that relapses may have influenced the analysis of T3MCDW, an analysis of the subpopulation from study 2302 that had no relapses at any time during the trial is shown in **Figure 12**.

Figure 11: Time to 3MCDW, FAS, study 2302

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	43	436	0.654	0.652 (0.445, .957) p=0.029
TER 14mg	62	411		
Combined	105	847		

Tests Between Groups

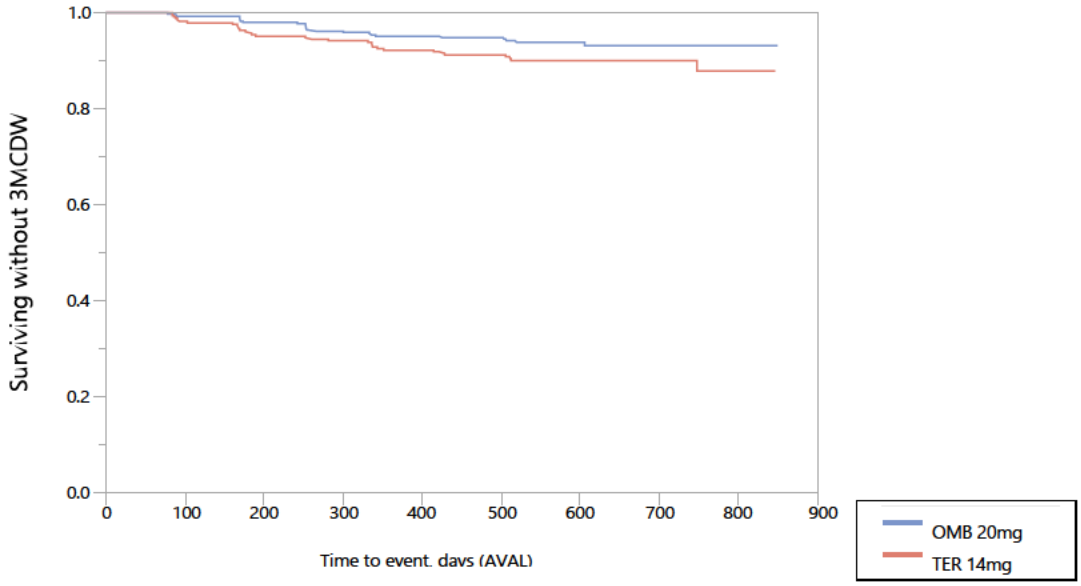
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.2969	1	0.0382*

Test	ChiSquare	DF	Prob>ChiSq
Wilcoxon	4.2268	1	0.0398*

Source: T3MCDE study 2302.jrp

Figure 12: Time to 3-month CDW, FAS, subjects with no relapses at any time

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL of STUDYID_COMB157G2302 Subset of ADTTCD ISE
Censored by CNSR
Censor Code 1
Grouped by TRT01P of STUDYID_COMB157G2302 Subset of ADTTCD ISE

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	24	383	0.593	0.614 (0.362, 1.044) p=0.072
TER 14mg	32	303		
Combined	56	686		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.5851	1	0.0583
Wilcoxon	3.5410	1	0.0599

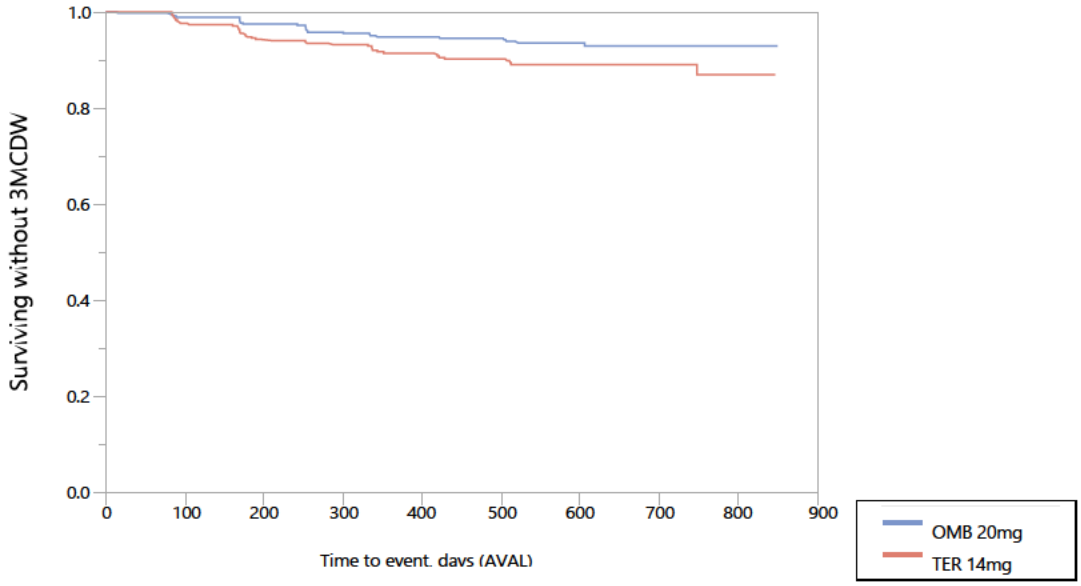
Source: T3MCDW no relapses Survival.jrp; PARAM_T3MCDW Subset of Join AVAL_0 of NCFRLSTY of ADARR c Study 2302 subset of ADTTCD ISE.jmp

Reviewer Comment: The above is in agreement with the sponsor's analysis of the relapse-free population provided in Table C2 1.3.6-1a - page 330 of SCE Appendix 1.

An analysis similar to the above analysis but including subjects in the analysis who did have a relapse prior to the start of an otherwise confirmed period of disability worsening, but censoring those subjects at the day of the progression event is shown in Figure 13.

Figure 13: Time to 3MCDW, FAS, study 2302, censor at any prior relapse

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	27	452	0.629	0.544, (0.351, 0.843) P=0.006
TER 14mg	41	432		
Combined	68	884		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.2214	1	0.0223*
Wilcoxon	5.1635	1	0.0231*

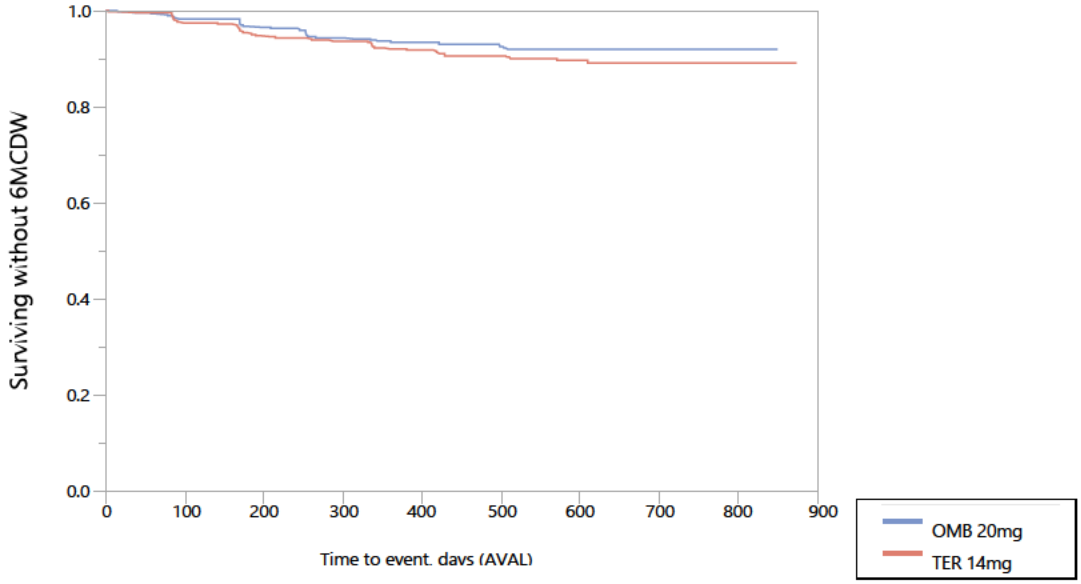
Source: T3MIPCW study 2302 Survival.jrp; PARAM_T3MIPCW Subset of STUDYID_COMB157G2302 Subset of ADTTCD ISE.jmp

6-month confirmed disability worsening

The analysis of time to 6-month confirmed disability worsening for study 2301 alone is shown in Figure 14. Because this analysis did not exclude relapses that may have occurred just before or during the period of worsened disability, an analysis of the population that did not experience a relapse at any time during the trial was conducted and is shown in Figure 15.

Figure 14: Time to 6-month confirmed disability worsening, FAS

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	36	443	0.754	0.756 (0.489, 1.170) P=0.209
TER 14mg	46	427		
Combined	82	870		

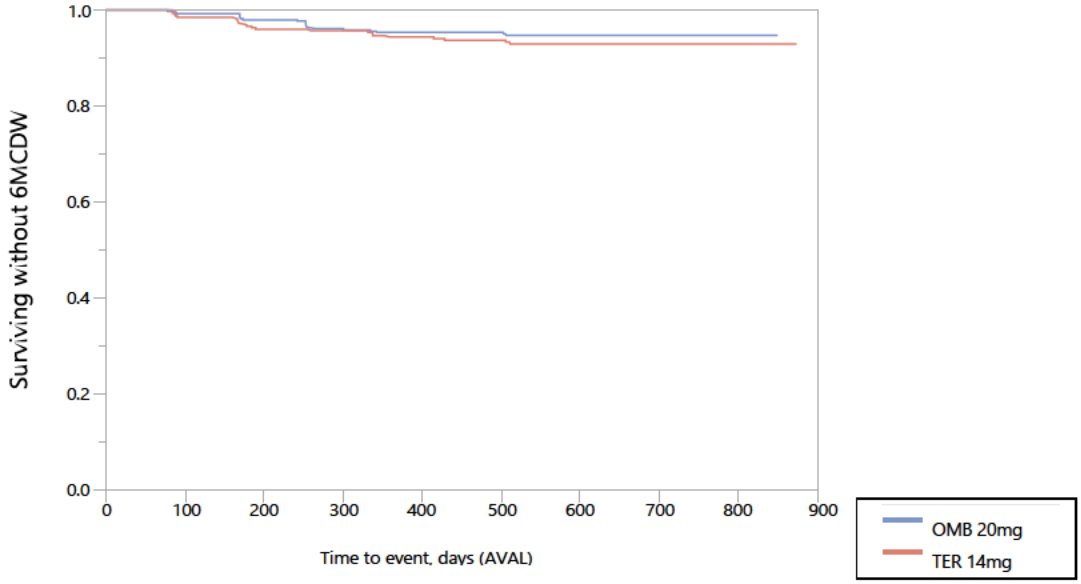
Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	1.5358	1	0.2152
Wilcoxon	1.3150	1	0.2515

Source: T6MCDW study 2302.jrp

Figure 15; Time to 6-month confirmed disability worsening, FAS, study 2302, subjects with no relapse at any time

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL of STUDYID_COMB157G2302 Subset of ADTTCD ISE
Censored by CNSR
Censor Code 1
Grouped by TRT01P of STUDYID_COMB157G2302 Subset of ADTTCD ISE

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	20	387	0.735	0.758 (0.414, 1.390) P=0.370
TER 14mg	22	313		
Combined	42	700		

Tests Between Groups

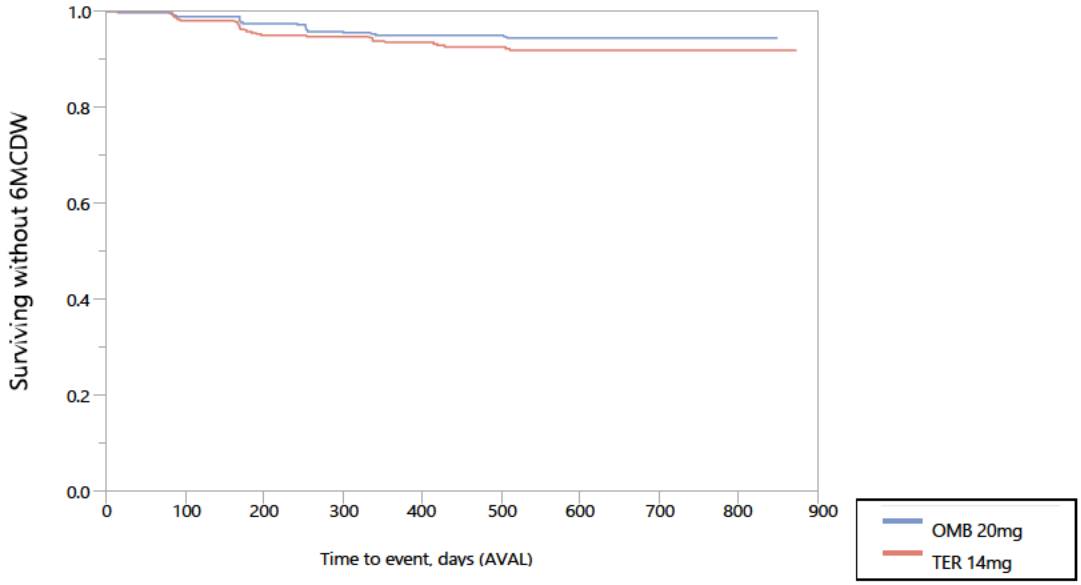
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.9420	1	0.3318
Wilcoxon	0.9285	1	0.3353

Source: T6MCDW no relapses study 2302 Survival.jrp; PARAM_T6MCDW Subset of Join AVAL_0 of NCFRLSTY of ADARR c Study 2302 subset of ADTTCD ISE.jmp

An analysis that is similar to the above analysis but including subjects in the analysis who did have a relapse prior to the start of an otherwise confirmed period of disability worsening, but censoring those subjects at the day of the progression event is shown in **Figure 16**.

Figure 16: Time to 6-month confirmed disability worsening, censor at any preceding relapse, FAS, study 2302

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	23	456	0.745	0.525 (0.325, 0.848) P=0.008
TER 14mg	30	443		
Combined	53	899		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	1.9962	1	0.1577
Wilcoxon	1.9260	1	0.1652

Source: T6MIPCW study 2302Survival.jrp; PARAM_T6MIPCW Subset of STUDYID_COMB157G2302 Subset of ADTTCD ISE.jmp

Reviewer Comment: Although the odds ratio and hazard ratio are slightly higher when subjects with relapses are excluded or censored if they occurred prior to a period of disability worsening, the results clearly favor ofatumumab

treatment compared to teriflunomide which itself has shown a benefit on disability in other studies.

MRI lesions

Number of gadolinium-enhancing lesions per scan

For the treatment period there were 0.04 lesions per scan for those treated with ofatumumab and 0.62 per scan for those treated with teriflunomide. The percent reduction was 93.1%. The sponsor's analysis using a negative binomial model and adjusting for region, age and the number of GdE lesions at baseline yielded adjusted means of 0.0317 lesions per scan for ofatumumab and 0.514 lesions per scan for teriflunomide for a 93.8% reduction.

Annualized rate of new T2 lesions

For the treatment period, the annual rate of new T2 lesions was 0.96 for the ofatumumab group and 5.27 for the teriflunomide group. The percent reduction was 81.8%. The sponsor's analysis using a negative binomial model and adjusting for region, age and the baseline volume of T2 lesions yielded an adjusted mean annual rate of 0.64 for the ofatumumab group and 4.2 for the teriflunomide group (to the end of study visit). The percent reduction was 84.5%.

Dose/Dose Response

A single dose was studied in studies 2301 and 2302

Durability of Response

The durability of the response was not studied.

Persistence of Effect

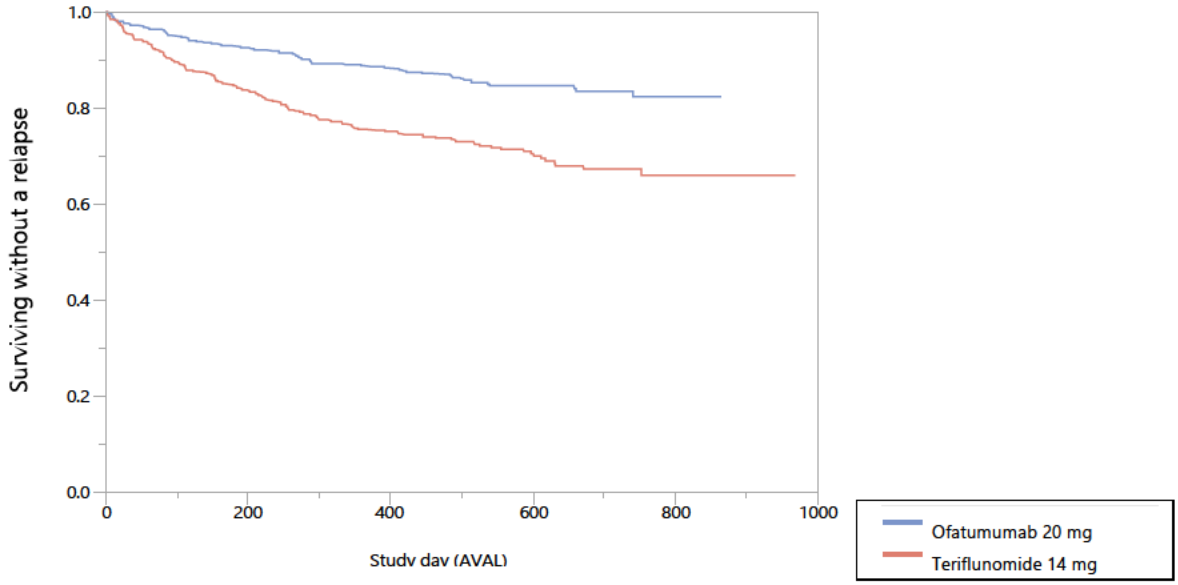
The persistence of the effect was not studied.

Additional Analyses Conducted on the Individual Trial

The time to the first confirmed relapse was significantly prolonged with ofatumumab treatment (**Figure 17**). If all relapses are included in the analysis, the result is similar with an OR of 0.456.

Figure 17: Time to first confirmed relapse, study 2302

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR
Ofatumumab 20 mg	72	409	0.429
Teriflunomide 14 mg	138	336	
Combined	210	745	

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	28.1504	1	<.0001*
Wilcoxon	26.8236	1	<.0001*

Source: Time to first confirmed relapse study 2302.jrp

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoint

Although the ARR was higher in study 2302 compared to study 2301, the percent reduction was essentially the same. The results based on an unadjusted raw ARR are consistent with those using the negative binomial model with adjustments. The results for confirmed relapses are consistent with those when all relapses are included (Table 50).

Table 50: ARR across studies

	2301		2302	
	OMB	TER	OMB	TER
ARR- confirmed				
Unadjusted/sponsor	0.117/0.11	0.239/0.22	0.124/0.10	0.26/0.25
Rate ratio	0.49/0.50		0.47/0.42	
ARR – all				
Unadjusted/sponsor	0.16/0.15	0.32/0.30	0.17/0.14	0.33/0.32
Rate ratio	0.50/0.50		0.51/0.45	

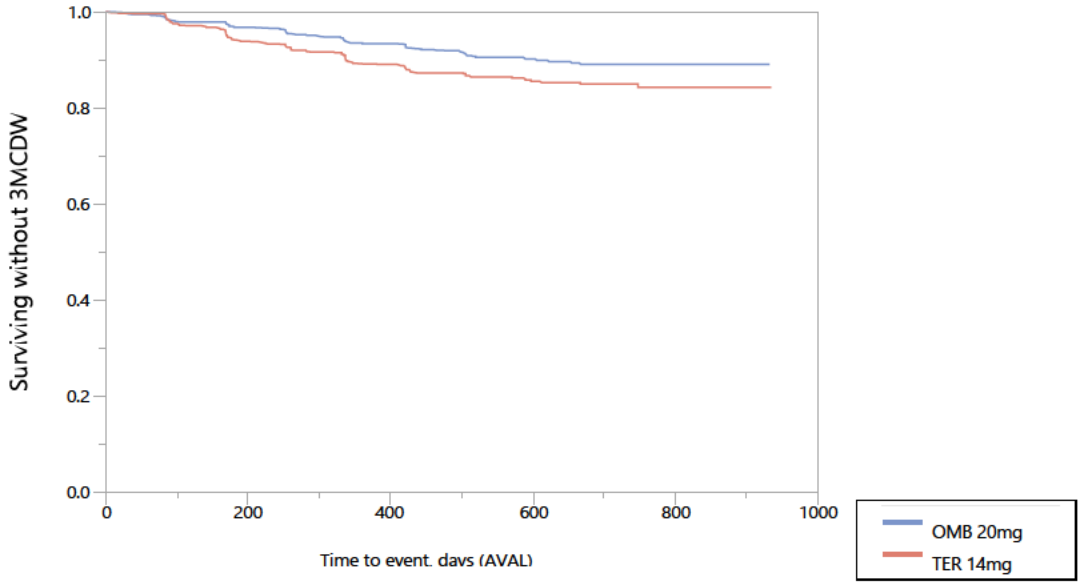
7.1.2. Secondary and Other Endpoints

Time to 3-month confirmed disability worsening

The time to the first 3-month confirmed disability worsening using the sponsor's primary analysis method, for the combined study 2301 and 2302 populations is shown in Figure 18. Because this analysis may be influenced by the occurrence of relapses that occurred just before or during the period of confirmation, an analysis that excludes all subjects with a relapse at any time during the trial was conducted (reviewer analysis) and is shown in Figure 19.

Figure 18: Time to first 3-month confirmed disability worsening, FAS, combined populations

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	88	856	0.664	0.656 (0.499, 0.862) p=0.002
TER 14mg	125	807		
Combined	213	1663		

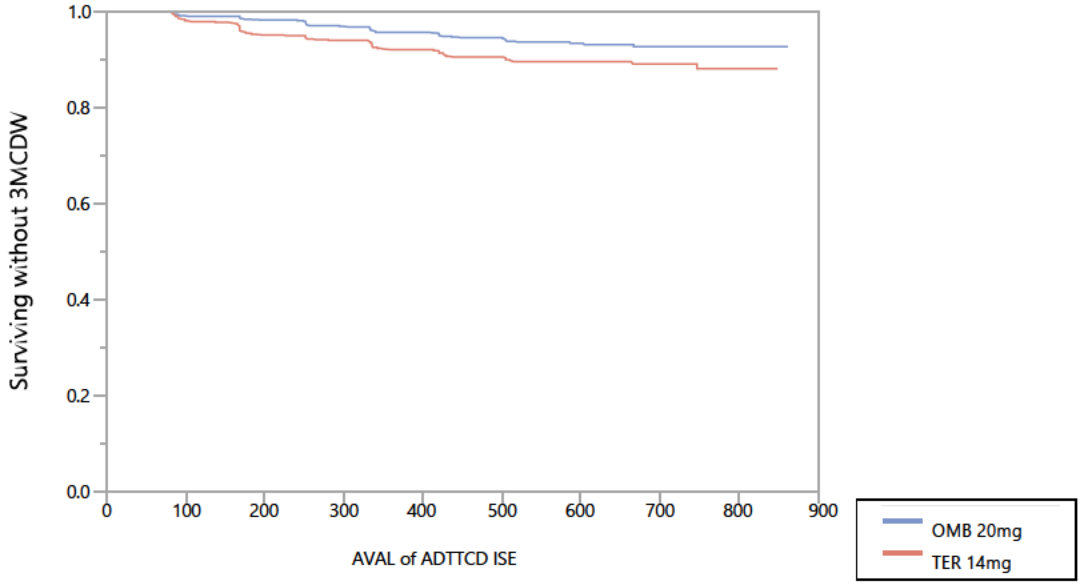
Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	8.3913	1	0.0038*
Wilcoxon	9.0357	1	0.0026*

Source: T3MCDW ISE.jrp

Figure 19: Time to first 3-month confirmed disability worsening, FAS, combined studies, subjects with no relapse at any time (reviewer analysis)

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL of ADTTCD ISE
Censored by CNSR
Censor Code 1
Grouped by TRT01P of ADTTCD ISE

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	50	743	0.598	0.587 (0.407, 0.848) p=0.004
TER 14mg	67	595		
Combined	117	1338		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	7.4086	1	0.0065*
Wilcoxon	7.9689	1	0.0048*

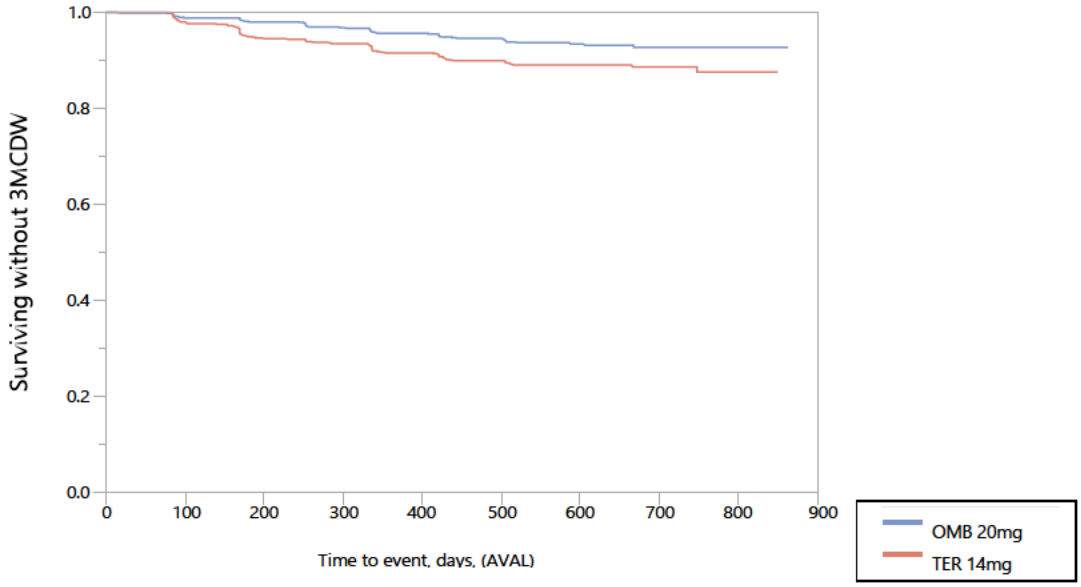
Source: PARAM_3MCDW subset Join AVAL_0 of ADARR c ADTTCD ISE survival.jrp

Reviewer Comment: The above analysis corresponds to the sponsor analysis of a subset of subjects without relapses on study (Table C2 1.3.6-1a page 329 of SCE Appendix 1).

An additional analysis in which any subject with a relapse prior to a period of 3-month confirmed disability worsening was included as censored at the onset of the relapse is shown in Figure 20.

Figure 20: Time to 3MCDW, IPCW analysis, PoolC2

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	53	891	0.617	0.540 (0.396, 0.738) p=<0.001
TER 14mg	82	850		
Combined	135	1741		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	10.8449	1	0.0010*
Wilcoxon	11.8312	1	0.0006*

T3MIPCW ISE Survival.jrp; PARAM_T3MIPCW Subset of ADTTCD ISE.jmp

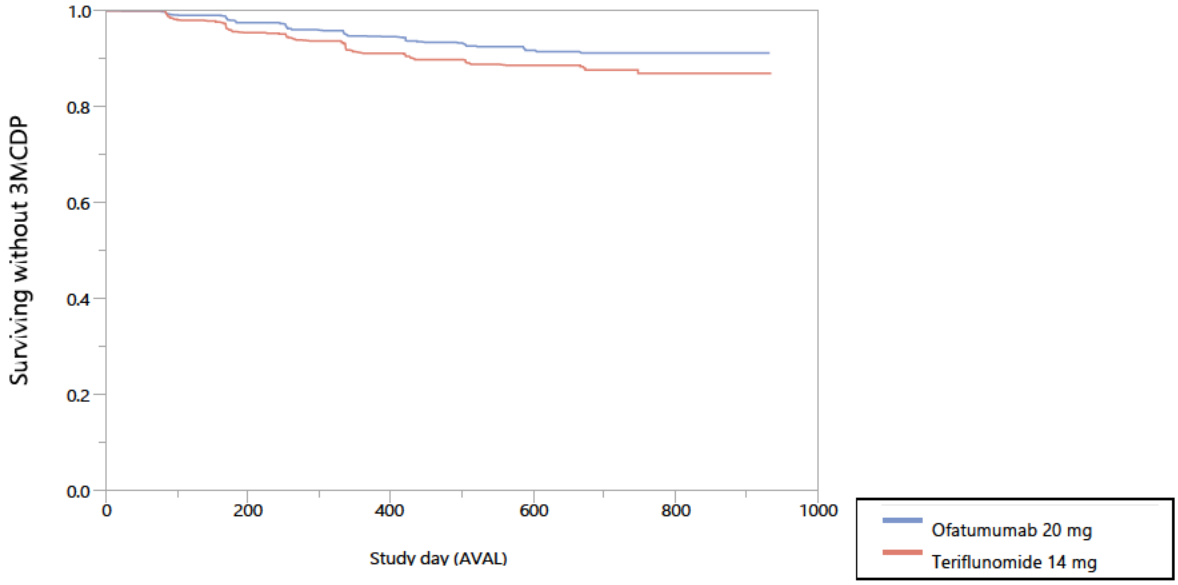
Reviewer Comment: The following request was sent to the sponsor: "Provide an analysis of 3- and 6-month confirmed disability worsening using the following criteria:

a. The onset may not start within 30 days of a preceding relapse
b. A relapse may not occur during the potential period of CDW
c. Confirmation may not occur at the time of a relapse
d. The applicable criterion for progression by EDSS score must be met throughout the period
e. An intervention for relapse prevention, or a symptomatic treatment such as dalfampridine, may not have been started or increased during the potential period of CDW.

The sponsor provided the requested analyses in sequence 0264. The analysis of 3-month confirmed disability progression using the above criteria are shown in **Figure 21**.

Figure 21: Time to 3-month confirmed disability progression, Pool C2, Reviewer criteria

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
Ofatumumab 20 mg	72	872	0.749	0.648 (0.478, 0.890) P = 0.007
Teriflunomide 14 mg	102	830		

Group	Number failed	Number censored	Simple OR	HR (sponsor)
Combined	174	1702		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.6035	1	0.0102*
Wilcoxon	6.9897	1	0.0082*

Source: T3MCDP ISE FDA criteria.jrp

Reviewer Comment: The various methods for analysis of the 3-month endpoint of disability worsening, in which relapses may contribute to the worsening, or progression, in which there is an attempt to eliminate the role of relapses by various means are shown in **Table 51** *below. Because the population was selected to have a high likelihood of relapses occurring during the trial, and because the drug clearly reduces the occurrence of relapses, it is not possible to totally eliminate their role in any assessment of the assessment of disability over time. The "Reviewer criteria" have been used to reduce the role of relapses as much as possible in these analyses. The result using those criteria is a more clinically meaningful measure of any effect on disability not attributable to an effect on relapses (***Figure 21***).*

Summary of analyses of 3-month confirmed disability worsening and progression

Table 51: Summary of analyses of 3MCDW

	T3MCDW[1]		T3MPIRA[2]		T3MCDW-No relapses[3]		T3MIPCW[4]	
	OMB	TERI	OMB	TERI	OMB	TERI	OMB	TERI
Study 2301								
Odds	45:420	63:396	37:427	52:407	26:360	35:292	26:439	41:418
Odds ratio	0.674		0.697		0.603		0.604	
p-value (KM, log rank)	0.0424		0.0871		0.0502		0.0171	
HR (sponsor)	0.652 (0.445, .957)				0.564 (0.339, 0.937)		0.536 (0.344, 0.837)	
p-value (sponsor)	0.029				0.027		0.006	
Study 2302								
Odds	43:436	62:411	37:442	53:420	24:383	32:303	27:452	41:432
Odds ratio	0.654		0.663		0.593		0.629	
p-value (KM, log rank)	0.0382		0.0614		0.0583		0.0223	
HR (sponsor)	0.660 (0.447, 0.974)				0.614 (0.362, 1.044)		0.544, (0.351, 0.843)	
p-value (sponsor)	0.036				0.072		0.006	
Pooled Studies 2301&2302								
Odds	88:856	125:807	75:869	105:827	50/743	67:595	53:891	82:850
Odds ratio	0.664		0.680		0.598		0.617	
p-value (KM, log rank)	0.0038		0.0122		0.0065		0.0010	
HR (sponsor)	0.656 (0.499, 0.862)				0.587 (0.407, 0.848)		0.540 (0.396, 0.738	
p-value (sponsor)	0.002				0.004		<0.001	

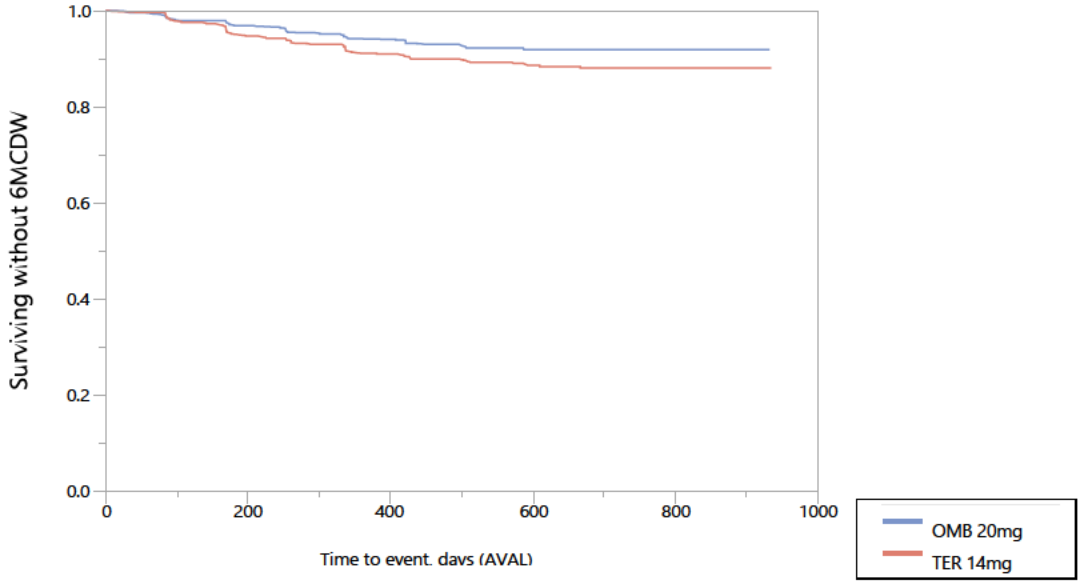
1: Time to 3-month confirmed disability worsening of EDSS in days (Full Analysis Set) – sponsor analysis method
2: Time to 3-month progression independent of relapses in days – sponsor analysis method
3: Time to 3-month progression of disability – sponsor analysis method of subgroup with no relapses; review analysis of subgroup derived from subgroup of ADARR with no relapses
4: T3MIPCW Time to 3-month Inverse Probability Censoring Weight

6-month confirmed disability worsening

An analysis of the time to the first 6-month confirmed disability worsening using the sponsor's primary analysis method is shown in Figure 22. Because this analysis method may be influenced by the occurrence of relapses just before or during the period of confirmed disability worsening, an analysis of the population that had no relapses at any time during the trial (reviewer analysis) was conducted and is shown in Figure 23.

Figure 22: Time to first 6-month confirmed disability worsening, FAS, combined studies

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	71	873	0.684	0.675 (0.498, 0.916) P=0.012
TER 14mg	99	833		
Combined	170	1706		

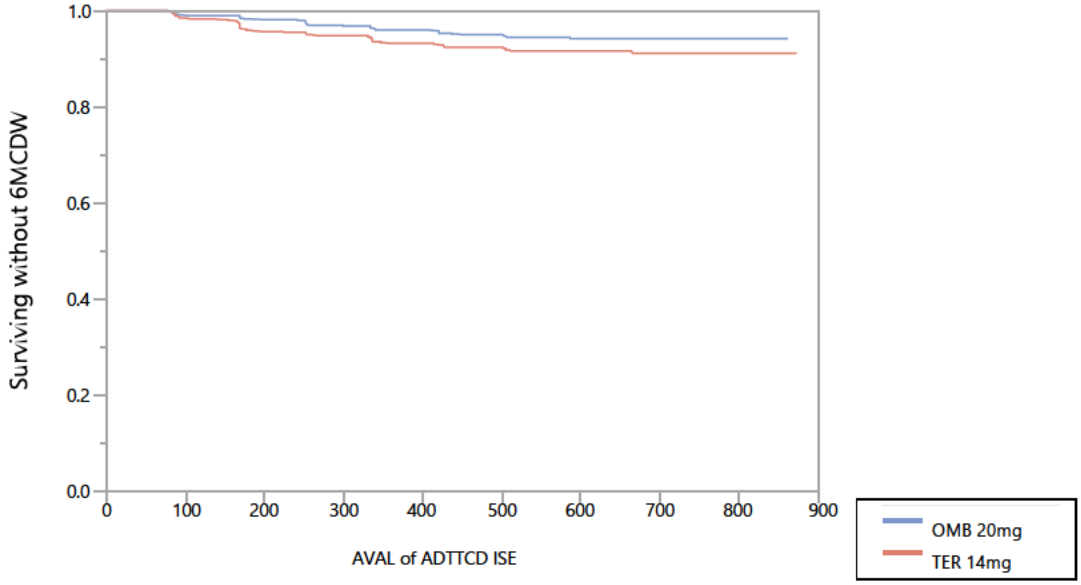
Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.7596	1	0.0164*
Wilcoxon	5.3470	1	0.0208*

Source: T6MCDW ISE.jrp

Figure 23: Time to 6-month confirmed disability worsening, FAS, combined studies, subjects with no relapses at any time (reviewer analysis)

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL of ADTTCD ISE
Censored by CNSR
Censor Code 1
Grouped by TRT01P of ADTTCD ISE

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
OMB 20mg	42	751	0.643	0.632 (0.421, 0.947) p=0.026
TER 14mg	53	609		
Combined	95	1360		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.4783	1	0.0343*
Wilcoxon	4.6034	1	0.0319*

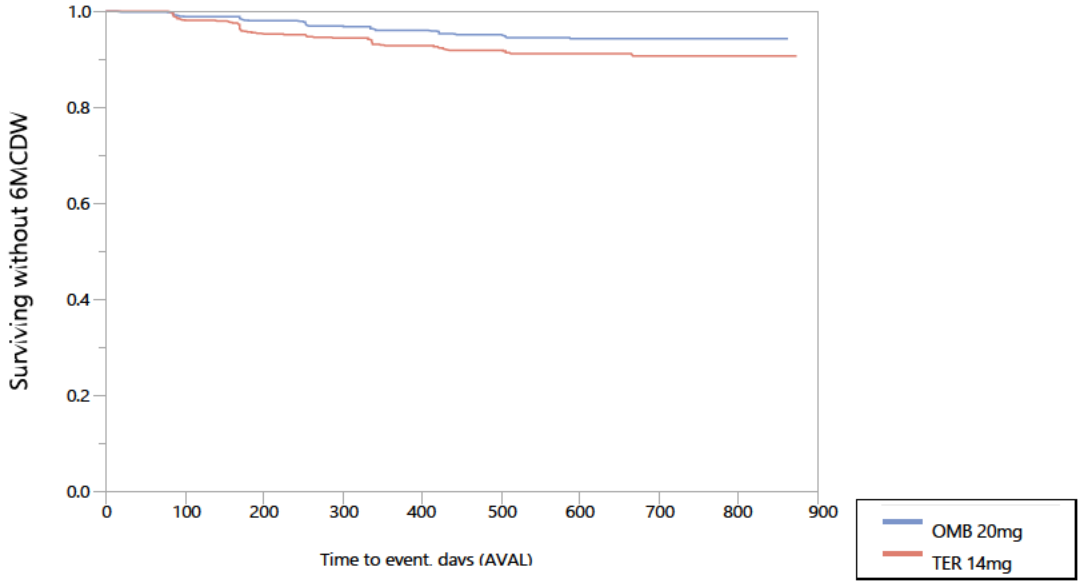
Source: PARAM_T6MCDW subset Join AVAL_0 of ADARR ISE c ADTTCD ISE Survival.jrp

Reviewer Comment: Corresponds to C2 1.3.6-1b page 331 of SCE Appendix 1. Sponsor HR = 0.632 (0.421, 0.947), p=0.026

An additional analysis that includes subjects with a relapse prior to a period of 6-month confirmed disability, but which censors those subjects at the onset of the relapse is shown in Figure 24.

Figure 24: Time to 6-month confirmed disability worsening, FAS, combined studies, subjects with relapse prior censored

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Unadjusted OR	HR (sponsor)
OMB 20mg	45	899	0.657	0.575 (0.409, 0.808) p=0.001
TER 14mg	66	866		
Combined	111	1765		

Tests Between Groups

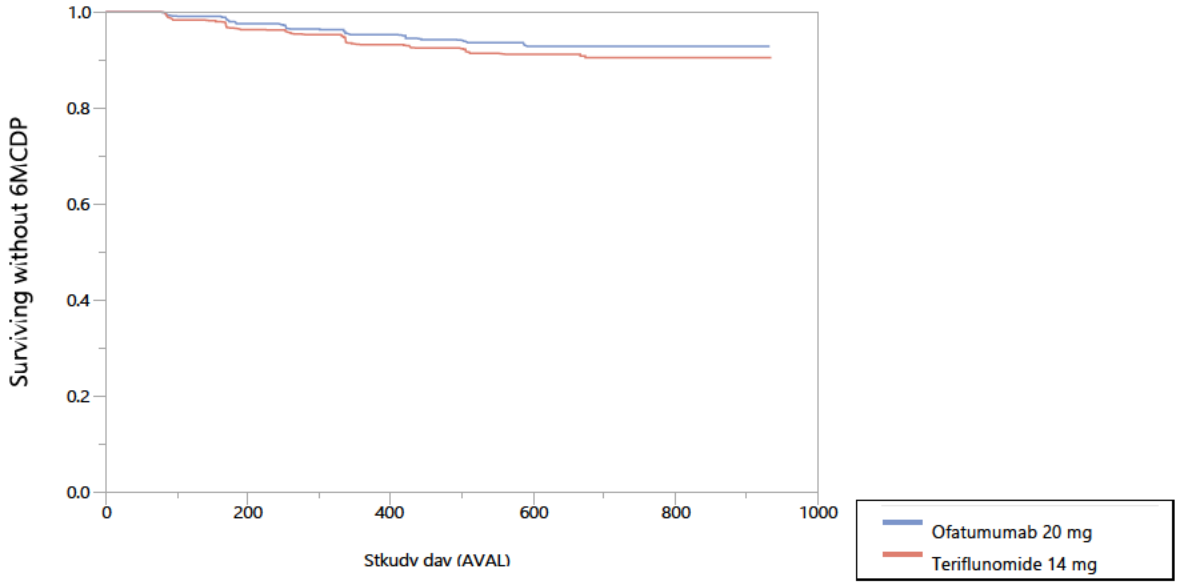
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	7.0000	1	0.0082*
Wilcoxon	7.2734	1	0.0070*

Source: T6MIPCW ISE Survival.jrp; PARAM_T6MIPCW Subset of ADTTCD ISE.jmp

Reviewer Comment: As for the analysis of 3-month confirmed disability progression, the sponsor reanalyzed 6-month confirmed disability progression using the criteria listed earlier (Figure 25).

Figure 25: Time to 6-month confirmed disability progression, Pool C2, Reviewer criteria

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P

Summary

Group	Number failed	Number censored	Simple OR	HR (sponsor)
Ofatumumab 20 mg	60	884	0.754	0.735 (0.524, 1.030) P = 0.074
Teriflunomide 14 mg	77	855		
Combined	137	1739		

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.7616	1	0.0966
Wilcoxon	2.8171	1	0.0933

Source: T6MCDP ISE FDA criteria.jrp

Reviewer Comment: The various methods for analysis of the 6-month endpoint of disability worsening, in which relapses may contribute to the worsening, or progression, in which there is an attempt to eliminate the role of relapses by various means are listed in below in Table 52. Because the population was selected to have a high likelihood of relapses occurring during the trial, and because the drug clearly reduces the occurrence of relapses, it is not possible to

totally eliminate their role in any assessment of the assessment of disability over time. The "Reviewer criteria" have been used to reduce the role of relapses as much as possible in these analyses. The result using those criteria is a more clinically meaningful measure of any effect on disability not attributable to an effect on relapses (Figure 25).

APPEARS THIS WAY ON ORIGINAL

Summary of 6-month progression of disability analyses

Table 52: Summary of analyses of 6MCDW

	T6MCDW[1]		T6MPIRA[2]		T6MCDW - No relapses[3]		T6MIPCW[4]	
	OMB	TERI	OMB	TERI	OMB	TERI	OMB	TERI
Study 2301								
Odds	35:430	53:406	32:433	44:415	22:364	31:296	22:443	36:423
Odds ratio	0.624		0.697		0.577		0.584	
p-value (KM, log rank)	0.0314		0.1144		0.0484		0.0202	
HR (sponsor)	0.607 (0.396, 0.930)				0.546 (0.315, 0.944)		0.525 (0.325, 0.848)	
p-value (sponsor)	0.022				0.30		0.008	
Study 2302								
Odds	36:443	46:427	33:446	36:437	20:387	22:313	23:456	30:443
Odds ratio	0.754		0.898		0.735		0.745	
p-value (KM, log rank)	0.2152		0.6423		0.3318		0.1577	
HR (sponsor)	0.756 (0.489, 1.170)				0.758 (0.414, 1.390)		0.525 (0.325, 0.848)	
p-value (sponsor)	0.209				0.370		0.008	
Pooled Studies 2301&2302								
Odds	71:873	99:833	65:879	80:852	42:751	53:609	45:899	66:866
Odds ratio	0.684		0.788		0.643		0.657	
p-value (KM, log rank)	0.0164		0.1444		0.0343		0.0082	
HR (sponsor)	0.675 (0.498, 0.916)				0.632 (0.421, 0.947)		0.575 (0.409, 0.808)	
p-value (sponsor)	0.012				0.026		0.001	

1: Time to 3-month confirmed disability worsening of EDSS in days (Full Analysis Set) – sponsor analysis method
2: Time to 3-month progression independent of relapses in days – sponsor analysis method
3: Time to 3-month progression of disability – sponsor analysis method of subgroup with no relapses; review analysis of subgroup derived from subgroup of ADARR with no relapses
4: T3MIPCW Time to 3-month Inverse Probability Censoring Weight

7.1.3. Subpopulations

Annualized Relapse Rate

The rate ratio for the ARR was similar in subgroups based on sex, region and age category (Table 53). There were too few subjects in the non-white race categories to assess the ARR in these subgroups. The ARR was higher in the 18- to 30-year old age group, as expected, but the rate ratio remained similar to the other age groups.

Table 53: ARR by subgroups, FAS, PoolC2 ISE

Subgroup	N	Relapse free %		ARR		Rate ratio
		OMB	TER	OMB	TER	
Sex						
F	1273	83	73	0.134	0.237	0.57
M	609	87	68	0.092	0.284	0.32
Region						
Europe	974	84	72	0.121	0.239	0.51
North America	421	81	70	0.132	0.250	0.53
ROW	487	87	71	0.108	0.277	0.39
Age category						
≥18 - ≤30	442	82	62	0.147	0.344	0.43
>30 - ≤40	651	87	71	0.097	0.25	0.39
>40 - ≤55	785	83	76	0.124	0.201	0.62

*: There are not enough subjects in the non-white categories to assess RACE

Disability worsening or progression

For the purpose of assessing subgroups, the "IPCW" method was used in which the influence of relapses with reduced by censoring subjects at the time of a relapse at the time of any relapse that occurred on or before the start of a period of disability worsening/progression. The treatment effect favors treatment with ofatumumab for all subgroups Table 54.

Table 54: 3- and 6-month CDW by subgroups, PoolC2, ISE

Subgroup		3-month CDW		6-month CDW	
		T3MIPCW		T6MIPCW	
	N	OR	p-value*	OR	p-value*
Sex					
Female	1271	0.537	0.0016	0.604	0.0160

Subgroup	N	3-month CDW T3MIPCW		6-month CDW T6MIPCW	
		OR	p-value*	OR	p-value*
Male	605	0.796	0.1932	0.768	0.2317
Region					
Europe	970	0.652	0.0323	0.629	0.0390
North America	419	0.648	0.0950	0.758	0.3163
ROW	487	0.477	0.0477	0.595	0.1588
Race					
Asian	71	0.627	0.7368	0.628	0.7368
Black or African-American	65	0.397	0.1525	0.492	0.2676
Other	87	0.957	0.5780	0.844	0.5280
White	1653	0.602	0.0019	0.657	0.0166
Age group					
≤40	1087	0.563	0.0069	0.654	0.0431
>40	789	0.643	0.0447	0.642	0.0791
Baseline EDSS					
≤3.5	1344	0.602	0.0094	0.618	0.0270
>3.5	532	0.614	0.0280	0.691	0.1080
Relapses in the last 24 months					
≤2	1357	0.712	0.0324	0.691	0.0402
>2	519	0.413	0.0064	0.573	0.0948
Baseline GdE lesions					
0	1142	0.569	0.0023	0.595	0.0114
>0	698	0.716	0.1849	0.735	0.2511
Baseline volume of T2 lesions by quartiles					
< 3.46	465	0.453	0.0429	0.470	0.0705
≥3.46 and <8.46	464	0.666	0.1138	0.584	0.1037
≥8.46 and <18.43	464	0.630	0.1707	0.811	0.5463
≥18.43	466	0.606	0.0350	0.658	0.0785
Baseline Timed 25 MWT					
10 sec or less	1636	0.624	0.0058	0.653	0.0219
Over 10 sec	237	0.600	0.0964	0.678	0.2132

*: log-rank test; nominal

7.1.4. Dose and Dose-Response

One dose was studied in the pivotal trials.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The onset and duration of the treatment effect was not studied.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Post-market Setting

There are no specific considerations for the benefit after approval.

7.2.2. Other Relevant Benefits

There are no additional relevant benefits

7.3. Integrated Assessment of Effectiveness

See the Sections above

There was no significant change in EDSS score from baseline to the End of Study visit for either treatment group and no difference between the treatment groups (Table 55).

Table 55: EDSS change from baseline to EOS visit, ISE

TRT01P	N	EDSS Change from Baseline				
		Mean	Std Dev	Min	Max	Median
OMB 20mg	883	-0	0.86	-4.5	4	0
TER 14mg	875	0.07	0.85	-3.5	4.5	0

Source: VISIT_EOS Subset of PARAM_EDSS Subset of ADEDSS ISE CHG By (TRT01P).jmp

8. Review of Safety

8.1. Safety Review Approach

The safety population is identified by the "SAFFL" flag. These subjects received at least one dose of investigational treatment. The "On Treatment" flag only indicates that the treatment start date precedes the start date of any adverse event. The key flag is the "SAFRFL" flag which indicates that the event started on or after the start of investigational treatment and ended within the interval of treatment start date to treatment end date plus 100 days. This allows for the pharmacodynamic effect of either investigational treatment. The population defined by both the SAFFL flag and the SAFRFL flag is therefore used for key safety analyses. The key subject pool is the "C2" pool which includes subjects from the 2 pivotal trials, 2102 and 2103.

> *Reviewer Comment: The use of the "SAFRFL" flag instead of the "ONTRTFL" flag only adds a small number of AEs or SAEs from the 100-day period after the end of treatment.*

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The overall number of RMS subjects exposed to any ofatumumab dose and route of administration and the duration of exposure are listed in Table 56. Over 824 subjects were exposed to the proposed clinical dose regimen of ofatumumab for one year or more (Table 57).

Table 56: Overall exposure to ofatumumab

Study	N		Exposure (patient-years)	
	Ofatumumab	Teriflunomide	Ofatumumab	Teriflunomide
Studies in RMS				
2311+2302 (Phase 3 in RMS)	946	936	1486.7	1397.8
115102 (Dose ranging IV in RMS)	38			
112831 POC, dose ranging in RMS)	167		38.4	
OMB 30mg q12w	32		7.4	
OMB 3mg q12w	34		7.9	
OMB 60mg q12w	34		8.0	
OMB 60mg q4w	64		15.0	
G2102 (PFS vs. autoinjector)	284		68.5	
Any OMB 20mgSC	1230		1555	

Source: ADEX ISS

Table 57: Duration of exposure to ofatumumab, 20 mg SC q4W, or teriflunomide comparator, pool L2

Duration of exposure	Number of subjects	
	OMB	TER
≥ 6 months	889	871
≥ 12 months	824	805
≥ 18 months	551	506
Total	1230	936

Source: PARAM_EXDUR days Subset of PoolL2FL_Y Subset of ADEX ISS AVAL By (TRT01A).jmp

8.2.2. Relevant characteristics of the safety population:

The demographic characteristics of the pooled safety population from studies 2301 and 2302 are listed in Table 58. The characteristics are well balanced by treatment group and typical of an RMS population. The sources of subjects by region and country support translation of the results to the US population.

Table 58: Demographic characteristics, studies 2301 and 2302 pooled

	OMB 20mg n=946	TER 14mg n=936	Totals n=1882
SEX - count subjects and %			
F	637 (67.3%)	636 (67.9%)	1273 (67.6%)
M	309 (32.7%)	300 (32.1%)	609 (32.4%)
AGE			
AGE - mean	38.36	37.96	38.16
AGE - std.dev.	9.04	9.22	9.13
AGE - min	18	18	18
AGE - max	56	56	56
AGE - median	39	38	38
AGEGR - count subjects and %			
<=40	529 (55.9%)	564 (60.3%)	1093 (58.1%)
>40	417 (44.1%)	372 (39.7%)	789 (41.9%)
RACE - count subjects and %			
WHITE	829 (87.6%)	829 (88.6%)	1658 (88.1%)
ASIAN	36 (3.8%)	35 (3.7%)	71 (3.8%)
OTHER	42 (4.4%)	28 (3.0%)	70 (3.7%)
BLACK OR AFRICAN AMERICAN	28 (3.0%)	38 (4.1%)	66 (3.5%)
UNKNOWN	11 (1.2%)	6 (0.6%)	17 (0.9%)
RACEGR1 - count subjects and %			
White	829 (87.6%)	829 (88.6%)	1658 (88.1%)
Other	53 (5.6%)	34 (3.6%)	87 (4.6%)
Asian	36 (3.8%)	35 (3.7%)	71 (3.8%)
Black or African American	28 (3.0%)	38 (4.1%)	66 (3.5%)
COUNTRY - count subjects and over 10 %			
USA	194 (20.5%)	199 (21.3%)	393 (20.9%)
RUS	176 (18.6%)	176 (18.8%)	352 (18.7%)
POL	113 (11.9%)	130 (13.9%)	243 (12.9%)
REGION1 - count subjects and %			
Eastern Europe	280 (29.6%)	278 (29.7%)	558 (29.6%)
Others	242 (25.6%)	240 (25.6%)	482 (25.6%)
North America and AUS	213 (22.5%)	213 (22.8%)	426 (22.6%)
Western Europe	211 (22.3%)	205 (21.9%)	416 (22.1%)
RGSUBGR1 - count subjects and %			
Europe	491 (51.9%)	483 (51.6%)	974 (51.8%)
Rest of world	245 (25.9%)	242 (25.9%)	487 (25.9%)
North America	210 (22.2%)	211 (22.5%)	421 (22.4%)
RGSUBGR2 - count subjects and %			
Rest of world	914 (96.6%)	905 (96.7%)	1819 (96.7%)
Asian	32 (3.4%)	31 (3.3%)	63 (3.3%)
RGSUBGR3 - count subjects and %			
Europe	491 (51.9%)	483 (51.6%)	974 (51.8%)
Rest of world	213 (22.5%)	211 (22.5%)	424 (22.5%)

	OMB 20mg n=946	TER 14mg n=936	Totals n=1882
North America	210 (22.2%)	211 (22.5%)	421 (22.4%)
Asian	32 (3.4%)	31 (3.3%)	63 (3.3%)

Source: JRevISSSelADSLSAFFL_Y POOLC2FL_Y DEMSUMMREPORT2

8.2.3. Adequacy of the safety database:

The size of the individual study databases and the pooled pivotal studies are adequate to assess safety.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The were no issues related to data integrity or quality.

8.3.2. Categorization of Adverse Events

Adverse events were categorized using the standard MedDRA terms. A review of those preferred terms that did not match the verbatim term exactly did not reveal any significant miscoding.

8.3.3. Routine Clinical Tests

Routine hematologic tests included a standard CBC plus CD19+ B-cell counts. Clinical chemistry included electrolytes, calcium, magnesium, phosphorus, glucose, total protein, BUN, creatinine albumin, alkaline phosphatase, liver transaminases, bilirubin, creatinine, amylase, total, HDL and LDL cholesterol, triglycerides, and C-reactive protein. Total IgG and IgM levels were collected at regular intervals. Teriflunomide levels were collected periodically. An ECG was done at screening and at the end of treatment. The timing of the key assessments is described in Appendix 13.5.

8.4. Safety Results

8.4.1. Deaths

Study 2301

There were no deaths during any phase of study 2301.

Study 2302

There was one death in study 2302 (subject COMB157G2302 (b) (6)). An aortic and vertebral artery dissection occurred 152 days after the last dose of teriflunomide. Transthoracic echocardiography showed left ventricular dysfunction, hypokinesis of the anteroseptal left ventricular region, severe aortic insufficiency. Resuscitation was required during attempted cardiothoracic surgery. Death due to aortic rupture occurred on the day of surgery.

Reviewer Comment: This death is not likely to be related to teriflunomide.

8.4.2. Serious Adverse Events

Study 2301

One or more serious adverse events occurred in 48 subjects (10.3%) treated with ofatumumab and in 38 subjects (8.2%) of subjects treated with teriflunomide (Table 59). The most common SAEs were in the Infections and Infestations SOC. Events occurring in 2 or more subjects treated with ofatumumab are shown by preferred term in Table 60. The serious infections are listed in Table 61. Appendicitis was the most common serious infection, occurring in 3 ofatumumab subjects and 1 teriflunomide subject. Nine ofatumumab subjects had a serious psychiatric AE compared to no teriflunomide subjects. The preferred terms for these nine subjects are listed in Table 62. Five of 9 of these events were related to depression or suicidality.

Table 59: Serious adverse events by SOC, Safety population, EOT* + 100 days, study 2301

Body System or Organ Class	OMB 20 mg	TERI 14 mg
Infections and infestations	12 (2.6%)	7 (1.5%)
Psychiatric disorders	9 (1.9%)	0 (0.0%)
Injury, poisoning and procedural complications	6 (1.3%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	4 (0.9%)	6 (1.3%)
Gastrointestinal disorders	4 (0.9%)	3 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.9%)	2 (0.4%)
Reproductive system and breast disorders	3 (0.6%)	3 (0.6%)
Nervous system disorders	3 (0.6%)	11 (2.4%)
Ear and labyrinth disorders	3 (0.6%)	0 (0.0%)
Hepatobiliary disorders	3 (0.6%)	1 (0.2%)
Blood and lymphatic system disorders	2 (0.4%)	0 (0.0%)
Investigations	2 (0.4%)	1 (0.2%)
General disorders and administration site conditions	1 (0.2%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	1 (0.2%)	3 (0.6%)
Immune system disorders	1 (0.2%)	0 (0.0%)
Renal and urinary disorders	0 (0.0%)	3 (0.6%)
Vascular disorders	0 (0.0%)	1 (0.2%)
Metabolism and nutrition disorders	0 (0.0%)	1 (0.2%)
Subjects(filtered)	48 (10.3%)	38 (8.2%)
1stColItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevSelADSLSAFFL_Y SOCbyTRT01AfiltAESER_Y SAFRFL_Y
*: EOT = End of Treatment

Table 60: Serious adverse events by preferred term, Safety population, 2 or more OMB subjects, FAS, EOT + 100 days, study 2301

Dictionary Derived Term	OMB 20 mg	TERI 14 mg
Appendicitis	3 (0.6%)	1 (0.2%)
Injection related reaction	2 (0.4%)	0 (0.0%)
Suicidal ideation	2 (0.4%)	0 (0.0%)
Vertigo	2 (0.4%)	0 (0.0%)
Back pain	2 (0.4%)	1 (0.2%)
Gastroenteritis	2 (0.4%)	0 (0.0%)
Total Subjects(filtered)	48 (10.3%)	38 (8.2%)
1stCollItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyTRT01AfiltAESER_Y SAFRFL_Y

Table 61: SAEs, Infections and infestations by preferred term, safety population, EOT plus 100 days, study 2301

Dictionary Derived Term	OMB 20 mg	TERI 14 mg
Appendicitis	3 (0.6%)	1 (0.2%)
Gastroenteritis	2 (0.4%)	0 (0.0%)
Escherichia urinary tract infection	1 (0.2%)	0 (0.0%)
Cystitis	1 (0.2%)	0 (0.0%)
Influenza	1 (0.2%)	0 (0.0%)
Kidney infection	1 (0.2%)	0 (0.0%)
Neutropenic sepsis	1 (0.2%)	0 (0.0%)
Osteomyelitis	1 (0.2%)	0 (0.0%)
Upper respiratory tract infection	1 (0.2%)	0 (0.0%)
Urinary tract infection	1 (0.2%)	0 (0.0%)
Campylobacter infection	0 (0.0%)	1 (0.2%)
Pneumonia	0 (0.0%)	1 (0.2%)
Influenzal Pneumonia	0 (0.0%)	1 (0.2%)
Salpingo-oophoritis	0 (0.0%)	1 (0.2%)
Tick-borne viral encephalitis	0 (0.0%)	1 (0.2%)
Abscess sweat gland	0 (0.0%)	1 (0.2%)
Subjects(filtered)	12 (2.6%)	7 (1.5%)
1stCollItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyTRT01AfiltAESER_Y SAFRFL_Y SOC_INFINF

Table 62: SAEs, Psychiatric SOC, by preferred term, safety population, EOT plus 100 days, study 2301

Dictionary Derived Term	OMB 20 mg
Suicidal ideation	2 (0.4%)
Mental status changes	1 (0.2%)

Dictionary Derived Term	OMB 20 mg
Psychotic disorder	1 (0.2%)
Somatic symptom disorder	1 (0.2%)
Stress	1 (0.2%)
Depression suicidal	1 (0.2%)
Suicide attempt	1 (0.2%)
Depression	1 (0.2%)
Subjects(filtered)	9 (1.9%)
1stCollItemSubjects	465 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyTRT01AfiltSAFRFL_Y AESER_Y SOC_PSYCH

Study 2302

One or more serious adverse events occurred in 38 subjects (7.9%) treated with ofatumumab and in 36 subjects (7.6%) treated with teriflunomide (Table 63). As in study 2301, appendicitis was the most common serious infection, occurring in 5 ofatumumab subjects and one teriflunomide subject (Table 64). There were no notable imbalances by treatment group.

Reviewer Comment: The disproportionate incidence of psychiatric SAEs in the ofatumumab group noted in study 2301 (Table 62) was not seen in study 2302.

Table 63: Serious adverse events by SOC, safety population, EOT* + 100 days, study 2302

Body System or Organ Class	OMB 20 mg	TERI 14 mg
Infections and infestations	12 (2.5%)	10 (2.1%)
Injury, poisoning and procedural complications	7 (1.5%)	8 (1.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.0%)	2 (0.4%)
Musculoskeletal and connective tissue disorders	4 (0.8%)	2 (0.4%)
Gastrointestinal disorders	4 (0.8%)	1 (0.2%)
Nervous system disorders	4 (0.8%)	4 (0.8%)
Cardiac disorders	3 (0.6%)	1 (0.2%)
General disorders and administration site conditions	2 (0.4%)	1 (0.2%)
Hepatobiliary disorders	2 (0.4%)	2 (0.4%)
Psychiatric disorders	1 (0.2%)	2 (0.4%)
Reproductive system and breast disorders	1 (0.2%)	5 (1.1%)
Respiratory, thoracic and mediastinal disorders	1 (0.2%)	1 (0.2%)
Skin and subcutaneous tissue disorders	1 (0.2%)	0 (0.0%)
Renal and urinary disorders	0 (0.0%)	1 (0.2%)
Vascular disorders	0 (0.0%)	2 (0.4%)
Eye disorders	0 (0.0%)	1 (0.2%)
Subjects(filtered)	38 (7.9%)	36 (7.6%)
1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: SAFFL_Y Subset of ADAE 2302 By (USUBJID, TRT01A, AEBODSYS) NUSUBJIDbyTRT01A By (AEBODSYS)
*: EOT = End of Treatment

Table 64: Serious adverse events by preferred term, safety population, 2 or more OMB subjects, FAS, EOT + 100 days, study 2302

Dictionary Derived Term	OMB 20 mg	TERI 14 mg
Appendicitis	5 (1.0%)	1 (0.2%)
Ankle fracture	2 (0.4%)	0 (0.0%)
Syncope	2 (0.4%)	0 (0.0%)
Uterine leiomyoma	2 (0.4%)	1 (0.2%)
Basal cell carcinoma	2 (0.4%)	1 (0.2%)
Urinary tract infection	2 (0.4%)	2 (0.4%)
Cholelithiasis	2 (0.4%)	0 (0.0%)
Subjects(filtered)	38 (7.9%)	36 (7.6%)
1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyTRT01AfiltSAFRFL_Y AESER_Y

Table 65: SAEs, Infections and infestations SOC by preferred term, safety population, EOT plus 100 days, study 2302

Dictionary Derived Term	OMB 20 mg	TERI 14 mg
Appendicitis	5 (1.0%)	1 (0.2%)
Urinary tract infection	2 (0.4%)	2 (0.4%)
Lower respiratory tract infection	1 (0.2%)	0 (0.0%)
Pneumonia	1 (0.2%)	0 (0.0%)
Respiratory tract infection viral	1 (0.2%)	0 (0.0%)
Influenza	1 (0.2%)	0 (0.0%)
Gastroenteritis	1 (0.2%)	0 (0.0%)
Urosepsis	1 (0.2%)	0 (0.0%)
Osteomyelitis	0 (0.0%)	1 (0.2%)
Paronychia	0 (0.0%)	1 (0.2%)
Peritonitis	0 (0.0%)	1 (0.2%)
Postoperative abscess	0 (0.0%)	1 (0.2%)
Sepsis	0 (0.0%)	1 (0.2%)
Viral infection	0 (0.0%)	1 (0.2%)
Cystitis	0 (0.0%)	1 (0.2%)
Subjects(filtered)	12 (2.5%)	10 (2.1%)
1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyTRT01AfiltSAFRFL_Y AESER_Y SOC_INFINF

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study 2301

Study treatment was discontinued due to an adverse event in 5.8% of subjects treated with ofatumumab and in 5.2% of subjects treated with teriflunomide (Table 66). A reduction in immunoglobulins accounted for 15 (3.2%) of the ofatumumab subjects compared to 4 (0.9%) in the teriflunomide group (Table 67).

Table 66: Discontinuation of Study Treatment due to a treatment emergent adverse event, study 2301, EOT+100 days, safety population

Dictionary Derived Term	Ofatumumab 20 mg	Teriflunomide 14 mg
Blood immunoglobulin M decreased	10 (2.2%)	3 (0.6%)
Alopecia	0 (0.0%)	4 (0.9%)
Immunoglobulins decreased	3 (0.6%)	0 (0.0%)
Diarrhoea	0 (0.0%)	3 (0.6%)
Multiple sclerosis relapse	0 (0.0%)	3 (0.6%)
Blood immunoglobulin G decreased	1 (0.2%)	1 (0.2%)
Dyspnoea	1 (0.2%)	0 (0.0%)
Flatulence	1 (0.2%)	0 (0.0%)
Gamma-glutamyltransferase increased	1 (0.2%)	0 (0.0%)
Gastroenteritis	1 (0.2%)	0 (0.0%)
Depression suicidal	1 (0.2%)	0 (0.0%)
Blood immunoglobulin M abnormal	1 (0.2%)	0 (0.0%)
Intentional overdose	1 (0.2%)	0 (0.0%)
Invasive breast carcinoma	1 (0.2%)	0 (0.0%)
Blood creatinine increased	1 (0.2%)	0 (0.0%)
Liver function test increased	1 (0.2%)	0 (0.0%)
Pulmonary sarcoidosis	1 (0.2%)	0 (0.0%)
Respiratory tract infection	1 (0.2%)	0 (0.0%)
Suicide attempt	1 (0.2%)	0 (0.0%)
Upper respiratory tract infection	1 (0.2%)	0 (0.0%)
Weight increased	1 (0.2%)	0 (0.0%)
Abdominal pain	0 (0.0%)	1 (0.2%)
Abdominal pain upper	0 (0.0%)	1 (0.2%)
Aspartate aminotransferase increased	1 (0.2%)	0 (0.0%)
Blood pressure increased	0 (0.0%)	1 (0.2%)
Cervix carcinoma	0 (0.0%)	1 (0.2%)
Colitis microscopic	0 (0.0%)	1 (0.2%)
Dehydration	0 (0.0%)	1 (0.2%)
Leukopenia	1 (0.2%)	0 (0.0%)
Dyspepsia	0 (0.0%)	1 (0.2%)
Hepatic enzyme increased	0 (0.0%)	1 (0.2%)
Interstitial lung disease	0 (0.0%)	1 (0.2%)
Metrorrhagia	0 (0.0%)	1 (0.2%)
Alanine aminotransferase increased	1 (0.2%)	0 (0.0%)
Nausea	0 (0.0%)	1 (0.2%)
Pain in extremity	0 (0.0%)	1 (0.2%)
Rash	0 (0.0%)	1 (0.2%)
Rash erythematous	0 (0.0%)	1 (0.2%)
Tachycardia	0 (0.0%)	1 (0.2%)
Vomiting	0 (0.0%)	1 (0.2%)
Subjects(filtered)	27 (5.8%)	24 (5.2%)
1stColItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevADSLTRT01AbyAEDECODfiltSAFRFL_Y AEACN_WD

Table 67: TEAE related to Immunoglobulin reduction leading to discontinuation of treatment, EOT+100 days safety population, study 2301

Dictionary Derived Term	Ofatumumab 20 mg	Teriflunomide 14 mg
Blood immunoglobulin M decreased	10 (2.2%)	3 (0.6%)
Immunoglobulins decreased	3 (0.6%)	0 (0.0%)
Blood immunoglobulin G decreased	1 (0.2%)	1 (0.2%)
Blood immunoglobulin M abnormal	1 (0.2%)	0 (0.0%)
Subtotal	15 (3.2%)	4 (0.9%)
1stCollItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevADSLTRT01AbyAEDECODfiltSAFRFL_Y AEACN_WD

Study 2302

Study treatment was discontinued due to an adverse event in 5.6% of subjects treated with ofatumumab and in 5.3% of subjects treated with teriflunomide (Table 68). A reduction in immunoglobulins accounted for 20 (4.2%) of these subjects in the ofatumumab group and 3 (0.6%) subjects in the placebo group (Table 69).

Table 68: Discontinuation of Study Treatment due to a treatment emergent adverse event, safety population, study 2302

AEDECOD	Ofatumumab 20 mg	Teriflunomide 14 mg
Blood immunoglobulin M decreased	9 (1.9%)	3 (0.6%)
Immunoglobulins decreased	7 (1.5%)	0 (0.0%)
Blood immunoglobulin G abnormal	2 (0.4%)	0 (0.0%)
Dizziness	1 (0.2%)	0 (0.0%)
Enlarged uvula	1 (0.2%)	0 (0.0%)
Blood immunoglobulin M abnormal	1 (0.2%)	0 (0.0%)
Blood immunoglobulin G decreased	1 (0.2%)	0 (0.0%)
Injection related reaction	1 (0.2%)	1 (0.2%)
Mechanical urticaria	1 (0.2%)	0 (0.0%)
Myocardial infarction	1 (0.2%)	0 (0.0%)
Pharyngeal swelling	1 (0.2%)	0 (0.0%)
Pulmonary sarcoidosis	1 (0.2%)	0 (0.0%)
Pyrexia	1 (0.2%)	0 (0.0%)
Rash generalised	1 (0.2%)	0 (0.0%)
Rheumatic disorder	1 (0.2%)	0 (0.0%)
Urinary incontinence	1 (0.2%)	0 (0.0%)
Vertigo	1 (0.2%)	0 (0.0%)
Abdominal pain	0 (0.0%)	1 (0.2%)
Alanine aminotransferase increased	0 (0.0%)	5 (1.1%)
Alopecia	0 (0.0%)	1 (0.2%)
Anxiety disorder	0 (0.0%)	1 (0.2%)
Aspartate aminotransferase increased	0 (0.0%)	2 (0.4%)
Blood alkaline phosphatase increased	0 (0.0%)	1 (0.2%)
Blood pressure increased	0 (0.0%)	1 (0.2%)

AEDECOD	Ofatumumab 20 mg	Teriflunomide 14 mg
Delusion	0 (0.0%)	1 (0.2%)
Gamma-glutamyltransferase increased	0 (0.0%)	1 (0.2%)
Hepatic enzyme increased	0 (0.0%)	1 (0.2%)
Hepatitis B core antibody positive	0 (0.0%)	1 (0.2%)
Latent tuberculosis	0 (0.0%)	1 (0.2%)
Liver function test increased	0 (0.0%)	1 (0.2%)
Lymphopenia	0 (0.0%)	1 (0.2%)
Mood altered	0 (0.0%)	1 (0.2%)
Multiple sclerosis relapse	0 (0.0%)	1 (0.2%)
Nausea	0 (0.0%)	1 (0.2%)
Oedema peripheral	0 (0.0%)	1 (0.2%)
Rash pruritic	0 (0.0%)	2 (0.4%)
Sepsis	0 (0.0%)	1 (0.2%)
Transaminases increased	0 (0.0%)	1 (0.2%)
Subjects(filtered)	27 (5.6%)	25 (5.3%)
1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRev2302ADSLTRT01AbyAEDECODfiltSAFRFL_Y AEACN_DC

Table 69: TEAE related to Immunoglobulin reduction leading to discontinuation of treatment, safety population, study 2302

AEDECOD	Ofatumumab 20 mg	Teriflunomide 14 mg
Blood immunoglobulin M decreased	9 (1.9%)	3 (0.6%)
Immunoglobulins decreased	7 (1.5%)	0 (0.0%)
Blood immunoglobulin G abnormal	2 (0.4%)	0 (0.0%)
Blood immunoglobulin M abnormal	1 (0.2%)	0 (0.0%)
Blood immunoglobulin G decreased	1 (0.2%)	0 (0.0%)
Subtotal	20 (4.2%)	3 (0.6%)
1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRev2302ADSLTRT01AbyAEDECODfiltSAFRFL_Y AEACN_DC

8.4.4. Significant Adverse Events

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study 2301

One or more adverse events occurred in 82.2% of subjects treated with ofatumumab and in 82.3% of those treated with teriflunomide. Infections were the most common adverse events in both treatment groups (Table 70). There were no notable differences by SOC between the treatment groups, with the possible exception of the Skin and Subcutaneous Tissue Disorders SOC where there were more events in the teriflunomide group. Although hepatobiliary disorders were uncommon, there were twice as many events in the ofatumumab group. The most common adverse event terms are listed by treatment group in Table 71.

Table 70: Adverse events by SOC, Safety population, EOT +100 days, study 2301

Body System or Organ Class	OMB 20 mg	TERI 14 mg
Infections and infestations	229 (49.2%)	238 (51.5%)
Nervous system disorders	128 (27.5%)	148 (32.0%)
General disorders and administration site conditions	126 (27.1%)	107 (23.2%)
Musculoskeletal and connective tissue disorders	123 (26.5%)	124 (26.8%)
Injury, poisoning and procedural complications	117 (25.2%)	111 (24.0%)
Gastrointestinal disorders	104 (22.4%)	135 (29.2%)
Investigations	94 (20.2%)	86 (18.6%)
Psychiatric disorders	74 (15.9%)	60 (13.0%)
Skin and subcutaneous tissue disorders	71 (15.3%)	116 (25.1%)
Respiratory, thoracic and mediastinal disorders	48 (10.3%)	56 (12.1%)
Reproductive system and breast disorders	34 (7.3%)	44 (9.5%)
Renal and urinary disorders	27 (5.8%)	37 (8.0%)
Ear and labyrinth disorders	24 (5.2%)	22 (4.8%)
Metabolism and nutrition disorders	24 (5.2%)	27 (5.8%)
Eye disorders	22 (4.7%)	29 (6.3%)
Vascular disorders	20 (4.3%)	32 (6.9%)
Blood and lymphatic system disorders	13 (2.8%)	21 (4.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (2.4%)	11 (2.4%)
Immune system disorders	10 (2.2%)	18 (3.9%)
Cardiac disorders	9 (1.9%)	15 (3.2%)
Hepatobiliary disorders	9 (1.9%)	4 (0.9%)
Endocrine disorders	4 (0.9%)	2 (0.4%)
Social circumstances	2 (0.4%)	2 (0.4%)
Subjects(filtered)	382 (82.2%)	380 (82.3%)
1stCollItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevSelADSLSAFFL_Y SOCbyTRT01AfiltSAFRFL_Y

Table 71: Adverse events by PT, 5% or more of either treatment group, safety population, EOT + 100 days, study 2301

Dictionary Derived Term	OMB 20 mg	TERI 14 mg
Nasopharyngitis	82 (17.6%)	69 (14.9%)
Injection related reaction	76 (16.3%)	77 (16.7%)
Headache	57 (12.3%)	51 (11.0%)
Upper respiratory tract infection	48 (10.3%)	73 (15.8%)
Fatigue	46 (9.9%)	40 (8.7%)
Urinary tract infection	42 (9.0%)	41 (8.9%)
Injection site reaction	42 (9.0%)	26 (5.6%)
Back pain	37 (8.0%)	34 (7.4%)
Influenza	32 (6.9%)	29 (6.3%)
Nausea	31 (6.7%)	32 (6.9%)
Alopecia	27 (5.8%)	64 (13.9%)
Blood immunoglobulin M decreased	26 (5.6%)	13 (2.8%)
Arthralgia	25 (5.4%)	23 (5.0%)

Dictionary Derived Term	OMB 20 mg	TERI 14 mg
Diarrhoea	21 (4.5%)	62 (13.4%)
Pain in extremity	23 (4.9%)	36 (7.8%)
Paraesthesia	16 (3.4%)	31 (6.7%)
Hypertension	15 (3.2%)	24 (5.2%)
Subjects(filtered)	382 (82.2%)	380 (82.3%)
1stCollItemSubjects	465 (100.0%)	462 (100.0%)

Source: JRevSelADSLSAFFL_Y AEDECODbyTRT01AfiltSAFRFL_Y

Study 2302

One or more adverse events occurred in 85.0% of subjects treated with ofatumumab and in 86.1% of those treated with teriflunomide (Table 72). Infections were the most common adverse events in both treatment groups. No single infection or type of infection was more common in one treatment group. Fungal infections were uncommon in both groups. There were no cases of PML. The most common individual preferred terms are listed in Table 73. Both injection-related and injection site-related adverse events were more common in the ofatumumab group.

Table 72: Treatment emergent adverse events by SOC, EOT + 100 days, study 2302

AEBODSYS	OMB 20 mg	TERI 14 mg
Infections and infestations	259 (53.8%)	255 (53.8%)
Injury, poisoning and procedural complications	161 (33.5%)	115 (24.3%)
Nervous system disorders	144 (29.9%)	152 (32.1%)
General disorders and administration site conditions	131 (27.2%)	96 (20.3%)
Musculoskeletal and connective tissue disorders	124 (25.8%)	106 (22.4%)
Gastrointestinal disorders	120 (24.9%)	151 (31.9%)
Investigations	107 (22.2%)	106 (22.4%)
Skin and subcutaneous tissue disorders	87 (18.1%)	122 (25.7%)
Psychiatric disorders	80 (16.6%)	75 (15.8%)
Respiratory, thoracic and mediastinal disorders	58 (12.1%)	61 (12.9%)
Vascular disorders	35 (7.3%)	45 (9.5%)
Eye disorders	33 (6.9%)	30 (6.3%)
Metabolism and nutrition disorders	29 (6.0%)	45 (9.5%)
Renal and urinary disorders	25 (5.2%)	36 (7.6%)
Reproductive system and breast disorders	24 (5.0%)	35 (7.4%)
Blood and lymphatic system disorders	19 (4.0%)	23 (4.9%)
Cardiac disorders	17 (3.5%)	18 (3.8%)
Ear and labyrinth disorders	17 (3.5%)	12 (2.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (2.7%)	12 (2.5%)
Hepatobiliary disorders	8 (1.7%)	13 (2.7%)
Immune system disorders	6 (1.2%)	9 (1.9%)
Endocrine disorders	5 (1.0%)	1 (0.2%)
Social circumstances	1 (0.2%)	0 (0.0%)
Congenital, familial and genetic disorders	1 (0.2%)	1 (0.2%)
Subjects(filtered)	409 (85.0%)	408 (86.1%)

AEBODSYS	OMB 20 mg	TERI 14 mg
1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRev2302 AEBODSYSbyADSLTRT01AfiltSAFRFL_Y

Table 73: Treatment emergent adverse events by preferred term, EOT+100days, 5% or more in either treatment group, study 2302

AEDECOD	Ofatumumab 20 mg	Teriflunomide 14 mg
Injection related reaction	119 (24.7%)	66 (13.9%)
Nasopharyngitis	88 (18.3%)	87 (18.4%)
Headache	69 (14.3%)	65 (13.7%)
Injection site reaction	61 (12.7%)	26 (5.5%)
Urinary tract infection	55 (11.4%)	37 (7.8%)
Upper respiratory tract infection	49 (10.2%)	47 (9.9%)
Back pain	35 (7.3%)	24 (5.1%)
Blood immunoglobulin M decreased	30 (6.2%)	8 (1.7%)
Influenza	30 (6.2%)	30 (6.3%)
Nausea	30 (6.2%)	32 (6.8%)
Diarrhoea	28 (5.8%)	49 (10.3%)
Anxiety	28 (5.8%)	18 (3.8%)
Alopecia	27 (5.6%)	74 (15.6%)
Fatigue	25 (5.2%)	32 (6.8%)
Insomnia	24 (5.0%)	19 (4.0%)
Depression	24 (5.0%)	24 (5.1%)
Arthralgia	24 (5.0%)	21 (4.4%)
Pain in extremity	23 (4.8%)	30 (6.3%)
Hypertension	20 (4.2%)	31 (6.5%)
Subjects(filtered)	409 (85.0%)	408 (86.1%)
1stCollItemSubjects	481 (100.0%)	474 (100.0%)

Source: JRev2302 AEDECODbyADSLTRT01AfiltSAFRFL_Y

8.4.6. Laboratory Findings

Study 2301

Hematology

Leukocytes: The median change during the RCP was +3% for those treated with ofatumumab compared to -9% for those treated with teriflunomide. The proportion of subjects with a leukocyte count below the LLN at any visit was 8% in the ofatumumab group compared to 23.8% in the teriflunomide group. There were no subjects in the ofatumumab group with a grade 3 reduction (1-2X10^9/L) compared to 5 teriflunomide subjects.

Reviewer Comment: One subject treated with ofatumumab (Subject (b) (6)) did have a grade 3 reduction on one occasion at study week 48 but that was 12

weeks after discontinuation of study treatment due to a new diagnosis of invasive breast cancer.

Neutrophils: The median change during the RCP was +5% for those treated with ofatumumab and -15% for teriflunomide subjects. The proportion with a neutrophil count below the LLN at any visit was 16.1% of the ofatumumab group compared to 39% for the teriflunomide group. Three ofatumumab subjects and 4 teriflunomide subjects had a grade 4 reduction ($<0.2X10^9/L$).

Lymphocytes: The median reduction during the RCP for both treatment groups was 10%. Five percent of ofatumumab subjects and 7% of teriflunomide subjects had a level below the LLN at any assessment. There were no reductions above a toxicity grade of 1.

Reviewer Comment: In general, reductions in white cell counts were more prominent in the teriflunomide group. Adverse events related to a reduction of WBCs are not prominent in either treatment group. Ofatumumab subject (b) (6) ***had an SAE of neutropenic sepsis. This subject had not received any immunotherapy prior to being randomized to ofatumumab in this trial. She developed mouth ulcerations on day 518 while on treatment. On Day 520, she was hospitalized and was diagnosed with neutropenic sepsis. The neutrophil count was 0.26 × 10^9/L (CTCAE grade 2). Treatment included meropenem. The event was considered resolved by day 522.***

Hemoglobin, Hematocrit, RBCs, platelets: There were no significant changes in any red blood cell assessments or in platelet counts.

Chemistry

Liver transaminases, bilirubin, alkaline phosphatase

ALT: For all visits, the median change in ALT was a decline of 6% in the ofatumumab group and an increase of 10% in the teriflunomide group. The proportion of subjects with one or more values above the ULN was 13% in the ofatumumab group and 25% in the teriflunomide group. One subject in each treatment group had a grade 3 elevation (>5 but ≤20X).

AST: For all visits, the median change in AST was zero for the ofatumumab group and an increase of 7% in the teriflunomide group. The proportion of subjects with one or more values above the ULN was 8% in the ofatumumab group and 14% in the teriflunomide group. One subject in each treatment group a grade 3 elevation (>5 but ≤20X).

Bilirubin: For all visits, the median change in bilirubin was zero for both treatment groups. The proportion of subjects with a value above the ULN was 7% for the ofatumumab group and 8% for the teriflunomide group. Eleven ofatumumab subjects (2%) and 9 teriflunomide subjects had a grade 3 elevation (>3 but ≤10X).

Hy's Law criteria: No subject in either treatment group met the Hy's Law criteria. No subjects met the Hy's Law criteria for ALT and AST elevation regardless of ALP changes. Four ofatumumab subjects had a greater than 5X elevation of AST or ALT. One of these subjects (COMB157G2301_(b) (6)) had a transient elevation at the end of follow-up assessment. One subject (COMB157G2301_(b) (6) had an elevation of ALT only but the drug was nevertheless discontinued. One subject (COMB157G2301_(b) (6)) had elevations of transaminases, bilirubin, GGT, and ALP; these changes resolved without discontinuing the drug; an AE of a drug-related hepatic disorder was reported. One subject (COMB157G2301(b) (6) had elevation of all liver assessments due to acute cholecystitis.

Renal function

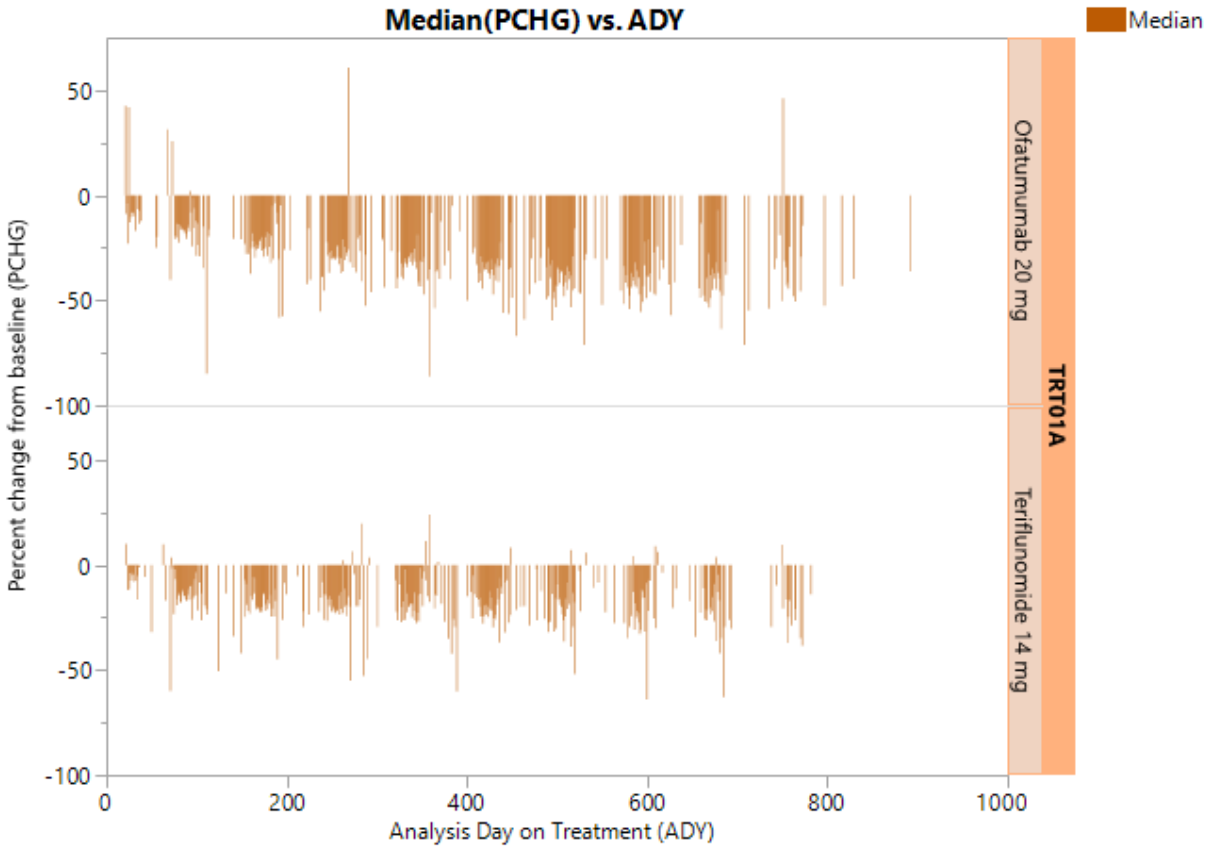
Patients with a GFR below 30 mL/min/1.73m^2 were excluded from the trial. There was no significant change in creatinine level during treatment in either treatment group. No subject treated with ofatumumab had a GFR below 30 during treatment. One subject in the teriflunomide group had a single GFR of essentially zero. This occurred 12 weeks after the end of treatment and appears to be due to a creatinine level that was most likely a lab error.

Immunoglobulins

IgM: There was a reduction in IgM levels in both treatment groups. For all assessments, the median reduction was 28% in the ofatumumab group and 17% in the teriflunomide group. The reduction was seen soon after the start of treatment and remained stable thereafter (**Figure 26**).

IgG: The median reduction in IgG levels over all assessments was 2% and 9% for the ofatumumab and teriflunomide treatment groups, respectively.

Figure 26: Median percent change in IgM level, by study day of treatment, study 2301



Source: IgM median PCHG on TRT 2301.jrp

CD19 positive cells – see review of ISS (**8.10**).

Study 2302

Hematology

Leukocytes: The median change during the RCP was +3% for those treated with ofatumumab compared to -8% for those treated with teriflunomide. The proportion of subjects with a leukocyte count below the LLN at any visit was 9% in the ofatumumab group compared to 21% in the teriflunomide group. There were no subjects in the ofatumumab group with a grade 3 reduction (1-2X10^9/L) compared to 1 teriflunomide subject.

Neutrophils: The median change during the RCP was +3% for those treated with ofatumumab and -14% for teriflunomide subjects. The proportion with a neutrophil count below the LLN at any visit was 15% of the ofatumumab group compared to 38% for the teriflunomide group. Two

ofatumumab subjects and no teriflunomide subjects had a grade 4 reduction (<0.2X10^9/L).

> ***Reviewer Comment: One ofatumumab subject had a grade 4 reduction on one occasion, week 60, with no associated AEs and one subject had a grade 4 reduction on one occasion, week 48; this subject had no AEs at any time.***

Lymphocytes: The median reduction during the RCP for subjects treated with ofatumumab was -6% and for those treated with teriflunomide the reduction was -7%. Six percent of ofatumumab subjects and 7% of teriflunomide subjects had a level below the LLN at any assessment. There were no reductions above a toxicity grade of 1.

> ***Reviewer Comment: As for study 2301, reductions in white blood cell counts were more prominent in the teriflunomide group. For the SMQ "haematopoietic leukopenia, the proportion of subjects was 1.66% for ofatumumab subjects compared to 3.38% for teriflunomide.***

Hemoglobin, Hematocrit, RBCs, platelets: There were no significant changes in any red blood cell assessments or in platelet counts.

Chemistry

Liver transaminases, bilirubin, alkaline phosphatase

ALT: For all visits, the median change in ALT was a decline of 5% in the ofatumumab group and an increase of 9% in the teriflunomide group. The proportion of subjects with one or more values above the ULN was 14% in the ofatumumab group and 24% in the teriflunomide group. No ofatumumab subjects had a grade 3 or 4 increase; 6 teriflunomide subjects had a grade 3 increase and one had a grade 4 increase.

AST: For all visits, the median change in AST was zero for the ofatumumab group and an increase of 6% in the teriflunomide group. The proportion of subjects with one or more values above the ULN was 7% in the ofatumumab group and 10% in the teriflunomide group. One subject in the ofatumumab group had a grade 3 increase; 3 teriflunomide subjects had a grade 3 elevation (>5 but ≤20X) and one had a grade 4 elevation (> 20X).

Bilirubin: For all visits, the median change in bilirubin was zero for both treatment groups. The proportion of subjects with a value above the ULN was 7% for both treatment groups. Thirteen ofatumumab subjects (3%) and 12 (3%) teriflunomide subjects had a grade 3 elevation (>3 but ≤10X).

Hy's Law criteria: No subject in the ofatumumab group met the Hy's Law criteria. One teriflunomide subject did meet Hy's Law criteria - COMB157G2302_ (b) (6) Five ofatumumab subjects had a greater than 5X elevation of AST or ALT on one or more occasions. Four of these subjects had transient elevations of no apparent cause. One (COMB157G2302 (b) (6) had elevations of all transaminases, bilirubin, and ALP attributable to an acute cholecystitis.

> ***Reviewer Comment: The narrative for the teriflunomide subject who met Hy's Law criteria is in Section 13.6.***

Renal function

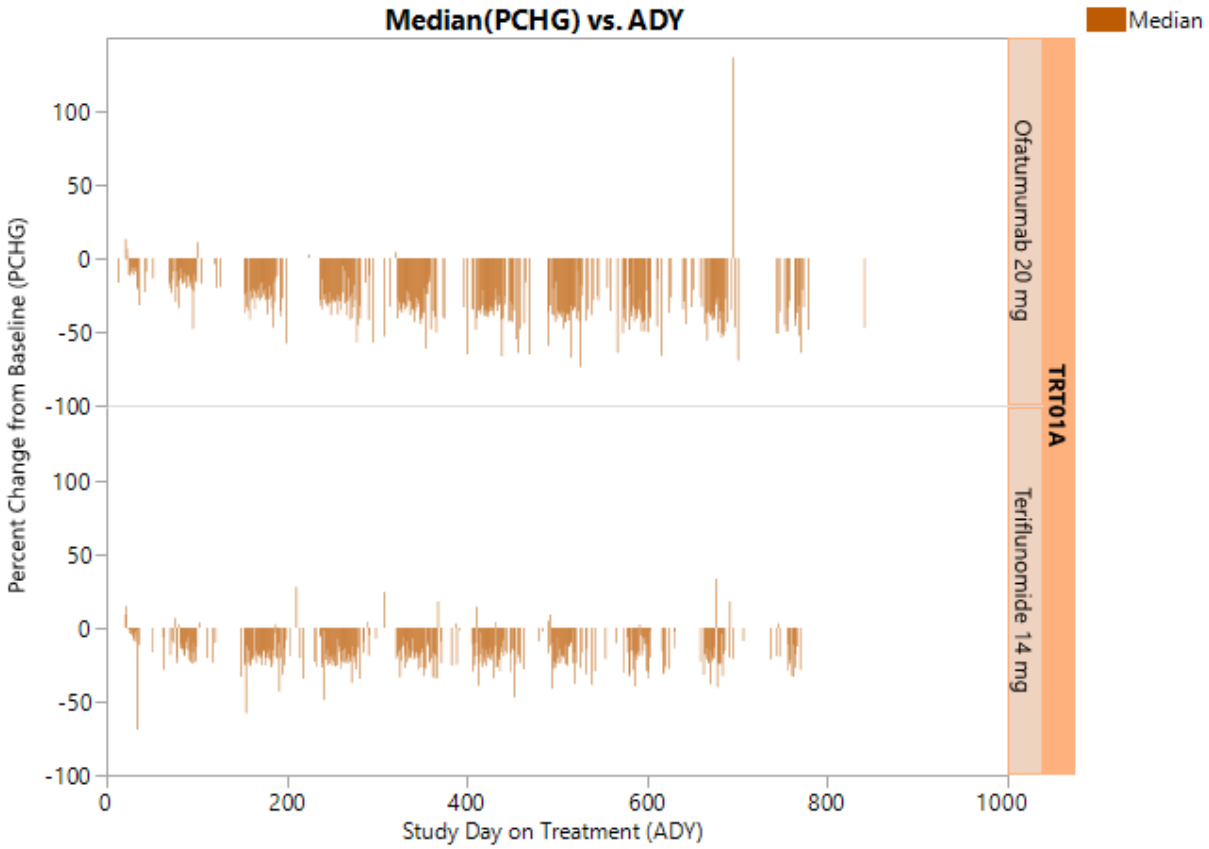
Patients with a GFR below 30 mL/min/1.73m^2 were excluded from the trial. There was no significant change in creatinine level during treatment in either treatment group. No subject had a GFR below 30 during treatment.

Immunoglobulins

IgM: The median reduction in IgM level for all visits on treatment was 28% for those treated with ofatumumab and 17% for those treated with teriflunomide. The reduction was seen soon after the start of treatment and remained relatively stable thereafter (**Figure 27**).

IgG: The median reduction in IgG level for all visits on treatment was 2% for the ofatumumab group and 9% for the teriflunomide group.

Figure 27: Median percent change in IgM level, by study day on treatment, study 2302



Source: IgM median PCHG in TRT study 2302.jrp

CD19 positive cells – see review of ISS (**8.10**).

8.4.7. Vital Signs

Study 2301

Blood pressure and pulse rate: A systolic blood pressure (SBP) below 90 mm Hg or above 160 mm Hg was very infrequent in both treatment groups. A diastolic blood pressure (DBP) below 50 mm Hg was very infrequent in both treatment groups. A DBP above 100 mm Hg occurred in 0.86% of ofatumumab subjects but in 5.84% of subjects treated with teriflunomide. There was no significant alteration of pulse rate.

> ***Reviewer Comment:** The proportion of subjects with a DBP above 100 mm Hg was somewhat more common in the teriflunomide group, but this difference is not as prominent in study 2302. In the Investigations SOC there were 2*

ofatumumab subjects and 7 teriflunomide subjects with an AE of increased blood pressure.

Weight: There were no subjects in either treatment group with significant weight loss. The proportion of subjects with 7% or greater weight increase was 21.7% in the ofatumumab group and 10.6% in the teriflunomide group.

Reviewer Comment: The modest gain in weight was more prominent in the ofatumumab group in both trials. However, the median percent change was less than 2% for both treatment group. Under the Investigations SOC, there were 2 ofatumumab subjects with an AE of weight gain compared to 9 teriflunomide subjects. The difference is therefore most likely a chance finding in a small trial and not likely to be of clinical significance.

Body temperature: The were no significant alterations in body temperature

Study 2302

Blood pressure and pulse rate: An SBP below 90 mm Hg or above 160 mm Hg was very infrequent in both treatment groups. A DBP below 50 mm Hg was very infrequent in both treatment groups. A DBP above 100 mm Hg occurred in 3.5% of ofatumumab subjects and in 5.3% of subjects treated with teriflunomide. There was no significant alteration of pulse rate.

Reviewer Comment: In the investigations SOC there were 7 ofatumumab subjects and 6 teriflunomide subjects with an AE of increased blood pressure. There are no AEs of a decreased blood pressure.

Weight: There were no subjects in either treatment group with significant weight loss. The proportion of subjects with 7% or greater weight increase was 23.9% in the ofatumumab group and 15.4% in the teriflunomide group.

Reviewer Comment: In the investigations SOC there were 5 ofatumumab subjects and 9 teriflunomide subjects with an AE of weight loss; there were 8 ofatumumab subjects and 7 teriflunomide subjects with an AE of weight gain.

Body temperature: The were no significant alterations in body temperature

8.4.8. Electrocardiograms (ECGs)

Study 2301

There are no events related to ECG changes under the Investigations SOC. The broad SMQ for Cardiac arrhythmias does not indicate a significant incidence in either treatment group.

Study 2302

There are no events related to ECG changes under the Investigations SOC. The broad SMQ for Cardiac arrhythmias does not indicate a significant incidence in either treatment group.

8.4.9. QT

Study 2301

The occurrence of changes in the QT interval, corrected by Fridericia's formula, were infrequent and generally small in both treatment groups (Table 74).

Table 74: QTcF changes during RCP, study 2301

QTcF parameter	OMB 20 mg N = 465		TER 14 mg N = 462	
	N	%	N	%
CRIT4 flag*	9	1.9	18	3.9
QTcF > 450 msec**	11	2.4	8	1.7
QTcF > 480 msec**	0	0	1	0.2
QTcF >500 msec**	0	0	0	0
ΔQTcF ≥ 30 msec**	24	5.2	23	5
ΔQTcF ≥ 60 msec**	2	0.4	3	0.7

Source: PARAM_SPQTCFS Subset of SAFRFL_Y Subset of EPOCH_RCP Subset of ADEG 2301 By (X parameter, USUBJID, TRT01A) NUSUBJID By (X parameter).jmp
*: QTcF = <350 or >450 for males and <360 or >460 for females
**: reviewer flags

Study 2302

The occurrence of changes in the QT interval, corrected by Fridericia's formula, were infrequent and generally small in both treatment groups (Table 75).

Table 75: QTcF changes during RCP, study 2302

QTcF parameter	OMB 20 mg N = 481		TER 14 mg N = 474	
	N	%	N	%
CRIT4 flag*	6	1.25	20	4.22
QTcF > 450 msec**	6	1.25	20	4.22
QTcF > 480 msec**	2	0.42	4	0.84
QTcF >500 msec**	0	0	1	0.21
ΔQTcF ≥ 30 msec**	34	7.1	23	4.9
ΔQTcF ≥ 60 msec**	4	0.83	4	0.84

Source: SPQTCFS Subset of SAFRFL_Y Subset of EPOCH_RCP Subset of ADEG 2302 By (X parameter, USUBJID, TRT01A) NUSUBJID By (X parameter).jmp
*: QTcF = <350 or >450 for males and <360 or >460 for females
**: reviewer flags

8.4.10. Immunogenicity

Study 2301

At baseline there were 4 subjects subsequently treated with ofatumumab who were positive for ADA OMB157 and 3 who were positive for anti-OMB157. At any visit during treatment with ofatumumab, 2 subjects were positive for ADA OMB157 antibody and 3 subjects were positive for anti-OMB antibodies. Two subjects were negative for neutralizing antibody. Only one subject who was positive at baseline was also positive during treatment with ofatumumab (b) (6)). There was therefore only one subject who was negative for ADA OMB157 at baseline but positive during treatment and two subjects who were negative at baseline for anti-OMG who were positive during treatment.

Reviewer Comment: See the Clinical Pharmacology review of the accuracy of the ADA assays.

Study 2301

At baseline there were 7 subjects subsequently treated with ofatumumab who were positive for ADA OMB157 and 8 who were positive for anti-OMB157. There were no subjects with neutralizing antibodies at baseline. At any visit during treatment, 3 subjects were positive for ADA OMB157 and 2 were positive for anti-OMB157. No subject had neutralizing antibodies. Two subjects who were positive for both ADA OMB157 and anti-OMB157 at baseline were also positive during treatment, leaving just one subject who was not positive at baseline but became positive during treatment with ofatumumab.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Injection-related reactions

For the pooled populations from studies 2301 and 2302 (Pool C2) a TEAE with the preferred term of injection-related reaction occurred in 20.6% of subjects treated with ofatumumab and in 15.2% of those who received a placebo injection during the RCP (Table 83). Two of the events were serious, both in the ofatumumab group. One in each treatment group led to discontinuation of study drug. Systemic symptoms were most commonly musculoskeletal or a change in vital signs. There are no features that distinguish these reactions in the group treated with ofatumumab compared to those who received a placebo injection (Table 76). The IRR occurred on day 1 (84%) or day 2 (13%) after ofatumumab injections and in essentially 100% of those treated with placebo. Pre-medication may have lowered the incidence, although this was the case in the placebo group as well (Table 77).

Table 76: Systemic symptoms in subjects with a treatment emergent IRR, ISS pool C2

PARCAT2	OMB 20mg	TER 14mg
Other manifestations	160 (16.9%)	103 (11.0%)
Musculoskeletal/connective tissue symptoms	44 (4.7%)	20 (2.1%)
Gastrointestinal symptoms	27 (2.9%)	28 (3.0%)
Related to change in vital signs	34 (3.6%)	20 (2.1%)
Skin/mucosal tissue symptoms	20 (2.1%)	28 (3.0%)
Respiratory compromise	7 (0.7%)	14 (1.5%)
Subjects(filtered)	191 (20.2%)	140 (15.0%)
1stCollItemSubjects	946 (100.0%)	936 (100.0%)

Source: JRevISS IRR SelADSLSAFFL_Y POOLC2FL_Y PARCAT2byTRT01AfiltANL01FL_Y PARCAT1_SYST

Table 77: Proportion with an IRR by pre-medication, ISS, PoolC2

Premedication	OMB 20mg	TER 14mg
None	114 (12.1%)	80 (8.5%)
Steroids	65 (6.9%)	65 (6.9%)
NSAIDs	43 (4.5%)	41 (4.4%)
Any	100 (10.6%)	87 (9.3%)

Source: JRev ISS IRR SelADSLSAFFL_Y POOLC2FL_Y CRIT1, 2, 3, 4 byTRT01AfiltANL01FL_Y PARCAT1_SYST

8.6. Safety Analyses by Demographic Subgroups

Reviewer Comment: Safety analyses by demographic subgroup are included in 8.10.

8.7. Specific Safety Studies/Clinical Trials

Study 112831

Study OMS112831 was the initial proof of concept study intended to explore the safety of a several dose levels administered subcutaneously and to explore efficacy using MRI markers of disease activity. Treatment was for 12 weeks with a placebo comparator arm, at which point the placebo group was treated with the lowest dose ofatumumab for 12 weeks so that the total duration of treatment was 24 weeks. In addition to an assessment of multiple dose levels, the study also explored the usefulness of a "conditioning" dose of ofatumumab. The conditioning dose was a "a sub-depleting dose of ofatumumab given one week prior to a fully-depleting dose to reduce post-injection systemic reactions (PISRs) to the SQ formulation".

There are 231 subjects in the safety dataset. The dosing regimens that were explored are listed in **Table 78**.

Table 78: Dosing regimens, study 112831

Dosing regimen (TRT01A)	N
Ofa30mg q12w	16
Ofa30mg q12wc*	16
Ofa3mg q12w	34
Ofa60mg q12w	17
Ofa60mg q12wc*	17
Ofa60mg q4w	32
Ofa60mg q4wc*	32
PBO	67

Source: SAFFL_Y Subset of ADSL 112831 By (TRT01A).jmp
*: "c" indicates a conditioning dose of 3mg at day 0.

The overall proportion of subjects with any AE varied from 38% to 72% compared to 27% in the placebo group. There was no clear relationship to dose or dose frequency. The most common AEs were similar to those in the larger pivotal studies. There were 19 SAE's in those treated with ofatumumab and 6 in the placebo group.

There was one SAE of interest, namely a report of "cytokine release syndrome" in a subject (OMS112831 (b) (6)) treated with ofatumumab 60 mg q12W. The event occurred 7 days after the start of ofatumumab and 4.5 hours after the most recent dose (0 mg on day 1 and 60 mg on day 7). Symptoms were shivering at 4.5 hours after the dose, followed by nausea and vomiting. There was no rash or fever. The subject was hospitalized for observation and was treated with cetirizine and paracetamol. The event resolved within hours.

There was one non-serious AE of "anaphylaxis" (OMS112831- (b) (6) but this event occurred during the 24-week follow-up period and was attributed to erythromycin.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

The incidence of malignant neoplasms was relatively low for both treatment groups (Table 79). No single type of malignancy is prominent. Because the comparator in most of the trials was an immunosuppressant, the lack of a difference between the treatment groups must be interpreted with caution.

Reviewer Comment: The duration of exposure was relatively short and may limit interpretation of the incidence of neoplasms.

Table 79: Proportion of subjects with a neoplasm, ISS all

Preferred term (AEDECOD)	OMB 20mg	TER 14mg
Uterine leiomyoma	6 (0.5%)	4 (0.4%)
Melanocytic naevus	3 (0.2%)	1 (0.1%)
Basal cell carcinoma	2 (0.2%)	2 (0.2%)
Seborrhoeic keratosis	2 (0.2%)	0 (0.0%)
Skin papilloma	2 (0.2%)	4 (0.4%)
Fibroadenoma of breast	2 (0.2%)	1 (0.1%)
Dysplastic naevus	1 (0.1%)	0 (0.0%)
Benign neoplasm of skin	1 (0.1%)	0 (0.0%)
Invasive breast carcinoma	1 (0.1%)	0 (0.0%)
Lipoma	1 (0.1%)	2 (0.2%)
Malignant melanoma in situ	1 (0.1%)	0 (0.0%)
Benign neoplasm of pineal gland	1 (0.1%)	0 (0.0%)
Non-Hodgkin's lymphoma recurrent	1 (0.1%)	0 (0.0%)
Anogenital warts	1 (0.1%)	0 (0.0%)
Haemangioma of skin	1 (0.1%)	0 (0.0%)
Adrenal adenoma	1 (0.1%)	0 (0.0%)
Acoustic neuroma	0 (0.0%)	1 (0.1%)
Benign breast neoplasm	0 (0.0%)	3 (0.3%)
Cervix carcinoma	0 (0.0%)	1 (0.1%)
Colon adenoma	0 (0.0%)	1 (0.1%)
Fibrosarcoma	0 (0.0%)	1 (0.1%)
Haemangioma of liver	0 (0.0%)	1 (0.1%)
Intracranial haemangioma	0 (0.0%)	1 (0.1%)
Neoplasm skin	0 (0.0%)	1 (0.1%)
Vulvovaginal warts	0 (0.0%)	1 (0.1%)
Subjects(filtered)	25 (2.0%)	23 (2.5%)
1stCollItemSubjects	1230 (100.0%)	936 (100.0%)

Source: JRevSelADSLISSALL SAFFL_Y AEDECODbyADSLTRT01AfiltADAESAFRFL_Y SOC_NEOPLASMS

8.8.2. Human Reproduction and Pregnancy

There were 4 pregnancies reported in studies 23012 and 2302, 3 in female subjects treated with ofatumumab and one in a female partner of a male subject treated with ofatumumab. Two of the pregnancies in females treated with ofatumumab were terminated, one elective and one therapeutic at 8 weeks due to a blighted ovum. The other two resulted in normal newborns. Four pregnancies were reported in ofatumumab subjects in study OMS112831. One resulted in a normal newborn, two were terminated electively, and one was ongoing at the time of the report. No pregnancies were reported in study COMB1572102 or OMS115102.

8.8.3. Pediatrics and Assessment of Effects on Growth

Subjects in the pediatric age group were not studied.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no cases of overdose. The potential for drug abuse is minimal. No subjects were identified that may have had drug withdrawal symptoms. There was no indication of an increase in relapses after discontinuation of treatment although this was not specifically studied.

8.9. Safety in the Post-market Setting

8.9.1. Safety Concerns Identified Through Post-market Experience

There is post-approval experience with the treatment of CLL with ofatumumab, marketed as Arzerra®. Experience with the safety of Arzerra is confounded by the concurrent use of other chemotherapeutic drugs and the nature of the disease being treated, namely CLL. There is a black box warning for reactivation of hepatitis B. While this event was not seen during the trials of ofatumumab for RMS, it is a concern with more widespread use of the drug for RMS. PML has also been reported with Arzerra but was not seen in trials for RMS. This too is a risk with more widespread and more prolonged use.

8.9.2. Expectations on Safety in the Postmarket Setting

In addition to the concerns raised by the experience with Arzerra, there are concerns raised by the results of the trials in RMS. The reduction in IgM seen with ofatumumab raises a concern that infections may become more prominent with longer term use.

8.9.3. Additional Safety Issues From Other Disciplines

No specific safety concerns have been raised up to the time of this review by other disciplines. However, the pharmacology/toxicology and clinical pharmacology reviews are not completed at this time.

8.10. Integrated Assessment of Safety

Pooled Pivotal Studies 2301 and 2302 (Pool C2)

The primary population for the analysis of safety for the CSS/ISS includes subjects in studies 2301 and 2302 from the start of treatment to the end of treatment plus 100 days (SAFRFL flag). Adverse events are attributed to the treatment actually taken (TRT01A).

Treatment Emergent Adverse Events

The most common TEAEs by System Organ Class were infections for both treatment groups (Table 80). There were no notable imbalances by SOC by treatment group.

Table 80: TEAEs by SOC, RCP, EOT+100days, ISS

AEBODSYS	OMB 20mg	TER 14mg
Infections and infestations	507 (53.6%)	505 (54.0%)
Nervous system disorders	279 (29.5%)	311 (33.2%)
Gastrointestinal disorders	234 (24.7%)	292 (31.2%)
Injury, poisoning and procedural complications	288 (30.4%)	231 (24.7%)
Musculoskeletal and connective tissue disorders	260 (27.5%)	241 (25.7%)
General disorders and administration site conditions	266 (28.1%)	210 (22.4%)
Investigations	215 (22.7%)	200 (21.4%)
Skin and subcutaneous tissue disorders	162 (17.1%)	245 (26.2%)
Psychiatric disorders	166 (17.5%)	142 (15.2%)
Respiratory, thoracic and mediastinal disorders	114 (12.1%)	126 (13.5%)
Metabolism and nutrition disorders	64 (6.8%)	85 (9.1%)
Reproductive system and breast disorders	63 (6.7%)	81 (8.7%)
Vascular disorders	56 (5.9%)	82 (8.8%)
Renal and urinary disorders	57 (6.0%)	77 (8.2%)
Eye disorders	57 (6.0%)	62 (6.6%)
Blood and lymphatic system disorders	45 (4.8%)	49 (5.2%)
Ear and labyrinth disorders	44 (4.7%)	36 (3.8%)
Cardiac disorders	33 (3.5%)	38 (4.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	27 (2.9%)	24 (2.6%)
Immune system disorders	19 (2.0%)	29 (3.1%)
Hepatobiliary disorders	17 (1.8%)	17 (1.8%)
Endocrine disorders	10 (1.1%)	3 (0.3%)
Social circumstances	3 (0.3%)	2 (0.2%)
Congenital, familial and genetic disorders	2 (0.2%)	1 (0.1%)
Subjects(filtered)	946 (100.0%)	936 (100.0%)
1stColItemSubjects	946 (100.0%)	936 (100.0%)

Source: JRevISS SelADSLPOOLC2_Y SOCbyADSLTRT01AfiltSAFRFL_Y

Infections and Infestations

The 5 most common preferred terms in the SOC Infections and Infestations are listed in Table 81. There is no notable infection or group of infections that was more common in one treatment group. This conclusion is supported by the results from the ODE1 custom MedDRA term group analysis where there were no apparent differences between the treatment groups for the various groupings of terms for infections (Table 84).

Table 81: Most common non-serious events in the SOC Infections and Infestations during the RCP, ISS

AEDECOD	OMB 20mg	TER 14mg
Nasopharyngitis	170 (18.0%)	156 (16.7%)
Upper respiratory tract infection	97 (10.3%)	120 (12.8%)
Urinary tract infection	97 (10.3%)	78 (8.3%)
Influenza	62 (6.6%)	59 (6.3%)
Sinusitis	30 (3.2%)	31 (3.3%)

Source: JRevISS SelADSLPOOLC2FL_Y AEDECODbyADSLTRT01AfiltSAFRFL_Y SOC_INF

General disorders and administration site conditions: The only term in this SOC of note was Injection site reaction, which occurred in 10.9% of ofatumumab subjects and in 5.6% of teriflunomide subjects receiving a placebo injection during the RCP.

> *Reviewer Comment: There is one event with the preferred term of Drug Withdrawal Syndrome – the verbatim term was sertraline withdrawal.*

Investigations

Terms related to a reduction in immunoglobulins are more frequent in subjects treated with ofatumumab and terms related to an increase in transaminases and a decrease in white cells are more common in subjects treated with teriflunomide (Table 82).

Table 82: Selected preferred terms, Investigations SOC, RCP, ISS

AEDECOD	OMB 20mg	TER 14mg
Blood immunoglobulin M decreased	56 (5.9%)	21 (2.2%)
Alanine aminotransferase increased	17 (1.8%)	37 (4.0%)
Aspartate aminotransferase increased	17 (1.8%)	23 (2.5%)
Immunoglobulins decreased	15 (1.6%)	2 (0.2%)
White blood cell count decreased	3 (0.3%)	13 (1.4%)
Blood immunoglobulin G decreased	4 (0.4%)	9 (1.0%)
Neutrophil count decreased	1 (0.1%)	9 (1.0%)
Liver function test increased	2 (0.2%)	7 (0.7%)
Hepatic enzyme increased	2 (0.2%)	6 (0.6%)
Lymphocyte count decreased	3 (0.3%)	4 (0.4%)
Transaminases increased	1 (0.1%)	3 (0.3%)
Monocyte count decreased	1 (0.1%)	3 (0.3%)
Blood immunoglobulin G abnormal	2 (0.2%)	0 (0.0%)

AEDECOD	OMB 20mg	TER 14mg
Blood immunoglobulin M abnormal	2 (0.2%)	0 (0.0%)
Aspartate aminotransferase abnormal	0 (0.0%)	1 (0.1%)
Subjects(filtered)	201 (21.2%)	192 (20.5%)
1stCollItemSubjects	946 (100.0%)	936 (100.0%)

Source: JRevISS SelADSLPOOLC2FL_Y AEDECODbyADSLTRT01AfiltSAFRFL_Y SOC_INVESTIG

Reviewer Comment: Despite the increased incidence of elevated transaminases in the Investigations SOC for subjects treated with teriflunomide, there is no evidence of an increase in clinical AE's in the Hepatobiliary SOC. In the MAED analysis of narrow SMQs, there is a suggestion of an increased risk for teriflunomide for severe drug-related hepatic disorders (3 events in 2 subjects vs. none for ofatumumab), consistent with the black box warning for severe and fatal liver failure for Aubagio. Although hepatitis B reactivation is included in the Warning and Precautions section of the Arzerra label, no such events occurred during the MS trials.

Blood and lymphatic system disorders: The terms neutropenia and leukopenia occurred in 6 subjects treated with ofatumumab 22 subjects treated with teriflunomide.

Reviewer Comment: In the MAED analysis, the narrow SMQ for haematopoietic leukopenia yields a risk ratio of 0.391 (0.198, 0.737; p=0.002) indicative of a statistically significantly higher risk for the teriflunomide group. There is no indication of a higher risk of cytopenias in MS patients treated with ofatumumab. Cytopenias are included in the Warnings and Precautions section of the Arzerra label. However, Arzerra is most commonly used in combination with other chemotherapeutic drugs for the treatment of chronic lymphocytic leukemia.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125326s063lbl.pdf

Neoplasms: There is no single type of neoplasm that raises a safety concern for either treatment group.

Injury, poisoning and procedural complications

The increased incidence of Injection-related reactions in the ofatumumab group, 20.6% compared to 15.3% in teriflunomide group that received placebo injections during the RCP.

Reviewer Comment: There are no notable imbalances for the individual preferred terms in the remaining SOCs. The MAED analysis of narrow SMQs

also does not raise any additional safety issues. It should be noted that conclusions about the safety of ofatumumab may be limited by the use of an active comparator. Some safety issues may be common to both drugs, in which case no difference is seen.

Adverse events by preferred term

The most common TEAEs by preferred term are listed in **Table 83**. Injection-related reactions, i.e. those with more systemic symptoms compared to injection-related reactions, were the most common single adverse event. Terms that most likely represent viral upper respiratory infections were the most common as a group (**Table 84**), occurring in 38.8% of ofatumumab subjects and in 37.1% of teriflunomide subjects.

Reviewer Comment: The sponsor proposed comparable incidence rates of upper respiratory infections for the label.

Table 83: TEAEs by preferred term, EOT+100days, ISS, 2% or more in either treatment group

AEDECOD	OMB 20mg	TER 14mg
Injection related reaction	195 (20.6%)	143 (15.3%)
Nasopharyngitis	170 (18.0%)	156 (16.7%)
Headache	126 (13.3%)	116 (12.4%)
Injection site reaction	103 (10.9%)	52 (5.6%)
Upper respiratory tract infection	97 (10.3%)	120 (12.8%)
Urinary tract infection	97 (10.3%)	78 (8.3%)
Back pain	72 (7.6%)	58 (6.2%)
Fatigue	71 (7.5%)	72 (7.7%)
Influenza	62 (6.6%)	59 (6.3%)
Nausea	61 (6.4%)	64 (6.8%)
Blood immunoglobulin M decreased	56 (5.9%)	21 (2.2%)
Alopecia	54 (5.7%)	138 (14.7%)
Diarrhoea	49 (5.2%)	111 (11.9%)
Arthralgia	49 (5.2%)	44 (4.7%)
Pain in extremity	46 (4.9%)	66 (7.1%)
Depression	45 (4.8%)	48 (5.1%)
Anxiety	43 (4.5%)	33 (3.5%)
Insomnia	39 (4.1%)	33 (3.5%)
Dizziness	39 (4.1%)	32 (3.4%)
Pyrexia	37 (3.9%)	26 (2.8%)
Oropharyngeal pain	36 (3.8%)	32 (3.4%)
Hypertension	35 (3.7%)	55 (5.9%)
Sinusitis	30 (3.2%)	31 (3.3%)
Pharyngitis	28 (3.0%)	19 (2.0%)
Paraesthesia	27 (2.9%)	52 (5.6%)
Abdominal pain	27 (2.9%)	31 (3.3%)
Gastroenteritis	27 (2.9%)	22 (2.4%)
Cough	25 (2.6%)	37 (4.0%)
Hypoaesthesia	25 (2.6%)	34 (3.6%)
Oral herpes	25 (2.6%)	25 (2.7%)
Rhinitis	25 (2.6%)	22 (2.4%)
Bronchitis	24 (2.5%)	33 (3.5%)
Muscle spasms	24 (2.5%)	31 (3.3%)
Vertigo	24 (2.5%)	21 (2.2%)
Constipation	24 (2.5%)	14 (1.5%)
Muscular weakness	23 (2.4%)	13 (1.4%)
Viral upper respiratory tract infection	22 (2.3%)	13 (1.4%)
Migraine	21 (2.2%)	17 (1.8%)
Influenza like illness	21 (2.2%)	10 (1.1%)
Abdominal pain upper	20 (2.1%)	31 (3.3%)
Rash	20 (2.1%)	23 (2.5%)
Vomiting	19 (2.0%)	33 (3.5%)
Cystitis	19 (2.0%)	15 (1.6%)
Blood creatinine increased	19 (2.0%)	12 (1.3%)
Subjects(filtered)	791 (83.6%)	788 (84.2%)
1stColItemSubjects	946 (100.0%)	936 (100.0%)

Source: JRevISS SelADSLPOOLC2FL_Y AEDECODbyADSLTRT01AfiltSAFRFL_Y

Injection-related reactions

The most common individual preferred term was an injection related reaction. Nearly all of these events occurred on the first or second day after the most recent dose, both for those receiving an injection of ofatumumab and those receiving an injection of placebo. All but 2 in the ofatumumab group were mild or moderate in severity.

One of these 2 grade 3 events occurred in subject G2301-(b) (6). The event was considered serious because the subject was hospitalized. This event occurred on day 1 with the first injection. "It was reported that, 4 hours after the injection, the patient was presented with injection related reaction with symptoms of fever (body temperature of 38°C), tremors, tachycardia, vomiting, and nausea, which resulted in hospitalization on the same day ((b) (6) (b) (6). Treatment for the event (injection related reaction) included dexamethasone, ondansetron, and pheniramine (all once on (b) (6)). No action was taken with the study medication due to this event (injection related reaction). On Day 3 (b) (6), the patient recovered from the symptoms of tachycardia, vomiting, nausea, fever and the event (injection related reaction) was considered resolved. The patient was discharged from the hospital on Day 3 ((b) (6)".

One event in subject G2302_(b) (6) was not considered serious but did result in discontinuation of study treatment. "The patient received the first injection of study medication on Day 1 (b) (6)). Premedication with methylprednisolone was administered prior to the injection. On the same day ((b) (6), 10 minutes after the injection, the patient experienced an injection systemic reaction with symptoms of asthenia, abdominal pain, urticaria and pruritus general. The patient was treated with clemastine fumarate for injection related reaction. Treatment with the study medication was permanently discontinued due the event (injection related reaction)."

Table 84: ODE1 grouping of MedDRA terms, ISS, 5% or more in OMB group

Analysis Columns	OMB 20mg		TER 14mg	
	N	%	N	%
Infection, All	493	52.1%	493	52.7%
URI, Cold, Rhinitis, Upper Resp Tract Infection, Flu-Like Illness	367	38.8%	347	37.1%
Allergic RXN, Hypersensitivity	208	22.0%	166	17.7%
Infection, Viral	150	15.9%	138	14.7%
Headache	147	15.5%	140	15.0%
UTI	113	11.9%	90	9.6%
Injection Site Reaction (All)	106	11.2%	54	5.8%

Analysis Columns	OMB 20mg		TER 14mg	
	N	%	N	%
Asthenia, Fatigue, Malaise, Weakness, Narcolepsy	102	10.8%	99	10.6%
Diarrhea, Colitis, Enteritis, Proctitis, Gastroenteritis, C-Difficile	90	9.5%	146	15.6%
Dyspepsia, N, V, Indigestion, Epigastric Pain, Gastritis, Duodenitis	87	9.2%	103	11.0%
Somnolence, Fatigue, Sedation	79	8.4%	78	8.3%
Abdominal Pain, Distension, Bloating, Spasm, IBS, Megacolon	76	8.0%	86	9.2%
Nausea, Vomiting	68	7.2%	84	9.0%
Depression	63	6.7%	60	6.4%
Influenza	62	6.6%	59	6.3%
Fall, Dizziness, Balance Disorder	58	6.1%	52	5.6%
Fall, Dizziness, Balance Disorder, Gait Disturbance, Difficulty Walking	58	6.1%	52	5.6%
Arthralgia, Arthritis, Arthrosis	57	6.0%	52	5.6%
Anxiety, Nervousness, Panic Attacks	51	5.4%	41	4.4%
Insomnia, Sleep Disturbance, Abnormal Dreams	49	5.2%	45	4.8%

Adverse events by subgroups

By Sex

The distribution of subjects for the ISS by sex is listed in Table 85. The incidence of an AE was slightly higher for females.

Table 85: Distribution of subjects by sex, RCP, ISS

	OMB 20mg		TER 14mg	
SEX	F	M	F	M
N	637	309	636	300
N, (%) with any AE	543 (85.2%)	248 (80.3%)	551 (86.6%)	237 (79%)
Total	946		936	

Source: SAFFL_Y Subset of PoolC2FL_Y Subset of ADSL ISS lr TRT01A By (SEX).jmp

There were generally no major differences by sex and actual treatment for the proportion of subjects with a TEAE (Table 86). The largest difference was the increased proportion infections in females for both treatment groups. This is largely attributable to the occurrence of non-serious urinary tract infections in females (Table 87). TEAEs in the Investigations SOC are more common in males for the ofatumumab group but there is no difference in the teriflunomide group. This appears attributable to a higher occurrence of decreased immunoglobulins in males treated with ofatumumab (Table 88).

Table 86: TEAEs by SOC by SEX, RCP, ISS

AEBODSYS	OMB 20mg				TER 14mg			
	Female N = 637		Male N = 309		Female N = 636		Male N = 300	
	N	%	N	%	N	%	N	%
Infections and infestations	363	57.0%	125	40.5%	368	57.9%	125	41.7%
Nervous system disorders	197	30.9%	75	24.3%	227	35.7%	73	24.3%
Gastrointestinal disorders	169	26.5%	55	17.8%	205	32.2%	81	27.0%
Injury, poisoning and procedural complications	203	31.9%	75	24.3%	163	25.6%	63	21.0%
Musculoskeletal and connective tissue disorders	178	27.9%	69	22.3%	165	25.9%	65	21.7%
General disorders and administration site conditions	185	29.0%	72	23.3%	148	23.3%	55	18.3%
Skin and subcutaneous tissue disorders	125	19.6%	33	10.7%	196	30.8%	42	14.0%
Investigations	115	18.1%	86	27.8%	131	20.6%	61	20.3%
Psychiatric disorders	118	18.5%	36	11.7%	102	16.0%	33	11.0%
Respiratory, thoracic and mediastinal disorders	77	12.1%	29	9.4%	86	13.5%	31	10.3%
Reproductive system and breast disorders	46	7.2%	12	3.9%	68	10.7%	11	3.7%
Vascular disorders	41	6.4%	14	4.5%	60	9.4%	17	5.7%
Metabolism and nutrition disorders	33	5.2%	20	6.5%	53	8.3%	19	6.3%
Renal and urinary disorders	41	6.4%	11	3.6%	52	8.2%	21	7.0%
Eye disorders	41	6.4%	14	4.5%	45	7.1%	14	4.7%
Blood and lymphatic system disorders	24	3.8%	8	2.6%	39	6.1%	5	1.7%
Ear and labyrinth disorders	31	4.9%	10	3.2%	25	3.9%	9	3.0%
Cardiac disorders	17	2.7%	9	2.9%	28	4.4%	5	1.7%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	19	3.0%	5	1.6%	19	3.0%	4	1.3%
Immune system disorders	12	1.9%	4	1.3%	20	3.1%	7	2.3%
Hepatobiliary disorders	13	2.0%	4	1.3%	11	1.7%	6	2.0%
Endocrine disorders	8	1.3%	1	0.3%	3	0.5%	0	0.0%
Social circumstances	3	0.5%	0	0.0%	2	0.3%	0	0.0%
Congenital, familial and genetic disorders	1	0.2%	0	0.0%	1	0.2%	0	0.0%

Source: SAFRFL_Y Subset of PoolC2 Subset of ADAE ISS By (USUBJID, AEBODSYS, SEX, TRT01A) TRT01AbySEX By (AEBODSYS)
*: N = NUSUBJID

Table 87: TEAEs, Infection and Infestations, most frequent, RCP, ISS

AEBODSYS	OMB 20mg				TER 14mg			
	Female		Male		Female		Male	
	N = 637		N = 309		N = 636		N = 300	
	N	%	N	%	N	%	N	%
Nasopharyngitis	123	19.3%	47	15.2%	106	16.7%	50	16.7%
Upper respiratory tract infection	69	10.8%	28	9.1%	87	13.7%	33	11.0%
Urinary tract infection	86	13.5%	11	3.6%	73	11.5%	5	1.7%
Influenza	50	7.8%	12	3.9%	50	7.9%	9	3.0%

Source: SOC_INF Subset of SAFRFL_Y Subset of PoolC2 Subset of ADAE ISS By (USUBJID, AEDECOD, TRT01A, SEX) TRT01AbySEX By (AEDECOD)
*: N = NUSUBJID

Table 88: TEASs related to immunoglobulins, Investigations, RCP, ISS

AEDECOD	OMB 20mg				TER 14mg			
	Female		Male		Female		Male	
	N = 637		N = 309		N = 636		N = 300	
	*N	%	*N	%	*N	%	*N	%
Blood immunoglobulin M decreased	25	3.9%	31	10.0%	14	2.2%	7	2.3%
Immunoglobulins decreased	10	1.6%	5	1.6%	1	0.2%	1	0.3%
Blood immunoglobulin G decreased	1	0.2%	3	1.0%	5	0.8%	4	1.3%
Blood immunoglobulin G abnormal	1	0.2%	1	0.3%	0	0.0%	0	0.0%
Blood immunoglobulin M abnormal	0	0.0%	2	0.6%	0	0.0%	0	0.0%
Total		5.8%		13.6%		3.1%		4.0%

Source: SOC_INVESTIG Subset of SAFRFL_Y Subset of PoolC2 Subset of ADAE ISS By (USUBJID, AEDECOD, TRT01A, SEX) TRT01AbySEX By (AEDECOD)
*: N = NUSUBJID

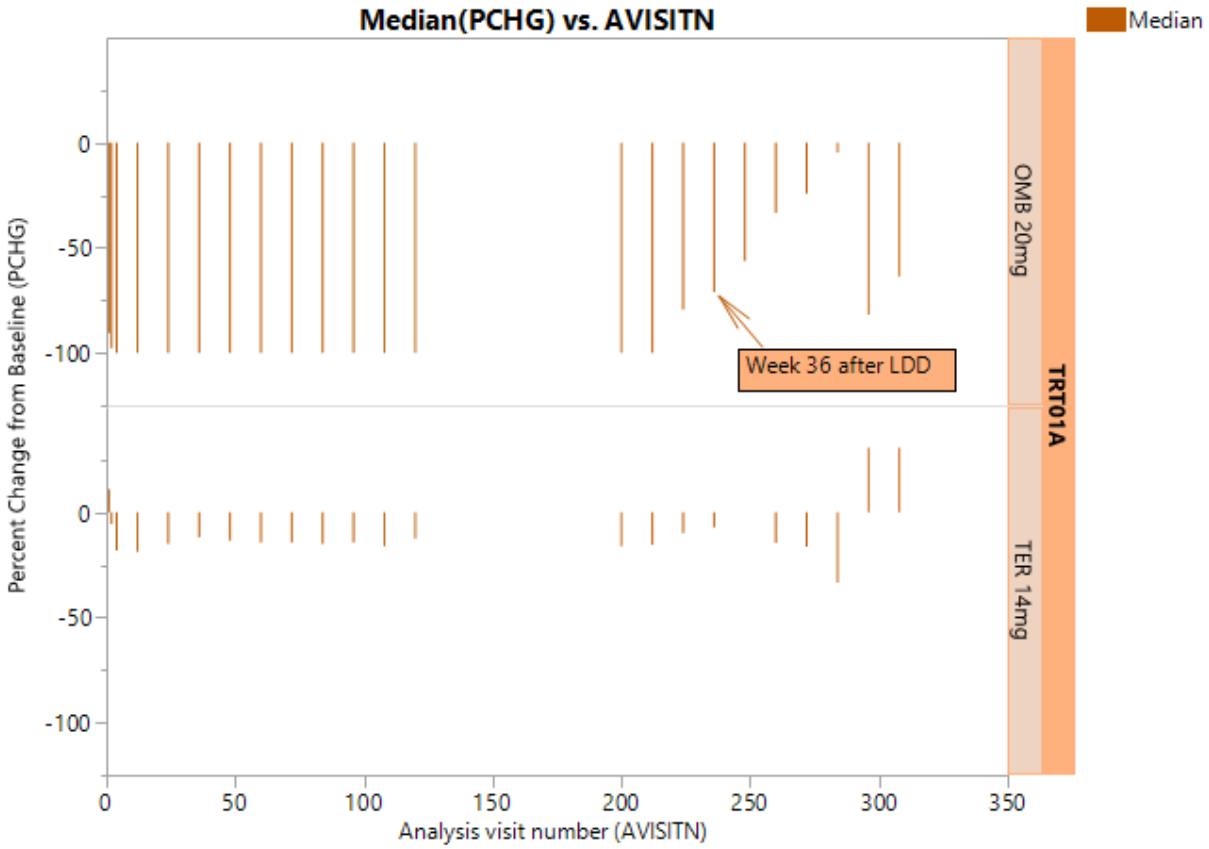
For the ISS population, the median reduction in IgM during treatment with ofatumumab was 29% compared to 17% for teriflunomide. For IgG the reduction was 2% for ofatumumab and 9% for teriflunomide. The reduction in CD19 positive cells for PoolC2 of the ISS is shown in Table 89 and graphically in Figure 28. The reduction in those treated with ofatumumab is nearly 100% by week 2 and remains at that level until approximately 24 weeks after the last dose of the drug.

Table 89: Percent change from baseline, CD19+ cells, PoolC2, ISS

AVISIT	N	Percent Change from baseline					
		Mean		Std Dev		Median	
		OMB 20mg	TER 14mg	OMB 20mg	TER 14mg	OMB 20mg	TER 14mg
Week 1	1780	-85	18.7	19.7	63.4	-91	11.1
Week 2	1791	-94	2.68	18.5	64.4	-98	-5.6
Week 4	1801	-96	-12	19.9	45.5	-100	-18
Week 12	1791	-99	-11	8.51	52.5	-100	-19
Week 24	1766	-98	-6	13	54	-100	-15
Week 36	1738	-98	-2.8	7.77	56.8	-100	-12
Week 48	1693	-97	-2.6	14.3	58.8	-100	-13
Week 60	1670	-96	-4.2	17.4	64.7	-100	-14
Week 72	1629	-95	-3.1	21.8	70.6	-100	-14
Week 84	1105	-95	-3.4	20.9	59.4	-100	-15
Week 96	685	-95	1.84	23.6	83.7	-100	-14
Week 108	381	-94	3.17	20.4	99.5	-100	-16
Week 120	117	-93	15.4	27.1	98.6	-100	-13
Last assessment on study drug	1877	-97	-6.9	16.5	56.8	-100	-16
Week 12 after LDD	1215	-97	3.05	14.4	165	-100	-15
Week 24 after LDD	160	-72	10.1	27	123	-79	-9.8
Week 36 after LDD	119	-62	5.6	37.3	116	-71	-7
Week 48 after LDD	75	-45	20.2	49.4	145	-56	0
Week 60 after LDD	39	-33	19.4	44.4	141	-33	-14
Week 72 after LDD	20	-32	90.4	59.5	225	-24	-16
Week 84 after LDD	10	-7.5	174	93.7	418	-4.5	-33
Week 96 after LDD	7	-67	165	45	259	-82	30.8
Week 108 after LDD	4	-40	30.8	75.1		-64	30.8

Source: ANL01FL_Y Subset of CD19 cell count Subset of PARCAT1_HEME Subset of ADLBOTH ISS PCHG By (AVISIT).jmp

Figure 28: Percent change from baseline, CD19+ cells, PoolC2, ISS



Source: Median PCHGbyAVISITNbyTRT01A CD19cells POOLC2 ISS.jrp
LDD = Last Dose of Drug

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting is not recommended.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

See the final Prescribing Information.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not recommended at this time.

12. Postmarketing Requirements and Commitments

See the approval letter for the post-marketing requirements and commitments.

13. Appendices

13.1. References

1. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
2. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain 1989;112 (Pt 1):133-46.
3. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a

geographically based study. 2. Predictive value of the early clinical course. Brain 1989;112 (Pt 6):1419-28.
4. Confavreux C, Aimard, Devic M. Course and Prognosis of Multiple Sclerosis assessed by the Computerized Data Processing Of 349 Patients. Brain 1980;103:281-300.
5. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. N Engl J Med 2000;343:1430-8.
6. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology 2003;61:1528-32.
7. Paz Soldan MM, Novotna M, Abou Zeid N, et al. Relapses and disability accumulation in progressive multiple sclerosis. Neurology 2015;84:81-8.
8. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 2003;126:770-82.
9. Liu C, Blumhardt LD. Disability outcome measures in therapeutic trials of relapsing-remitting multiple sclerosis: effects of heterogeneity of disease course in placebo cohorts. J Neurol Neurosurg Psychiatry 2000;68:450-7.
10. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology 2014;83:278-86.
11. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66:1485-9.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Studies 2301, 2302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1310 (study 2301); 1322 (study 2302)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7 (study 2301); 6 (study 2302)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: 0 Significant payments of other sorts: 9 Proprietary interest in the product tested held by investigator: 3 Significant equity interest held by investigator in $: >50,000 held by 4 investigators Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1269 (study 2301); 1307 (study 2302)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Eligibility Criteria

Inclusion criteria

1. Written informed consent must be obtained before any assessment is performed
2. Male or female patients aged 18 to 55 years (inclusive) at Screening
3. Diagnosis of MS according to the 2010 Revised McDonald criteria (Polman et al. 2011)
4. Relapsing MS: relapsing-remitting course (RRMS), or secondary progressive (SPMS) course with disease activity, as defined by Lublin et al 2014
5. Disability status at Screening with an EDSS score of 0 to 5.5 (inclusive)
6. 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 randomization. Note: Screening MRI scan may be used if no positive Gd-enhancing scan exist from prior year.
7. Neurologically stable within 1 month prior to randomization

Exclusion criteria

1. Patients suspected of not being able or willing to cooperate or comply with study protocol requirements in the opinion of the Investigator
2. Patients with primary progressive MS (Polman et al. 2011) or SPMS without disease activity (Lublin et al. 2014)
3. Patients meeting criteria for neuromyelitis optica (Wingerchuk et al. 2006)
4. Disease duration of more than 10 years in patients with EDSS score of 2 or less
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 12 months after stopping study medication. Given the long elimination time of teriflunomide of up to 2 years, women planning to become pregnant may undergo the accelerated elimination process (as per teriflunomide label) after the 12- month period. Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject, if accepted by the local regulation). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male partner sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner.
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study drug.

      Note: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate
      clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or
      tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when

the reproductive status of the woman has been confirmed by follow up hormone level
assessment is she considered not of child bearing potential.

7. Sexually active males, unless they agree to use a condom during active treatment. Male patients should not father a child in this period. Given the long elimination time of teriflunomide of up to 2 years, the male patient wishing to father a child during the study should discontinue study drug and undergo the accelerated elimination process (refer to Section 7.8). A condom is required to be used also by vasectomized males in order to prevent accidental exposure of their female partner to study via seminal fluid
8. Patients with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g. rheumatoid arthritis, scleroderma, Sjögren's syndrome, Crohn's disease, ulcerative colitis, etc.) or with immunodeficiency syndrome (hereditary immune deficiency, drug-induced immune deficiency)
9. Patients with active systemic bacterial, viral or fungal infections, or known to have AIDS or to test positive for HIV antibody at Screening
10. Patients with neurological findings consistent with PML or confirmed PML
11. Patients at risk of developing or having reactivation of syphilis or tuberculosis (e.g. patients with known exposure to or history of syphilis or tuberculosis). Testing for syphilis and tuberculosis will be done at Screening unless such testing has been performed in the past 6 months prior to Screening with documented negative result. Testing should be done per local clinical practice (for syphilis e.g. by positive rapid plasma reagin (RPR); for tuberculosis e.g. skin test or blood test as per local practice).

    NOTE: The Investigator may consult with an infectious disease expert if e.g. test results are unclear or there is suspicion of false positive test results. If the infectious disease expert considers the test results false positive and not clinically relevant, the Investigator
    must document (in source data and as a comment in the electronic case report form (eCRF)) that the test results are considered false positive and may then randomize the patient.

12. Patients at risk of developing or having reactivation of hepatitis: Positive results at Screening for serological markers for hepatitis (H) A, B, C, and E indicating acute or chronic infection:

    - anti-HA Immunoglobulin (Ig) M (IgM)
    - HBs Ag and/or anti-HBc IgM and/or HB virus deoxyribonucleic acid (DNA)
    - anti-HBs negative and Anti-HBc positive
    - anti-HC IgG or IgM

- anti-HE IgM (if positive IgG and/or IgM, perform HE-RNA PCR and if negative, patient can be randomized)

  NOTE: If the Investigator suspects false positive hepatitis serology results, such as an antibody pattern indicating acute hepatitis infection but no corresponding elevated liver enzymes and no signs or symptoms of liver disease, an infectious disease expert may be consulted. If the infectious disease expert finds no evidence of acute or chronic
  hepatitis infection and considers the serology results false positive and not clinically relevant, the Investigator must document (in source data and as a comment in the eCRF) that the serology results are considered false positive and may then randomize
  the patient.

13. Have received any live or live-attenuated vaccines (including for varicella-zoster virus or measles) within 2 months prior to randomization
14. Have been treated with any of the medications listed below (Note: no wash-out period is required in the case of prior treatment with interferon-β or glatiramer acetate):

Medication	Exclusionary if used/used within required wash-out period
Systemic corticosteroids, adrenocorticotropic hormone	30 days prior to Screening MRI scan
Dimethyl fumarate	1 month prior to randomization
Intravenous immunoglobulin, fingolimod, natalizumab (patients who have discontinued natalizumab in the 6 months prior to randomization should be evaluated to rule out PML)	2 months prior to randomization
Teriflunomide	3.5 months prior to randomization or 1 month prior to randomization if patient undergoes AEP and has documented teriflunomide plasma level below 0.02 mg/L before randomization (if discontinued for reason related to safety or lack of efficacy, patient is not eligible, see below)
Mildly to moderately immunosuppressive/chemotherapeutic medications (e.g. azathioprine, methotrexate)	6 months prior to randomization
Highly immunosuppressive/chemotherapeuticmedications (mitoxantrone, cyclophamide, cladribine) B-cell targeted therapies such as rituximab, ocrelizumab Laquinimod	2 years prior to randomization
Mitoxantrone (with evidence of cardiotoxicityfollowing treatment or cumulative life-time dose > 60 mg/m²) Alemtuzumab Lymphoid irradiation; bone marrow transplantation	Any time

Medication	Exclusionary if used/used within required wash-out period
Other strongly immunosuppressive treatments (with effects potentially lasting over 6 months) Ofatumumab Teriflunomide (if discontinued for reasons related to safety or lack of efficacy)	

15. Patients currently treated with or needing treatment with cholestyramine (unless for accelerated teriflunomide elimination, Section 7.8) or leflunomide during the study
16. Use of other investigational drugs at the time of enrolment (Screening) or within the prior 30 days, or five elimination half-lives, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer
17. History of malignancy of any organ system (other than basal cell carcinoma, in situ squamous cell carcinoma of skin, or in situ carcinoma of cervix of the uterus that have been radically treated e.g. completely excised with clear margins), within the past 5 years, regardless of whether or not there is evidence of local recurrence or metastases
18. Any of the following conditions or treatments that may impact the safety of the patient:

    - History of, or current, significant cardiac disease including cardiac failure (NYHA functional class II-IV), myocardial infarction (within 6 months), unstable angina (within 6 months), transient ischemic attack (within 6 months), stroke, cardiac arrhythmias requiring treatment or uncontrolled arterial hypertension
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second- or third-degree AV block without a pacemaker on Screening electrocardiogram (ECG)
    - History of familial long QT syndrome or known family history of Torsades de Pointe
    - History of or active severe respiratory disease, including Chronic Obstructive Pulmonary Disease, interstitial lung disease or pulmonary fibrosis
    - Patients with asthma requiring regular treatment with oral steroids
    - Severe hepatic impairment (Child-Pugh class C) or any chronic liver or biliary disease
    - Patients with severe renal impairment (Glomerular Filtration Rate < 30 ml/min/1.73 m^2)
    - Any medically unstable condition as determined by the Investigator

19. Any of the following abnormal laboratory values prior to randomization:

    - Total or conjugated bilirubin (BIL) greater than 1.5 times upper limit of normal (ULN) range, unless in the context of Gilbert's syndrome
    - Alkaline phosphatase (AP) greater than 1.5 times the ULN range
    - AST or ALT greater than 1.5 times ULN or gamma-glutamyl-transferase (GGT) greater than 2 times ULN range

- White blood cell (WBC) count < 3,500/mm3 (< 3.5 x 109/L)
- Lymphocyte count < 800/mm3 (< 0.8 x 109/L)
- Serum IgG and IgM < lower limit of normal (according to central laboratory range)
- Any other clinically significant laboratory assessment as determined by the Investigator (e.g. significant anemia, neutropenia, thrombocytopenia, signs of impaired bone marrow function)

20. Patients with severe hypoproteinaemia e.g. in nephrotic syndrome
21. Patients with any of the following neurologic/psychiatric disorders prior to randomization:

    - Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the Columbia - Suicide Severity Rating Scale (C-SSRS), if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for the "Non -Suicidal Self-Injurious Behavior" (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years
    - Ongoing substance abuse (drug or alcohol) or any other factor (i.e. serious psychiatric condition, recurrent substance abuse) that may interfere with the subject's ability to cooperate and comply with the study procedures
    - History of clinically significant CNS disease (e.g. stroke, traumatic brain or spinal injury, history or presence of myelopathy) or neurological disorders which may mimic MS

22. Patients unable or unwilling to undergo MRI scans
23. History of hypersensitivity to any of the study drugs or excipients (including lactose intolerance) or to drugs of similar chemical classes

Note: If a patient fails on one or more laboratory (or other) assessment criteria, as part of the Screening process, the assessment(s) may be repeated at the discretion of the Investigator, and the patient may be included if criteria are then met, provided the assessments are completed within the Screening or Baseline time window.

*If additional restrictions and/or assessments are required in order to comply with the local legal (e.g. in regard to a higher legal age for study participation) or regulatory (e.g. in regards to compliance with local prescribing information) requirements, the local requirements must be followed.

13.4. Relapse severity criteria

MILD	MODERATE	SEVERE
EDSS increase of 0.5 point	EDSS increase of 1 or 2 points	Exceeding Moderate criteria
OR	OR	OR
1-point FS change in one to	2-point FS change in one or	Exceeding Moderate criteria

MILD	MODERATE	SEVERE
three systems	two systems	
	OR	OR
	1-point change in four or more systems	Exceeding Moderate criteria

APPEARS THIS WAY ON ORIGINAL

13.5. Schedule of Assessments

Visit	SCR D -45 to -8	BL D -7 to D1	D1	D7	D14	M1	M3	M6	M9	M12/24	M15/21/27	M18	EOT	EOS
Phone Interview				X	X	Monthly between scheduled visits								
PE	X	X						X		X				
VS, Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine labs	X					X	X	X	X	X	X	X	X	X
B-cells	X	X		X	X	X	X	X	X	X	X	X	X	X
TER level														X
IgG, IgM	X	X				X	X	X	X	X	X	X	X	X
ECG	X	X											X	X
MRI	X									X			X	X
eCSSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EDSS	X	X	X			X	X	X	X	X	X	X	X	X
T25FWT	X	X				X	X	X	X	X	X	X	X	X
9HPT	X	X						X		X		X	X	X

13.6. Narratives

Subject G2302-(b) (6)

Patient [G2302(b) (6)] – SAE (hepatic failure); AE leading to study drug discontinuation (transaminases increased)
Patient details: 38-year-old, female, Caucasian
Treatment group: Teriflunomide
Relationship to study treatment: Suspected
Treatment prematurely discontinued: Yes (transaminases increased)

A 38-year-old, Caucasian female ((b) (6), with relapsing multiple sclerosis (RMS) subtype relapsing remitting multiple sclerosis (RRMS) was randomized in study COMB157G2302, at site (b) (6) in (b) (6). The patient received the first dose of study medication (teriflunomide) on Day 1 ((b) (6)).

Prior disease-modifying treatment for MS included interferon beta-1b, which was started on [redacted] and discontinued on [redacted], due to lack of efficacy, glatiramer acetate which was started on [redacted] and discontinued on [redacted], due to lack of efficacy, and fingolimod hydrochloride which was started on [redacted] and discontinued on [redacted] due to lack of efficacy.

At Screening [redacted]), the patient's alcohol consumption was less than 1 drink per day. At screening ([redacted]), the patient's aspartate aminotransferase (AST) was 21 U/L (RR: ≤ 41 U/L), alanine aminotransferase ALT was 20 U/L (RR: ≤ 45 U/L), alkaline phosphatase was 48 U/L (RR: 30 to125 U/L), total bilirubin was 36 µmol/L (RR: 2 to 21 µmol/L), direct bilirubin was 12 µmol/L (RR: ≤ 7 µmol/L), and gamma-glutamyl transferase (GGT) was 30 U/L (RR: 2 to 65 U/L).

The patient's relevant medical history included goiter [redacted]. The patient's relevant medical conditions ongoing at time of screening included Gilbert's syndrome (since [redacted]) for which the patient did not receive any treatment, arthralgia (since [redacted] for which the patient received treatment with ibuprofen, headache (since [redacted] for which the patient received treatment with ibuprofen, metamizole, flatulence (since [redacted] for which the patient received treatment with pantoprazole sodium sesquihydrate, domperidone, esomeprazole, , and hepatic cyst (since [redacted]) for which the patient did not receive any treatment.

At the time of event onset, treatment with study medication was ongoing.

On Day 15 ([redacted]), the patient was noted with increased transaminases with AST at 240 U/L (RR: 10 to 35 U/L), ALT at 372 U/L (RR: 10 to 35 U/L), and GGT at 33 U/L (RR: < 40 U/L) and had no clinical symptoms.

No treatment was reported for this event. Treatment with study medication was permanently discontinued due to the event (transaminases increased) and the patient received the last dose of study medication on Day 16 [redacted].

On [redacted], the patient's abdominal ultrasound showed gastritis (non-serious) and patient was treated with omeprazole ([redacted] to [redacted]). It was reported that, the patient underwent teriflunomide accelerated elimination procedure from [redacted] to [redacted].

On [redacted] 14 days after the last dose of study medication, another laboratory work-up showed further increase in the transaminases (see the table below). No alcohol, drug nor Acetaminophen/paracetamol use was reported for that patient. On [redacted], 20 days after the last dose of study medication, the patient was reported with symptoms of bloating, nausea and vomiting, fatigue, itching, loss of appetite sickness, emesis and flatulence, but she refused admission in the hospital. On the same day [redacted]), the patient showed signs of jaundice

on the skin, clinical hematoma due to coagulation deficit were detected and the patient was diagnosed with hepatic failure with AST at 643 U/L, ALT at 818 U/L, GGT at 43 U/L, and total bilirubin at 129 µmol/L. On the same day (b) (6)), hepatitis serology was negative. No treatment was reported for this event. On an unspecified date, an abdominal ultrasound was normal. The events (transaminases increased, hepatic failure) were considered resolved on (b) (6) (b) (6) with normal serum transaminases level.

> ***Reviewer Comment: A table of laboratory results is provided in the CSR. The laboratory abnormalities peaked on (b) (6) and then gradually declined. The results were normal on (b) (6).***

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAWRENCE D RODICHOK
06/17/2020 04:22:03 PM

PAUL R LEE
08/14/2020 01:57:22 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326Orig1s070

NON-CLINICAL REVIEW(S)

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 19, 2020

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist, Division of Neurology 2
Acting Director, Division of Pharmacology/Toxicology-Neuroscience
Office of Neuroscience

Subject: BLA 125326 (ofatumumab)

Ofatumumab (Arzerra), a fully human type 1 IgG1κ monoclonal antibody targeting CD20+ B cells, was originally approved on October 26, 2009, for the treatment of chronic lymphocytic leukemia (CLL). The sponsor (Novartis Pharmaceuticals Corporation) submitted a Prior Approval Supplement to BLA 125326 on December 20, 2019, proposing a new indication for ofatumumab, relapsing forms of multiple sclerosis (RMS). Clinical development of ofatumumab for the treatment of RMS was conducted under IND 111116.

For the new indication, the sponsor conducted pharmacology (proof-of-concept) and reproductive and developmental toxicology (male and female fertility and enhanced pre- and postnatal development [ePPND]) studies to support clinical development and marketing authorization. The Division agreed with the sponsor that a standard assessment of carcinogenic risk was not required because ofatumumab is not pharmacologically active in rodent species.

The nonclinical studies submitted to support the new indication were reviewed by Dr. Melissa Banks-Muckenfuss (Pharmacology/Toxicology BLA Review and Evaluation, BLA 125326, Supplement 70, July 9, 2020). Dr. Banks-Muckenfuss also references previous reviews of the nonclinical data submitted to support approval of ofatumumab for CLL.

The proposed mechanism by which ofatumumab exerts therapeutic effects in patients with RMS is through binding to $CD20^+$ B cells (EC_{50} of 287 ng/mL) resulting in B-cell lysis, possibly through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). ADCC and CDC were demonstrated in in vitro assays with ofatumumab. In vivo studies demonstrated depletion of $CD20^+$ B-cell populations in blood and lymphoid tissues following subcutaneous (SC) or intravenous (IV) administration of ofatumumab to cynomolgus monkeys.

The fertility study in sexually mature male and female cynomolgus monkeys, in which ofatumumab was administered IV weekly for 5 doses (0, 10, and 100 mg/kg) followed by 4 biweekly doses (0, 3, and 20 mg/kg), resulted in no adverse effects on male or female reproductive parameters, including hormones, menstrual cycle, and sperm analysis, or on histopathological evaluation of reproductive organs. Anti-drug antibodies reduced plasma exposures at the low dose (LD) but not notably at the high dose (HD). Plasma exposures (M-F; $AUC_{(0\text{-}168\ hr)}$) at the HD (an NOAEL) were 247000-222000 and 162000-124000 µg*hr/mL on Days 1 and 85, respectively.

In an ePPND study, ofatumumab was administered IV to pregnant cynomolgus monkeys (14/group) according to the same doses and frequency as in the fertility study, except the 5 weekly doses were initiated on gestation day (GD) 20 and the biweekly maintenance doses (0, 3, and 20 mg/kg) were administered from GD 62 to GD 160. (Offspring were not directly dosed.) Of the initial 14/group, 12, 10, and 13 dams (LD, MD, and HD, respectively) delivered an infant; of these infants, 1 LD infant was stillborn, and 1 C and 1 HD infant died or was sacrificed on day of birth (postnatal day [PND] 0). In addition, 1 C and 5 HD infants died or were sacrificed moribund during PNDs 1-37. (One high-dose dam was sacrificed on lactation day 96 because of severe glomerulonephropathy.) Ten C, 9 LD, and 7 HD infants survived to terminal sacrifice (PND 180).

Of the HD infants that died during the postnatal period, deaths were attributed to maternal injury (1 male), adrenal inflammatory cell infiltration and hemorrhage (1 female), hepatocellular degeneration and necrosis (1 male), and pulmonary inflammation and maternal rejection and injury (1 male); cause of death was not identified in 1 female. The adrenal, hepatic, and pulmonary findings were attributed by the sponsor to the severe depletion of $CD20^{+}$-positive B cells in HD infants.

There was no ofatumumab-related maternal toxicity or effects on developmental parameters in infants, including body weight, morphology, neurobehavioral assessments (e.g., reflexes, postural tonus, eye tracking), grip strength, or skeletal development (bone mineral density, mineral content); however, immune function (TDAR, using KLH immunization) was clearly impaired in HD female infants.

While the high dose was a no-effect dose for adverse developmental effects, a no-effect dose for mortality and immune effects in offspring was not established because of the limited number of evaluable offspring at the low dose. Only 5 LD infants had dams who did not develop antidrug antibodies and were, therefore, adequately exposed to ofatumumab throughout pregnancy. Plasma exposure ($AUC_{(0\text{-}336\ hr}$) at the high dose in dams was 111000 µg*hr/mL on GD 146.

An embryofetal development study was conducted for the approval of ofatumumab for CLL, and the results are described in labeling for that indication. Ofatumumab was administered (GDs 20-50) by intravenous infusion to pregnant monkeys at weekly doses 0, 20, and 100 mg/kg. Plasma exposures ($AUC_{(0\text{-}7d)}$) were 87860 and 622600 µg*hr/mL, respectively, on GD 48.

For comparison, plasma exposure ($AUC_{(0\text{-}tau)}$) in humans at the recommended monthly maintenance dose of 20 mg is 483 µg*hr/mL.

Conclusions and Recommendations

Only reproductive and developmental toxicology studies in monkey were conducted to support clinical development and a supplemental BLA for treatment of patients with RMS, as agreed to by the Division. The fertility study is adequate and demonstrated no adverse effects of ofatumumab on male or female reproductive systems at plasma exposures substantially higher than that in humans at the recommended human maintenance dose. The expanded pre- and postnatal development study had limitations, primarily the lack of an adequate number of low-dose offspring exposed to ofatumumab during pregnancy, which precluded an assessment of dose-response. However, there were clear adverse effects, including those resulting from pharmacologically-mediated immunosuppression, which led to deaths and reduced functional immune response in offspring at the high dose. Therefore, the study does not need to be repeated.

The nonclinical data submitted by the sponsor are adequate to support approval of ofatumumab for the proposed indication.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LOIS M FREED
08/19/2020 03:47:44 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	125326, Supplement 70
Supporting document/s:	SDN594, eCTD 0248
Applicant's letter date:	12/20/2019
CDER stamp date:	12/20/2019
Product:	Ofatumumab, Kesimpta (OMB157)
Indication:	Relapsing forms of multiple sclerosis (RMS)
Applicant:	Novartis Pharmaceuticals Corp.
Review Division:	DN 2
Reviewer:	Melissa Banks-Muckenfuss, PhD
Supervisor:	Lois Freed, PhD
Acting Division Director:	Nicholas Kozauer, MD
Project Manager:	Candido Alicea, PhD

TABLE OF CONTENTS

Abbreviations Used in This Review:

LD= Low Dose
HD= High Dose
IV= Intravenous
SC= Subcutaneous
GD = Gestation Day
LacD = Lactation Day
PND = Postnatal Day

1 Executive Summary

1.1 Introduction

Ofatumumab, a recombinant fully human IgG1 kappa monoclonal antibody directed at human CD20 antigen, for intravenous (IV) administration was approved in 2009 as Arzerra® for the treatment of chronic lymphocytic leukemia (CLL). The Sponsor has developed a formulation of ofatumumab for subcutaneous (SC) administration for the treatment of relapsing forms of multiple sclerosis (RMS).

1.2 Brief Discussion of Nonclinical Findings

The nonclinical toxicology package for the original BLA for ofatumumab was comprised of several pharmacology, pharmacokinetics, and toxicology studies, including an embryofetal development study in monkeys. At the time Arzerra was approved, several nonclinical issues relevant to clinical use were noted in the review (see the BLA 125326 Nonclinical review by Dr. A. McDougal, dated 8/10/2009). Based on the toxicology studies by the IV route, the following were identified as clinically-relevant risks: increased risk of infection, infusion-reaction/cytokine response, delayed onset anemia, fetal toxicity (i.e., decreased placental, fetal spleen, and fetal thymus weights), and clinical chemistry alterations (i.e., increased lactate dehydrogenase, increased C-reactive protein). These toxicities were considered to be "extensions of the pharmacology of the product, … reflected in the clinical studies, and… monitorable in the clinical setting." While the toxicities remain potential risks of ofatumumab administration, the potential for these risks may be lower because of the considerably lower dose for SC administration in this indication (i.e., the proposed dose for RMS is 20 mg SC QW for 3 weeks followed by monthly maintenance doses, compared to up to 2000 mg ofatumumab IV at varying intervals for up to approximately 2 years for CLL).

The change from IV to SC administration in the Phase 2 and 3 clinical studies was supported by a 2-dose (Q2W) SC administration study of ofatumumab (0, 20, or 100 mg/kg SC or 100 mg/kg IV) with a 33-week recovery period in female cynomolgus monkeys. CD20+ B cells were depleted, and CD40+ B cells were markedly reduced, in all ofatumumab-dosed groups. During the dosing period, increases in eosinophils were observed in the SC administration groups (LD > HD) and slight RBC reductions were observed in the HD SC and IV groups. During the recovery period, WBC were mildly reduced in the LD SC group but were increased in the HD SC and IV groups. Recovery of CD20+ and CD40+ B cells occurred earliest in the LD SC group, followed by the HD SC group and the IV group. Relative bioavailability was variable after SC dosing, especially at the LD, and evidence of ADA development was observed in 3 of 6 animals in the LD SC group (compared to 1 of 6 animals in the HD SC group and no IV-dosed animals). The study had limitations but supported the change in route for Phase 2 and Phase 3 clinical studies, in which clinical experience was gained.

To address reproductive toxicology, an embryofetal development (EFD) study was submitted to support the approval of Arzerra (see BLA 125326 nonclinical review by Dr. McDougal, dated 8/10/2009). In the EFD study, both ofatumumab and ADA (believed to

be maternal ADA) were observed in fetal blood. CD20+CD40+ B cells showed depletion at both doses in fetal cord blood (approximately 10% of control) on GD100. Teratogenicity was not observed but decreased placental weights and reduced fetal spleen and thymus weights (at the HD) were observed, with marked reductions in B cells in the spleens of most fetuses at both doses.

To support approval for indications with populations requiring chronic treatment (such as RMS), fertility and enhanced pre- and post-natal development studies were submitted. These studies provide an assessment of potential toxicity to reproductive tissues (i.e., the majority of the animals used in the toxicology studies had been sexually immature, as noted in the original BLA review) and pre- and postnatal development, including potential functional effects of the fetal immune alterations observed in the EFD study, respectively.

A fertility study was conducted by IV administration in cynomolgus monkeys. The monkeys were administered ofatumumab (0, 10, or 100 mg/kg weekly for 5 weeks then 0, 3, or 20 mg/kg every 2 weeks) for 3 months followed by an 8-week recovery period. Marked B-cell depletion occurred at both doses, with dose-dependent decreased cellularity of the lymphoid follicles and absence/reduction of germinal centers in the spleen and lymph nodes. By immunohistochemistry, CD20+ cells were depleted in the spleen and lymphatic tissues (with reduced CD3+ cells considered secondary to reduced germinal centers reflecting marked depletion of CD20+ cells). ADA were observed at both doses, and neutralizing ADA were observed at the LD. Clearly drug-related adverse effects on reproductive tissues were not observed in females. Minimal evidence suggested an effect in HDM, i.e., an apparent increase in total sperm alterations, although the data were highly variable, and bilateral moderate testicular depletion/degeneration of germ cells in a single animal. The NOAEL/LOAEL (females/males) for drug-related adverse reproductive effects was the HD.

An ePPND study was conducted by IV administration in pregnant cynomolgus monkeys. Beginning on GD20, the monkeys were administered ofatumumab (0, 10 or 100 mg/kg) weekly for 5 weeks, followed by doses of 0, 3, or 20 mg/kg administered once every 2 weeks beginning GD62 until birth of the infants. Maternal ofatumumab exposures were observed until Lactation Day 28 (LacD28; in the LD group) or LacD91 (in the HD group). The LD maternal animals showed slightly reduced red cell mass and apparent increased prenatal loss. CD20+ B cells were depleted in blood of the maternal animals at both doses. In the maternal animals, repletion of CD20+ cells occurred by approximately LacD91 (in the LD group) or LacD175 (in the HD group), except for early repletion in 4 of 14 LD maternal animals that developed neutralizing ADA.

Infant postnatal survival was reduced at the HD; the early postnatal deaths were attributed to accidents (i.e., not considered drug-related) or secondary infection (i.e., considered drug-related). Birth weights were slightly reduced in the ofatumumab-dosed groups and reduced body weights persisted in female offspring during the observation period. Ofatumumab exposures were present in only three LD infants but were observed in all HD infants; seven LD infants (and no HD infants) exhibited ADA. Infants

of the LD maternal animals that developed neutralizing ADA did not show B-cell depletion. Otherwise, CD20+ B-cell depletion was observed, with repletion in the infants beginning on PND63 in the LD group and PND91/119 (males/females) in the HD group. Immune alterations were observed in the offspring of ofatumumab-dosed females, particularly at the HD. CD3+ and CD3+CD4+ T cells were increased in HD female infants from PND28 to PND119. IgG levels were reduced in the HD infants on PND70, recovering in males by PND175 but remaining reduced in female infants. The T Cell-Dependent Antibody Response (TDAR) assay, using immunizations on PND119 and PND147, demonstrated persistent problems with immune responsivity in the HD offspring of ofatumumab-dosed females. IgM responses to the first KLH immunization were absent or reduced in the HD infants (males and females) and were also reduced after the second immunization in the HD male infants. IgG responses were reduced and delayed after the first immunization in the HD female infants and were still reduced after the second immunization. Overall, there was no clear no-effect level for body weight and immune effects in the offspring. Increased postnatal mortality and persistent alterations in immune function were observed in infants of the HD maternal animals.

Overall, the systemic toxicities observed after high dose IV ofatumumab are notable concerns (e.g., long-lasting immunosuppression and potential delayed onset anemia); however, the proposed RMS treatment regimen uses considerably lower doses administered by SC administration. Clearly drug-related adverse effects on fertility were not observed in females, but there was a suggestion of an adverse effect (assessment was complicated by highly variable data) in HD males. Adverse neonatal/postnatal effects (e.g., increased postnatal mortality and persistent alterations in immune function) were evident in the ePPND study, demonstrating functional sequelae for the fetal B-cell alterations observed in the previously conducted EFD study. These issues should be addressed in labeling.

1.3 Recommendations

1.3.1 Approvability

Although the nonclinical studies conducted demonstrated several limitations, there is no objection to the approval of 20 mg SC ofatumumab (monthly maintenance doses) for the treatment of RMS. The adverse reproductive and developmental findings should be clearly addressed in labeling.

1.3.2 Additional Nonclinical Recommendations

1.3.3 Labeling

The following suggestions, below, are provided for proposed labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
KESIMPTA is a CD20-directed cytolytic antibody indicated…

USE IN SPECIFIC POPULATIONS
Pregnancy: Based on animal data, may cause fetal harm (8.1).
Contraception: Use effective contraception during treatment and for … after the last treatment. (8.3)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
… Ofatumumab crosses the placenta and can cause peripheral and splenic fetal B-cell depletion based on findings from animal studies *(see Data)*. Increased postnatal mortality and persistent adverse immune effects occurred in offspring whose mothers were administered ofatumumab intravenously throughout gestation until delivery. Teratogenicity was not observed after intravenous administration of ofatumumab to pregnant monkeys during organogenesis.

Ofatumumab can cause fetal B-cell depletion *[See Data]*. Avoid administering live vaccines to neonates and infants exposed to KESIMPTA in utero until B-cell recovery occurs *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

Data
Animal Data
Embryo-fetal development and enhanced pre- and postnatal development studies in monkeys showed that exposure to ofatumumab given intravenously during gestation did not cause teratogenicity but showed increased postnatal mortality, persistently reduced postnatal body weights in females, and persistent adverse immune effects in the offspring that were maternally-exposed to the HD. A no-effect level was not determined for B-cell depletion in the offspring. The low adverse effect level (LOAEL) level for ofatumumab exposure during gestation was 10/3 mg/kg; based on maternal systemic exposure, the AUC was >20-fold the human AUC at 20 mg monthly.

In the EFD study, pregnant cynomolgus monkeys were administered 0, 20, or 100 mg/kg ofatumumab IV weekly beginning GD 20 through GD 50, with Cesarean sections performed on GD 100. Ofatumumab was detected in the fetal cord blood, showing placental transfer and fetal exposure to ofatumumab. Exposure to ofatumumab during gestation resulted in depletion of CD20+ B cells in maternal animals and their offspring, along with reduced spleen weights and splenic B cells in the fetuses. Teratogenicity was not observed.

In the ePPND study, cynomolgus monkeys were administered 0, 10/3, or 100/20 mg/kg ofatumumab IV from GD 20 until birth; doses of 0, 10 or 100 mg/kg were administered weekly for 5 weeks followed by doses of 0, 3 or 20 mg/kg administered once every 2 weeks beginning on GD 62. Ofatumumab was detected in the blood of the maternal animals and in the blood of the offspring (that persisted postnatally at 100/20 mg/kg). Increased postnatal mortality was observed in the offspring of females administered 100/20 mg/kg ofatumumab. Reduced birth weights were observed in the offspring of

ofatumumab-dosed females, and body weight reductions persisted into the maturation period in female offspring maternally exposed to ofatumumab. Depletion of CD20+ B-cells in the maternal animals and their offspring was observed, with reduced spleen weights and persistently reduced humoral immune responses (to Keyhole Limpet hemocyanin (KLH)) in the offspring at 100/20 mg/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which ofatumumab exerts its therapeutic effects in multiple sclerosis is unknown, but it is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes and certain subsets of T cells. Following cell surface binding to lymphocytes, ofatumumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.

…

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been performed to assess the carcinogenic potential of KESIMPTA.

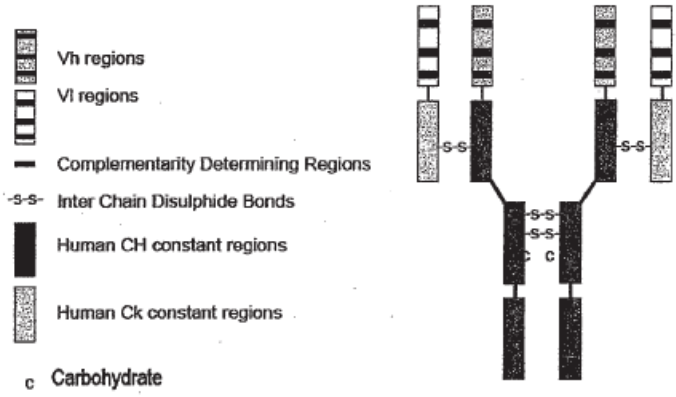
No studies have been performed to assess the mutagenic potential of KESIMPTA. As an antibody, KESIMPTA is not expected to interact directly with DNA.

Male and female monkeys were administered ofatumumab by intravenous injection (0, 10, and 100 mg/kg weekly for 5 weeks, followed by doses of 0, 3, and 20 mg/kg every 2 weeks for 8 weeks). No clear effects on reproductive tissues were observed in females. No effects on the estrus cycle were observed in females. Although variable, evidence of effects on sperm were suggested in males administered 100/20 mg/kg. The no-effect/low-effect level (females/males) was 100/20 mg/kg. The AUC at 100/20 mg/kg was >250-fold the AUC in humans at the 20 mg monthly dose; at 10/3 mg/kg, the AUC was >20-fold the AUC in humans at the 20 mg monthly dose.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)	
Generic Name	Ofatumumab
Code Name	OMB157
Molecular Weight	Approximately 149 kDa. Each light chain is approximately 25 kDa, each heavy chain is approximately 50 kDa.
Structure or Biochemical Description	Recombinant monoclonal IgG1 kappa antibody against an epitope on CD20 (see below, from Dr. McDougal's BLA 125326 review)



Pharmacologic Class CD20-directed cytolytic antibody

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 111116	MS	
BLA 125326	CLL	Arzerra approved in 2009
[redacted] (b) (4)		

2.3 Drug Formulation

Ofatumumab (Arzerra) was initially approved as a citrate buffered formulation (20 mg/mL) for IV infusion; this formulation was replaced [redacted] (b) (4) [redacted] (b) (4) to "minimize particle formation and to provide a more concentrated DS also more favorable for DP subcutaneous (s.c.) delivery." All materials were identified as "comparable based on CMC characterizations."

Two single-use formulations, each 20 mg/0.4 mL (i.e., 50 mg/mL), developed: in a pre-filled pen (auto-injector containing a PFS) and in a pre-filled syringe (PFS). See the Sponsor's summary Table 2-1, below.

Table 2-1 Composition of the drug product

Ingredient	Concentration (mg / 1.0 mL)	Theoretical amount per syringe (mg / 0.4 mL)	Total amount per syringe including overfill (mg)	Function	Reference to standards
Ofatumumab (OMB157)	50.000	20.000	(b) (4)	Drug substance	Novartis monograph
Arginine [1) 2)] / (b) (4)	(b) (4)	4.000		(b) (4)	Ph. Eur.; USP/NF; JP
Sodium acetate trihydrate [1) 2)] / (b) (4)		2.722			Ph. Eur.; USP/NF; JP
Sodium chloride		1.192			Ph. Eur.; USP/NF; JP
Polysorbate 80 [a)]		0.080			Ph. Eur.; USP/NF; JP
Disodium edetate [1) 2)] / (b) (4)		0.007			Ph. Eur.; USP/NF; JP
Hydrochloric acid (b) (4)		(b) (4)		pH adjusting agent	Ph. Helv.
(b) (4)	(b) (4)			(b) (4)	Ph. Eur.; USP/NF; JP
Water for injection [2) 3)]					

Note: The syringes are filled with a declared volume of 0.4 mL with an overfill of (b) (4)% to allow injection of the complete declared dose.

(b) (4)

2.4 Comments on Novel Excipients

No novel excipients were identified; the excipients are identified in the Sponsor's Table 1-1, below.

Table 1-1 Excipients used in Ofatumumab drug product

Excipients	Functions
Arginine [1) 2)] (b) (4)	(b) (4)
Sodium acetate trihydrate [1) 2)] (b) (4)	
Sodium chloride	
Polysorbate 80 [a)]	
Disodium edetate [1) 2)] (b) (4)	
Hydrochloric acid (b) (4)	pH adjusting agent
(b) (4) Water for injection [2) 3)]	(b) (4)
(b) (4)	

2.5 Comments on Impurities/Degradants of Concern

None were identified for nonclinical assessment.

2.6 Proposed Clinical Population and Dosing Regimen

Ofatumumab subcutaneous injection is proposed for the treatment of relapsing forms of multiple sclerosis (RMS); dosing is by SC injection on Days 1, 7, and 14, followed by SC injection every month thereafter starting on Day 28.

2.7 Regulatory Background

Ofatumumab for IV infusion was previously approved (Arzerra®) on October 26, 2009, for the treatment of Chronic Lymphocytic Leukemia (CLL). Novartis acquired the rights to ofatumumab from GSK in 2015, with the transfer of IND 111116 (for the treatment of RMS) to Novartis in February 2016.

3 Studies Submitted

3.1 Studies Reviewed

Study RD-2018-00361: *In vitro* comparison of the mode of action of anti-CD20 antibodies: ofatumumab and ocrelizumab

Study RD-2019-00356: Determination of kinetic rate constants and affinities of ofatumumab and ocrelizumab on CD20 expressing cells

Study RD-2019-00021: Imaging Mass Cytometry and Single-cell Genomics Reveals Differential Depletion and Repletion of B cell Populations Following Ofatumumab Treatment in Cynomolgus Monkeys

Study RD-2019-00332: MAPPs analysis of ofatumumab

Study CD2007-01024 (G07285): (b) (4) 1841157A: 2-Dose Subcutaneous and Intravenous Toxicity Study in Female Cynomolgus Monkeys Followed by a 33-Week Off-Dose Period

Study Pcs-r1670402 ((b) (4) #8364864): 13 Week intravenous administration for effects on female and male fertility in the cynomolgus monkey with at least an 8 week recovery period.

Study 1670033 ((b) (4) #8345086): Enhanced study for effects on pre- and postnatal development in cynomolgus monkey

3.2 Studies Not Reviewed

Study 2010n109133 (514630): Pilot Study in Cynomolgus Monkeys for Evaluating HuMab-CD20 (Clone 11B8) in Comparison with Ofatumumab

3.3 Previous Reviews Referenced

Nonclinical review for BLA 125326 (dated 07/29/2009, by Dr. Andrew McDougal) (b) (4)

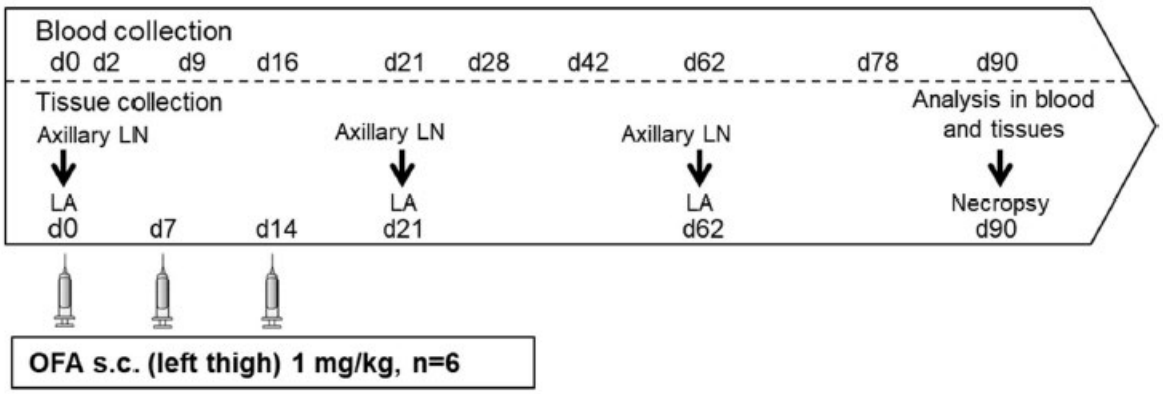
4 Pharmacology

4.1 Primary Pharmacology

Ofatumumab is a recombinant fully human monoclonal immunoglobulin G1 (IgG1) kappa antibody expressed in murine NS0 cells. It binds human CD20 with high affinity and specificity, and acts as a B cell-depleting agent (presumably via antibody-dependent cell-mediated cytotoxicity [ADCC] and complement-dependent cytotoxicity [CDC]). Ofatumumab bound rhesus and cynomolgus monkey CD20 with equal or greater affinity compared with human CD20 (EC_{50} values of 97.4, 139, and 287 ng/mL, respectively). Ofatumumab did not bind CD20 of other species; therefore, cynomolgus monkey was the only nonclinical species used for testing.

In vitro and in vivo pharmacology studies were submitted in support of the sBLA. An in vitro assay was conducted comparing the binding of ofatumumab and ocrelizumab to CD20 antigen on BJAB cells (a Burkitt lymphoma-derived line; Study RD-2019-00356). The obtained K_D values were 167±59 pM for ofatumumab and 206±65 pM for ocrelizumab using directly labeled target antibody. Using the indirect labeling approach, the obtained K_D value was 395±73 pM for ofatumumab and 467±117 pM for ocrelizumab. In vitro assays comparing the modes of action of ofatumumab, ocrelizumab, and rituximab in primary human B (or RAJI) cells were conducted (Study RD-2018-00361). In these assays, ofatumumab was shown to act through both ADCC and CDC; in the CDC assays (2-hr direct and delayed), ofatumumab showed high potency and long-lasting B-cell depletion.

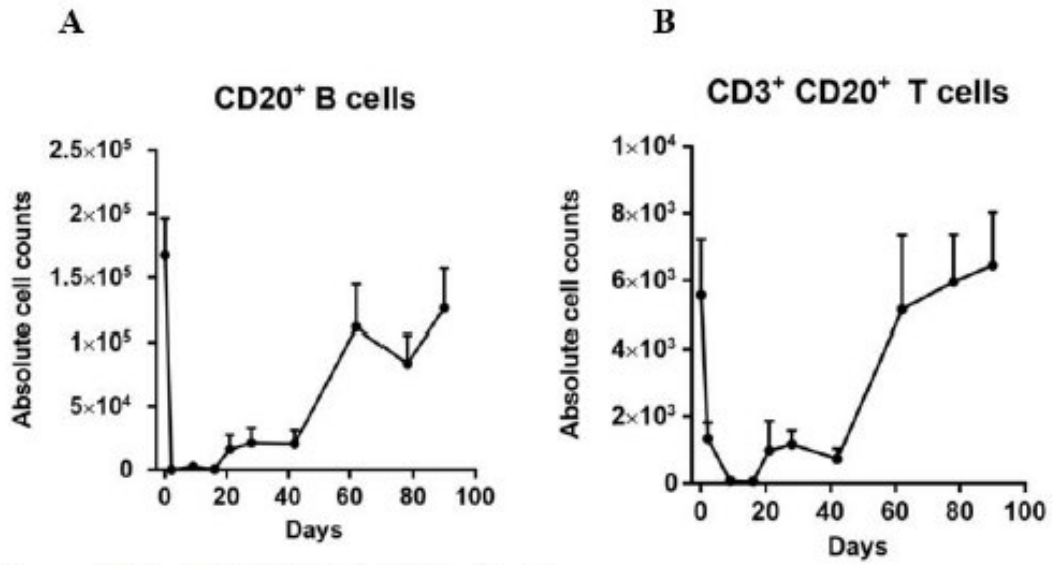
The Sponsor also used an in vivo transcriptional animal model to help elucidate the mode of action of ofatumumab administered SC (non-GLP Study RD-2019-00021). Six monkeys were treated on Days 0, 7, and 14 with ofatumumab (1 mg/kg; 100 mg/5 mL). Axillary lymph nodes (LN) were collected on Days 0, 21, 62, and 90; at termination (Day 90), lymphocytes were isolated from whole blood, and spleen and additional lymph nodes were collected (with cells mechanically dissociated for evaluation). See the Sponsor's summary design figure, below.



Supplementary Figure 1. Study design.
d, day; LA, lymphadenectomy; LN, lymph node; OFA, ofatumumab; s.c., subcutaneous

Changes in lymphocyte subsets were explored by flow cytometry, molecular imaging cytometry, immunohistochemistry, and single cell transcriptome analyses. In blood, ofatumumab resulted in a rapid reduction of CD20+ B cells, followed by a reduction in CD3+CD20+ T cells. B cells were depleted as early as Day 2 and showed a biphasic repletion (i.e., partial repletion on Days 21 to 42 and substantial repletion by Day 62); CD3+CD20+ T cells (these were identified as B cells in the original study report) followed a similar pattern. See the Sponsor's Figure 2-4 (taken from the pharmacology written summary), below.

Figure 2-4 **Changes in lymphocyte counts in blood samples from cynomolgus monkeys treated acutely with subcutaneous ofatumumab. A: CD20+ B cells. B: CD3+CD20+ T cells. Data are expressed as means plus/ minus standard error of the mean**



Source: [Table 2.6.3.2-RD-2019-00021, Fig. 1]

In axillary LN, naïve and mature B-cell counts were generally reduced over Days 1 to 62 but showed repletion (and an apparent rebound) on Day 90. The Sponsor reported complete CD21+ B-cell (i.e., mature B cell) depletion in the perifollicular and interfollicular areas of the axillary LN, with less severe depletion in the lymphoid follicles (i.e., depletion primarily of the germinal center core). By Day 62, the perifollicular and interfollicular areas were infiltrated by CD21+ B cells and the distribution was considered similar to baseline cytoarchitecture by Day 90. In the spleen, no clear changes were observed on Day 90. The Sponsor submitted figures for the other LN assessed, both draining (inguinal) and non-draining (deep cervical, axillary, and popliteal); any pattern of effects among the LNs was difficult to assess based on the limited information provided.

4.2 Secondary Pharmacology

The Sponsor conducted a MAPPS assay (Study RD-2019-00332), an indicator of immunogenic potential, comparing four antibodies including ofatumumab. In order (highest to lowest), the highest numbers of total and different clusters (i.e., indicating greater potential for immunogenicity) were observed for adalimumab, ofatumumab, ocrelizumab, and ustekinumab. The Sponsor noted that the presentation of clusters does not necessarily result in T-cell recognition.

6 General Toxicology

Repeated dose toxicity studies were conducted in cynomolgus monkeys, up to 7 months in duration (see the original BLA 125326 nonclinical review by Dr. McDougal, dated 8/10/2009); the main findings from the review of the 7-month study are summarized below.

In **Study 25052** (CD2008/01521/00), cynomolgus monkeys (3/sex/dose main study + 4/sex/dose recovery) were administered 0, 20, or 100 mg/kg ofatumumab by 30-minute IV infusion weekly for 8 weeks, then monthly for 5 months. Both doses of ofatumumab, 20 mg/kg and 100 mg/kg, were reported to saturate the receptor. A dose-response relationship was observed for the duration but not the magnitude of the pharmacological effect. Circulating B cells were depleted at both doses and remained low for up to four months after the cessation of dosing; recovery was generally (except in mortalities) observed at the end of the 6-month recovery period.

Mortality occurred at both doses; several of these animals showed reduced body weights. Three deaths were attributed to infection (2 LD and 1 HD); these deaths were considered indirectly related to treatment and relevant to patient safety. Two deaths were attributed to hemolytic anemia (1 LD and 1 HD); the relevance of these mortalities to human risk was unclear. Clinical signs of increased heart force and heart rate were observed. Reduced red cell parameters were observed in both ofatumumab groups and continued through the recovery period; the LD animals showed recovery (Day 372). Ofatumumab bound RBCs were observed in 2 of 14 ofatumumab-treated animals. It was posited that the observed anemia may represent a humoral immune response to

ofatumumab in monkeys; such a toxicity would not be expected to be predictive of toxicity in humans. Lymph node biopsies also showed marked B-cell depletion, with recovery between Day 274 and Day 350. Histopathological findings observed in the survivors included minimal to moderate lymphoid atrophy, lymphoid depletion, and/or follicular atrophy in the lymph nodes (submandibular and mesenteric), Peyer's patches (ileum), and spleen. Signs of inflammatory cell infiltration were also in several organs (e.g., kidneys, brain, sciatic nerve, eye, lungs, and trachea); the inflammatory cell infiltration continued to be observed at the end of the recovery period. Assessments of humoral immune function (KLH) showed reduced responses in HD animals during the dosing period and in LD and HD during the recovery period.

Systemic exposure was variable; detection of ADA (observed in 1 LDF early mortality out of 24 animals) was not deemed reliable based on the study observations and higher incidences observed in other studies. The elimination half-life (in the recovery phase) was approximately 10 days. See the summary TK Tables C and D, below, taken from Dr. McDougal's review. A NOAEL for the study was not identified, based on the observed mortalities believed related to immune effects and infection.

Table C: Geometric Mean (CV%) Parameter Estimates Indicative of Systemic Exposure to HuMax-CD20 Following i.v. Infusion on Days 1, 50, 134 and 190 in Male Cynomolgus Monkeys

Dose (mg/kg)	Day	Part	AUC(0-∞) (µg.h/mL) (CV%)	AUC(0-t) (µg.h/mL) (CV%)	AUC(0-6.5 h) (µg.h/mL) (CV%)	AUC(0-168 h) (µg.h/mL) (CV%)	Cmax(obs) (µg /mL) (CV%)
20	1	Main & Recovery	73950 [n=5] (35.4)	41375 (24.9)	2096 (37.0)	41299 (24.9)	531 (21.9)
	50	Main & Recovery	405835 (20.5)	304126 (14.7)	6473 (31.7)	119208 (15.2)	1239 (27.4)
	134	Main & Recovery	140268 [n=3] (30.5)	81235 (18.5)	3443 (15.7)	62492 (18.5)	695 (21.5)
	190	Main	- -	1088 [n=3] (5.1)	3467 [n=1] -	- -	697 [n=7] (10.0)
		Recovery	202732 (55.9)	189796 (56.3)	2841 (35.7)	58439 (5.6)	
100	1	Main & Recovery	402347 [n=6] (15.7)	265410 (19.3)	13948 (6.5)	264893 (19.3)	2699 (9.9)
	50	Main & Recovery	2065198 [n=3] (20.1)	1277280 (26.7)	27499 (32.9)	545047 (18.2)	6382 (15.7)
	134	Main & Recovery	560464 [n=5] (36.9)	276325 (42.8)	16024 (34.3)	304533 [n=6] (22.5)	3735 (26.9)
	190	Main	- -	54892 [n=3] (25.9)	16244 [n=3] (27.3)	- -	3110 [n=7] (29.9)
		Recovery	903407 (32.3)	765564 (24.4)	13464 (18.0)	287241 (16.4)	

n=7 for Day 1, 50 and 134 (Main & Recovery), n=4 for Day 190 (both Main and Recovery animals) unless otherwise specified

Table D: Geometric Mean (CV%) Parameter Estimates Indicative of Systemic Exposure to HuMax-CD20 Following i.v. Infusion on Days 1, 50, 134 and 190 in Female Cynomolgus Monkeys

Dose (mg/kg)	Day	Part	AUC(0-∞) (µg.h/mL) (CV%)	AUC(0-t) (µg.h/mL) (CV%)	AUC(0-6.5 h) (µg.h/mL) (CV%)	AUC(0-168 h) (µg.h/mL) (CV%)	Cmax(obs) (µg /mL) (CV%)
20	1	Main & Recovery	62783 (25.9)	41293 (25.7)	1699 (104.9)	41202 (25.7)	462 (49.6)
	50	Main & Recovery	292676 (23.4)	225584 (24.6)	5842 (37.4)	96208 (29.4)	1114 (36.6)
	134	Main & Recovery	93746 (66.1)	25392 (253.6)	3000 (14.6)	48493 (27.2)	638 (20.2)
	190	Main	-	1072 (13.0)	-	-	567 (28.3)
		Recovery	128482 (15.2)	120394 (12.3)	2404 (14.2)	46397 (5.5)	
100	1	Main & Recovery	423185 (5.1)	117697 (284.1)	12557 (56.6)	272379 (12.2)	2676 (36.1)
	50	Main & Recovery	1458986 (44.8)	1204139 (51.3)	26832 (17.7)	487785 (26.0)	5414 (18.8)
	134	Main & Recovery	421266 (25.2)	243873 (45.5)	18862 (29.5)	282951 (26.3)	4034 (21.1)
	190	Main	112886 -	59183 (4.4)	18789 (19.4)	112298 (-)	3460 (19.3)
		Recovery	809700 (7.7)	757219 (6.4)	15928 (10.1)	272484 (5.5)	

n=7 for Day 1, 50 and 134 (Main & Recovery), n=4 for Day 190 (both Main and Recovery animals) unless otherwise specified

6.2 Repeat-Dose Toxicity

The Sponsor conducted a 2-week dosing study (with a 33-week recovery period) of ofatumumab administered SC and IV to support a change in the route of administration. This study (b) (4) supported SC dosing in the Phase 2 and 3 clinical studies.

Study title: (b) (4) 1841157A: 2-Dose Subcutaneous and Intravenous Toxicity Study in Female Cynomolgus Monkeys Followed by a 33-Week Off-Dose Period

Study no.:	CD2007-01024 (G07285)
Study report location:	EDR, BLA 125326
Conducting laboratory and location:	(b) (4)
Date of study initiation:	9/24/2007
GLP compliance:	Yes (US FDA)
QA statement:	Yes
Drug, lot #, and % purity:	(b) (4) 1841157A, batch # FXK-206544-115, 100% pure

Methods (see the Sponsor's summary table, below)

Frequency of dosing: Days 1 and 15

Dose volume: SC: 1 mL/kg
IV:10 mL/kg (infusion approximately 30 minutes)

Formulation/Vehicle: (b) (4) Sodium acetate trihydrate, (b) (4) Disodium edetate (b) (4) Arginine (b) (4) Sodium Chloride, and (b) (4) Polysorbate 80 in sterile water for injection (pH 5.5)

Species/Strain: Cynomolgus moneys- Mauritian (b) (4)

Age: 3 to 5 years old

Weight: 3.04-4.66 kg

Group Number	Dose[1] (mg/kg/day)	Dose Concentration (mg/mL)	Dosing Regimen	Number/Sex
1	0	0	Subcutaneous[2]	4F
2	20	20	Subcutaneous[2]	6F
3	100	100	Subcutaneous[2]	6F
4	100	10	Intravenous infusion[3]	6F

1. Doses and concentrations are expressed in terms of the parent compound.
2. Interscapular region used for site of dose administration.
3. Duration of dosing was 30 minutes/dose at an infusion rate of 0.333 mL/kg/minute.

No mortality occurred and no clearly drug-related changes in body weight were observed. During the dosing period, eosinophils were increased on Day 1 in the HD SC group (approximately 1.7-fold) and on Days 1, 15, and 20 in the LD SC group (approximately 2.0-2.3-fold). RBC were slightly reduced on Days 15 and 20 in the HD SC and IV groups. During the recovery period, WBC counts were reduced in the LD SC group compared to the controls; reductions of approximately 20% to 30% through Day 195 and approximately 50% from Day 222 to Day 250 were observed (including neutrophils, lymphocytes, and monocytes). In contrast, WBC counts were increased up to 1.5-fold compared to controls in the HD SC and IV groups. In particular, neutrophils were increased 1.8-fold to 2.5-fold in the HD SC and IV groups from Day 47 to Day 104. The IV-dosed animals showed sporadic increases (approximately 10%-15%) in RBC counts on Day 76 and Day 128. No clearly drug-related changes in clinical chemistry parameters were noted at the end of the dosing week (Day 20). During the recovery period, increased total bilirubin was observed in 1 LD SC-dosed animal (approximately 1.9-fold) and 1 HD SC-dosed animal (+45%), compared to controls (N=2). One of 3 HD SC-dosed animals showed increased creatinine (+57%), compared to controls.

CD20+ B cells were not detectable on Days 15 or 20 in any ofatumumab-treated group, regardless of route; CD40+ B cells were also reduced by 50% to 100% of control counts. The LD SC group animals began to show CD20+ B-cell recovery between Days 47 and 128; by Day 163, CD20+ B cells were recovered. In comparison, CD20+ B-cell

recovery was delayed in the HD SC and IV group animals; recovery began on Day 76 to Day 195 in the HD SC group and on Day 195 in the IV group. Only 50% recovery of CD20+ B cells was observed by Day 250 in the HD SC and IV groups. Results for CD40+ B cells were similar to those for CD20+ B cells. The observed differences in CD20+ and CD40+ B-cell recovery rates, as well as systemic exposure [i.e., AUC], were attributed to the presence of ADA; the effects were considered similar in the HD SC and IV groups, in the absence of ADA. CD3+ lymphocyte (T cell) counts were variable, which complicated assessment. In the LD SC group, a slight reduction (approximately 10%-20%) in CD3+ T cells, compared to controls, was observed throughout the majority of the recovery period.

The anatomical pathology assessment was primarily focused on evaluation of local toxicity. A separate, signed pathology report was not provided (this is a limitation of the study); a peer review was conducted but not provided. Relative (to body) spleen weights were slightly increased (approximately 10%) on Day 21 and Day 258 in the HD SC group and were reduced (approximately 10%) in the IV group on Day 21 and Day 258. Relative thymus weights were increased on Day 21 (approximately 2-fold) in the IV group but were reduced in the LD SC and IV groups compared to the control and HD SC groups on Day 258. Misshapen, thickened, and firm caudate liver lobe (with irregular surface and accentuated lobular pattern) was observed in one HD SC group animal; however, there were no microscopic correlates. Limited tissues were evaluated microscopically, including: macroscopic findings, injection site, ileum and jejunum [Peyer's patches], lymph nodes [inguinal, mandibular/cervical, mesenteric, and axillary], spleen, and thymus). At terminal sacrifice, changes were observed in the lymph nodes and injection sites. Minimal to moderate extramedullary hematopoiesis in the mandibular/cervical lymph node was observed in one animal from the LD SC and HD SC groups (severity not dose-related). The Sponsor also indicated that "a high degree of variability was observed between animals in the number and size of primary and secondary lymphoid follicles in the spleen and lymph nodes," but considered this variability within normal limits as it "depends on the immunologic state of the animal." At the injection site, minimal subcutaneous fibrosis (with lymphocytic and granulomatous inflammation) and perivascular and/or focal lymphocytic inflammation of the dermis were observed in one to two animals of the SC-dosed groups. Minimal fibrosis of the dermis and minimal inflammatory cell infiltrate of the intima were observed in one to two IV-dosed animals. At the recovery sacrifice, no drug-related changes were reported.

Overall, three of six LD SC and one of six HD SC group animals showed ADA. See the Sponsor's table, below, for details. ADA were detected beginning on Day 20 in two animals of the LD SC group. ADA were not detected in IV-dosed animals. TK was affected for 2 LD SC group animals and 1 HD SC group animal on Day 47 and/or throughout the recovery period; the presence of ADA may have contributed to accelerated drug clearance and B-cell recovery.

Anti-GSK1841157 Antibody Concentrations in Female Cynomolgus Monkey Serum (ng/mL)

Group No. Dose (biweekly)	Animal Number	Day -6	Day 15	Day 20	Day 47	Day 76	Day 104	Day 128	Day 163	Day 195	Day 222	Day 250
Group 1	2877	NQ[a]	NQ	NQ								
0 mg/kg	2878	NQ	NQ	NQ								
	2879	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ
	2880	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ
Group 2	2881	NQ	NQ	NQ								
20 mg/kg	2882	NQ	NQ	NQ								
	2883	NQ	NQ	65.2								
	2884	NQ	NQ	5.6	4220	21800	20900	18700	14700	10400	83400	67200
	2885	NQ	NQ	NQ	4.7	200	1210	1720	2930	3060	2810	3440
	2886	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ
Group 3	2887	NQ	NQ	NQ								
100 mg/kg	2888	5.7	NQ	NQ								
	2889	NQ	NQ	NQ								
	2890	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ
	2891	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ
	2892	NQ	NQ	NQ	35.6	1420	3700	2150	1850	2040	1590	1310
Group 4	2893	NQ	NQ	NQ								
100 mg/kg	2894	NQ	NQ	NQ								
	2895	NQ	NQ	NQ								
	2896	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ
	2897	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ
	2898	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ	NQ

[a] The sample tested was below the lowest limit of quantification (LLQ = 4.0 ng/mL) and is designated as NQ (Not-Quantifiable)

Following SC and IV administration, ofatumumab was quantifiable for at least 336 hr after the first dose and at least 72 hr after the Day 15 dose in all groups. In the recovery animals, ofatumumab was quantifiable in at least 2 of 3 animals per group up to Day 61, Day 128 or Day 163 for the LD SC, HD SC, and IV-dosed groups, respectively. Mean relative bioavailability was approximately 75% on both Days 1 and 15 in the HD SC group, but was approximately 85% on Day 1 and 40% on Day 15 in the LD SC group. See the Sponsor's summary TK table, below.

Parameter	Period	Female (n = 6)		
		Dose of GSK1841157 (mg/kg/dose)		
		20 (SC)	100 (SC)	100 (IV)
AUC_{0-t} [a] (mg.h/mL)	Day 1[c]	57.9 [44.6 - 77.0]	257 [225 - 283]	340 [322 - 398]
	Day 15[d]	46.4 [18.7 – 67.9]	274 [134 - 347]	392 [375 - 423]
	Off-dose[e]	80.0 [18.7 – 136]	753 [136 - 1110]	1005 [889 - 1156]
Relative Bioavailability F% [a]	Day 1	85.1 [65.6 – 113]	75.6 [66.3 – 83.3]	NA
	Day 15 with Off-dose [f]	39.8 [9.29 – 67.6]	74.9 [13.5 – 110]	NA
AUC_{0-72} [a] (mg.h/mL)	Day 15[f]	16.7 [5.75 - 31.7]	88.9 [78.6 – 99.7]	145 [141-151]
C_{max} [a] (mg/mL)	Day 1	0.218 [0.186 - 0.269]	1.00 [0.923 - 1.17]	2.76 [2.47 - 3.32]
	Day 15	0.297 [0.0916 - 0.637]	1.51 [1.16 - 2.01]	3.27 [2.93 - 3.93]
T_{max} [b] (h)	Day 1	120 [36.0 - 168]	48.0 [24.0 - 48.0]	0.50 [0.50-0.50]
	Day 15	60.0 [24.0 - 72.0]	48.0 [24.0 - 72.0]	1.00 [0.50 - 6.00]
$T_{1/2}$ [b] (h)	Off-dose	76.8 [26.5 - 210]	226 [72.2 - 353]	320 [265 - 345]

NA = Not applicable.
The relative bioavailability was calculated by comparison between the dose normalized individual AUC_{0-t} following SC administration and the mean AUC_{0-t} following IV administration on Day 1 and Day 15, respectively

a. Results are reported as Mean and [Range].
b. Results are reported as Median and [Range].
c. AUC_{0-t} was calculated from time 0 to the last sampling time 336 hours after dosing on Day 1.
d. n = 3, AUC_{0-t} was calculated from time 0 up to the sampling time 312 hours after dosing on Day 15.
e. n = 3, AUC_{0-t} was calculated from time 0 up to the last quantifiable time-point during the off-dose period.
f. n = 3.

8 Carcinogenicity

The Sponsor submitted a carcinogenicity assessment to justify the lack of a carcinogenicity study (IND 111116, Seq No. 0097, dated 8/9/2016); the justification was found acceptable upon review (see email correspondence dated 6/11/2017).

9 Reproductive and Developmental Toxicology

The reproductive toxicology assessment supporting the original BLA consisted of an embryofetal development study in cynomolgus monkey. The nonclinical review of the original BLA (see review by Dr. A. McDougal, dated 8/10/09) noted that the toxicology

studies were “of limited utility to assess reproductive toxicity” because most of the animals were sexually immature. To support the use of ofatumumab in indications requiring chronic treatment in a population such as RMS, fertility and enhanced pre- and postnatal development studies were submitted.

9.1 Fertility and Early Embryonic Development

Study Title: 13 Week Intravenous Administration for Effects on Female and Male Fertility in the Cynomolgus Monkey with at Least An 8 Week Recovery Period

Study no.:	Pcs-r1670402 (b) (4)
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7/12/2017
GLP compliance:	Yes (OECD, (b) (4), except: OECD/(b) (4): bioanalysis, TK, cytokine analysis, & IHC Non-GLP: ADA evaluation & pathology peer review
QA statement:	Yes
Drug, lot #, and % purity:	Ofatumumab (OMB157), Batch # 152394721, 99.6% pure

Methods (See the Sponsor’s Table 1.1, below.)

Frequency of Dosing	Days 1, 8, 15, 22, 29, 43, 57, 71 and 85
Route of administration:	IV infusion
Formulation/Vehicle:	See Table 3.1.2, below.
Species/Strain:	Cynomolgus monkeys (Vietnamese) 3.5-7 years old M: 4.7-8.2 kg; F: 2.7-4.0 kg

Table 1.1: Study Design

Group Number	Group Description	Dose Level[a] (mg/kg)	Dose Volume[b] (mL/kg)	Animals/Group Males/Females	Necropsy after ... 13 Weeks[c]	Necropsy after ... 21 Weeks[d]
1	Control	0 mg/kg weekly / 0 mg/kg bi-weekly	10	6/6	4 M / 4 F	2 M / 2 F
2	Low	10 mg/kg weekly / 3 mg/kg bi-weekly	10	6/6	4 M / 4 F	2 M / 2 F
3	High	100 mg/kg weekly / 20 mg/kg bi-weekly	10	6/6	4 M / 4 F	2 M / 2 F

F = Females; M = Males
a = First five weeks weekly / every 2 weeks thereafter starting on study Day 43.
b = Based on most recent individual body weight.
c = End of treatment period
d = End of treatment-free period

3.1.2 Control Item (Vehicle)

The control item (vehicle) components were supplied as follows.

Components	Storage	Batch No.	Expiry Date	Composition per mL [mg]
Sodium acetate trihydrate		AM0940967	31 Jan 2018	(b) (4)
Sodium chloride		K48705904	28 Feb 2022	
(b) (4)		K49022887	31 May 2022	
Hydrochloride acid (b) (4)		HC60667757	30 Sep 2019	
(b) (4)	(b) (4)	HC60683437	31 Oct 2019	
Disodium edetate (b) (4)		17C244111	Dec 2021	
Polysorbate 80 (b) (4)		K49092461	31 May 2019	
(b) (4)				
Water for injection		NA	NA	

NA = Not applicable.

Observations and Results

Mortality

There were no early deaths.

Clinical Signs

Drug-related clinical signs or changes in respiration rate or body temperature were not observed. One LDM was reported to show moderate hypoactivity, excessive salivation, lying body position, and swollen eyelids between Day 71 and Day 85; incomplete B-cell depletion was observed in this animal on Day 85, and the effects were considered potentially ADA-related.

Body Weight

No drug-related changes in body weight were observed.

Clinical Pathology

Hematology & Coagulation
In males, reticulocytes were reduced in the ofatumumab-dosed groups (approximately 20% on Day 85 and 30-40% on Recovery Day 50 [not d-r]). WBC were increased 40% to 50% in ofatumumab-dosed males on Recovery Day 50; increased neutrophils accounted for most of the observed increase (approximately 70%).

In females, lymphocytes were reduced in the ofatumumab-dosed groups on Day 85 (approximately 40% in the HD group) and at the end of recovery (approximately 25% in the LD and 40% in the HD groups). Eosinophils were dose-dependently reduced on Day 85; partial recovery was observed (see the Sponsor's table, below).

Table
Summary of Hematology
Test Item (dosage) 1 2 3
OMB157 mg/kg weekly first 5 weeks 0 10 100
OMB157 mg/kg biweekly from day 43 0 3 20

AEOS. 10E9/L

	Phase	Predose		Dosing	Recovery
Group/ Sex	Day	65	71	85	52
	Session	1	1	1	1
	Name	Hema/IPT	Hema/IPT	Hema/IPT	Hema/IPT
1/F	Mean	0.25	0.31	0.43	0.29
	SD	0.218	0.429	0.366	0.304
	N	6	6	6	2
2/F	Mean	0.20	0.18	0.11	0.14
	SD	0.186	0.142	0.133	0.113
	N	6	6	6	2
	%-Diff	-20%	-42%	-74%	-52%
3/F	Mean	0.14	0.17	0.04**	0.18
	SD	0.131	0.171	0.038	0.170
	N	6	6	6	2
	%-Diff	-44%	-45%	-91%	-38%
	Statistics	A	A	AT	X7

* P<=0.05
** P<=0.01
*** P<=0.001
A = ANOVA and Dunnett's
T = Rank-transformed data
X7 = Not analyzed (mean of too small)

Clinical Chemistry
Reductions in IgG and IgM were observed (approximately 10% to 40%) in both ofatumumab-dosed groups in the recovery period; however, it is noted that the values were based on two animals per group.

Urinalysis
Urine volume was reduced in the HDM at the end of dosing (see the Sponsor's Table 4.3, below).

Table 4.3: Summary of Urinalysis

Test Item (dosage) 1 2 3
OMB157 mg/kg weekly first 5 weeks 0 10 100
OMB157 mg/kg biweekly from day 43 0 3 20

		UVOL. mL		
	Phase	Predose	Dosing	Recovery
Group/ Sex	Day	9	85	50
	Session	1	1	1
	Name	Urine	Urine	Urine
1/M	Mean	76.8	98.8	190.0
	SD	43.97	103.38	35.36
	N	6	6	2
2/M	Mean	106.3	78.8	104.0
	SD	29.73	53.44	93.34
	N	6	6	2
	%-Diff	38%	-20%	-45%
3/M	Mean	114.2	29.6	109.5
	SD	39.50	24.01	50.20
	N	6	6	2
	%-Diff	49%	-70%	-42%
	Statistics	A	AT	X7

A = ANOVA and Dunnett's
T = Rank-transformed data
X7 = Not analyzed (mean of actual group sizes too small)

Cytokines
No effects on IFN-γ, TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-8, or IL-10 levels were reported.

Immunophenotyping (IPT)
Circulating CD20+ B cells were depleted in both ofatumumab-dosed groups. Only animals with neutralizing ADA showed CD20+ B-cell counts exceeding the limit of quantitation on Day 85 and Recovery Day 50. See the Sponsor's tables, below.

CD20+ B cells absolute (10E9/L) and % of Lymphocytes

Group/ Sex	Phase	Predose Day 8 (10E9/L)	Predose Day 8 (%)	Predose Day 16 (10E9/L)	Predose Day 16 (%)	Dosing Day 85 (10E9/L)	Dosing Day 85 (%)	Recovery Day 50 (10E9/L)	Recovery Day 50 (%)
1/M	Mean	1.42	34.09	1.60	30.16	1.29	33.25	1.56	43.94
	SD	1.09	15.83	0.96	15.75	1.18	14.69	-	-
	N	6	6	6	6	6	6	2	2
2/M	Mean	1.24	23.80	1.26	21.22	0.32 **	6.36 **	0.82	17.44
	SD	0.38	6.16	0.48	6.16	0.37	7.00	-	-
	N	6	6	6	6	6	6	2	2
3/M	Mean	1.90	25.86	2.09	23.59	0.00 ***	0.01 ***	0.00	0.00
	SD	0.93	7.37	1.04	7.03	0.00	0.01	-	-
	N	6	6	6	6	6	6	2	2
	Statistics	A	AT	A	AT	AT	AT	X	X

Standard deviation not calculated for less than three values

Statistical analysis was performed using SAS release 9.2
A = ANOVA and Dunnett's
T = Rank-transformed data
X = No analysis performed
* P≤ 0.05
** P≤ 0.01
*** P≤ 0.001

CD20+ B cells absolute (10E9/L) and % of Lymphocytes

Group/ Sex	Phase	Predose Day 65 (10E9/L)	Predose Day 65 (%)	Predose Day 71 (10E9/L)	Predose Day 71 (%)	Dosing Day 85 (10E9/L)	Dosing Day 85 (%)	Recovery Day 52 (10E9/L)	Recovery Day 52 (%)
1/F	Mean	0.96	23.87	1.14	21.40	0.86	25.40	1.15	28.28
	SD	0.47	8.65	0.49	5.97	0.25	8.09	-	-
	N	6	6	6	6	6	6	2	2
2/F	Mean	0.71	23.17	0.86	21.87	0.12 ***	4.19 **	0.00	0.09
	SD	0.46	10.02	0.52	7.99	0.29	10.24	-	-
	N	6	6	6	6	6	6	2	2
3/F	Mean	1.15	30.09	1.60	30.34	0.00 ***	0.00 ***	0.00	0.00
	SD	0.58	8.00	0.75	7.87	0.00	0.00	-	-
	N	6	6	6	6	6	6	2	2
	Statistics	A	A	A	A	AT	AT	X	X

Standard deviation not calculated for less than three values

Statistical analysis was performed using SAS release 9.2
A = ANOVA and Dunnett's
T = Rank-transformed data
X = No analysis performed
* P≤ 0.05
** P≤ 0.01
*** P≤ 0.001

Assessment of T cell counts (i.e., CD3+, CD3+CD8+ cytotoxic, and CD3+CD4+ helper) was complicated by high variability (i.e., predose differences between the groups, particularly in males). T cell counts tended to be reduced at the end of the dosing and/or recovery period compared to their predose counts in individual HDMs.

Toxicokinetics & ADA

TK was evaluated on Day 1 and Day 85. The non-GLP ADA assessment was performed using a qualified but non-validated method.

Systemic exposure to ofatumumab increased approximately dose-proportionally on Day 1 and slightly more than dose-proportionally on Day 85. No clear sex difference was observed. See the Sponsor's summary Table 4.1, below.

Table 4.1: Summary of Mean Ofatumumab C_{max}, DN C_{max}, AUC_{0-168}, and DN AUC_{0-168} in Male and Female Monkey Serum

Dose Level* (mg/kg)	Interval	Sex	n	C_{max} (µg/mL)	DN C_{max}	AUC_{0-168} (µg·h/mL)	DN AUC_{0-168}
10/3 (Group 2)	Day 1	M	6	275	27.5	22600	2260
		F	6	248	24.8	1670	167
	Day 85	M	2**	113	37.6	11300	3780
		F	5**	136	45.3	13900	4620
100/20 (Group 3)	Day 1	M	6	2760	27.6	247000	2470
		F	6	2530	25.3	222000	2220
	Day 85	M	6	1340	67.2	162000	8090
		F	6	1090	54.7	124000	6200

* Dose administered weekly (first 5 occasions)/dose administered biweekly (last 4 occasions)
** 4 male and 1 female animals were excluded due to being ADA positive on Day 22/57

Five of 12 LD animals (i.e., 4 LDM and 1 LDF) showed ofatumumab concentrations below the LLOQ from Day 22/57, correlating with a neutralizing ADA response and recovery of CD20+ B cells in blood and lymphoid tissues. Five other LD animals and two of 12 HD animals (on Day 22 only) were positive for ADAs without a clear effect on ofatumumab TK.

Dosing Solution Analysis

Formulation analyses on Day 1 and during Weeks 7 and 13 showed that the formulations were between 92.5% and 100.2% of the nominal concentration. Drug was not found in the vehicle control formulations.

Necropsy

A separate, signed pathology report was submitted. A non-GLP peer review was conducted but not included in the report. A full necropsy was conducted, and organ weights were collected for adrenal gland, brain, epididymides, heart, kidneys, liver, ovaries, pituitary, prostate, spleen, testes, thymus, thyroid/parathyroid, and uterus/cervix. Epididymal sperm motility was assessed. The tissues evaluated histologically included: epididymides, mammary glands, gross lesions, injection sites, mandibular and mesenteric lymph nodes, ovaries, Peyer's patches (ileum), prostate, seminal vesicles, spleen, testes, thymus, and uterus/cervix.

Organ Weights

At the end of the dosing period, thymus weight was reduced approximately 50% in the LDM but was increased approximately 20% at the HD in both males and females.

Dose-dependent increases in epididymal (approximately 20% at the LD and approximately 40% at the HD) and testicular (approximately 20% at the LD and approximately 60% at the HD) weights were observed. Uterine weights were reduced (approximately 20%) in the HDF. The Sponsor considered the observations reflective of normal variation.

At the end of the recovery period, thymus weight was increased approximately 2-fold in the LDM, but slight reductions in spleen weight (approximately 10%-40%) were observed in ofatumumab-dosed males and females. Dose-dependent increases in epididymal weight (approximately 30% at the LD and 2-fold at the HD) were observed. Prostate weight was increased approximately 50% at the HD. Ovarian weight was slightly reduced (approximately 20%) but uterine weight was increased (approximately 50%) at the HD. Slight increases (20-30%) in other organ weights (heart in both sexes and liver in females at the HD) were attributed to individual variation.

Macroscopic

No clearly drug-related findings were observed.

Histopathology

Microscopic changes were observed in lymphatic tissues and spleen, with few observations in other evaluated tissues. See selected data from the Sponsor's summary table, below.

At the end of the dosing period, dose-dependent slight to severe reductions in germinal centers and minimal to moderate extramedullary hematopoiesis were observed in the lymph nodes. In the spleen, dose-dependent decreased cellularity in the lymphoid follicles and moderate to severe reductions in germinal centers were observed.

One HDM showed bilateral moderate depletion/degeneration of germ cells in the testis; changes observed in the other animals were unilateral. Low incidence uterine changes were observed, but similar changes have been reported as background lesions in cynomolgus monkeys (see Cline et al., 2008). Moderate hemorrhage and slight GALT hyperplasia in the cecum were observed with low incidence (i.e., each in 1 HDF).

Summary of Severity of Microscopic Observations
Terminal Sacrifice

Test Item	(dosage)	1	2	3
OMB157	mg/kg weekly first 5 weeks	0	10	100
OMB157	mg/kg biweekly from day 43	0	3	20

Tissue/ Observation	Group/Sex: Number of Animals:	1/M 4	2/M 4	3/M 4	1/F 4	2/F 4	3/F 4
Lymph Node, Mandibular	Number Examined:	4	4	4	4	4	4
	Unremarkable:	4	0	0	3	2	1

Germinal centers, absent/reduced						
finding not present -	4	0	0	4	2	1
slight 2	0	4	1	0	2	0
moderate 3	0	0	0	0	0	3
marked 4	0	0	3	0	0	0
Total Incidence:	0	4	4	0	2	3
Hematopoiesis, extramedullary						
finding not present -	4	4	2	3	4	3
minimal 1	0	0	1	1	0	1
moderate 3	0	0	1	0	0	0
Total Incidence:	0	0	2	1	0	1
Lymph Node, Mesenteric						
Number Examined:	4	4	4	4	4	4
Unremarkable:	4	2	0	4	2	1
Germinal centers, absent/reduced						
finding not present -	4	2	0	4	2	1
slight 2	0	1	0	0	1	0
moderate 3	0	0	0	0	1	1
marked 4	0	1	3	0	0	1
severe 5	0	0	1	0	0	1
Total Incidence:	0	2	4	0	2	3
Hematopoiesis, extramedullary						
finding not present -	4	4	3	4	4	4
slight 2	0	0	1	0	0	0
Total Incidence:	0	0	1	0	0	0
Spleen						
Number Examined:	4	4	4	4	4	4
Unremarkable:	4	1	0	3	1	1
Decreased cellularity, lymphoid follicles						
finding not present -	4	3	0	4	4	2
slight 2	0	0	1	0	0	1
moderate 3	0	1	2	0	0	1
marked 4	0	0	1	0	0	0
Total Incidence:	0	1	4	0	0	2
Germinal centers, absent/reduced						
finding not present -	4	1	0	3	1	1
moderate 3	0	1	0	0	0	0
marked 4	0	0	1	1	0	0
severe 5	0	2	3	0	3	3
Total Incidence:	0	3	4	1	3	3
Testis						
Number Examined:	4	4	4	0	0	0
Unremarkable:	3	4	2	0	0	0
Depletion/degeneration, germ cells						
finding not present -	3	4	2	0	0	0
minimal 1	0	0	1	0	0	0
moderate 3	1	0	1	0	0	0
Total Incidence:	1	0	2	0	0	0

Uterus/Cervix	Number Examined:	0	0	0	4	4	4
	Unremarkable:	0	0	0	4	3	3
Adenomyosis							
	finding not present -	0	0	0	4	3	4
	minimal 1	0	0	0	0	1	0
	Total Incidence:	0	0	0	0	1	0
Dilatation							
	finding not present -	0	0	0	4	4	3
	slight 2	0	0	0	0	0	1
	Total Incidence:	0	0	0	0	0	1

After an 8-week recovery period, changes persisted in the spleen and LN. See selected data from the Sponsor's summary table, below.

Table 7.8: Summary of Severity of Microscopic Observations - Recovery Sacrifice

Report Run: 3:19 P

Test Item (dosage)		1	2	3
OMB157	mg/kg weekly first 5 weeks	0	10	100
OMB157	mg/kg biweekly from day 43	0	3	20

Tissue/Observation	Group/Sex: / Number of Animals:	1/M 2	2/M 2	3/M 2	1/F 2	2/F 2	3/F 2
Lymph Node, Mandibular	Number Examined:	2	2	2	2	2	1
	Unremarkable:	2	2	0	2	1	0
Germinal centers, absent/reduced							
	finding not present -	2	2	0	2	1	0
	slight 2	0	0	0	0	1	0
	moderate 3	0	0	0	0	0	1
	marked 4	0	0	2	0	0	0
	Total Incidence:	0	0	2	0	1	1
Lymph Node, Mesenteric	Number Examined:	2	2	2	2	2	2
	Unremarkable:	2	1	0	2	0	0
Germinal centers, absent/reduced							
	finding not present -	2	1	0	2	0	0
	slight 2	0	1	0	0	2	2
	marked 4	0	0	1	0	0	0
	severe 5	0	0	1	0	0	0
	Total Incidence:	0	1	2	0	2	2
Spleen	Number Examined:	2	2	2	2	2	2
	Unremarkable:	2	2	0	2	0	0
Decreased cellularity, lymphoid follicles							
	finding not present -	2	2	0	2	0	0
	slight 2	0	0	1	0	0	2
	moderate 3	0	0	1	0	2	0
	Total Incidence:	0	0	2	0	2	2
Germinal centers, absent/reduced							
	finding not present -	2	2	0	2	0	0
	moderate 3	0	0	0	0	0	1
	severe 5	0	0	2	0	2	1
	Total Incidence:	0	0	2	0	2	2

Uterus/Cervix	Number Examined:	0	0	0	2	2	2
	Unremarkable:	0	0	0	2	1	2
Hyperplasia, endometrium							
	finding not present -	0	0	0	2	1	2
	moderate 3	0	0	0	0	1	0
	Total Incidence:	0	0	0	0	1	0

Immunohistochemistry

T-cell (anti-CD3) and B-cell (anti-CD20) staining was used to visualize depletion in the lymphoid tissues.

Lymphoid tissues (i.e., spleen, LN, GALT, and thymus) showed marked decreases in the intensity, quantity, and distribution of staining of CD20+ cells. After the recovery period, depletion was still present in the lymphoid tissues at the HD but showed partial recovery at the LD (although this is confounded by the effects of neutralizing ADA). "Minor" dose-dependent reductions in the distribution and quantity of staining of CD3+ cells in the lymphoid tissues were observed, with some evidence of recovery at the LD (see comment above regarding ADA); the changes in CD3+ cell staining were considered secondary to the reduction in size/number of germinal centers reflecting the marked reductions in CD20+ cells.

Fertility Parameters

In females, menstrual cycles were monitored; clearly drug-related changes in menstrual cycle length were not observed. One HDF showed "many extra bleedings" after 4 regular cycles; the cycles were described as regular, with "stronger bleeding"; uterine/cervical tissues in this animal were reported as microscopically normal. A few individuals showed microscopic changes in the uterus (see **Histopathology**; i.e., adenomyosis, slight lumen dilatation, and moderate focal hyperplasia of the endometrial lumen of the uterus); however, these changes have been reported as background lesions in cynomolgus monkeys, with endometrial hyperplasia reported as "rare" (see Cline et al., 2008).

In males, semen evaluation was performed during the predose period and during Weeks 1, 7, and 13; sperm count, motility, and morphology were assessed. Testicular size, volume, homogeneity, and echogenicity were also assessed. No clearly drug-related changes were observed for ejaculate weight or sperm count. A slight reduction in epididymal sperm motility at the HD (77.8%, compared to 88.7% in controls) at necropsy was not clearly observed in the semen evaluations; no clear differences were observed after the recovery period. Sperm morphology was variable but suggested increased sperm defects in HDM; the Sponsor attributed this observation to two individuals, but those individuals were not clearly outliers. See tables below, from the Sponsor. Clearly drug-related changes in testicular volume were not observed.

Table
Summary of Sperm Morphology (%)

Test Item	(dosage)	1	2	3
OMB157	mg/kg weekly first 5 weeks	0	10	100
OMB157	mg/kg biweekly from day 43	0	3	20

Occasion		Dosing Phase Week 1					
Group/ Sex		normal	head defects	mid piece defects	tail defects	total amount of defects	multiple defects
1/M	Mean	84.4	0.6	9.2	8.6	18.3	2.3
	SD	8.1	0.6	5.3	5.9	9.0	1.5
	N	6	6	6	6	6	6
2/M	Mean	87.5	1.1	8.4	5.3	14.8	2.0
	SD	7.2	0.5	5.2	3.0	7.4	1.3
	N	6	6	6	6	6	6
3/M	Mean	69.8	1.0	8.3	23.0	32.3	1.9
	SD	25.3	0.9	6.2	25.6	25.6	1.1
	N	6	6	6	6	6	6
	Statistics	AT	AT	AT	AT	AT	AT

Statistical analysis was performed using SAS release 9.2

A = ANOVA and Dunnett's
T = Rank-transformed data

Table
Summary of Sperm Morphology (%)

Test Item	(dosage)	1	2	3
OMB157	mg/kg weekly first 5 weeks	0	10	100
OMB157	mg/kg biweekly from day 43	0	3	20

Occasion		Dosing Phase Week 7					
Group/ Sex		normal	head defects	mid piece defects	tail defects	total amount of defects	multiple defects
1/M	Mean	91.4	0.8	5.0	5.1	10.8	1.8
	SD	3.8	0.9	1.5	3.8	5.9	1.7
	N	6	6	6	6	6	6
2/M	Mean	92.7	0.5	4.1	3.8	8.3	0.8
	SD	2.4	0.4	2.3	1.4	2.6	0.4
	N	6	6	6	6	6	6
3/M	Mean	74.8	1.7	14.0	11.3	26.9	1.2
	SD	16.6	1.8	12.1	7.7	17.9	1.0
	N	6	6	6	6	6	6
	Statistics	AT	AT	AT	AT	AT	AT

Statistical analysis was performed using SAS release 9.2

A = ANOVA and Dunnett's
T = Rank-transformed data

Table
Summary of Sperm Morphology (%)

Test Item	(dosage)	1	2	3
OMB157	mg/kg weekly first 5 weeks	0	10	100
OMB157	mg/kg biweekly from day 43	0	3	20

Occasion: Dosing Phase Week 13

Group/ Sex		normal	head defects	mid piece defects	tail defects	total amount of defects	multiple defects
1/M	Mean	89.5	0.9	5.2	6.8	12.9	2.0
	SD	6.5	1.2	2.9	4.1	7.2	1.4
	N	5	5	5	5	5	5
2/M	Mean	78.0	0.4	6.2	16.8	23.4	1.2
	SD	22.4	0.4	3.9	22.3	22.8	0.7
	N	5	5	5	5	5	5
3/M	Mean	82.2	0.8	7.0	12.3	20.1	2.0
	SD	10.8	1.1	2.6	8.4	10.2	0.7
	N	6	6	6	6	6	6
	Statistics	AT	AT	AT	AT	AT	AT

Statistical analysis was performed using SAS release 9.2

A = ANOVA and Dunnett's
T = Rank-transformed data

Table
Summary of Sperm Morphology (%)

Test Item	(dosage)	1	2	3
OMB157	mg/kg weekly first 5 weeks	0	10	100
OMB157	mg/kg biweekly from day 43	0	3	20

Occasion: Recovery Phase

Group/ Sex		normal	head defects	mid piece defects	tail defects	total amount of defects	multiple defects
1/M	Mean	90.5	0.0	4.5	5.8	10.3	0.8
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
2/M	Mean	85.5	1.3	5.3	10.8	17.3	2.8
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
3/M	Mean	52.3	0.8	11.0	36.5	48.3	0.5
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
	Statistics	X	X	X	X	X	X

X = No analysis performed

Overall, no clearly drug-related alterations in reproductive tissues were observed in females. There was inconsistent evidence of changes in sperm at the HD and one HDM showed microscopic testicular depletion/degeneration of germ cells. The NOAEL/LOAEL (females/males) for findings in reproductive tissues was the HD (i.e., 100/20 mg/kg over 13 weeks).

9.2 Embryonic Fetal Development

An embryofetal development study was conducted to support the BLA for Arzerra (see BLA 125326 by Dr. McDougal, dated 8/10/2009). In Study 2148-010, pregnant cynomolgus monkeys (12/group) were administered 0, 20, or 100 mg/kg ofatumumab IV weekly beginning GD20 and continuing through GD50 (i.e., 5 infusions total). Saturating levels of ofatumumab were reportedly present in maternal blood on GD100, when Cesarean sections were performed. Weekly dosing of ofatumumab resulted in accumulation; the half-life ranged from approximately 4 to 15 days. Ofatumumab and

ADA (believed to be maternal ADA) were observed in fetal blood, indicating placental cross-over. CD20+/CD40+ B cells showed nearly complete depletion at both doses in maternal blood throughout dosing until Day GD100 and in fetal cord blood (~10% of control) on GD100. Teratogenicity was not observed but decreased placental weights and reduced fetal spleen and thymus weights were observed. Immunophenotyping demonstrated marked B-cell reductions in the spleens of most fetuses at both doses.

Dr. McDougal's review noted the following:

- **Lack of postnatal recovery data for animals exposed during gestation**
  - **Because fetuses were evaluated on GD100, no postnatal B-cell recovery data are available. These data may be important for maximizing the benefit of early childhood immunizations.**
  - **No data are available regarding the distribution of ofatumumab into milk, or the gastrointestinal absorption of ofatumumab from milk.**

9.3 Prenatal and Postnatal Development

Study title: Enhanced Study for Effects on Pre- and Postnatal Development in Cynomolgus Monkeys

Study no.:	1670033 (b) (4)
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6/28/2017
GLP compliance:	Yes (OECD, FDA), except TK & TDAR Yes (OECD, (b) (4) Non-GLP: X-ray, ADA, IHC, EM
QA statement:	Yes
Drug, lot #, and % purity:	Ofatumumab (OMB157), batch 162395852, purity 99.7% IgG

Methods (see the Sponsor's study design table, below)

Frequency of dosing:	Weekly for 5 weeks (GD20, GD27, GD34, GD41, and GD48), followed by dosing every 2 weeks from GD62 until GD160 (GD62, GD76, GD90, GD104, GD118, GD132, GD146, and GD160)
Route of administration:	IV, 30-minute infusion
Formulation/Vehicle:	In sodium acetate trihydrate, sodium chloride (b) (4) arginine (b) (4) hydrochloric acid (b) (4) (b) (4) disodium edetate (b) (4) polysorbate 80, and water for injection
Species/Strain:	cynomolgus monkey 4-6 years old; 2.8 – 4.9 kg
Study design:	Doses were selected based on the previous EFD study and two repeat-dose toxicity studies. The 100 mg/kg dose was selected to "further characterize the B-cell depletion observed at this dose in the fetuses of the EFD study and to evaluate the postnatal reversibility of this effect… The once every other week (biweekly) dosing regimen was selected based on the long elimination half-life observed in the general toxicity studies and the desire to minimize the potential for formation of ADAs."
Deviation from study protocol:	Numerous deviations were noted but were not reported to affect the integrity or interpretation of the study.

Table 1.1: Study Design

Group Number	Group Description	Number of Pregnant Females	Dose Level (mg/kg)	Dose Volume[a] (mL/kg)
1	Control	14	0 mg/kg weekly / 0 mg/kg biweekly	10
2	Low	14	10 mg/kg weekly / 3 mg/kg biweekly	10
3	High	14	100 mg/kg weekly / 20 mg/kg biweekly	10

a Based on most recent individual body weight.

Observations and Results

The group size was small (N=14). The Sponsor stated that the group size was selected based on ICH S6(R1) Guideline Note 5 (i.e., the selected group size "… provided for 6-8 live infants per group on Day 7 p.p."; see Jarvis et al., 2010). The Sponsor also stated that, "Due to unexpected early pregnancy losses, additional two animals per group were recruited for the study." There were 10 or more surviving infants in the control and HD groups at PND4; however, the number of infants surviving for the duration of the study were 10, 9, and 7 in the control, LD and HD groups, respectively.

F_0 Animals

Survival

One HD maternal animal was euthanized on LacD96 for poor physical condition, including dehydration, body weight loss, and urine ammoniac odor. Clinical pathology alterations were observed as early as LacD71 and were considered secondary to severe bilateral glomerulonephropathy and tubular degeneration in the kidney, including: reduced red cell mass; increased creatinine concentration; increased neutrophil count, WBC counts, and fibrinogen concentration; and increased glucose and potassium concentrations. Depletion of CD20+ B cells as well as depletion of T-cell subsets, CD16+ NK cells, and CD3+CD14+ monocytes, were observed. Slight to moderate decreases in germinal centers were observed in the mesenteric lymph node and spleen. Inflammation and/or mononuclear cell infiltrates were observed in several tissues.

IHC staining of the kidneys showed moderate staining for cynomolgus monkey IgM in the glomeruli, with the majority located within the capillary lumen (i.e., representing circulating serum IgM). One vessel with apparent acute inflammatory changes had multifocal subendothelial deposition of IgM-positive material. The pathologist stated that, "… the observation of subendothelial IgM-positive deposits in an acutely inflamed vessel supports an immune-complex disease having contributed to the morbidity… the chronicity of the glomerular changes suggests the possibility of immune-complex formation and deposition at an earlier time point during this study." On this basis, the death of this animal was attributed to an adverse ADA-mediated event, supported by the presence of ADA on GD138 in blood and the IgM-positive deposits in an acutely inflamed vessel of the kidneys.

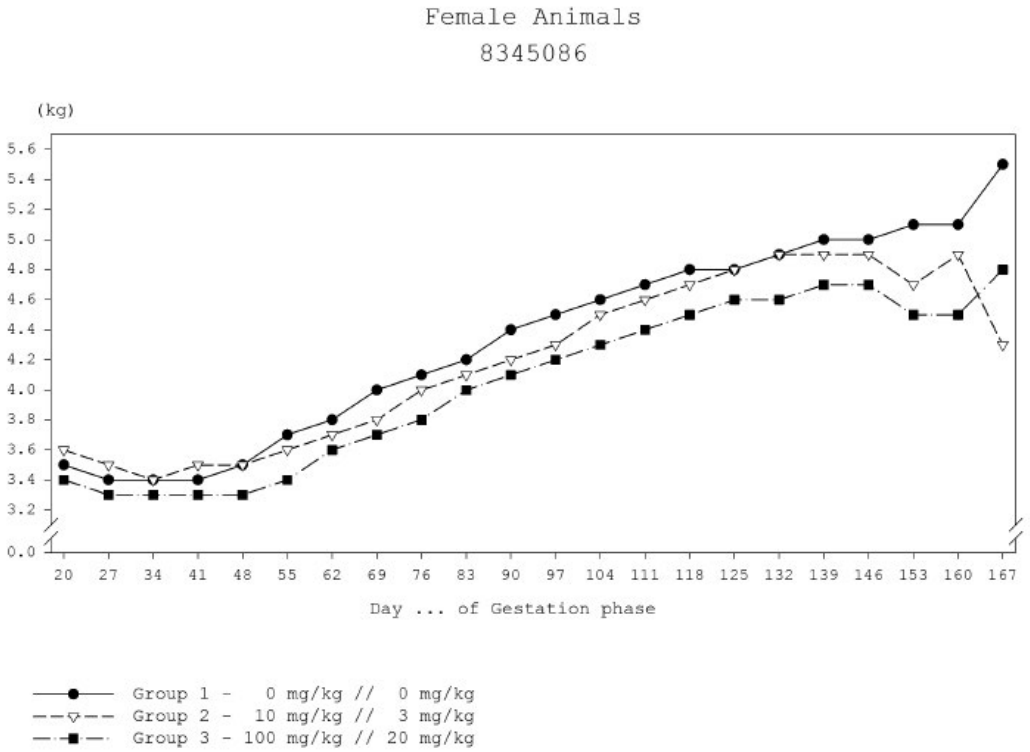
Clinical Signs

Oxytocin was administered to 3 LD and 2 HD ofatumumab-dosed animals within the first 7 days of birth "to increase maternal animal-infant bonding." Several maternal animals, including controls, were reported to have harmed their offspring during the study. No drug-related clinical signs, veterinary treatments, or effects on vaginal bleeding were reported.

Body Weight

During gestation, slightly reduced body weights (approximately 6%) were observed at the HD. See Figure 8.2, below, from the Sponsor. Note that for GD153, GD160, and GD167, fewer animals were included in the averages for the groups (i.e., 10, 8, and 8; 7, 5, and 3; and 2, 1, and 1; in the control, LD, and HD groups, respectively).

Figure 8.2: Group Mean Maternal Body Weights – During Gestation



Gestation Length

Gestation length was slightly reduced at the HD compared to controls (i.e., 159, 160, and 154 days in the control, LD, and HD groups), but was within the historical reference range (136-179 days, average 160 ±7 days).

Pregnancy Outcome

During the study, 2/14, 3/14, and 1/14 females aborted in the control, LD, and HD groups, respectively. Prenatal loss was 14.3%, 28.6%, and 7.1% in the control, LD, and HD groups, respectively; see the Sponsor's Table 4.1, below, for details. There were 3 early deliveries in the HD group (GD133-143), and 2 early deliveries in the control group (GD136-141). Each group showed one infant death on the day of birth (i.e., undetermined COD in the control group, stillborn in the LD group, and an infant with maternal injuries in the HD group).

Table 4.1: Pregnancy Outcome and Infant Loss

Group/ Dose	Animals N	Early Pregnancy Loss (GD 20 to 50)	Mid Pregnancy Loss (GD 51 to 100)	Late Pregnancy Loss (GD 101 to 175)	Stillbirths[a], Including Death During Birth or Infant loss PND 0	Total Pregnancy Loss (GD 20 to 175/PND 0)	Infant Loss Postnatal Days (1-181)
Group 1 (0/0 mg/kg)	14	P0002, P0013 (GD30)	-	-	P0014 (GD141)	3	P0001-1 (PND2)
		14.29%	-	-	7.14%		7.14%
Group 2 (10/3 mg/kg)	14	P0103, P0104 (GD30)	P0102 (GD58)	P0108 (GD140)	P0109 (GD166)	5	-
		14.29%	7.14%	7.14%	7.14%		-
Group 3 (100/20 mg/kg)	14	P0205 (GD30)	-	-	P0208 (GD133)	2	P0209-1 (PND1); P0211-1 (PND1); P0204-1 (PND4) P0206-1 (PND12); P0203-1 (PND37)
		7.14%			7.14%		35.71%

GD = Gestation Day; PND = Postnatal Day.
a Stillbirth is defined as a infant born with a lung not inflated with air (determined by a lung flotation test).

Clinical Pathology

Samples for hematology evaluation were taken on GD20, GD48, GD118, and GD146 and LacD28, LacD91, and LacD175. Samples for clinical chemistry evaluation were taken on GD20, GD146, and LacD175.

Overall, the LD group showed slightly reduced (~8%) RBC counts on GD118 and LacD28 compared to controls.

Immunophenotyping

Samples taken for hematology were used when possible; additional samples were collected on LacD28, LacD91, and LacD175.

During gestation, CD20+ B cells were reduced at both doses; see the Sponsor's summary data, below. On GD48, GD118, and GD146, CD20+ B cells were at the limit of detection in all maternal animals, except four LD animals. The four LD animals began to show repletion of the CD20+ B cells beginning on GD118; the repletion was attributed to high ADA levels leading to increased clearance of drug.

CD20+ B-cells absolute (10E9/L) and % of Lymphocytes

Group/ Sex	Phase	Gestation Day 20 (10E9/L)	20 (%)	48 (10E9/L)	48 (%)	118 (10E9/L)	118 (%)	146 (10E9/L)	146 (%)
1/F	Mean	1.41	33.36	1.35	24.76	0.82	19.38	0.66	23.47
	SD	0.68	9.91	0.54	6.97	0.32	5.55	0.28	9.67
	N	14	14	12	12	12	12	10	10
2/F	Mean	0.90 *	25.50	0.02 ***	0.57 ***	0.14 ***	3.16 ***	0.14 ***	4.13 ***
	SD	0.43	9.17	0.05	1.40	0.23	5.75	0.19	5.78
	N	14	14	12	12	11	11	10	10
3/F	Mean	0.84 *	24.48 *	0.00 ***	0.00 ***	0.00 ***	0.00 ***	0.00 ***	0.01 ***
	SD	0.43	9.04	0.00	0.00	0.00	0.01	0.00	0.01
	N	14	14	12	12	13	13	10	10
Statistics		A	A	AT	AT	AT	AT	AT	AT

Statistical analysis was performed using SAS release 9.2
A = ANOVA and Dunnett's
T = Rank-transformed data
* P≤ 0.05
** P≤ 0.01
*** P≤ 0.001

Clear effects on CD3+ T cell, CD3+CD4+ T helper cell, CD16+ natural killer cell, or CD14+ monocyte counts were not observed during the gestation period. Although complicated by variability (and similar to GD20 counts in the HD group), CD3+CD8+ cytotoxic T cell counts suggested a slight increase in the LD and HD groups on GD146 compared to controls. Overall, the relative percentage of T cells was increased (i.e., consistent with reductions in B cells). See the Sponsor's summary table, below.

CD3+CD8+ cytotoxic T-cells absolute (10E9/L) and % of Lymphocytes

Group/ Sex	Phase	Gestation Day 20 (10E9/L)	20 (%)	48 (10E9/L)	48 (%)	118 (10E9/L)	118 (%)	146 (10E9/L)	146 (%)
1/F	Mean	0.68	16.38	1.03	19.23	0.89	20.37	0.53	17.34
	SD	0.32	5.34	0.38	5.74	0.41	6.20	0.21	3.85
	N	14	14	12	12	12	12	10	10
2/F	Mean	0.65	18.52	1.03	25.24 *	1.19	26.91 *	0.82	24.00 *
	SD	0.32	4.73	0.58	5.83	0.65	7.04	0.41	7.67
	N	14	14	12	12	11	11	10	10
3/F	Mean	0.83	23.14 **	1.03	29.36 ***	1.22	31.66 ***	0.81	29.32 ***
	SD	0.41	6.33	0.28	5.67	0.44	5.64	0.39	5.97
	N	14	14	12	12	13	13	10	10
Statistics		A	A	A	A	A	A	AT	A

Statistical analysis was performed using SAS release 9.2
A = ANOVA and Dunnett's
T = Rank-transformed data
* P≤ 0.05
** P≤ 0.01
*** P≤ 0.001

During the lactation period, CD20+ B cells remained reduced through at least LacD28. In the LD animals, CD20+ B cells were markedly reduced on LacD28 (i.e., <20% of control counts) but were similar to control counts by LacD91. In the HD group, CD20+ B-cell counts were at the level of detection on LacD28 and LacD91 and reached approximately 70% of control counts on LacD175. See the Sponsor's summary table, below.

CD20+ B-cells absolute (10E9/L) and % of Lymphocytes

Group/ Sex	Phase Day	Lactation 28 (10E9/L)	28 (%)	91 (10E9/L)	91 (%)	175 (10E9/L)	175 (%)
1/F	Mean	1.38	23.15	1.43	23.54	1.31	27.47
	SD	0.59	6.71	0.52	5.85	0.61	9.81
	N	10	10	9	9	9	9
2/F	Mean	0.24 ***	4.33 ***	1.32	16.60	1.49	27.68
	SD	0.38	6.52	1.05	11.43	1.01	15.73
	N	9	9	9	9	9	9
3/F	Mean	0.00 ***	0.01 ***	0.02 ***	0.57 ***	0.94	20.52
	SD	0.00	0.01	0.03	0.81	0.58	11.54
	N	8	8	7	7	6	6
	Statistics	AT	AT	AT	AT	A	A

A = ANOVA and Dunnett's
T = Rank-transformed data

* P≤ 0.05
** P≤ 0.01
*** P≤ 0.001

During lactation, CD3+CD8+ cytotoxic T cells were slightly increased in the LD group (LacD28 and LacD91) and in the HD group (LacD28, LacD91, and LacD165), compared to controls. See the Sponsor's summary table, below. Clear effects on CD3+ T cells, CD3+CD4+ T helper cells, CD16+ natural killer cells, or CD14+ monocyte counts were not observed. Overall, the relative percentage of T cells was increased, consistent with the reduction in B cells.

CD3+CD8+ cytotoxic T-cells absolute (10E9/L) and % of Lymphocytes

Group/ Sex	Phase Day	Lactation 28 (10E9/L)	28 (%)	91 (10E9/L)	91 (%)	175 (10E9/L)	175 (%)
1/F	Mean	1.23	20.72	1.29	21.09	0.93	19.59
	SD	0.45	5.09	0.62	6.87	0.37	6.62
	N	10	10	9	9	9	9
2/F	Mean	1.73	30.83 *	2.08	28.11	1.15	22.98
	SD	0.91	7.89	1.11	5.51	0.61	6.63
	N	9	9	9	9	9	9
3/F	Mean	1.85	36.18 **	2.08	41.57 ***	1.62	32.45 **
	SD	1.49	11.49	0.97	8.69	0.69	8.10
	N	8	8	7	7	6	6
	Statistics	A	A	A	A	A	A

A = ANOVA and Dunnett's

* P≤ 0.05
** P≤ 0.01
*** P≤ 0.001

Necropsy Observations

No drug-related findings were observed in the heart, kidney, lung, liver, spleen, and stomach on LacD180; histological assessment was not conducted for the adult females, except for the early HD decedent.

Toxicokinetics

Maternal exposure increased approximately dose-proportionally after a single dose of 10 mg/kg or 100 mg/kg on GD20 and after multiple doses of 3 mg/kg or 20 mg/kg on GD146. No accumulation was observed. The Sponsor provided the following TK summary table, below.

Table 1.1: Summary of Mean OMB157 Cmax, Cmax/D, AUC0-168 and AUC0-168/D in Maternal Monkey Serum

Dose Level* (mg/kg)	Interval	Cmax (µg/mL)	Cmax/D [(µg/mL)/(mg/kg)]	AUC0-168 (h·µg/mL)	AUC0-168/D [(h·µg/mL)/(mg/kg)]
10 mg/kg weekly/ 3 mg/kg biweekly (Group 2)	GD 20	225	22.5	23800	2380
	GD 146	90.1	30.0	10500	3510
100 mg/kg weekly/ 20 mg/kg biweekly (Group 3)	GD 20	2400	24.0	250000	2500
	GD 146	733	36.6	77900	3900

Notes: Group 2 animals were dosed 10 mg/kg weekly through GD 48, then 3 mg/kg bi-weekly starting on GD 62.
Group 3 animals were dosed 100 mg/kg weekly through GD 48, then 20 mg/kg bi-weekly starting on GD 62.

ADA

ADA analysis was conducted for samples taken on GD20, GD48, GD76, GD118, GD146, LacD28, LacD91, and LacD180. The non-GLP assay was not validated. ADA were observed in 9 LD and 5 HD animals. Four of the LD animals showed neutralizing ADAs beginning on GD48, and their offspring did not show ofatumumab exposures on PND28. ADAs in the other females did not show an effect on exposure.

Formulation Analysis

Ofatumumab was not detected in the control formulations. Concentration analysis of the dosing formulations from GD20, GD76, and GD146 were 96.3% to 98.8% of the nominal concentration.

F_1 Generation

The maternal animals were dosed with ofatumumab until the birth of the infants (i.e., the offspring were not directly dosed with ofatumumab).

Survival

Infant survival was reduced in the HD group. See the Sponsor's summary Table 4.5.1, below.

4.5.1 Infant Survival

Study Group	Control	10/3 mg/kg	100/20 mg/kg
Prenatal Loss	2	4	1
Still Birth	0	1	0
Infant Loss Between PND 0 and 181	2	0	6
Surviving Infants on PND 181	10	9	7

A total of 10 control, 9 LD, and 7 HD infants survived until PND180. The Sponsor noted that “intra-alveolar squames was noted in the lung, indicating intrauterine respiration of amniotic fluid due to stress (unspecific)” in all infants that were delivered early. In HD infants, there were 6 early deaths between PND0 and PND180; of these deaths, three were considered “accidental” (i.e., not drug-related).

One male infant was euthanized on PND1, following injury by the adult female (considered COD); this animal also showed markedly reduced thymus size (no histological correlate), minimal extramedullary hematopoiesis in the liver, and agonal congestion/ hemorrhage in the brain. A female infant was delivered early (GD140) and found dead on PND1; no COD was determined, but markedly reduced thymic size was noted. Another male infant was found dead on PND37 with maternal injuries (considered COD); markedly reduced thymic size (correlating histologically with moderate atrophy), reduced RBC mass, and slight pigment deposition in the red pulp of the spleen were also observed.

The three remaining HD infant deaths occurred between PND1 and PND12; the Sponsor attributed these deaths to infection secondary to the pharmacologically-induced immune modulation, based on the histopathological findings. Descriptions of these early mortalities are provided below.

> One male infant was born early (GD143) and euthanized on PND1. On the day of birth, this infant showed an overall weak appearance, was hypoactive, showed panting respiration and a painful abdomen on palpation, and had no measurable body temperature; it was refused by the maternal female. Bilateral hematoma was observed in in the frontal lobes of the brain (correlating microscopically with moderate hemorrhage in the meninges and the cerebral cortex). Markedly reduced thymic size (without histologic correlate) was observed. Acute, locally-extensive, moderate alveolar inflammation was observed in the lung. Moderate intratubular eosinophilic granules in the kidneys and minimal extramedullary hematopoiesis in the liver were also observed. The COD was considered accidental by the pathologist, but the Sponsor highlighted the pulmonary inflammation.

> One female infant was found dead on PND4. Both the thymus and the spleen were markedly reduced in size, correlating microscopically with marked thymic atrophy and moderate, diffuse splenic atrophy of the white and red pulp, respectively. In the heart, the ductus arteriosus was not completely closed. Moderate bilateral necrosis was observed in the adrenal medulla, with moderate infiltration of inflammatory cells (mainly neutrophils) and slight hemorrhage. Moderate, diffuse hepatocellular vacuolation was also observed. Minimal multifocal tubular degeneration with protein and cellular casts was observed in the kidneys. Partial autolysis limited assessment of the GI tract. The COD was considered undetermined by the pathologist; the Sponsor highlighted the acute, bilateral adrenal lesions.

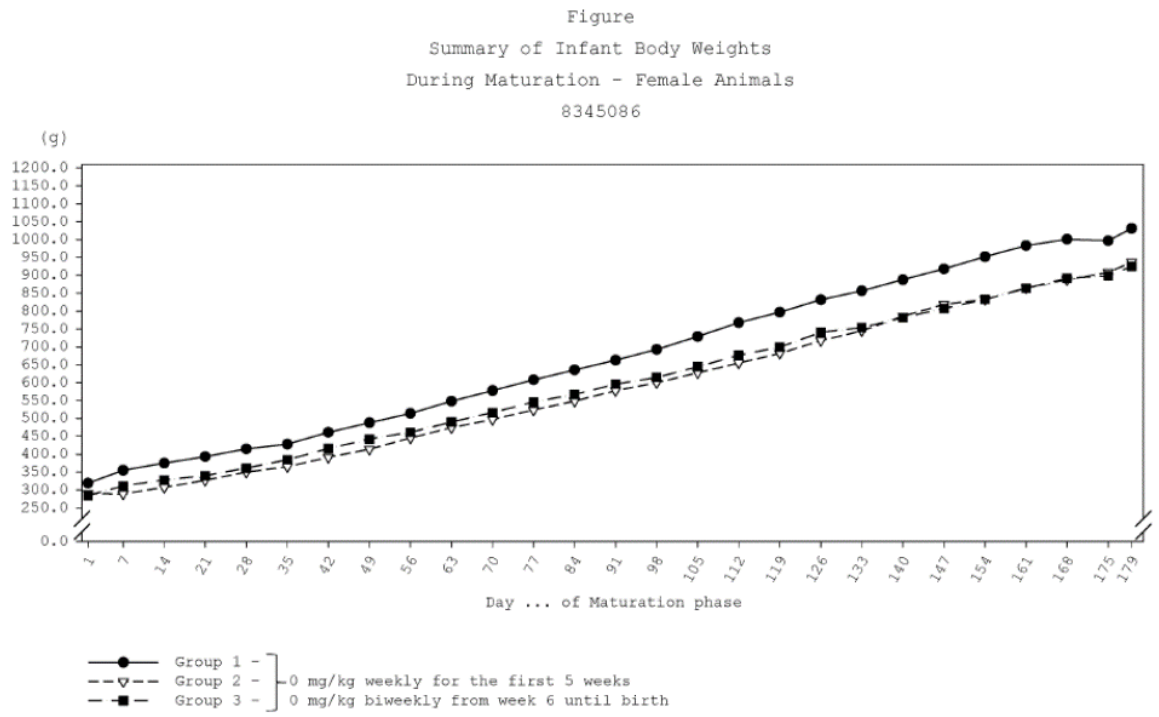
One male infant was euthanized on PND12 after being found in a lying position, jaundiced, and without a measurable body temperature. Yellow discoloration and minimal scaling of the skin were observed, correlating microscopically with slight focal epidermal hyperplasia and hyperkeratosis with focal infiltration of inflammatory cells. Markedly increased ALT, AST, GLDH, ALP, and total bilirubin were observed, with coagulopathy (i.e., increased prothrombin and partial thromboplastin times and decreased fibrinogen concentration). Markedly reduced thymic size was observed (not available at histology). In the liver, the following were observed: moderate, diffuse hepatocellular degeneration/necrosis; slight multifocal regeneration; slight, multifocal increased cellularity of mononuclear inflammatory cells in the portal tracts; and minimal, multifocal extramedullary hematopoiesis. Additionally, an acute, focal area of slight necrosis was observed in the myocardium of the heart, with slight infiltration of inflammatory cells (mainly neutrophils). Minimal focal hyaline deposit was observed in the kidney, and slightly increased cellularity of lymphoid cells was observed in the mesenteric lymph node. The COD was considered undetermined by the pathologist, but the hepatic findings were highlighted by the Sponsor.

Clinical Signs

Several infants were reported to show short episodes of vomiting. One HD infant was administered glucose and saline solution subcutaneously for body weight loss on PND49 and received supplemental food through PND180.

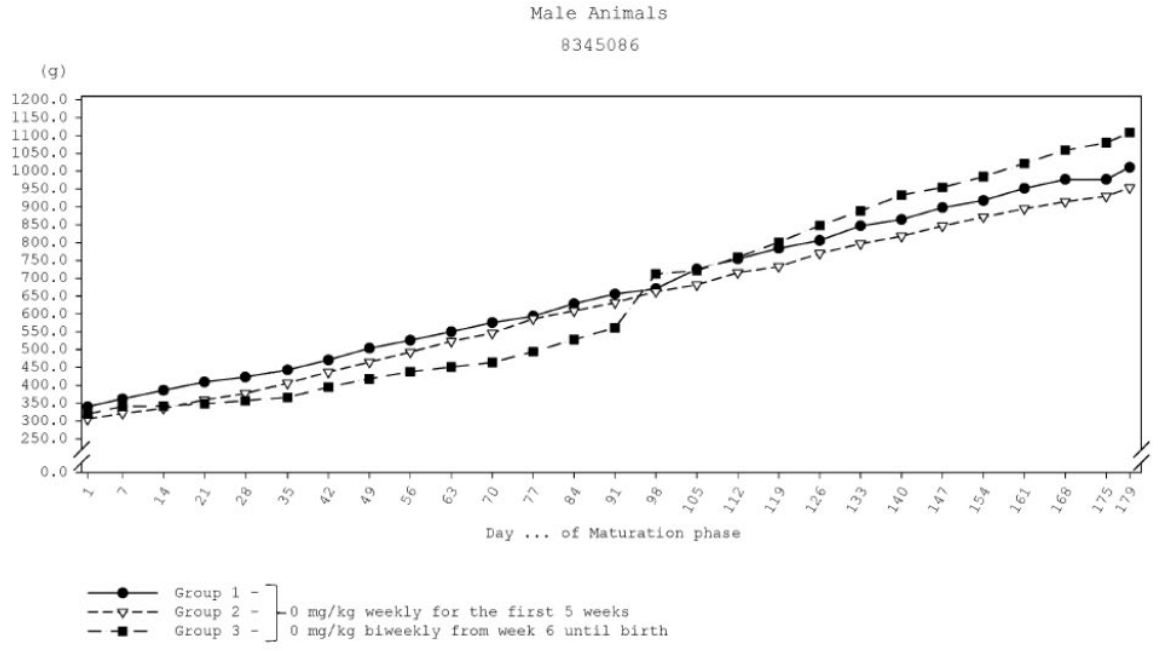
Body weight

At birth, mean body weights of the LD and HD infants were slightly reduced (approximately 10%) compared to those of the control group infants. During the first 7 days after birth, the LD female infants showed reduced mean body weights compared to the control group (i.e., PND1 to PND7: LDF infants: 290 ± 24.7 to 289 ± 27.6 g; control female infants: 319 ± 63.4 to 355 ± 37.7 g). The Sponsor's figure (below) shows a slight but persistent reduction in mean body weight (approximately 10-15%) for the female infants of the LD and HD groups. Overall body weight gains (i.e., PND1-PND179) were reduced 6% in the LD female infants and 8% in the HD female infants.



Mean body weights in the LD and HD male infants were also slightly reduced compared to controls at the beginning of the observation period (see the Sponsor's Figure 8.3, below). Interpretation of the data was complicated by the removal of several animals from the calculation dataset for various reasons (e.g., euthanasia, hand-feeding). Note that the observed change in the HD mean at PND98 is related to removal of an animal from the calculation (resulting in a group size of 1 for the remaining measures).

Figure 8.3: Group Mean Infant Body Weights – During Maturation



Morphological Exams

Exams (including head circumference, distance between the eyes, crown-rump length, crown-heel length, tail length, thorax circumference, length of right arm, length of left arm, length of right leg, length of left leg, and ano-genital distance) were conducted on PND1, PND21, PND56, PND84, and PND168. Generally, 4 to 6 infants per sex were assessed for each group; however, only 2 to 4 male infants were available for assessment in the HD group (because of early mortality). This is a limitation of the study; however, no clearly drug-related differences were observed.

Neurobehavioral Assessment

A neurobehavioral test battery was performed on PND1 and PND7, consisting of three parts:

Part 1- general examination in the cage and in the hand.
Part 2- postural tonus, dorsiflexion, grasp support, righting reflex, prone progression, clasp support, and buildup.
Part 3- following of the eyes, lip smack orientation, sucking, rooting, snout reflex, nystagmus, and moro (pupil response and glabellar tap) reflex.

Generally, 4 to 6 infants per sex per group were available for assessment. No learning and memory assessment was conducted; this was a limitation of the study. The LD and HD male infants showed slight deficiencies on the prone progression test on PND1 and PND7. Generally, the LD and HD infants were slightly more reactive on the buildup test.

Grip Strength

Grip strength was tested on PND28. Few animals were available for assessment (i.e., 3-5 infants/sex/group). Grip strength was not clearly affected.

Skeletal and bone mineral assessment

Skeletal development was evaluated by x-ray on PND35 (±2 days). Bone mineral density (BMD) and bone mineral content (BMC) were measured on PND100 (±2 days) by DEXA scan of the lumbar spine (vertebra L2 through L5).

Skeletal x-rays were conducted on 10 control, 9 LD, and 7 HD infants. DEXA data were presented for 4 or 5 infants per sex in each group except HDM (N=2). BMD and BMC were reduced in 2 LDM infants (group mean 0.167 g/cm^2 compared to 0.274 g/cm^2), compared to controls; these were reduced up to 80% in the most affected animal. One HDF infant (P0214-1) showed markedly reduced (approximately 70%) BMD and BMC, compared to controls. The Sponsor reported no drug-related findings.

Clinical Pathology

Blood samples were taken for hematology (PND28, PND63, PND91, PND119, and PND180), coagulation (PND56, PND84, PND112, and PND175), and clinical chemistry (PND70 and PND175) evaluations. Data for three animals were not available because

of errors. Additionally, IgG, IgM, and IgA were evaluated for 2 to 5 infants/sex/group. Interpretation was complicated by variability and the small number of animals per group.

WBC counts were reduced (approximately 40% compared to controls) in the HD male infants on PND28, PND63, and PND91. Lymphocyte counts were reduced in the LD male infants (25%) on PND21 and in the HD male infants (30-50%) on PND28, PND63, PND91, and PND119. Although the data were variable, eosinophil counts appeared increased in the HD male infants (1.8-2.8-fold), the LD female infants (2.1-2.3-fold), and the HD female infants (1.2-2.2-fold) during the maturation period. Neutrophil counts were increased (~80%) in the LD male infants. The clinical pathologist reported that two infants in the LD group showed minimal to mild reductions in red cell parameters but attributed the observation to the sampling procedure. Reductions in ALP (30-45%) and globulins (~20%) were observed in the HD male infants on PND70 and PND175.

Generally, reductions in immunoglobulins were reduced in the HD infants. IgG was reduced in the HD infants on PND70 (the means for males/females were BLOQ/1.10 g/L in the HD, compared to 2.67/3.09 g/L in the controls); on PND175, IgG was similar to controls in male infants but remained reduced (i.e., approximately 37% of the control value) in female infants. IgM appeared reduced in the HD female infants on PND70 but was not clearly affected on PND175. IgA was reduced approximately 50% on PND175 in the HD male infants.

Anatomical Pathology

Terminal organ weights and macroscopic and microscopic tissue evaluations were conducted for 5, 5, and 2 males and 5, 4, and 5 females in the control, LD, and HD groups, respectively. Assessments were also conducted for the infants that died early (see details for each of those animals under **Survival**).

Organ Weights

In the HD male infants, adrenal (approximately 40%) and testis (40-50%) weights were increased and spleen weight was reduced (20-25%), compared to controls. In the HD female infants, thymus weight was increased (approximately 24%) and spleen weight was reduced (approximately 35%). Liver weight was slightly reduced (approximately 20%) in the LD female infants.

Macroscopic Pathology

Clearly drug-related changes were not observed. Inguinal lymph node enlargement was observed in one HD male infant.

Histopathology

No clearly drug-related findings were reported.

A marked ovarian cyst was observed in one HD female infant (also minimal in one LD female infant). A few observations suggesting inflammatory or immune changes were observed. Slight to moderate increased lymphoid cellularity of the inguinal or mesenteric lymph nodes was observed in two HD male infants. In the stomach, slightly

increased lymphoid follicles were observed in one HD female infant and moderate chronic inflammation was observed in one HD male infant. Slight mononuclear cell infiltrates in the brain were observed in one HD female infant. Overall, minimal to slight mononuclear and/or inflammatory cells were observed sporadically in several tissues, including heart, kidney, brain, liver, lung, salivary gland, skeletal muscle, and GI tract.

Immunophenotyping

Blood samples were taken on PND28, PND63, PND91, PND119, and PND180. Few animals were assessed; three to five infants/sex/group were evaluated. Generally, CD20+ B cells were depleted or reduced in the HD male and female infants and were initially reduced in the LD male and female infants (showing recovery, or rebound, by PND63). See the Sponsor's summary data tables, below.

CD20+ B-cells absolute (10E9/L) and % of Lymphocytes

Group/ Sex		Phase: Maturation; Day: 28 (10E9/L)	28 (%)	63 (10E9/L)	63 (%)	91 (10E9/L)	91 (%)	119 (10E9/L)	119 (%)	180 (10E9/L)	180 (%)
1/M	Mean	3.83	37.10	4.79	38.56	4.99	40.75	5.71	37.48	3.30	35.10
	SD	1.41	7.71	2.84	9.93	2.46	17.42	4.63	18.54	1.84	15.40
	N	5	5	5	5	5	5	5	5	5	5
2/M	Mean	1.24 *	15.48	5.09	35.59	6.38	38.88	6.14	37.63	4.30	33.67
	SD	1.92	20.92	1.53	8.23	2.96	13.17	1.23	10.69	2.40	9.34
	N	5	5	5	5	5	5	5	5	5	5
3/M	Mean	0.00 *	0.00 **	0.02	0.44	1.52	18.09	3.00	31.43	1.73	38.96
	SD	0.00	0.01	-	-	-	-	-	-	-	-
	N	3	3	2	2	2	2	2	2	2	2
	Statistics	A	AT	A	A	A	A	A	A	A	A

Standard deviation not calculated for less than three values

A = ANOVA and Dunnett's
T = Rank-transformed data

* P≤ 0.05
** P≤ 0.01
*** P≤ 0.001

CD20+ B-cells absolute (10E9/L) and % of Lymphocytes

Group/ Sex		Phase: Maturation; Day: 28 (10E9/L)	28 (%)	63 (10E9/L)	63 (%)	91 (10E9/L)	91 (%)	119 (10E9/L)	119 (%)	180 (10E9/L)	180 (%)
1/F	Mean	3.00	31.61	2.98	31.94	3.60	29.65	3.44	30.23	2.56	26.45
	SD	1.32	10.41	0.57	4.94	1.07	9.32	0.82	8.16	1.11	9.25
	N	5	5	5	5	5	5	5	5	5	5
2/F	Mean	1.29	15.07	5.17	36.48	6.24	35.33	6.10	36.74	3.55	28.85
	SD	1.56	17.86	2.98	10.50	3.39	7.74	2.51	6.90	1.79	10.82
	N	4	4	4	4	4	4	4	4	4	4
3/F	Mean	0.00 ***	0.00 ***	0.00 **	0.00 **	0.01 **	0.04 **	1.42 **	10.32 **	2.74	22.63
	SD	0.00	0.00	0.00	0.00	0.01	0.06	0.95	7.23	0.83	1.41
	N	5	5	5	5	5	5	5	5	5	5
	Statistics	AT	AT	AT	AT	AT	AT	AT	A	A	AT

Standard deviation not calculated for less than three values

A = ANOVA and Dunnett's
T = Rank-transformed data

* P≤ 0.05
** P≤ 0.01
*** P≤ 0.001

CD3+ T cells and CD3+CD4+ T-helper cells were increased in the HD female infants (see the Sponsor's summary tables, below). CD3+CD8+ cytotoxic T cells tended to be slightly reduced in HD male infants. Otherwise, clearly drug-related effects on CD3+ T cells (males), CD3+CD4+ T-helper cells (males), CD16+ NK cells, and CD14+ monocytes were not observed.

CD3+ T-cells absolute (10E9/L) and % of Lymphocytes

Group/ Sex		Phase: Maturation; Day: 28 (10E9/L)	28 (%)	63 (10E9/L)	63 (%)	91 (10E9/L)	91 (%)	119 (10E9/L)	119 (%)	180 (10E9/L)	180 (%)
1/F	Mean	5.62	58.73	5.87	60.59	7.96	63.36	7.55	62.69	6.13	63.19
	SD	2.47	13.01	2.26	5.70	2.38	8.20	3.13	7.58	1.40	7.91
	N	5	5	5	5	5	5	5	5	5	5
2/F	Mean	4.96	71.05	7.00	55.01	9.87	55.66	8.61	53.51	7.28	59.46
	SD	1.36	16.78	1.77	8.62	5.57	6.33	2.78	5.47	2.74	9.43
	N	4	4	4	4	4	4	4	4	4	4
3/F	Mean	9.64 *	92.94 **	10.13 *	94.33 ***	12.45	94.47 ***	12.19	83.67 ***	8.60	71.90
	SD	2.81	3.35	2.64	1.86	3.27	2.22	3.78	6.67	2.32	2.74
	N	5	5	5	5	5	5	5	5	5	5
	Statistics	A	A	A	A	A	A	A	A	A	A

Standard deviation not calculated for less than three values

A = ANOVA and Dunnett's

* P≤ 0.05
** P≤ 0.01
*** P≤ 0.001

CD3+CD4+ T-helper-cells absolute (10E9/L) and % of Lymphocytes

Group/ Sex		Phase: Maturation; Day: 28 (10E9/L)	28 (%)	63 (10E9/L)	63 (%)	91 (10E9/L)	91 (%)	119 (10E9/L)	119 (%)	180 (10E9/L)	180 (%)
1/F	Mean	4.35	45.56	4.37	45.05	5.73	45.63	5.20	42.84	3.97	41.23
	SD	1.97	10.95	1.78	6.05	1.95	8.26	2.51	8.94	1.19	10.01
	N	5	5	5	5	5	5	5	5	5	5
2/F	Mean	3.97	57.33	5.27	41.51	6.07	36.28	5.37	33.93	4.53	37.85
	SD	1.14	15.99	1.40	7.61	2.60	10.09	1.59	7.60	1.45	9.79
	N	4	4	4	4	4	4	4	4	4	4
3/F	Mean	7.42 *	71.41 **	7.43 *	69.49 ***	8.94	67.93 **	8.35	57.82 *	5.74	48.08
	SD	2.22	5.18	1.80	5.79	2.32	1.61	2.35	7.62	1.67	5.39
	N	5	5	5	5	5	5	5	5	5	5
	Statistics	A	A	A	A	A	AT	A	A	A	A

Standard deviation not calculated for less than three values

A = ANOVA and Dunnett's
T = Rank-transformed data

* P≤ 0.05
** P≤ 0.01
*** P≤ 0.001

TDAR

A T Cell-Dependent Antibody Response (TDAR) assay was conducted; four to five animals/sex/group were assessed, except 2 males were assessed for the HD group. The levels of anti-Keyhole limpet hemocyanin (KLH) IgG and anti-KLH IgM were measured in serum from infants immunized with KLH on PND119 and PND147. Serum samples were obtained prior to and 14, 21, and 28 days after KLH injection to assess primary and recall (memory) responses. Generally, the humoral immune responses of the infants were highly variable.

After the first KLH immunization on PND119, an IgM response was observed shortly after immunization followed by an IgG response peaking between 2 to 3 weeks after immunization in controls. The Sponsor stated that the ofatumumab-exposed infants with the lowest B-cell levels on PND91 showed reduced IgG and IgM levels, compared to controls. In males, only one of 2 infants of the HD group showed an IgM response (which was delayed and reduced, approximately 35% of the control average), and the IgG response was slightly delayed. In females, there was no IgM response to the first KLH injection in the HD group (also no IgM response in one female of the LD group), and the IgG response was both delayed and reduced (i.e., IgG peaked 3 weeks after immunization at approximately 21% of the control group mean). The Sponsor attributed

the reduced response in females of the HD group to reduced B-cell counts. See the Sponsor's tables, below.

After the second KLH immunization on PND147, only one of 2 HD male infants showed an IgM response (which was reduced, approximately 25% of the control average), but IgG responses similar to controls were observed. In females of the HD group, there was a clear IgM response, but the IgG response remained reduced (approximately 22% of the control group average). See the Sponsor's summary tables below.

Table 6.6: Summary of Anti-KLH IgM Data - Males

Summary of KLH IgM (Male)

Test Item	(dosage)	1	2	3
OMB157	mg/kg weekly for the first 5 weeks	0	10	100
OMB157	mg/kg biweekly from week 6 until birth	0	3	20

Group/ Sex	Phase / Day	KLHM Maturation 112	133	140	161	168	175
1/M	Mean	125	866	324	1169	291	295
	SD	55.5	628.0	139.7	844.2	185.2	185.8
	N	5	5	5	5	5	5
2/M	Mean	100	773	656	926	446	257
	SD	0.0	551.1	735.1	1004.1	427.7	204.7
	N	5	5	5	5	5	5
3/M	Mean	100	114	201	193	167	142
	SD	0.0	19.8	142.1	131.5	33.9	59.4
	N	2	2	2	2	2	2
	Statistics	X1	A	A	A	AT	A

X1 = No analysis required
A = ANOVA and Dunnett's
T = Rank-transformed data

Table 6.7: Summary of Anti-KLH IgM Data - Females

Summary of KLH IgM (Female)

Test Item	(dosage)	1	2	3
OMB157	mg/kg weekly for the first 5 weeks	0	10	100
OMB157	mg/kg biweekly from week 6 until birth	0	3	20

Group/ Sex	Phase / Day	KLHM Maturation 112	133	140	161	168	175
1/F	Mean	100	626	198	254	181	165
	SD	0.0	548.2	152.1	163.5	150.8	100.3
	N	5	5	5	5	5	5
2/F	Mean	100	727	636	595	293	282
	SD	0.0	918.5	689.2	617.0	211.2	145.7
	N	4	4	4	4	4	4
3/F	Mean	100	100**	100	546	229	136
	SD	0.0	0.0	0.0	647.9	161.6	81.4
	N	5	5	5	5	5	5
	Statistics	X1	AT	AT	A	A	A

* P<=0.05
** P<=0.01
*** P<=0.001
T = Rank-transformed data
X1 = No analysis required
A = ANOVA and Dunnett's

Table 6.4: Summary of Anti-KLH IgG Data - Males

Summary of KLH IgG (Male)

Test Item	(dosage)	1	2	3
OMB157	mg/kg weekly for the first 5 weeks	0	10	100
OMB157	mg/kg biweekly from week 6 until birth	0	3	20

Group/ Sex	Phase Day	KLHG Maturation 112	133	140	161	168	175
1/M	Mean	100	3307	3334	42575	30543	32955
	SD	0.0	4160.9	3582.4	19193.2	16940.7	23272.3
	N	5	5	5	5	5	5
2/M	Mean	100	1953	5607	53438	41321	20989
	SD	0.0	491.7	3914.8	29260.3	21701.6	19621.5
	N	5	5	5	5	5	5
3/M	Mean	107	1514	5651	54153	51188	39803
	SD	9.2	213.5	4642.9	5612.3	4839.4	5631.4
	N	2	2	2	2	2	2
	Statistics	X1	A	A	A	A	A

X1 = No analysis required
A = ANOVA and Dunnett's

Table 6.5: Summary of Anti-KLH IgG Data - Females

Summary of KLH IgG (Female)

Test Item	(dosage)	1	2	3
OMB157	mg/kg weekly for the first 5 weeks	0	10	100
OMB157	mg/kg biweekly from week 6 until birth	0	3	20

Group/ Sex	Phase Day	KLHG Maturation 112	133	140	161	168	175
1/F	Mean	100	2424	2867	41792	26266	12167
	SD	0.0	1915.8	2624.8	20015.0	16119.3	9984.1
	N	5	5	5	5	5	5
2/F	Mean	100	1591	6130	86470	75849	32119
	SD	0.0	818.8	4207.4	105084.4	79494.3	42299.6
	N	4	4	4	4	4	4
3/F	Mean	100	149***	616	9301	9966	5135
	SD	0.0	107.7	487.2	2622.3	7131.7	3740.7
	N	5	5	5	5	5	5
	Statistics	X1	AT	A	AT	AT	AT

* P<=0.05
** P<=0.01
*** P<=0.001
X1 = No analysis required
A = ANOVA and Dunnett's
T = Rank-transformed data

TK

Ofatumumab was present in the blood of 3 LD infants on PND28 (one until PND63) and in all HD infants until PND63 (males) or PND91 (females). Summary TK data for the infants were not provided (see selected from the Sponsor's Table 9.6, below).

Table 9.6 (Continued): Individual Concentrations (ng/mL) of OMB157 in Infant Monkey Serum: PND 28, 64, 91, 119, and 180 ± 1

Dose Group	Maternal Dose Level (mg/kg)	Animal	Post-Natal Day (PND) PND 28	PND 63	PND 91	PND 119	PND 180 ± 1
2	10/3	P0101-1	3890	< 400	< 400	< 400	< 400
		P0105-1	< 400	< 400	< 400	< 400	< 400
		P0106-1	2020	< 400	< 400	< 400	< 400
		P0107-1	< 400	3740	< 400	< 400	< 400
		P0110-1	< 400	< 400	< 400	< 400	< 400
		P0111-1	< 400	< 400	< 400	< 400	< 400
		P0112-1	< 400	< 400	< 400	< 400	< 400
		P0113-1	< 400	< 400	< 400	< 400	< 400
		P0114-1	1010	< 400	< 400	< 400	< 400

Note: Maternal animals were dosed 10 mg/kg weekly through GD 48, then 3 mg/kg bi-weekly starting on GD 62 through birth.

Table 9.6 (Continued): Individual Concentrations (ng/mL) of OMB157 in Infant Monkey Serum: PND 28, 64, 91, 119, and 180 ± 1

Dose Group	Maternal Dose Level (mg/kg)	Animal	Post-Natal Day (PND) PND 28	PND 63	PND 91	PND 119	PND 180 ± 1
3	100/20	P0201-1	76400	11700	< 400	< 400	< 400
		P0202-1	96600	13900	3060	< 400	< 400
		P0203-1	105000	NS	NS	NS	NS
		P0207-1	51400	456	< 400	< 400	< 400
		P0210-1	118000	14400	2300	< 400	< 400
		P0212-1	14800	7540	411	< 400	< 400
		P0213-1	67200	1330	< 400	< 400	< 400
		P0214-1	124000	45400	10400	< 400	< 400

NS No sample.
Note: Maternal animals were dosed 100 mg/kg weekly through GD 48, then 20 mg/kg bi-weekly starting on GD 62 through birth.

ADA

Blood samples for ADA were taken on PND180. ADAs were observed in 7 LD infants but were not observed in the HD infants. The assay was positive for one control group infant.

Overall, a no-effect dose was not identified for the study, based on birth weight reductions (that persisted into maturation in females), B-cell reductions, and immune effects. However, at the HD, clearly adverse effects (i.e., increased postnatal mortality and persistent adverse immune effects) were observed.

11 Integrated Summary and Safety Evaluation

Ofatumumab is a fully humanized IgG1 kappa monoclonal antibody directed at the human CD20 cell surface antigen. CD20 is expressed on B cells during differentiation and maturation and has also been reported on certain subsets of T cells. Ofatumumab binds human CD20 with high affinity and specificity and results in lysis of CD20+ B cells, presumably by inducing antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Ofatumumab was shown to bind human as well as cynomolgus and rhesus monkey CD20, but not CD20 of other species; therefore, cynomolgus monkey was used for toxicology testing.

Ofatumumab (for IV administration, as Arzerra) was previously approved for the treatment of chronic lymphocytic leukemia in 2009. To support the initial BLA, several repeat dose toxicity studies were conducted in cynomolgus monkeys, up to 7 months' duration (see BLA 125326 nonclinical review by Dr. McDougal, dated 8/10/2009).

In the 7-month repeated dose study (Study CD2008/01521/00), cynomolgus monkeys (3/sex/dose main study + 4/sex/dose recovery) were administered 0, 20, or 100 mg/kg ofatumumab weekly for 8 weeks, then monthly for 5 months. Both doses of ofatumumab were reported to saturate the receptor. Mortality occurred at both the LD and the HD. Three deaths (two LD and 1 HD) were attributed to infection, which was considered indirectly drug-related and relevant to patient safety. Two deaths were attributed to hemolytic anemia, which was considered indirectly related to drug and of uncertain relevance to human risk. Reductions in RBC parameters were observed in the ofatumumab-dosed animals beginning on Day 50 and continuing throughout the recovery period. Blood flow cytometry showed marked CD20+ B-cell depletion, with recovery of circulating B cells generally beginning on Day 246 (in the LD group) or Day 284/ Day 302 (in the HD group; females/males) followed by a rebound between Day 330 and Day 350/3, and returning to baseline by Day 372 (i.e., approximately 6 months after the last dose). Marked B-cell depletion was also observed in the lymph nodes (LN). Histologically, minimal to moderate lymphoid atrophy, lymphoid depletion, and follicular atrophy was observed in the LN, Peyer's patches (ileum), and spleen. Signs of inflammatory cell infiltration were observed in several tissues and continued to be observed at the end of the recovery period. Reduced humoral immune responses were observed during the dosing period in the HD group and in both ofatumumab-dosed groups during the recovery period. Overall, a NOAEL for the 7-month repeated dose study was not identified, based on the observed mortalities attributed to infection and hemolytic anemia (considered a potential humoral immune response to drug). The following were identified as clinically-relevant risks: increased risk of infection, infusion-reaction/cytokine response, delayed onset anemia, fetal toxicity (i.e., decreased placental, fetal spleen, and fetal thymus weights), and clinical chemistry alterations (i.e., increased lactate dehydrogenase, increased C-reactive protein). These remain potential risks, although the risk may be lower considering the lower dose given by the SC route of administration in the treatment of RMS.

The Sponsor indicated that a SC formulation of ofatumumab was developed because the potency at the target (i.e., CD20) allowed efficacy at a relatively low dose that could be administered in a small volume (i.e., 20 mg in 0.4 mL).

The change from IV to SC administration in the Phase 2 and 3 clinical studies was supported by a 2-dose SC administration study with a 33-week recovery period in female cynomolgus monkeys. Monkeys (6 females/group in the LD and HD groups; 4 females/group for the control group) were administered 0, 20, or 100 mg/kg ofatumumab SC or 100 mg/kg IV on Days 1 and 15. CD20+ B cells were depleted, and CD40+ B cells were markedly reduced, in the ofatumumab-dosed groups. Recovery of CD20+ and CD40+ B cells occurred earliest in the LD SC group, followed by the HD SC group and the IV group. During the dosing period, eosinophils were increased in the SC administration groups (LD > HD), and slight RBC reductions were observed in the HD SC and IV groups. During the recovery period, WBC were reduced in the LD SC group but were increased in the groups given 100 mg/kg SC or IV. ADA developed in the SC-dosed groups, and an effect of ADA on TK was observed in the LD SC group. Microscopic changes included extramedullary hematopoiesis in the lymph nodes and inflammatory and fibrotic changes at the injection site. Overall, the treatment duration was shorter than that generally requested in a bridging toxicity study for a chronic indication, but the expected pharmacodynamic effects were observed well into the recovery period. Use of a single sex and minimally adequate numbers of animals in the main study groups (i.e., 3 females/group in the drug-dosed main study groups) were limitations of the study. The study design primarily addressed local toxicity, with a limited list of tissues assessed microscopically (a separate pathology report was not provided). Although the study suffers from limitations, the study supported the use of SC dosing in the clinical program.

Fertility and enhanced pre- and postnatal development studies were submitted to support the sBLA, given the population and chronic dosing regimen for the RMS indication. An EFD study was previously submitted to support the original BLA. The nonclinical review of the original BLA (see review by Dr. McDougal, dated 8/10/2009) noted that the majority of the animals used in the toxicology studies had been sexually immature; therefore, a reliable assessment of potential toxicity to reproductive tissues could not be obtained in those studies.

In the IV fertility study, cynomolgus monkeys (4/sex/group in the main study and 2/sex/group recovery) were administered ofatumumab (0, 10/3 mg/kg, or 100/20 mg/kg) for approximately 3 months. The initial dose (10 or 100 mg/kg) was given weekly for 5 weeks (i.e., Days 1, 8, 15, 22 and 29) followed by a maintenance dose (3 or 20 mg/kg) given once every 2 weeks (i.e., Days 43, 57, 71 and 85). The main study animals were necropsied on Day 92, and the recovery animals were necropsied on Day 148. Marked CD20+ B-cell depletion was observed at both doses. After 8 weeks of recovery, circulating B cells remained depleted at the HD and showed only partial recovery at the LD. Dose-dependent decreased cellularity of the lymphoid follicles and absence/reduction of germinal centers were observed in the spleen and lymph nodes. By immunohistochemistry, CD20+ cells were depleted in the examined tissues,

including the spleen, LN, GALT, and thymus; dose-dependent reductions of CD3+ cells were also observed in most of these tissues (although this was considered secondary to the reduction in germinal centers reflecting the marked reductions in CD20+ cells). Clearly drug-related alterations in female reproductive tissues were not observed. There was some evidence for an effect in HD males (e.g., apparent, although highly variable, increases in total sperm alterations compared to controls and one HDM showing bilateral moderate testicular depletion/degeneration of germ cells); however, several measures such as testicular volume were not clearly affected. ADA were observed at both doses, but with greater incidence at the LD; neutralizing ADA were observed in 4 of 6 LDM and 1 of 6 LDF by Day 22/Day 57. The NOAEL/LOAEL (F/M) for reproductive effects was the HD.

In the ePPND study, groups of 14 pregnant females were administered ofatumumab (0, 10/3, or 100/20 mg/kg IV) from GD20 until birth. The initial dose (0, 10, or 100 mg/kg) was administered weekly for 5 weeks followed by maintenance doses (0, 3, or 20 mg/kg) administered once every 2 weeks beginning on GD 62. Maternal ofatumumab administration was stopped at birth, and the maternal animals and infants were followed for a 6-month observation period (i.e., LacD/PND180). One HD maternal animal was euthanized on LacD96 in moribund condition with reduced red cell mass, markedly reduced B and T cells, and severe bilateral glomerulonephropathy; this finding was believed to be ADA-mediated based on the presence of ADA in the blood on GD138 and subendothelial IgM deposits in an acutely inflamed renal vessel. In the LD maternal animals, slightly reduced red cell mass was observed on GD118 and LacD28 compared to controls, and increased prenatal loss was suggested (i.e., 28.6% compared to 14.3% in controls). CD20+ B cells were depleted in the blood of the maternal animals as well as their infants. In the maternal animals, repletion of CD20+ cells occurred by approximately LacD91 in the LD group and approximately LacD175 in the HD group, except for early repletion in 4 of 14 LD maternal animals that developed neutralizing ADA (i.e., ofatumumab was not detected beginning on GD48, and infants of these females did not show B-cell depletion). In total, 9 LD and 5 HD maternal animals developed ADA.

Infant survival was reduced at the HD in the ePPND study; the early postnatal deaths were attributed to accidents (i.e., not considered drug-related) and secondary infection (i.e., drug-related). Birth weights were slightly reduced in infants of the ofatumumab-dosed maternal animals and persisted in female infants during the observation period. IgG levels were reduced in the HD infants on PND70, recovering in males by PND175 but remaining reduced in females. Ofatumumab exposures were present in only three LD infants (until PND28 or PND63) but were observed in all HD infants until PND63 (males) or PND91 (females); seven LD infants (and no HD infants) showed ADA. In the infants of maternal animals showing persistent ofatumumab exposures, CD20+ B-cell repletion was observed beginning on PND63 in the LD infants and on PND91/119 (M/F) in the HD infants. CD3+ and CD3+CD4+ T cells were increased in female HD infants from PND28 to PND119. In the TDAR assay conducted, IgM responses were reduced after the first and second KLH administration in the HD male infants and were absent in HD female infants after the first immunization. IgG responses were reduced and

delayed in the HD female infants after the first immunization and remained reduced in the HD female infants after the second KLH administration. A no-effect level was not identified for the study, based on CD20+ B-cell depletion and reduced birth weights (that persisted into maturation in female infants); the LD is considered a LOAEL. Increased postnatal mortality and adverse immune alterations that resulted in persistent functional effects were observed in the HD infants.

Comparisons to human exposures at the proposed RHD

The Sponsor reported that monthly SC doses of 20 mg after the initial "loading dose regimen" produced a steady state mean AUC_{tau} of 483 mcg·hr/mL and a mean C_{max} of 1.425 mcg/mL. See the Sponsor's Table 4-3, below, comparing the exposures at the sponsor's NOAELs in the nonclinical studies and human exposures at "steady state" following monthly SC doses of 20 mg ofatumumab. It is noted that although the sponsor identified 100 mg/kg IV as the NOAEL for the 7-month study, a clear NOAEL was not identified for that study (based on mortalities at both doses, which were attributed to infection [which was considered relevant to patient safety but an extension of the pharmacology and monitorable] and hemolytic anemia [which was considered of unclear relevance to human risk because it potentially represented a humoral immune response to drug that would be of limited predictivity to humans]). For the fertility study, the HD (i.e., 100 mg/kg / 20 mg/kg) is considered a NOAEL/LOAEL for females and males. For the ePPND study, the LD (i.e., 10 mg/kg / 3 mg/kg) is considered the LOAEL, based on increased postnatal mortality and persistent adverse immune effects at the HD (i.e., 100 mg/kg / 20 mg/kg).

Table 4-3 Exposure multiples for animal findings based on a 20 mg subcutaneous 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

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)

12 Appendix/Attachments

References

Cline JM et al. (2008) Toxicologic Pathology, 36(7): 142s-163s.
Jarvis P et al (2010) Birth Defects Research (Part B), 89: 175-187.
Rojko JL et al. (2014) Toxicologic Pathology, 42: 725-764.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELISSA K BANKS-MUCKENFUSS
07/09/2020 02:04:42 PM

LOIS M FREED
07/09/2020 02:33:00 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326Orig1s070

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 125326 /S-70
Drug Name:	ofatumumab
Indication(s):	relapsing multiple sclerosis (RMS)
Applicant:	Novartis
Date(s):	Submission date: 12/20/2019
	PDUFA Date: 9/20/2020
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiang Ling, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader
	James Hung, Ph.D., Director
Medical Division:	Division of Neurology 2
Clinical Team:	Lawrence Rodichok, M.D., Clinical reviewer
	Paul Lee, M.D., Clinical Team Leader
Project Manager:	Candido Alicea

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The data overall provide adequate evidence for the efficacy of ofatumumab as treatment of patients with relapsing multiple sclerosis (RMS).

Ofatumumab demonstrated superiority over teriflunomide in lowering MS relapse rate in 2 independent, well-controlled trials. In Study G2301, ofatumumab compared with teriflunomide significantly reduced the annualized relapse rate (ARR: 0.11 vs 0.22) by 50.5% ($p<0.001$). In Study G2302, ofatumumab compared with teriflunomide significantly reduced the ARR (0.10 vs 0.25) by 58.5% ($p<0.001$). The robustness of the treatment effect was confirmed in all sensitivity and supportive analyses. The treatment effect also appeared consistent across the subgroups.

In both pivotal studies, ofatumumab resulted in statistically significant treatment effect on magnetic resonance imaging (MRI) and Neurofilament light chain (NfL) related key secondary endpoints, except for the rate of brain volume loss.

In the combined data from studies G2301 and G2302, ofatumumab significantly reduced the risk of 3-month confirmed worsening (3mCDW) compared with teriflunomide, with a consistent effect in both studies G2301 and G2302. Ofatumumab also significantly reduced the risk of 6-month confirmed worsening (6mCDW), but the statistical significance was lost when the disability event was assessed independent of relapses. Statistical significance was not achieved for the endpoint of 6-month confirmed improvement (6mCDI), although a positive trend was observed favoring the ofatumumab treatment group compared with the teriflunomide group.

2 INTRODUCTION

2.1 Overview

Ofatumumab intravenous injection was originally approved in 2009 for the treatment of chronic lymphocytic leukemia. Novartis has developed a subcutaneous formulation of ofatumumab for the treatment of patients with relapsing multiple sclerosis (RMS) under IND 111116. The Phase III clinical program comprised two studies of identical design (COMB157 G2301 and COMB157G2302; abbreviated as G2301 and G2302) with a total of 1882 RMS patients. Both studies were randomized, double-blind, double-dummy, active comparator-controlled, parallel-group, multi-center study with variable treatment duration. Eligible patients were randomized in a 1:1 ratio to receive either ofatumumab 20 mg s.c. injections every 4 weeks or teriflunomide 14 mg orally once daily. The maximum treatment duration for an individual patient was 30 study months (approximately 2.5 years). If the primary endpoint (annualized relapse rate) was successful in both studies, the disability-related key secondary endpoints were to be tested based on the combined data from the two studies.

Table 1. Pivotal Studies with Ofatumumab in MS

Study	Objective, population	No. of patients randomized / exposed to study treatment	Treatment dosing regimen	Primary efficacy endpoint
Phase III controlled studies in patients with RMS				
[G2301]	Double-blind, double-dummy, active-comparator controlled, parallel-group, multi-center study evaluating efficacy and safety of ofatumumab vs teriflunomide in patients with RMS (ASCLEPIOS I / ASCLEPIOS II)	927 / 927 Ofatumumab 465 / 465 Teriflunomide 462 / 462	Ofatumumab 20 mg s.c. (PFS) q4w [d] Teriflunomide 14 mg p.o. qd	ARR, defined as the number of confirmed MS relapses in a year
[G2302]		955 / 955 Ofatumumab 481 / 481 Teriflunomide 474 / 474		

ARR=annualized relapse rate; Gd=gadolinium; MS=multiple sclerosis; RMS=relapsing multiple sclerosis; RRMS=relapsing-remitting multiple sclerosis; PFS=pre-filled syringe

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directories: \\CDSESUB1\evsprod\BLA125326\0248 and \\CDSESUB1\evsprod\BLA125326\0264.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Datasets were sufficiently structured and defined, and documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

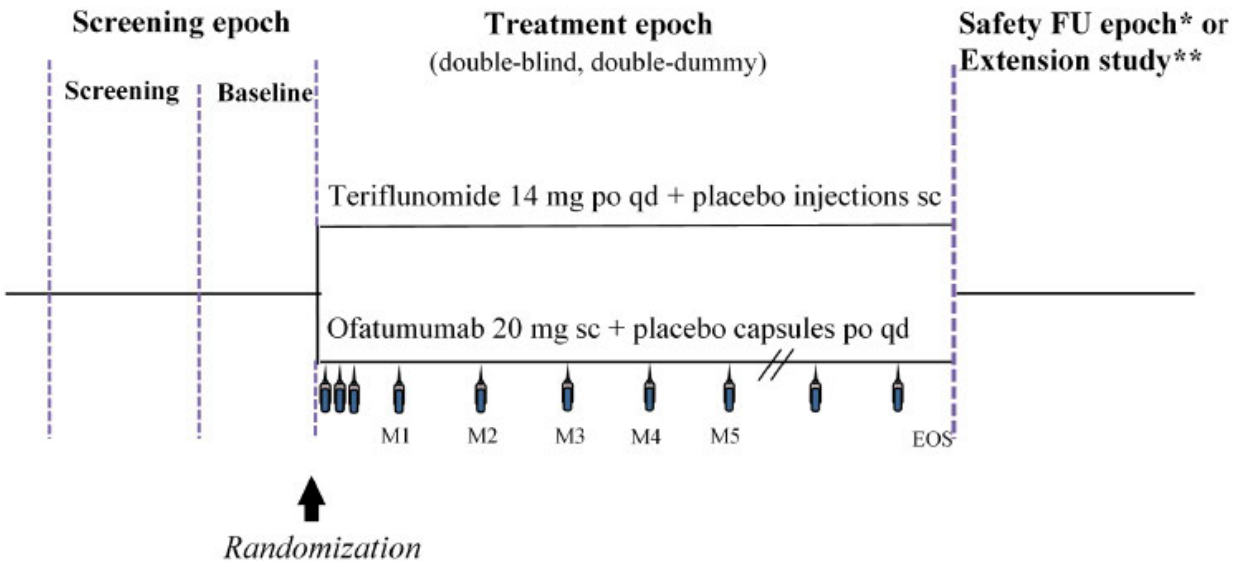
Study G2301 was initiated on September 20, 2016 and completed on July 5, 2019. Study G2302 was initiated on August 26, 2016 and completed on July 10, 2019. Database lock occurred on August 16, 2019. The study protocol was amended 2 times and the last version was dated August 6, 2018 to update the secondary objectives of the study. The original SAP was dated July 15, 2016 and the final SAP was dated October 17, 2019 after database lock to correct B-cell depletion analysis.

Study design

Studies G2301 and G2302 were randomized, double-blind, active comparator-controlled, parallel-group, multi-center studies in 927 patients (G2301) and 955 patients (G2302) with RMS. The studies were of identical design and conducted in parallel. Eligible patients were randomized (1:1) to receive either ofatumumab 20 mg s.c. injections every 4 weeks or teriflunomide 14 mg orally once daily. The randomization was stratified by geographical region and by MS subtype (relapsing-remitting MS, or secondary progressive MS).

The studies consisted of 3 epochs: Screening epoch (including Baseline), Treatment epoch (double-blind), and Safety follow-up epoch. The treatment duration for an individual patient was variable and based on when the End of Study (EOS) criteria were met. The maximal treatment duration for an individual patient was 30 study months (approximately 2.5 years). EOS was declared once sufficient information had been collected (based on blinded data) to ensure 90% power for the primary endpoint in each study individually, and sufficient power for the disability related endpoints (i.e. ≥90% power for 3mCDW and ≥80% power for 6mCDW).

Figure 1. Study design for ofatumumab Phase III clinical program in RMS



EOS=end-of-study; FU=follow-up; M=month

A blinded sample size review (BSSR) was conducted prior to the completion of enrollment to allow the number of randomized patients to be increased to a maximum of 1250 patients in each study. The planned sample size was not increased based on the BSSR.

Efficacy Endpoint

The primary endpoint was the annualized relapse rate (ARR), which was defined as the number of confirmed MS relapses in a year. Relapse confirmation occurred through the assessment of a clinically relevant change in the Expanded Disability Status Scale (EDSS) by an independent EDSS rater.

The key secondary endpoints were the following for each study:

- Number of Gd-enhancing T1 lesions per scan;
- Annualized rate of new or enlarging T2 lesions;
- Neurofilament light chain concentration (NfL) in serum;
- Brain volume loss;

and for pooled studies:

- 3-months confirmed disability worsening (3mCDW);
- 6-months confirmed disability worsening (6mCDW);
- 6-month confirmed disability improvement (6mCDI).

The 3mCDW or 6mCDW was defined as an EDSS increase from baseline sustained for at least 3 or 6 months, respectively. Disability worsening could have an onset in- or outside the influence of a relapse. A disability worsening could only be confirmed at a scheduled visit in the absence of (confirmed or unconfirmed) relapse if, over a period of 3 or 6 months time interval, all assessments met the worsening criterion as listed in Table 2.

Table 2. Criterion for disability worsening based on change in EDSS score

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

The 6mCDI was defined in a similar fashion based on the criterion in Table 3. For 6mCDI, patients with a baseline EDSS total score <= 1.5 could not contribute to the analysis as improvement was not possible for them.

Table 3. Criterion for disability improvement based on change in EDSS score

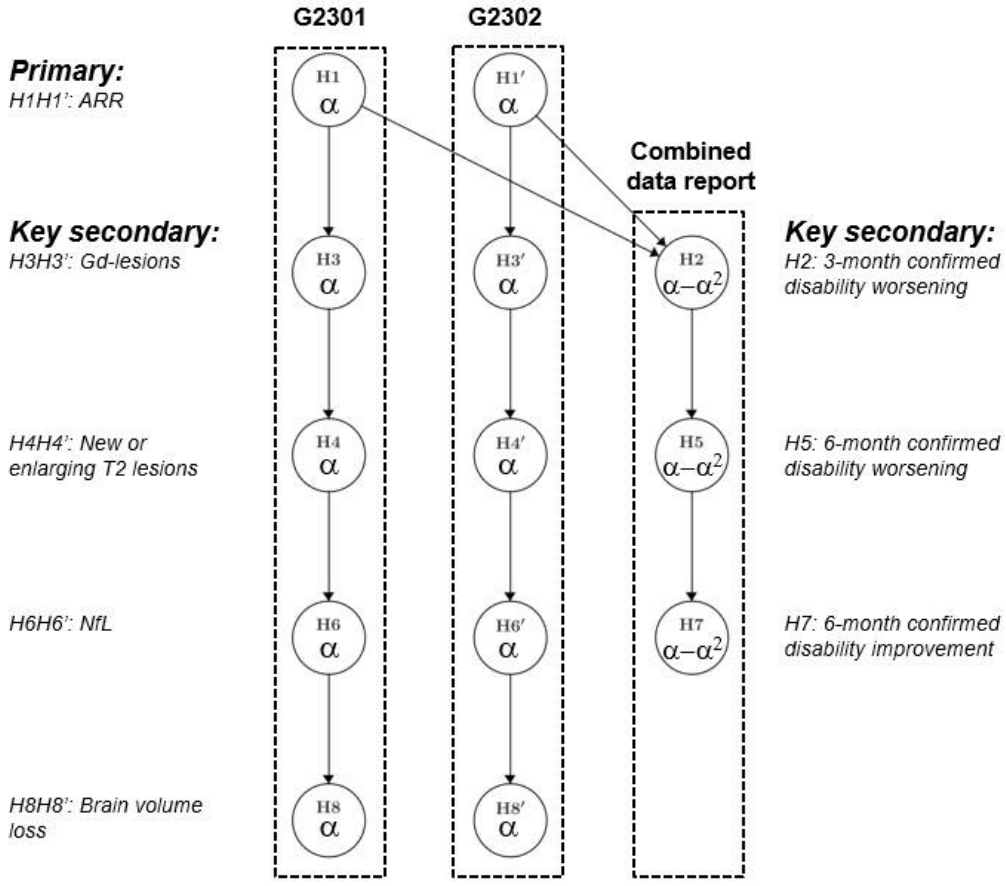
Total EDSS at baseline*	"Disability improvement" criterion
0 to 1.5	No improvement possible
≥2 to 6	≤ -1
≥6.5 to 9.5	≤ -0.5

3.2.2 Statistical Methodologies

Analysis Population
Statistical analyses of clinical endpoints were based on Full analysis set (FAS), comprised of all randomized patients.

Multiple Testing Procedures
To control the type I error rate, a testing strategy containing all primary and key secondary endpoints of studies G2301 and G2302, as illustrated in Figure 2 was implemented. Hypotheses were tested in hierarchical order as indicated by the arrows. The number associated with each hypothesis (α, or α-α^2, where α was 0.025 1-sided) indicates the significance level at which that hypothesis was tested. Within each study, the primary endpoint (ARR) was tested first, and if the null hypothesis could be rejected, key secondary endpoints were tested according to the following hierarchy: Gd-enhancing T1 lesions (MRI), T2 lesions (MRI), NfL levels, brain volume loss (MRI).

Figure 2. Testing procedure and type-I error control in studies G2301 and G2302



A meta-analysis for the combined data was pre-planned for key secondary disability-related endpoints, as the individual studies were not powered for these analyses. If both studies

successfully rejected the null-hypothesis of the primary endpoint, disability-related endpoints could be tested at 1-sided significance level of 0.024 (=0.025-0.025^2) using the combined data from both studies, regardless of the outcomes of MRI- and NfL-related endpoints. The testing procedure was pre-planned and agreed by the Agency.

The testing procedure controls the type-I error rate (one-sided) at the study-level to ≤0.025, and at combined studies level to ≤0.000625(= 0.025^2).

Analysis Methods

Annualized relapse rate (ARR)
The primary endpoint was analyzed using a negative binomial regression model with log-link, treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of T1 Gd-enhancing lesions and the patient's age at baseline as covariates. The patient's time in study, calculated as natural log of [(end of treatment epoch date - first dose date +1) /365.25], was used as an offset variable to adjust for the varying lengths of patient's time in the study.

The following sensitivity analyses were planned for the primary endpoint. The primary analysis was to be repeated to include all reported MS relapses (confirmed or unconfirmed). The primary was also repeated using the per-protocol set to provide an analysis of on-treatment data from patients who have no major protocol violations. In this analysis, only relapses with a start date during the on-treatment period were included, in comparison with the primary analysis which used all available data up to the end of treatment epoch date, irrespective of on or off study treatment. Additionally, the time-to-first relapse was analyzed in a Cox proportional hazards model. In comparison with the primary analysis using a negative binomial model, the Cox proportional hazards model does not assume constant relapse rates (but rather it assumes proportional hazards).

Disability related endpoints
Disability related endpoints were analyzed using a Cox proportional hazards model with study as stratum, treatment, and region as factors and baseline EDSS as a continuous covariate. Censoring occurred in those patients who did not experience an event, this included patients who had a "tentative" disability worsening/improving that could not be confirmed due to an early discontinuation or any another reason. The censoring time was defined as the time from the first dose to the last available EDSS assessment during the treatment epoch. If a patient dies due to MS (EDSS=10 at any time), it was considered a confirmed disability worsening.

As a supportive analysis, the log-rank test stratified by study was performed. Additionally, an analysis was conducted assigning all patients who discontinued from the study due to "lack of efficacy" or died (due to any reason) during the treatment epoch as patients with a confirmed event. The event time for these patients was calculated based on the date of the discontinuation from study. A worse-case type of analysis for 3mCDW or 6mCDW considered only those ofatumumab patients who discontinued the study due to lack of efficacy or died to have disability worsening.

MRI- and NfL-related key secondary endpoints

For gadolinium (Gd)-enhancing T1 lesions (which represent acute, transient inflammation on a specific scan), the data was analyzed in a negative binomial model with an offset for the number of MRI scans included in the analysis. The result was presented as the number of Gd-enhancing T1 lesions per MRI scan. The model included treatment and region, and age, and number of Gd-enhancing lesions at baseline as continuous covariates.

For the number of new or enlarging T2 lesions (which represent the cumulative increase in the number of lesions between baseline and the specific post-baseline scan), the data was analyzed in a negative binomial model with an offset for the time (in years) between the last post-baseline scan and the baseline (or screening) scan. The result was presented as the number of new or enlarging T2 lesions per year. The model included treatment and region, and age, and baseline volume of T2 lesions as continuous covariates.

NfL is a biomarker of neuroaxonal injury and neuronal loss. The data was analyzed in a repeated measure model (MMRM) with unstructured covariance assumed between assessments within patients. As the NfL level is expected to follow log-normal distribution, it was transformed by natural log before fitting the statistical model for analysis. The statistical hypothesis test was based on the treatment contrast and p-value obtained at month 3.

Percent brain volume change from baseline was analyzed in a random coefficient model (with random slope and intercept and unstructured covariance assumed for these random effects). Post-baseline assessments were done at Month 12, Month 24 (and EOT/EOS if discontinued prematurely). The hypothesis compared the slope of percent brain volume change between ofatumumab and teriflunomide groups.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In Study G2301, a total of 927 subjects were randomized. A higher proportion of patients in the teriflunomide treatment group (17.5%) discontinued prematurely from the Treatment epoch as compared to the ofatumumab group (10.3%). The difference mainly resulted from the discontinuations due to patient/guardian decision in the teriflunomide group vs the ofatumumab group (9.1% vs 3.4%) (Table 4).

Table 4. Study G2301: Subject Disposition

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)**
Completed study drug	400 (86.0)	359 (77.7)	759 (81.9)
Discontinued 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)
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)

Source: CSR Table 10-2.

In Study G2302, a total of 955 subjects were randomized. A similar proportion of patients discontinued prematurely in the ofatumumab and teriflunomide group (17.3% vs 17.7%) (Table 5).

Table 5. Study G2302: Subject Disposition

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)**
Completed study drug	383 (79.6)	370 (78.1)	753 (78.8)
Discontinued 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)

Source: CSR Table 10-2.

Demographics were generally balanced between the treatment groups for Study G2301 and G2302 populations. Most patients were female and White, with a mean age of 38 years (Table 6).

Table 6. Patient Demographics in Studies G2301 and G2302

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

Source: FDA reviewer.

Baseline disease characteristics were generally balanced between the treatment groups for Study G2301 and G2302. The mean disease duration since MS diagnosis was 5.7 years for Study G2301 and 5.6 years for Study G2302. The mean baseline EDSS was 2.96 for Study G2301 and 2.88 for Study G2302 (Table 7).

Table 7. Baseline Disease Characteristics in Studies G2301 and G2302

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

Source: Summary of Clinical Efficacy Table 3-2.

3.2.4 Results and Conclusions

3.2.4.1 Study G2301

Annualized Relapse Rate (ARR)

Treatment with ofatumumab significantly reduced the annualized relapse rate by 50.5% (ARR ratio=0.495, $p<0.001$). The adjusted ARR was 0.11 in the ofatumumab group, compared with 0.22 in the teriflunomide group (Table 8). Results of the all pre-specified sensitivity analyses were consistent with that of the primary analysis, including analysis of the ARR based on all relapses (confirmed and unconfirmed), analysis of confirmed relapses in the per-protocol population, as well as analysis of the time-to-first relapse.

Table 8. Study G2301: Summary of Annualized Relapse Rate

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

This endpoint was analyzed in a negative binomial model.
Source: CSR Table 11-1, confirmed by FDA reviewer.

Number of Gd-Enhancing Lesions

Treatment with ofatumumab compared with teriflunomide, significantly reduced the mean number of Gd-enhancing T1 lesions per scan (0.01 vs 0.45) by 97.5% ($p<0.001$; Table 9).

Table 9. Study G2301: Number of Gd-Enhancing Lesions per Scan

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

This endpoint was analyzed in a negative binomial model.
Source: CSR Table 11-4, confirmed by FDA reviewer.

Annualized 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 (0.72 vs 4.00) by 82.0% ($p<0.001$; Table 10).

Table 10. Study G2301: Number of New or Enlarging T2 Lesions per Year

	OMB 20 mg N=465	TER 14 mg N=462
N: number of patients included in the analysis	440	431
Adjusted annualized mean rate of new/Enlarging T2 lesions	0.72	4.00
(95% CI)	(0.61, 0.85)	(3.47, 4.61)
Rate ratio	0.18	
(95% CI)	(0.15, 0.22)	
Rate reduction	82.0%	
p-value	<0.001	

This endpoint was analyzed in a negative binomial model
Source: CSR Table 11-5, confirmed by FDA reviewer.

Neurofilament light chain (NfL) concentration

At Month 3, treatment with ofatumumab compared to teriflunomide demonstrated a significant relative reduction in NfL concentration by 7% (p=0.011; Table 11).

Table 11. Study G2301: Neurofilament light chain (NfL) Concentrations at Month 3

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

This endpoint was analyzed using repeated measures mixed effects model.
Source: CSR Table 11-6, confirmed by FDA reviewer.

Percent change in brain volume from baseline

The annual rate of brain volume loss, estimated as the slope in volume change, was not statistically different between the ofatumumab and teriflunomide treatment groups based on the random coefficients model (p=0.116; Table 12).

Table 12. Study G2301: Percent Change in Brain Volume from Baseline

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

This endpoint was analyzed using a random coefficients model.
Source: CSR Table 11-7, confirmed by FDA reviewer.

3.2.4.2 Study G2302

Annualized Relapse Rate (ARR)

Treatment with ofatumumab significantly reduced the annualized relapse rate by 58.5% (ARR ratio=0.415, p<0.001). The adjusted ARR was 0.10 in the ofatumumab treatment group, compared with 0.25 in the teriflunomide group (Table 13). Results of the all pre-specified sensitivity analyses were consistent with that of the primary analysis.

Table 13. Study G2302: Summary of Annualized Relapse Rate

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

This endpoint was analyzed in a negative binomial model.
Source: CSR Table 11-1, confirmed by FDA reviewer.

Number of Gd-Enhancing Lesions

Treatment with ofatumumab compared with teriflunomide, significantly reduced the mean number of Gd-enhancing T1 lesions per scan (0.03 vs 0.51) by 93.8% ($p<0.001$;Table 14).

Table 14. Study G2302: Number of Gd-Enhancing Lesions per Scan

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

This endpoint was analyzed in a negative binomial model.
Source: CSR Table 11-4, confirmed by FDA reviewer.

Annualized 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 (0.64 vs 4.15) by 84.5% ($p<0.001$;Table 15).

Table 15. Study G2302: Number of New or Enlarging T2 Lesions per Year

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

This endpoint was analyzed in a negative binomial model
Source: CSR Table 11-5, confirmed by FDA reviewer.

Neurofilament light chain (NfL) concentration

At Month 3, treatment with ofatumumab compared to teriflunomide demonstrated a significant relative reduction in NfL concentration by 11% ($p<0.001$; Table 16).

Table 16. Study G2302: Neurofilament light chain (NfL) Concentrations at Month 3

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

This endpoint was analyzed using repeated measures mixed effects model.
Source: CSR Table 11-6, confirmed by FDA reviewer.

Percent change in brain volume from baseline

The annual rate of brain volume loss, estimated as the slope in volume change, was not statistically different between the ofatumumab and teriflunomide treatment groups based on the random coefficients model ($p=0.129$; Table 17).

Table 17. Study G2302: Percent Change in Brain Volume from Baseline

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

This endpoint was analyzed using a random coefficients model.
Source: CSR Table 11-7, confirmed by FDA reviewer.

3.2.4.3 Pooled Studies G2301 and G2302

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

Disability worsening (time to 3mCDW)

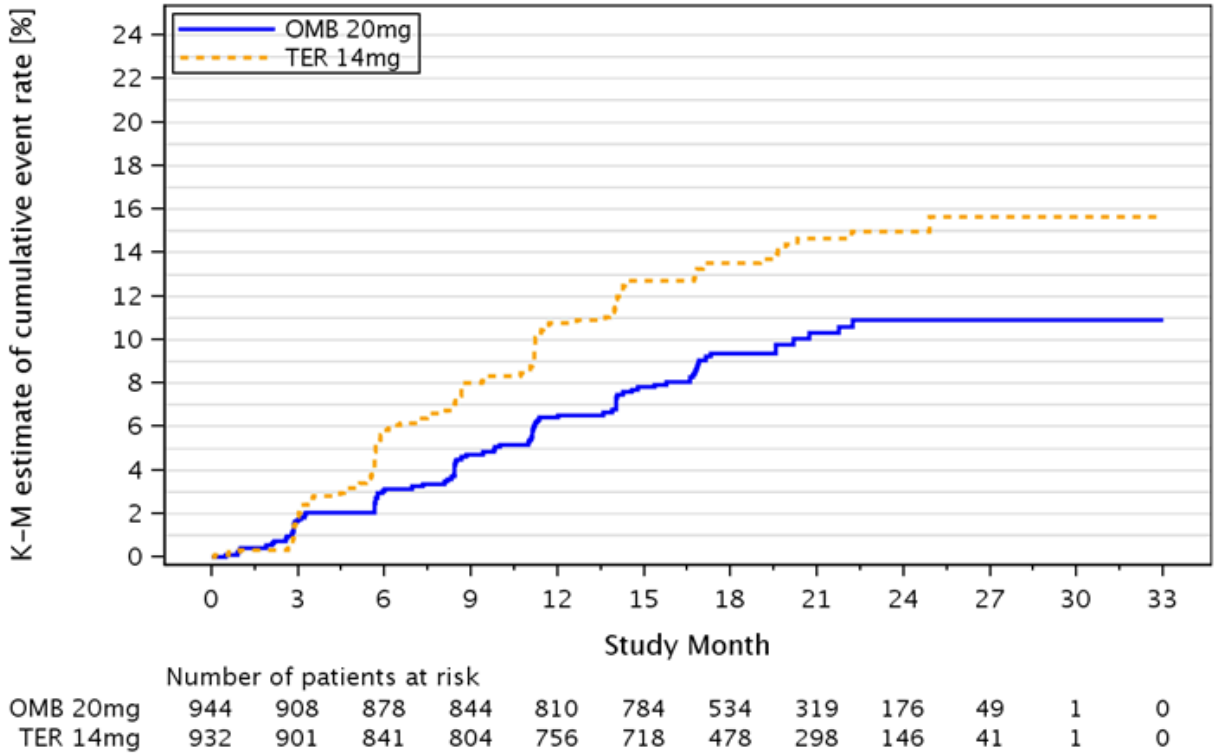
Ofatumumab significantly lowered the risk of a 3mCDW by 34.4%, compared to teriflunomide ($p=0.002$) in pooled Studies G2301 and G2302 (Table 18). There was a consistent trend in favor of ofatumumab in each individual study. Treatment with ofatumumab delayed the time to first 3mCDW as shown in the corresponding Kaplan-Meier curves (Figure 3).

Table 18. Time to First 3-month Confirmed Disability Worsening

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

Source: Meta-analysis report Table 11-1, confirmed by FDA reviewer.

Figure 3. Time to First 3-month Confirmed Disability Worsening



Source: Meta-analysis report Figure 11-2.

The pre-specified supportive and sensitivity analyses were generally consistent, including the worst-case type of analysis in which ofatumumab patients who discontinued from the study due to lack of efficacy and/or died were considered as having 3mCDW (a risk reduction for ofatumumab vs. teriflunomide of 32.9%, p=0.004; results not shown in table).

Additional analyses were conducted per the Agency's request. The protocol specified that disability worsening could have an onset in- or outside the influence of a relapse and the confirmation can only occur in the absence of relapse. To estimate the effect of ofatumumab on disability progression independent of relapse activity in patients with RMS, an analysis was conducted in which absence of relapses was required for the whole duration starting from the onset of disability progression event until the progression was confirmed. This is a common approach for analyzing the treatment effect on disease progression for RMS population. The analysis showed a risk reduction for ofatumumab vs. teriflunomide of 34.2% (p=0.007; Table 19).

In the second analysis, patients who had an onset of a tentative disability worsening but with no further EDSS assessments available for confirmation were defined as having confirmed disability worsening, instead of being censored. The analysis included over 100 additional events and showed a smaller risk reduction for ofatumumab vs. teriflunomide of 25.1% (p=0.009; Table 19) for 3mCDW.

Table 19. Additional Analyses on Time to First 3-month Confirmed Disability Worsening

	KM estimate at Month 24 % (95% CI)	n/N (%)	Hazard ratio (95% CI)	Risk reduction	P-value
Disability progression independent of relapse					
OMB 20mg	8.9 (7.0,11.2)	72/944 (7.6)	0.658 (0.487, 0.890)	34.2%	0.007
TER 14mg	12.4 (10.2,15.0)	102/931 (11.0)			
Patients without EDSS assessments available for confirmation assigned as having confirmed disability					
OMB 20mg	20.1 (16.9,23.8)	149/944 (15.8)	0.749 (0.603, 0.930)	25.1%	0.009
TER 14mg	23.9 (20.7,27.5)	182/931 (19.5)			

Source: FDA reviewer.

Disability worsening (time to 6mCDW)

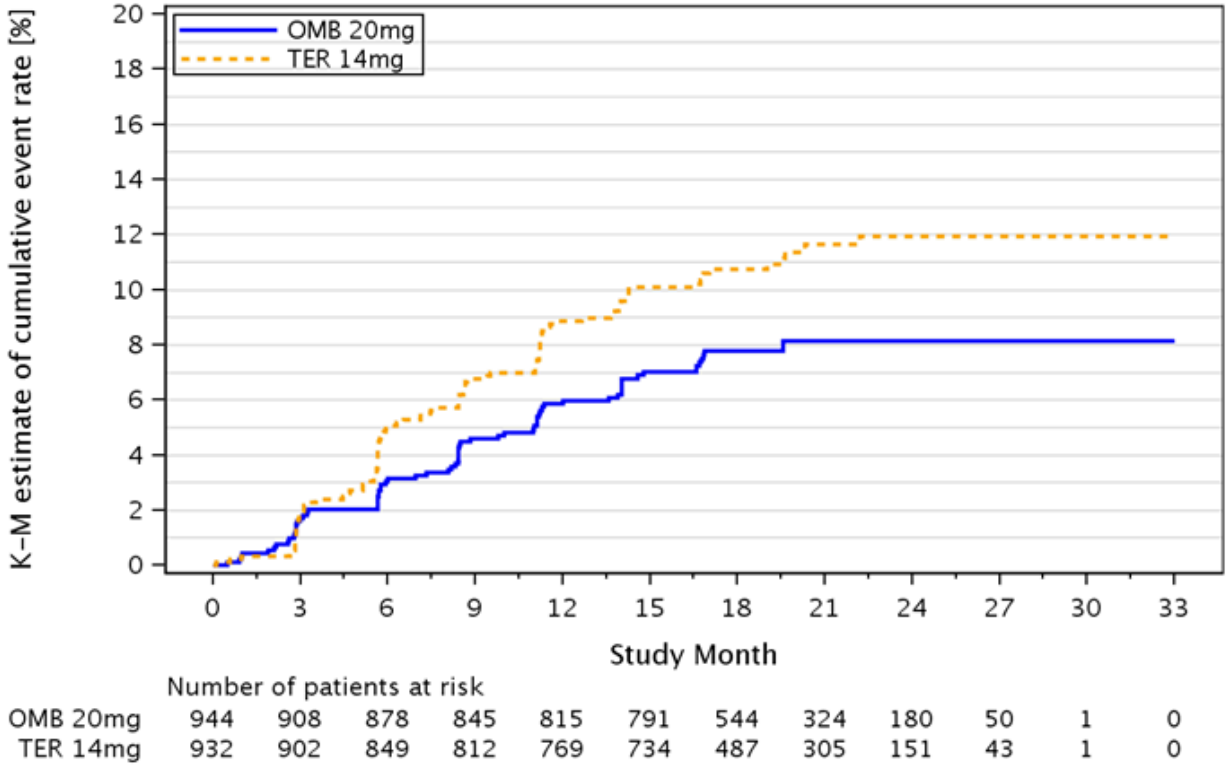
Ofatumumab significantly lowered the risk of a 6mCDW by 32.5%, compared to teriflunomide (p=0.012) in pooled Studies G2301 and G2302 (Table 20). Trends in favor of ofatumumab were observed in each individual study, and the risk reduction was numerically larger in Study G2301 than Study G2302. Treatment with ofatumumab delayed the time to first 6mCDW as shown in the corresponding Kaplan-Meier curves (Figure 4).

Table 20. Time to First 6-month Confirmed Disability Worsening

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

Source: Meta-analysis report Table 11-2, confirmed by FDA reviewer.

Figure 4. Time to First 6-month Confirmed Disability Worsening



Source: Meta-analysis report Figure 11-3.

The pre-specified supportive and sensitivity analyses were generally consistent, including the worst-case type of analysis in which ofatumumab patients who discontinued from the study due to lack of efficacy and/or died were considered as having 6mCDW (a risk reduction for ofatumumab vs. teriflunomide of 29.6%, p=0.022; results not shown in table).

Additional analysis of 6-month disability progression independent of relapses showed a risk reduction for ofatumumab vs. teriflunomide of 26.5% (p=0.074). The analysis in which patients without EDSS assessments available for confirmation were assigned as having confirmed disability included over 150 additional events and showed a smaller risk reduction for ofatumumab vs. teriflunomide of 24.3% (p=0.013) for 6mCDW (Table 21).

Table 21. Additional Analyses on Time to First 6-month Confirmed Disability Worsening

	KM estimate at Month 24 % (95% CI)	n/N (%)	Hazard ratio (95% CI)	Risk reduction	P-value
Disability progression independent of relapse					
OMB 20mg	7.1 (5.5,9.1)	60/944 (6.4)	0.735 (0.524, 1.030)	26.5%	0.074
TER 14mg	9.5 (7.6,11.8)	77/931 (8.3)			
Patients without EDSS assessments available for confirmation assigned as having confirmed disability					
OMB 20mg	19.6 (16.4,23.2)	145/944 (15.4)	0.757 (0.607, 0.943)	24.3%	0.013
TER 14mg	23.2 (20.0,26.8)	176/931 (18.9)			

Source: FDA reviewer.

Disability improvement (time to 6mCDI)

For 6mCDI, patients with a baseline EDSS total score <= 1.5 could not contribute to this analysis as improvement was not possible for them based on the definition. It is therefore an analysis in a subset of the total FAS population with 403 patients excluded from this meta-analysis.

Statistical significance was not achieved for the endpoint of 6mCDI, although patients treated with ofatumumab had a 35.2% increased probability for a 6mCDI as compared to patients treated with teriflunomide (p=0.094; Table 22).

Table 22. Time to First 6-month Confirmed Disability Improvement

Data source	KM estimate at Month 24 % (95% CI)	n/N (%)	Hazard ratio (95% CI)	Risk reduction	P-value
Combined data G2301 + G2302					
OMB 20mg	11.0 (8.8,13.7)	74/749 (9.9)	1.352 (0.950, 1.924)	-35.2%	0.094
TER 14mg	8.1 (6.2,10.6)	53/723 (7.3)			

Source: Meta-analysis report Table 11-3, confirmed by FDA reviewer.

3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Subgroup analysis results for the primary endpoint of annualized relapse rate for Study G2301 and Study G2302 are shown in Table 23 and Table 24, respectively. Ofatumumab demonstrated a higher efficacy than teriflunomide and the treatment effect appeared consistent across the subgroups except for small subgroups of race.

Table 23. Study G2301: Summary of annualized relapse rate by demographics subgroups

Subgroup	OMB 20 mg N/ Adjusted ARR (95% CI)	TER 14mg N/ Adjusted ARR (95% CI)	Rate Ratio (95% CI)
Age			
<=40	246/ 0.11 (0.08, 0.15)	282/ 0.27 (0.22, 0.33)	0.42 (0.29, 0.61)
>40	219/ 0.12 (0.09, 0.17)	180/ 0.20 (0.15, 0.26)	0.62 (0.40, 0.95)
Gender			
Female	318/ 0.12 (0.10, 0.16)	317/ 0.22 (0.18, 0.28)	0.55 (0.39, 0.76)
Male	147/ 0.10 (0.07, 0.16)	145/ 0.27 (0.21, 0.36)	0.38 (0.23, 0.63)
Race			
White	411/ 0.12 (0.10, 0.16)	412/ 0.24 (0.20, 0.29)	0.52 (0.39, 0.69)
Black or African American	15/ <0.01 (NA.)	20/ 0.33 (0.15, 0.72)	NA
Asian	15/ 0.05 (<0.01, 0.34)	16/ 0.08 (0.02, 0.34)	0.57 (0.05, 6.75)
Other	24/ 0.10 (0.04, 0.29)	14/ 0.32 (0.13, 0.79)	0.33 (0.08, 1.30)
Region			
Europe	249/ 0.13 (0.10, 0.18)	246/ 0.25 (0.20, 0.31)	0.54 (0.38, 0.77)
North America	103/ 0.12 (0.07, 0.19)	105/ 0.29 (0.20, 0.40)	0.41 (0.23, 0.72)
Rest of world	113/ 0.08 (0.05, 0.14)	111/ 0.19 (0.13, 0.27)	0.44 (0.23, 0.84)

Source: FDA reviewer.

Table 24. Study G2302: Summary of annualized relapse rate by demographics subgroups

Subgroup	OMB 20 mg N/ Adjusted ARR (95% CI)	TER 14mg N/ Adjusted ARR (95% CI)	Rate Ratio (95% CI)
Age			
<=40	283/ 0.12 (0.09, 0.17)	282/ 0.31 (0.25, 0.39)	0.39 (0.27, 0.57)
>40	198/ 0.13 (0.09, 0.18)	192/ 0.21 (0.15, 0.28)	0.61 (0.38, 0.97)
Gender			
Female	319/ 0.15 (0.11, 0.19)	319/ 0.26 (0.21, 0.32)	0.57 (0.40, 0.81)
Male	162/ 0.08 (0.05, 0.13)	155/ 0.30 (0.22, 0.41)	0.26 (0.15, 0.47)

Subgroup	OMB 20 mg N/ Adjusted ARR (95% CI)	TER 14mg N/ Adjusted ARR (95% CI)	Rate Ratio (95% CI)
Race			
White	418/ 0.13 (0.10, 0.16)	417/ 0.28 (0.24, 0.34)	0.45 (0.33, 0.62)
Black or African American	13/ 0.14 (0.04, 0.53)	18/ 0.13 (0.04, 0.42)	1.08 (0.19, 6.12)
Asian	21/ 0.12 (0.03, 0.41)	19/ 0.11 (0.03, 0.38)	1.06 (0.18, 6.33)
Other	29/ 0.05 (0.01, 0.22)	20/ 0.29 (0.11, 0.74)	0.18 (0.03, 1.00)
Region			
Europe	242/ 0.11 (0.08, 0.16)	237/ 0.24 (0.18, 0.32)	0.46 (0.30, 0.71)
North America	107/ 0.15 (0.10, 0.24)	106/ 0.23 (0.15, 0.34)	0.66 (0.36, 1.20)
Rest of world	132/ 0.13 (0.09, 0.20)	131/ 0.36 (0.26, 0.48)	0.37 (0.22, 0.62)

Source: FDA reviewer.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Patients with RMS can experience disability worsening either due to incomplete recovery from relapses, or due to a gradual disability progression independent (or in absence) of relapse activity. The applicant used the terminology 'confirmed disability worsening' (CDW) for the former case of disability worsening with or without relapse activity being accounted for; and 'confirmed disability progression' (CDP) for the latter case of disability progression independent (or in absence) of relapse activity. The disability event specified in the protocol was CDW as key secondary endpoints. However, CDP is usually used in RMS trials for regulatory purpose.

5.2 Collective Evidence

In both pivotal studies, ofatumumab resulted in statistically significant effects on relapses (primary endpoint) and MRI- and NfL-related key secondary endpoints, except for percent change in brain volume as assessed by comparing the slope of brain volume loss (Table 25).

In the combined data from studies G2301 and G2302, ofatumumab significantly reduced the risk of 3mCDW and 3mCDP compared with teriflunomide, with a consistent effect in both studies G2301 and G2302. Ofatumumab also significantly reduced the risk of 6mCDW but not 6mCDP. Statistical significance was not achieved for the endpoint of 6mCDI, although a positive trend was observed favoring the ofatumumab treatment group compared with the teriflunomide treatment group (Table 25).

Table 25. Summary of efficacy results

Endpoints	G2301		G2302	
	Ofatumumab 20 mg (n = 465)	Teriflunomide 14 mg (n = 462)	Ofatumumab 20 mg (n = 481)	Teriflunomide 14 mg (n = 474)
Endpoints based on separate studies				
Annualized relapse rate (primary endpoint)	0.11	0.22	0.10	0.25
Rate reduction	50.5% (p < 0.001)		58.5% (p < 0.001)	
Mean number of T1 Gd-enhancing lesions per MRI scan	0.01	0.45	0.03	0.51
Relative reduction	97.5% (p < 0.001)		93.8% (p < 0.001)	
Number of new or enlarging T2 lesions	0.72	4.00	0.64	4.15
Relative reduction	82.0% (p < 0.001)		84.5% (p < 0.001)	
Neurofilament light (NfL) at Month 3; pg/mL	8.80	9.41	8.92	10.02
Relative reduction	7% (p = 0.011)		11% (p < 0.001)	
Brain volume rate of change from baseline	-0.28	-0.35	-0.29	-0.35
Relative reduction	20% (p = 0.116)		17% (p = 0.129)	
Endpoints based on pooled studies				
Proportion of patients with 3mCDW Risk reduction	10.9% ofatumumab vs 15.0% teriflunomide 34.4% (p = 0.002)			
Proportion of patients with 3mCDP Risk reduction	8.9% ofatumumab vs 12.4% teriflunomide 34.2% (p = 0.007)			
Proportion of patients with 6mCDW Risk reduction	8.1% ofatumumab vs 12.0% teriflunomide 32.5% (p = 0.012)			
Proportion of patients with 6mCDP Risk reduction	7.1% ofatumumab vs 9.5% teriflunomide 26.5% (p = 0.074)			
Proportion of patients with 6mCDI Risk reduction	11.0% ofatumumab vs 8.1% teriflunomide -35.2% (p = 0.094)			

5.3 Conclusions and Recommendations

The data overall provide adequate evidence to support for the efficacy of ofatumumab as treatment of subjects with RMS.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XIANG LING
07/02/2020 11:12:35 AM

KUN JIN
07/02/2020 12:17:36 PM
I concur with the review.

HSIEN MING J HUNG
07/02/2020 12:22:22 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326Orig1s070

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

sBLA#	**125326/S0248**
Submission Date:	12/20/2019
Generic Name:	Ofatumumab (OMB157, Kesimpta)
Indication:	Multiple Sclerosis (MS).
Sponsor:	Novartis Pharmaceuticals
Review Team:	Jagan Mohan Parepally, Vishnu D Sharma, Atul Bhattaram, Angela Men
Submission Type:	Supplemental Biologics License Application (sBLA)

EXECUTIVE SUMMARY

The sponsor is seeking the approval for ofatumumab (Kesimpta), a recombinant, humanized monoclonal antibody that selectively targets CD20-expressing B cells to treat relapsing forms (RMS) of multiple sclerosis. This is a supplemental biologic licensing application (sBLA). The original Biologics License Application (BLA #125,326) with the trade name Arzerra® was submitted by GlaxoSmithKline (GSK) to the Division of Biologic Oncology Products to treat patients with chronic lymphocytic leukemia (CLL).

The proposed dosing regimen is 20 mg given by subcutaneous injection with initial dosing at Weeks 0, 1, and 2 followed by subsequent monthly dosing, starting at Week 4. The efficacy and safety of ofatumumab in multiple sclerosis patients was supported by two randomized, double-blind Phase 3 studies comparing the efficacy and safety of ofatumumab 20 mg s.c. versus teriflunomide 14 mg p.o. in 1882 patients with relapsing multiple sclerosis and an open label extension study. Two Phase 2 studies supporting dose-selection and exploratory efficacy and safety of ofatumumab were also included.

In addition, the sponsor submitted a PK study comparing ofatumumab administered via pre-filled syringe assembled with a safety needle device and via pre-filled syringe assembled with an autoinjector. A population PK modeling and analysis was performed using data from Phase 2 and 3 studies to determine the effect of covariates such as body weight and baseline B-cell count on the steady state PK metrics AUC and Cmax.

From a clinical pharmacology perspective, the proposed 20 mg with initial dosing at Weeks 0, 1, and 2 followed by subsequent monthly dosing, starting at Week 4 supported the indication in Multiple Sclerosis. The incidence of immunogenicity was low. The treatment-induced ADA were detected in 2 of 923 patients with RMS treated with ofatumumab in the Phase III studies. From the ADA positive samples, no neutralizing antibodies (nAb) were identified in studies.

The primary focus of the review is to review the relative bioavailability of ofatumumab between ofatumumab administered via pre-filled syringe assembled with a safety needle

device and via pre-filled syringe assembled with an autoinjector and population PK analysis focusing patient specific characteristics on the PK of ofatumumab.

BACKGROUND

Kesimpta (Ofatumumab, s.c injection) is an anti-CD20 monoclonal antibody targeting and leading to B-cell depletion. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the pre-B to mature B lymphocyte stage

Following studies were submitted supporting the sBLA:

Efficacy and Safety Studies

Phase 3 Studies

Ofatumumab has been investigated in two randomized, double-blind phase 3 studies (COMB157G2301 & COMB157G2302) comparing the efficacy and safety of ofatumumab 20 mg s.c. versus teriflunomide 14 mg p.o. in 1882 patients with relapsing multiple sclerosis (RMS).

The Phase 3 program also includes an open-label extension study (COMB157G2399) evaluating long-term safety, tolerability and effectiveness of ofatumumab in patients with RMS.

COMB157G1301: A study to support Japanese registration, assessing efficacy, safety, and tolerability in Japanese and ex-Japan Caucasian patients.

Phase 2 Studies

Dose-selection Study OMS112831: This study 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 s.c. in patients with RRMS.

Supportive efficacy Study OMS115102: This study was a randomized, multicenter, double-blind, placebo-controlled Phase II study. It was primarily designed to evaluate the safety of 3 different doses of ofatumumab i.v. (100 mg, 300 mg, and 700 mg), but also included descriptive analyses of PK parameters and exploratory analysis of efficacy endpoints.

Clinical Pharmacology Studies:

- COMB157G2102: A PK study (COMB157G2102) comparing ofatumumab administered via pre-filled syringe assembled with a safety needle device (PFS-NSD, pre-filled syringe presentation) and via pre-filled syringe assembled with an autoinjector (PFS-AI, pre-filled pen presentation).

- PopPK Modeling: Analysis of the ofatumumab concentration-time data was performed using data from 5 studies: G2301, G2302, G2102, OMS115102 and OMS112831.

Following PK study (COMB157G2102) comparing ofatumumab administered was conducted to support the PFS-NSD used in studies COMB157G2301, COMB157G2302 and COMB157G2102. At the request of Division of Neurology II, the Office of Scientific Investigations and surveillance (OSIS) declined to conduct audit of the current PK study, since the study sites were recently inspected, and the inspection results were found to be acceptable. The bioanalytical method validation and analytical performance of assay used to measure plasma concentrations of ofatumumab are acceptable.

COMB157G2102: A 12 week randomized open label parallel group multicenter study to evaluate bioequivalence of 20 mg subcutaneous ofatumumab injected by pre-filled syringe or autoinjector in adult RMS patients (Week 12 analysis)

Objectives:

The primary objective was to demonstrate bioequivalence of 20 mg ofatumumab injected s.c. by the pre-filled syringe assembled in a needle safety device (PFS) versus the pre-filled syringe assembled in an autoinjector device (AI).

The secondary objectives were:

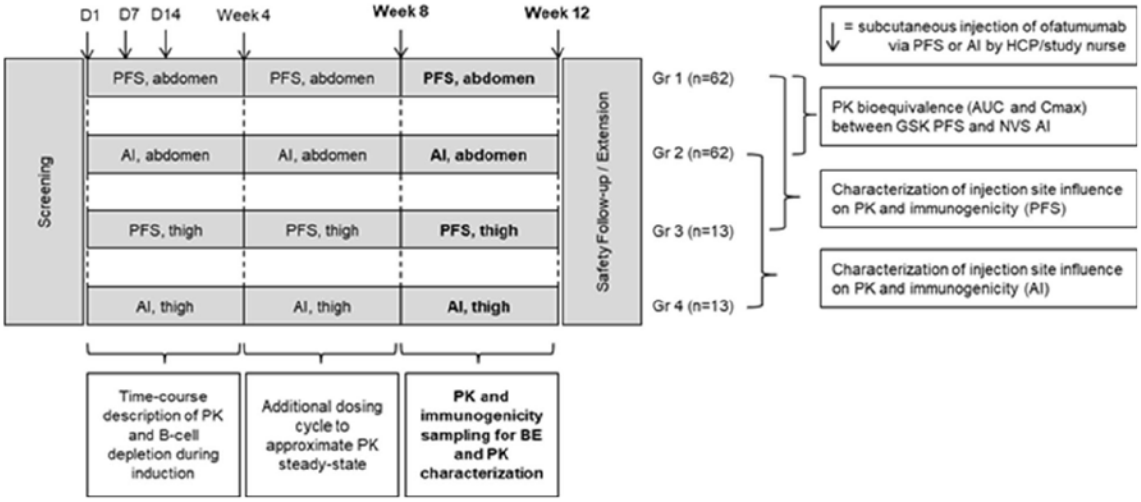
- To characterize the PK following s.c. administration of ofatumumab to either the abdominal region or the thigh.
- To assess the immunogenicity, safety and tolerability of ofatumumab.

Study Design	This study was a randomized, open-label, multi-center, parallel group, 12-week study originally planned in 150 patients. An assessment of the variability of data as measured by coefficient of variation for PK parameters, AUCtau and Cmax, was planned as interim analysis. This interim analysis was conducted before any results from the study were available, when 36 patients randomized to the PFS-abdomen and the AI-abdomen treatment groups completed Week 12. Based on results of interim analysis, sample size was increased from originally planned sample size of 150 patients to enroll the maximum per-protocol allowed sample size of 284 patients by adding more patients to the PFS-abdomen and AI-abdomen groups (approximately 129 patients per group). The study had 3 Parts: screening (Part 1), treatment (Part 2), and safety follow-up (Part 3). Part 1 - Screening: Lasted up to 30 days and consisted of Screening and Baseline assessments. Part 2 - Treatment: Treatment period consisted of an open-label administration of ofatumumab 20 mg s.c. as loading dose regimen (three

	weekly doses on Day 1, Day 7 and Day 14), followed by a maintenance dose regimen of 20 mg every 4 weeks starting at Week 4. Evaluation of primary endpoint, bioequivalence, was performed between the AI-abdomen and the PFS-abdomen groups. Part 3 -Safety follow-up/Extension study: The Safety-FU period was applicable for the patients who either completed the Treatment period (i.e. Week 12) on study drug and did not enter the planned extension study or prematurely discontinued the study treatment.
Study Population	Study enrolled male and female patients (aged 18-55 years) diagnosed with MS according to the 2010 Revised McDonald criteria or Relapsing MS and with an EDSS score of 0 to 5.5 (inclusive). Additionally, patients had to have a history of at least 1 relapse during previous year or 2 relapses during previous 2 years or a positive Gd-enhancing MRI scan during the previous 1 year, and had to be neurologically stable within 1 month prior to randomization.
Treatment Groups	Eligible patients were randomized in a 10:10:1:1 ratio into 1 of 4 ofatumumab treatment groups based on the type of injection device (PFS or autoinjector) and the injection location (abdomen or thigh): • Group 1: PFS-abdomen: ofatumumab 20 mg s.c. injection with PFS administrated on abdomen • Group 2: AI-abdomen: ofatumumab 20 mg s.c. injection with autoinjector administrated on abdomen • Group 3: PFS-thigh: ofatumumab 20 mg s.c. injection with PFS administrated on thigh • Group 4: AI-thigh: ofatumumab 20 mg s.c. injection with autoinjector administrated on thigh
Number of Subjects	Three hundred and forty-four patients were enrolled/randomized at 41 study centers, and 284 patients were randomized. All 284 patients were included in the Safety set and PK analysis set, and 258 patients from the AI-abdomen and the PFS-abdomen treatment groups were included in BE analysis set.
Pharmacokinetic Sampling	Ofatumumab was administered subcutaneously on Day 1, Day 7, Day 14, Week 4, Week 8 and Week 12. Blood samples for PK analysis were collected at baseline (Day 1), Days 4, 7, 14, Week 4, 6, 8, 9, 10, 11 and 12 (Day 84).
Sampling for Immunogenicity	Blood samples for anti-drug antibodies (ADA) analysis were collected at baseline (Day 1), Week 4, 8, and 12 (Day 84).
Pharmacokinetic Assessments	The primary variables are PK endpoints, namely AUCtau and Cmax calculated from PK concentration data collected in the dosing interval after Week 8 dose administration in accordance with the assessment schedule. Bioequivalence analysis between PFS and autoinjector involved the two groups (AI-abdomen and PFS-abdomen).
Safety Assessments	Safety assessments consisted of collecting all AEs, serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies.

	They included the regular monitoring of hematology, blood chemistry and regular assessments of vital signs, ECG and physical condition. Injection related reactions, infections and infestations, malignancy and suicidality assessment were the safety topic of interest. The number and percentage of patients with B-cells < LLN value (i.e., B-cell depleted) or with notable low level criteria in IgG or IgM at least once are presented by treatment group and visit-window.
Statistical Methods	Primary analysis to address the bioequivalence between PFS and autoinjector involved two groups (AI-abdomen (T) and PFS-abdomen (R)). The null hypothesis was that "Mean difference in ln (AUCtau) and/or ln (Cmax) greater than allowed-difference between these 2 groups" . The alternative hypothesis was that "Mean difference in ln (AUCtau) and ln (Cmax) less than allowed-difference between these 2 groups". Ln refers to the natural log function. As the testing for Average Bioequivalence (ABE) was based on a between-groups comparison, the variabilities of the R and T groups were expected to be high, with a coefficient of variation (CV) greater than 0.3. The reference-scaled ABE (RSABE) bioequivalence approach for highly variable drugs was also used. For this purpose, the current guidance for crossover design were modified for application in a parallel groups design. Testing was performed for AUCtau and Cmax separately on the BE analysis set.

Study Design Schematic



Note: This study was originally planned in 150 patients. Following interim analysis, sample size was increased from 150 to 284 patients by adding more patients to the PFS-abdomen and AI-abdomen groups (approximately 129 patients per group, see study design).

RESULTS:

Out of 284 randomized patients, 1 patient in the PFS-abdomen group discontinued the study.

Bioequivalence testing of AUCtau during Week 8 dosing interval

Statistics	OMB 20mg AI (ABD) N = 128	OMB 20mg PFS (ABD) N = 130	Trt. Comparison (AI vs. PFS)	Meet Criteria	Bioequivalence criteria ABE[1]	RSABE[2]
n	128	128*				
Mean (hr*ug/mL)	665.9	594.5				
SD (hr*ug/mL)	545.96	412.66				
CV (%)	81.98	69.41				
Min (hr*ug/mL)	23	62				
Q1 (hr*ug/mL)	307.2	295.6				
Median (hr*ug/mL)	513.7	494.2				
Q3 (hr*ug/mL)	845.0	740.2				
Max (hr*ug/mL)	2765	2106				
n (log)	128	128*				
Geo-mean (hr*ug/mL)	487.7	474.1				
Geo-CV (%)	103.5	79.7				
SDlog	0.854	0.701				
Log-scale mean difference (90% CI)			0.03 (-0.13, 0.19)	NA	[ln(0.8),ln(1.25)]	
Geo-mean ratio (GMR)			1.03	Yes		[0.8,1.25]
95% upper bound of the linearised criterion			-0.3131	Yes		<= 0

ABE (Average Bioequivalence) method: Concluded BE if 90% CI of log-scale mean difference meets the specified criteria [ln(0.8),ln(1.25)], i.e. [-0.223, 0.223].

Note: RSABE method is applied to replicated crossover study designs to establish BE. However, RSABE in addition to ABE was also used to evaluate BE though the current study involves parallel group design. ABE approach is more appropriate for these calculations.

According to the sponsor the between-subject variability for the reference group was used instead of within-subject variability for scaling to the reference variability (ie, the permitted window increases as the variability increases). The window calculated was between -0.223 to 0.223.

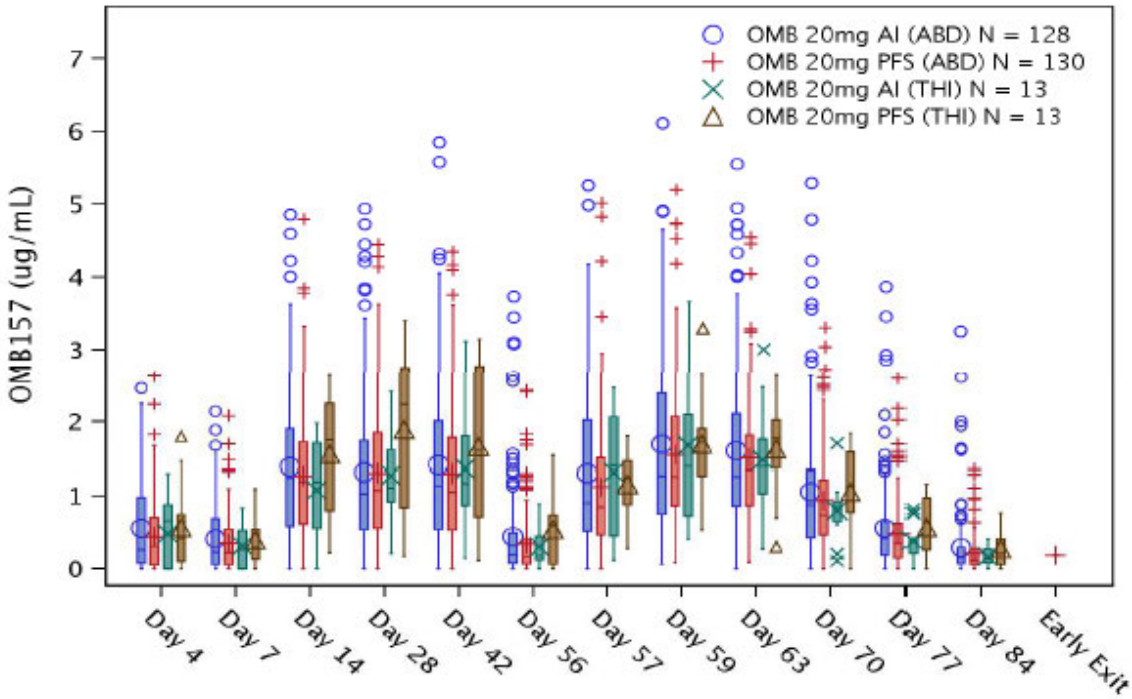
RSABE (Reference Scaled ABE) method (applies if SDlogr>=0.294): Concluded BE if both 1) GMR (Geo-mean ratio) and 2) 95% upper bound of the linearized criterion meet the specified criteria respectively. SDlogr=Standard deviation of reference group (PFS) in log-scale.

Bioequivalence testing of Cmax during Week 8 dosing interval

Statistics	OMB 20mg AI (ABD) N = 128	OMB 20mg PFS (ABD) N = 130	Trt. Comparison (AI vs. PFS)	Meet Criteria	Bioequivalence criteria ABE[1]	Bioequivalence criteria RSABE[2]
n	128	128*				
Mean (ug/mL)	1.827	1.684				
SD (ug/mL)	1.3016	1.0290				
CV (%)	71.2527	61.1189				
Min (ug/mL)	0.14	0.21				
Q1 (ug/mL)	0.868	0.984				
Median (ug/mL)	1.400	1.440				
Q3 (ug/mL)	2.465	2.245				
Max (ug/mL)	6.11	5.20				
n (log)	128	128*				
Geo-mean (ug/mL)	1.409	1.409				
Geo-CV (%)	89.2	67.9				
SDlog	0.765	0.616				
Log-scale mean difference (90% CI)			0.00 (-0.14, 0.14)	NA	[ln(0.8),ln(1.25)]	
Geo-mean ratio (GMR)			1.00	Yes		[0.8,1.25]
95% upper bound of the linearised criterion			-0.2446	Yes		<= 0

ABE (Average Bioequivalence) method: Concluded BE if 90% CI of log-scale mean difference meets the specified criteria [ln(0.8),ln(1.25)], i.e. [-0.223, 0.223].

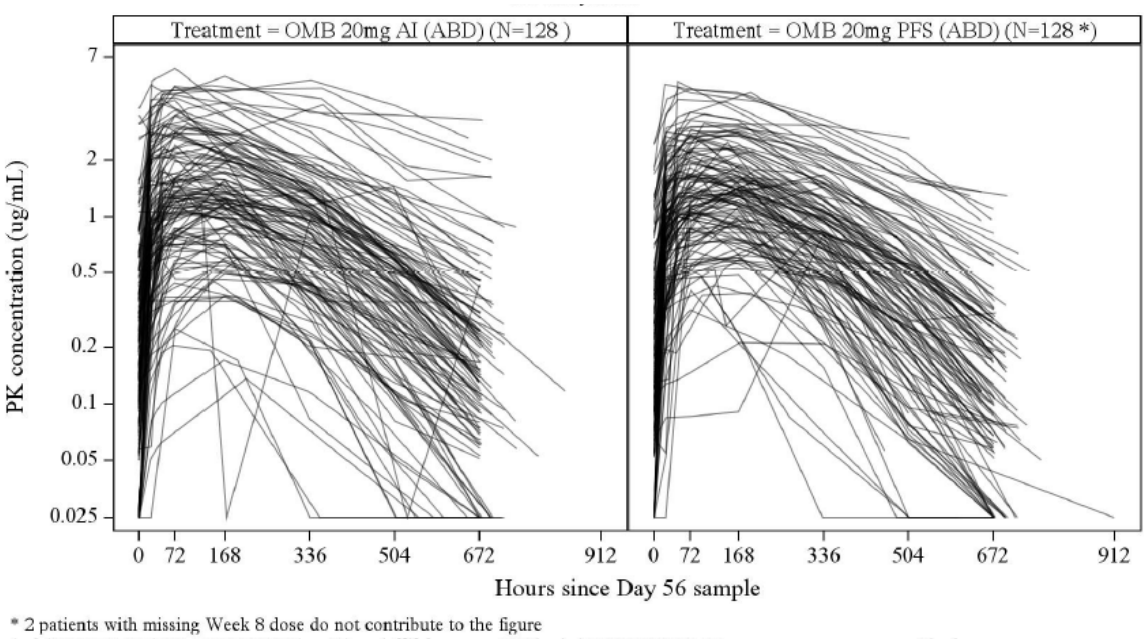
Ofatumumab PK concentrations by visit and injection site



OMB: ofatumumab, ABD: abdomen, THI: thigh, AI: autoinjector, PFS: pre-filled syringe

The PK profiles, Cmax and AUCtau values of ofatumumab from the abdomen and thigh injection areas were essentially similar.

Spaghetti plot of PK concentrations by treatment at Week 8 dosing interval.



* 2 patients with missing Week 8 dose do not contribute to the figure

Note: The spaghetti plots of PK concentrations by treatment show similar mean and variability for ofatumumab administered using AI or PFS in abdomen.

Ofatumumab administered subcutaneously either by pre-filled syringe in needle safety device or by pre-filled syringe in autoinjector resulted in similar depletion (< 10 cells/µL) of B-cell during the loading phase which was sustained through the maintenance phase.

Note: Both the average bioequivalence and reference-scaled average bioequivalence analysis methods were used for calculations showing that ofatumumab administered using AI and the PFS at abdomen site meeting BE criteria.

Study Conclusions:

Ofatumumab administered by pre-filled syringe assembled in an autoinjector device and the pre-filled syringe assembled in a needle safety device were bioequivalent.

Immunogenicity

The overall incidence of positive ADA in RMS patients from all the studies was low. The treatment-induced ADA were detected in 2 of 923 patients with RMS treated with ofatumumab in the Phase III studies. No patients with treatment-enhanced ADA were identified. From the ADA positive samples, no neutralizing antibodies (nAb) were identified in studies G2301, G2302 and G2102.

Dose adjustments based on intrinsic factors

No dose adjustment of ofatumumab is needed in patients based on age, sex, body weight, race, and baseline B-cell count. Please refer to Pharmacometric review in appendix for more details.

Recommended Labeling Revisions Summary:

The labeling language described in Sections 6.2 (Immunogenicity), 7 (Drug-Drug Interactions), and 12.3 (Pharmacokinetics) were revised to be consistent with previous product labels within the same indication.

Section 7, Drug-Drug Interactions: Statement [redacted] (b) (4) should be deleted, since this information is not relied on a clinically significant drug interaction.

Section 8.5 Geriatric Use: Statement [redacted] (b) (4) should be deleted.

Section 12.3: A statement related to specific populations that the population characteristics do not have a clinically meaningful effect on the pharmacokinetics of ofatumumab: body weight, sex, age, race and baseline B-cell count. The above information was not described in the proposed label.

Jagan Mohan Parepally, M.S., Ph.D.
Reviewer
Division of Neuropsychiatric Pharmacology (DNP)

Vishnu D Sharma, Ph.D.
Reviewer
Division of Pharmacometrics (DPM)

Atul Bhattaram, Ph.D.
Team Leader, DPM

Concurrence:
Angela Men, M.D., Ph.D._____
Team Leader, DNP

Appendix 1: Division of Pharmacometrics Review

EXECUTIVE SUMMARY

Novartis Pharmaceuticals is seeking an approval for KESIMPTA (Ofatumumab) injection for treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The recommended dose of KESIMPTA is 20 mg given by subcutaneous injection with initial dosing at Weeks 0, 1, and 2 followed by subsequent monthly dosing, starting at Week 4.

This document is a review of the sponsor's population pharmacokinetic (Pop PK) analysis which supports labeling statements. Few changes are suggested to Section 12 of the proposed label. Supportive information is also provided for these proposed changes in the document.

SPONSOR'S ANALYSIS

Objectives

- Characterize the PK relationship of ofatumumab concentrations and determine the covariate effects in the PK model to explain between-subject variability
- Explore the effect of covariates such as weight and baseline B-cell count on the steady state PK metrics AUC and C_{max} derived from the developed Pop PK model

Data

Th PK data from a total of 5 studies (COMB157G2301, COMB157G2302, COMB157G2102, OMS115102, and OMS112831) were used to develop Pop PK models for ofatumumab.

Method

Nonlinear mixed effect PK modeling was conducted using Monolix (version 2018R1). The base structural PK model was first developed in which various models including TMDD and its approximations and a range of absorption models were explored. Covariate analysis was performed using initially a priori selected covariates, then performing an exploratory analysis of covariates versus inter-subject random effects to select a full covariate model, which was then reduced to include only significant covariate effects according to the Wald test. The final model was evaluated by using the likelihood-based criteria, goodness-of-fit plots, convergence plots, the precision and correlations of parameter estimates, the distribution of random effects and visual predictive checks. The clinical relevance of the covariates was assessed by simulating the effect of the selected covariates on the steady state PK metrics AUC and C_{max}.

Results

The PK of ofatumumab was described by 2-compartments quasi-steady state (QSS) model, a first order absorption for the SC administration, and a monotonically declining time effect on the target synthesis rate, k_{syn}. Covariates such as weight was added on clearance, absorption rate, central volume of distribution, inter-compartmental clearance, elimination rate constant for complex, $k_{e(P)}$ and synthesis rate constant at time 0, k_{syn0}; gender was added on bioavailability; auto-injector was added on $k_{e(P)}$; and intravenous formulation was added on k_{syn0}. The parameter estimates of the final population PK model for ofatumumab are shown in **Table 2-1.**

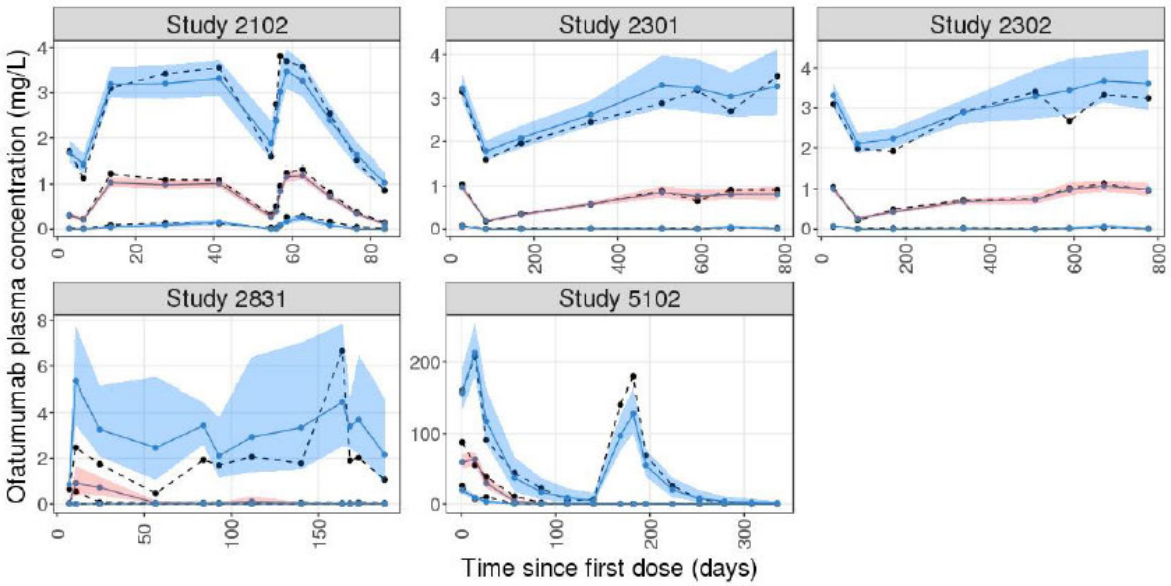
Table 2-1: Parameter estimates of sponsor's final population PK model

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,WT70)	-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,WT70)	1.47	(5.02)	NA		
Q (L/day)	0.0462	(5.3)	0.425	(10.3)	[92.2]
β(Q,WT70)	2.33	(8.98)	NA		
V_c (L)	2.8	(1.91)	0.2	(7.48)	[76.8]
β(V_c,WT70)	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($k_{e(p)}$,WT70)	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},WT70)	-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		

Source: Novartis population PK report: Table 5-11, Page 51

The population PK model for ofatumumab was assessed with diagnostics plots including goodness-of-fit (**Figure 3-1**) and visual predictive checks (VPC) (**Figure 2-1**). Overall, goodness-of-fit plots and VPC plots adequately describe the PK data of ofatumumab. The final pop PK model was used to simulate steady-state PK profiles of ofatumumab 20 mg (**Figure 2-2**). The effect of weight and sex on the simulated steady-state C_{max} and AUC of ofatumumab 20 mg is shown in **Figure 2-3**.

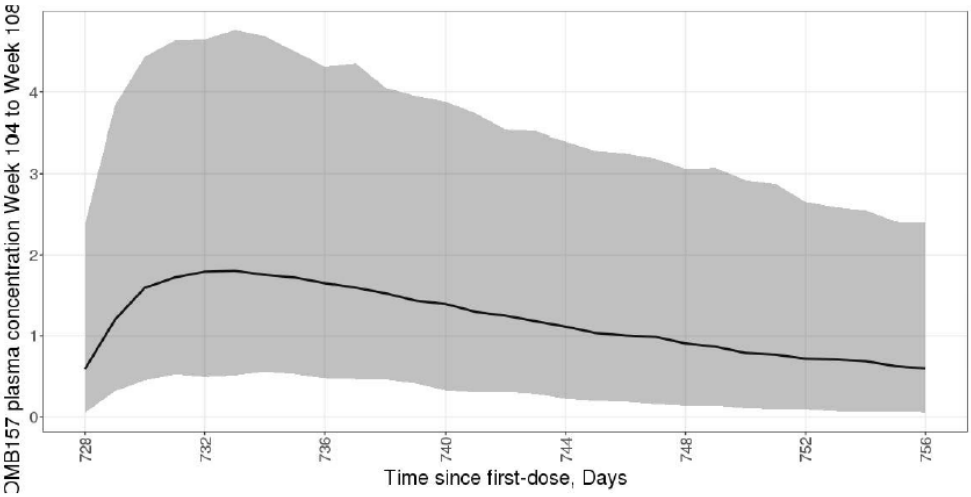
Figure 2-1: Visual Predictive Checks for the final population PK model following subcutaneous administration stratified by studies. OMB157 represents ofatumumab in the caption.



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

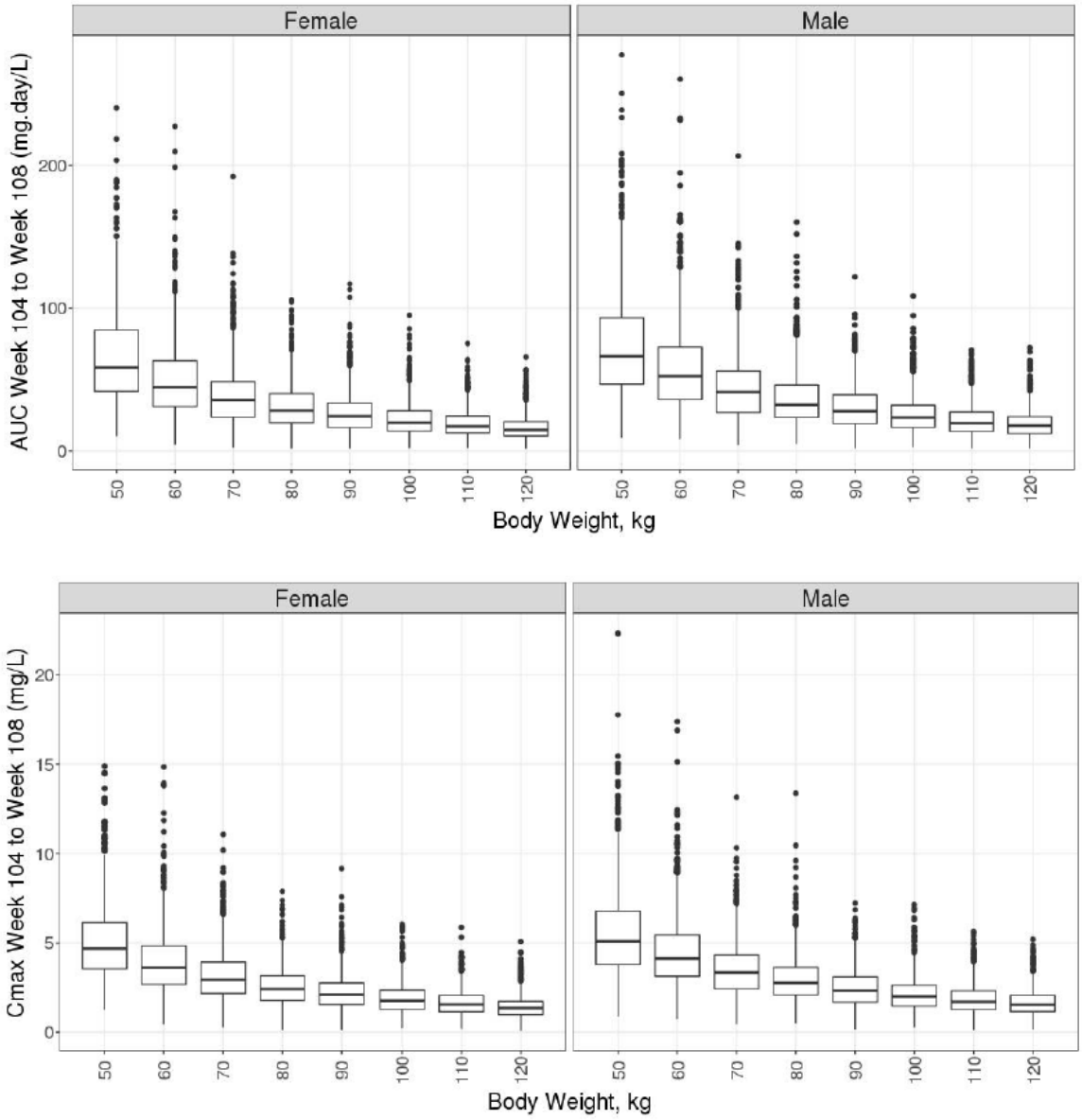
Source: Novartis population PK report: Table 5-16, Page 52

Figure 2-2: Simulated steady state PK profile of ofatumumab 20 mg administered with pre-filled syringe in the patient population



Source: Novartis population PK report: Table 5-19, Page 54

Figure 2-3: Simulated steady-state AUC (upper panel) and C_{max} (lower panel) of ofatumumab 20 mg by weight and stratified by sex.



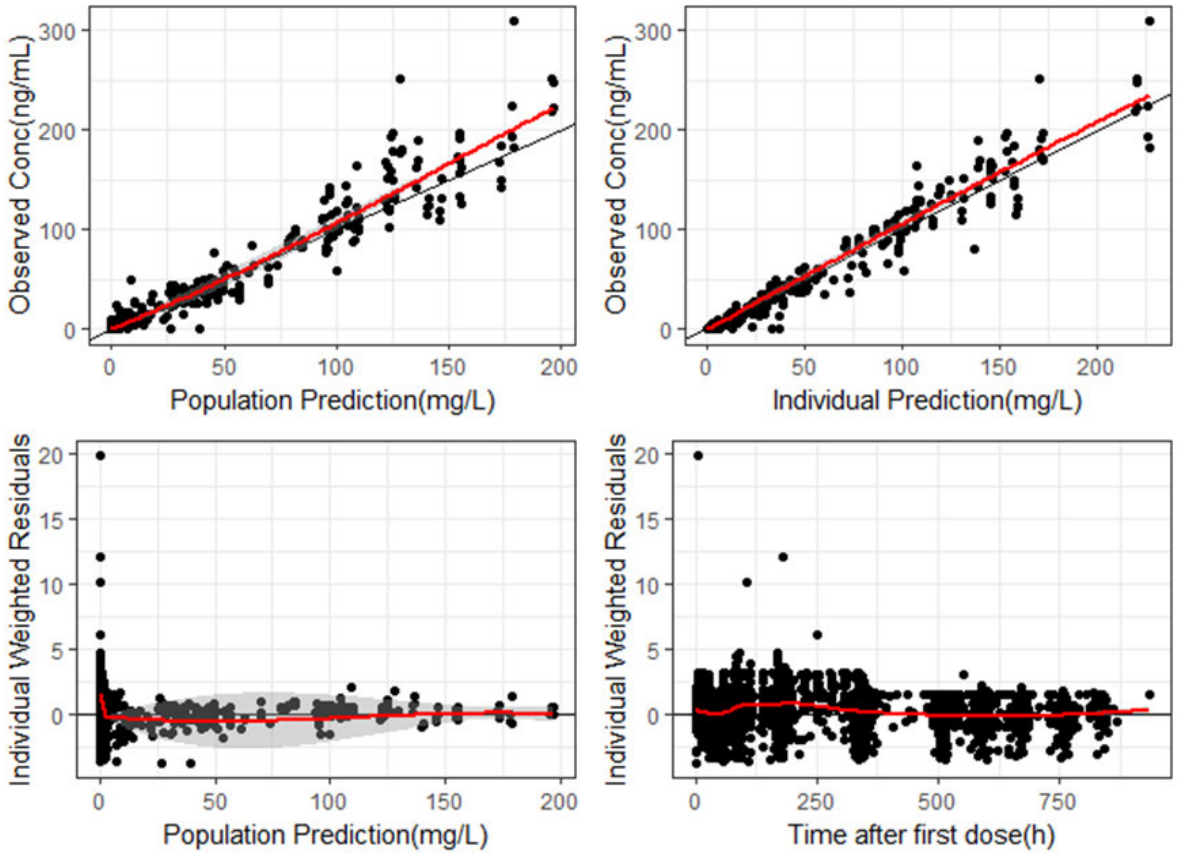
Source: Novartis population PK report: Table 5-20,5-21, Page 56

REVIEWER'S ANALYSIS

Sponsor's Pop PK model evaluation

The reviewer was able to run the sponsor's final PK model and obtained similar results. Model diagnostics for ofatumumab are shown in **Figure 3-1**. The population- and individual-predicted parameter estimates derived from the final PK model were used to evaluate the bioavailability (i.e. 0.358) and steady-state volume of distribution (i.e. 5.6 L) of ofatumumab. These parameters are consistent with the sponsor's provided values in the pop PK report and drug label.

Figure 3-1: Goodness-of-fit plots of sponsor's final population PK model for ofatumumab



Source: M:\Ofatumumab_BLA125326_VS\Reviewer\Rscripts\pk_analysis_ofatumumab.R

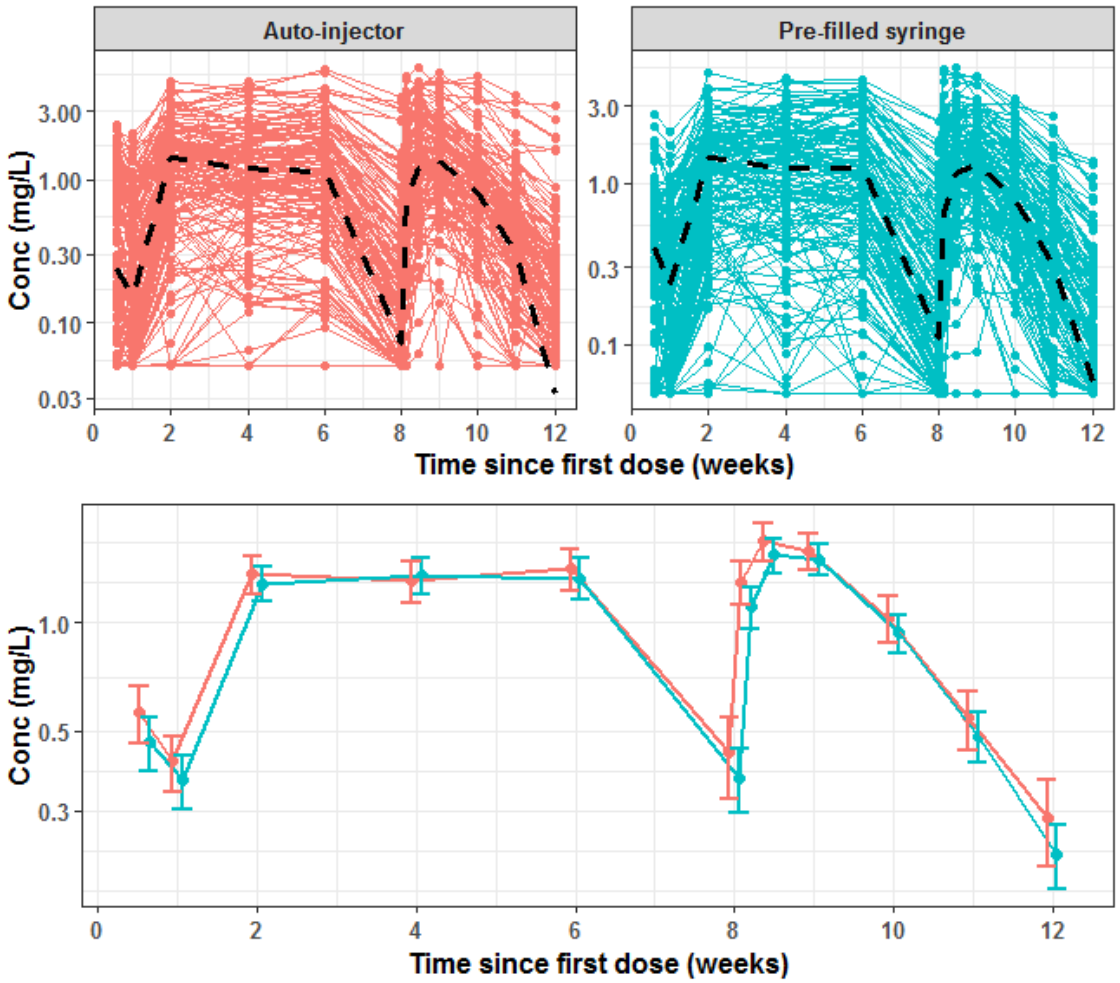
The effect of the covariates on the PK of ofatumumab was evaluated based on the population parameter estimates from the PK model and the observed data. Study 112102

was used to evaluate the impact of covariates on the PK of ofatumumab as it has reasonable amount of PK data at the proposed dosing regimen with rich PK sampling.

Type of Injector

The observed PK profiles of ofatumumab 20 mg from 141 subjects with auto-injector injections and 143 subjects with pre-filled syringe injections are plotted along with the corresponding median population predictions (**Figure 3-2**). Overlap of 95% confidence intervals (CI) of the PK profiles by injector type suggest lack of clinically relevant impact of injector type on ofatumumab PK.

Figure 3-2: Top row: Individual PK profiles of ofatumumab by type of injector. Black dashed line indicates median population predictions from sponsor's final PK model; Bottom row: Mean PK profiles of ofatumumab by injector type. Red color indicates subjects with auto-injector and strong cyan color indicates subjects with pre-filled syringe injection. Error bars indicates 95% confidence intervals.

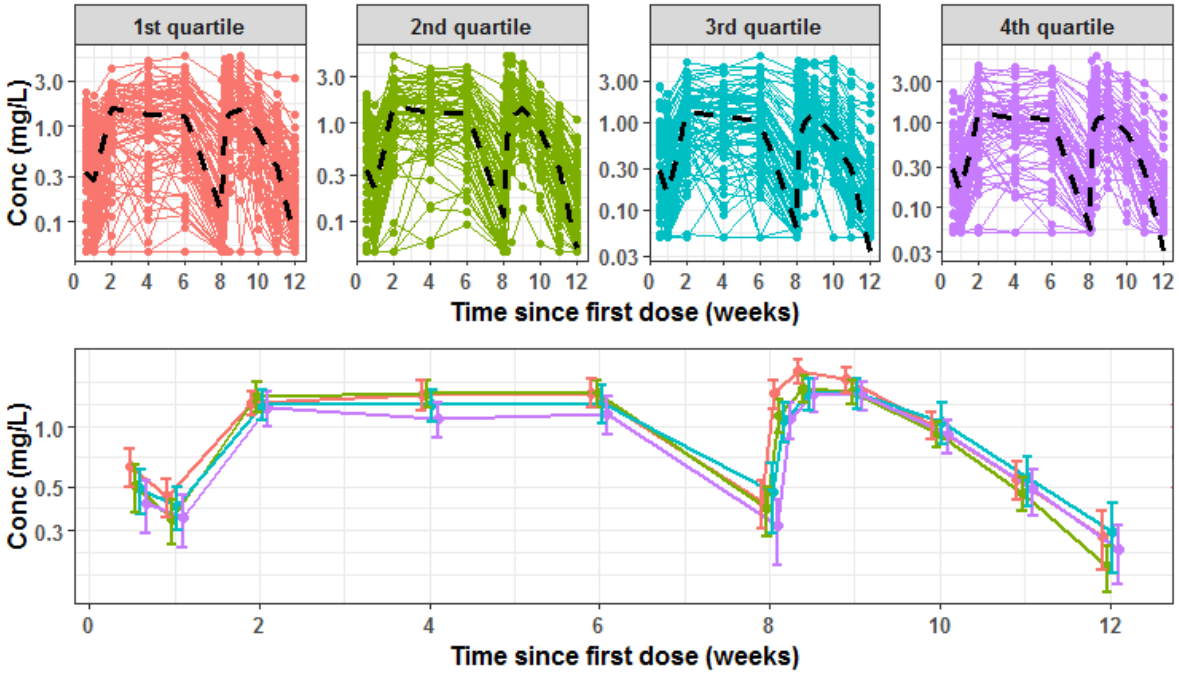


Source: M:\Ofatumumab_BLA125326_VS\Reviewer\Rscripts\pk_analysis_ofatumumab.R

Age effect

The observed PK data of 284 subjects dosed with ofatumumab 20 mg were distributed into quartiles (i.e. 1st quartile: n=80, 18-31; 2nd quartile: n=64, 31- 37; third quartile: n=74, 37-44; and 4th quartile: n=66, 44-55) based on their age distribution and plotted along with the corresponding median population predictions (**Figure 3-3**). Overlap of 95% CI of the PK profiles by age quartile suggest lack of clinically relevant impact of age on ofatumumab PK (**Figure 3-6**). However, PK data was not available from the elderly subjects (>65 years of age).

Figure 3-3: Top row: Individual PK profiles of ofatumumab by age quartiles. Black dashed line indicates median population predictions from sponsor's final PK model; Bottom row: Mean PK profiles of ofatumumab by age quartiles. Red, green, cyan and purple color indicates 1st, 2nd, 3rd and 4th quartile of body weights respectively. Error bars indicates 95% confidence intervals.

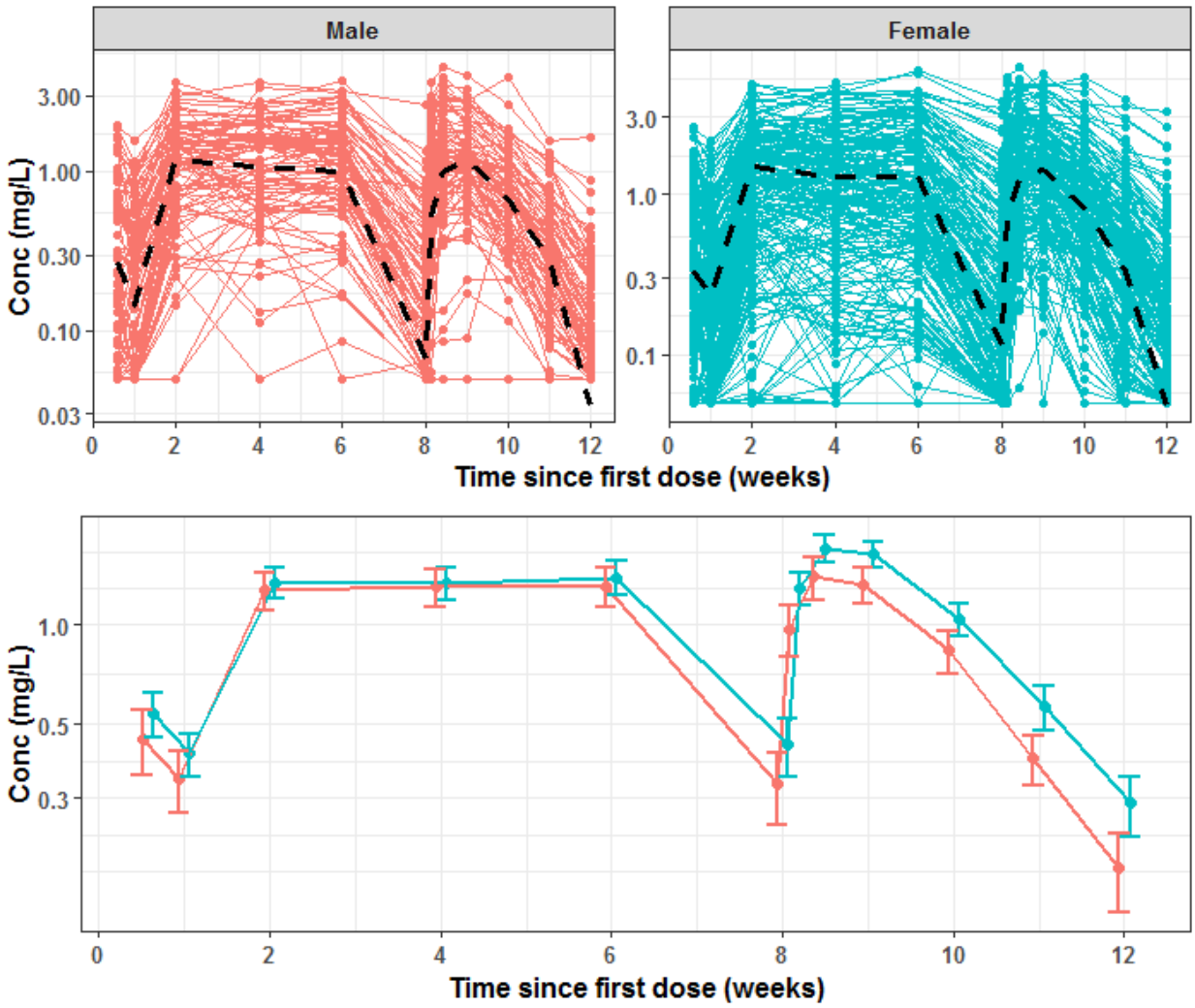


Source: M:\Ofatumumab_BLA125326_VS\Reviewer\Rscripts\pk_analysis_ofatumumab.R

Sex effect

The PK data of 85 males and 199 females dosed with ofatumumab 20 mg were compared and plotted along with the corresponding population predictions (**Figure 3-4**). The changes in steady-state $C_{max,SS}$ and AUC_{SS} for sex were within 20% across the weight range (**Figure 2-3** and **Table 3-1**) and thus do not suggest any clinical relevant impact of sex on the PK of ofatumumab (**Figure 3-6**).

Figure 3-4: Top row: Individual PK profiles of ofatumumab by sex. Black dashed line indicates median population predictions from sponsor's final PK model; Bottom row: Mean PK profiles of ofatumumab by sex. Red color indicates females and strong cyan color indicates female subjects. Error bars indicates 95% confidence intervals.



Source: M:\Ofatumumab_BLA125326_VS\Reviewer\Rscripts\pk_analysis_ofatumumab.R

Table 3-1: Effect of weight and sex on steady-state AUC and C_{max} of ofatumumab

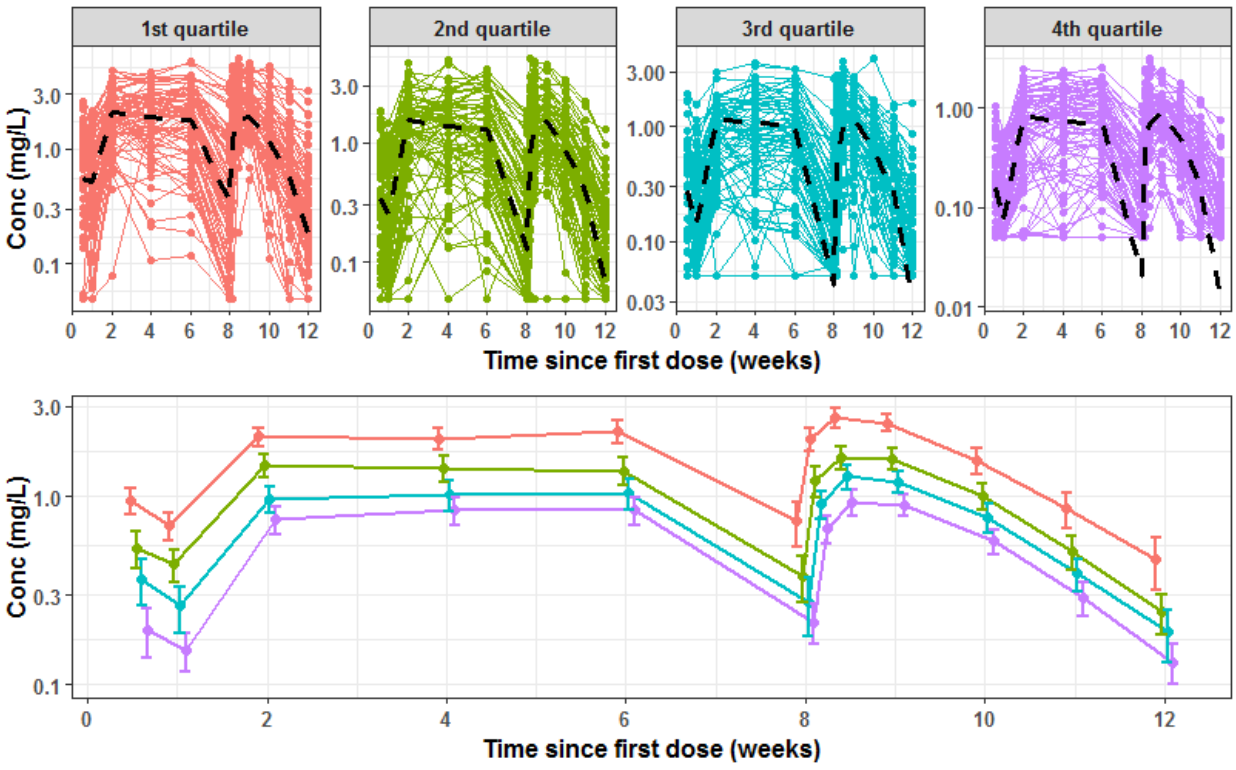
Weight (kg)	Median AUC_{ss} (mg.day/L)		Median $C_{max,ss}$ (mg/L)	
	Female	Male	Female	Male
50	58.3	66.3	4.67	5.09
70	35.6	41.2	2.93	3.34
120	14.6	17.6	1.34	1.53

Source: Novartis population PK report: Table 5-12, Page 57

Body weight effect

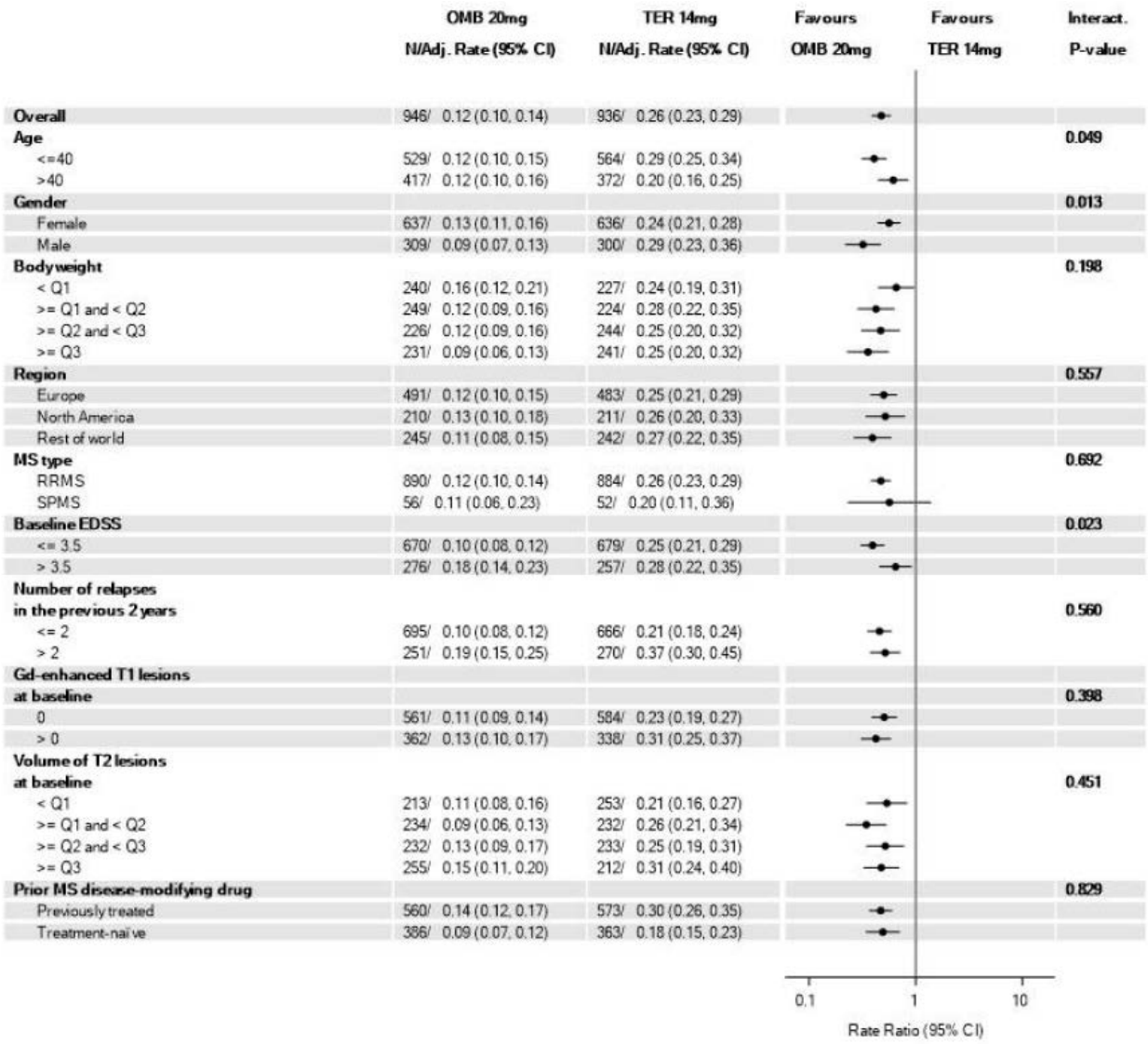
The PK data of 284 subjects dosed with ofatumumab 20 mg were distributed into quartiles (i.e. 1st quartile: n=72, 45-61; 2nd quartile: n=72, 61-70; third quartile: n=69, 70-85; and 4th quartile: n=71, 85-168) based on their weight distribution and plotted along with the corresponding median population predictions (**Figure 3-5**). Overall, increase in body weights resulted in lower AUC and C_{max} of ofatumumab. The corresponding changes in steady-state C_{max} and AUC were up to 60% when compared to the subject of 70 kg weight (**Figure 2-3** and **Table 3-1**). However, these differences do not have an impact on primary clinical endpoint (**Figure 3-6**).

Figure 3-5: Top row: Individual PK profiles of ofatumumab by body weight quartiles. Black dashed line indicates median population predictions from sponsor's final PK model; Bottom row: Mean PK profiles of ofatumumab by body weight quartiles. Red, green, cyan and purple color indicates 1st, 2nd, 3rd and 4th quartile of body weights respectively. Error bars indicates 95% confidence intervals.



Source: M:\Ofatumumab_BLA125326_VS\Reviewer\Rscripts\pk_analysis_ofatumumab.R

Figure 3-6: Annual relapse rates (time-based)- Confirmed relapses by subgroup: Ofatumumab 20 mg vs. Teriflunomide 14 mg (G2301 and G2302).



MS=multiple sclerosis; N=total number of patients included in the analysis; OMB=ofatumumab; Q=quartile; RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis TER=teriflunomide

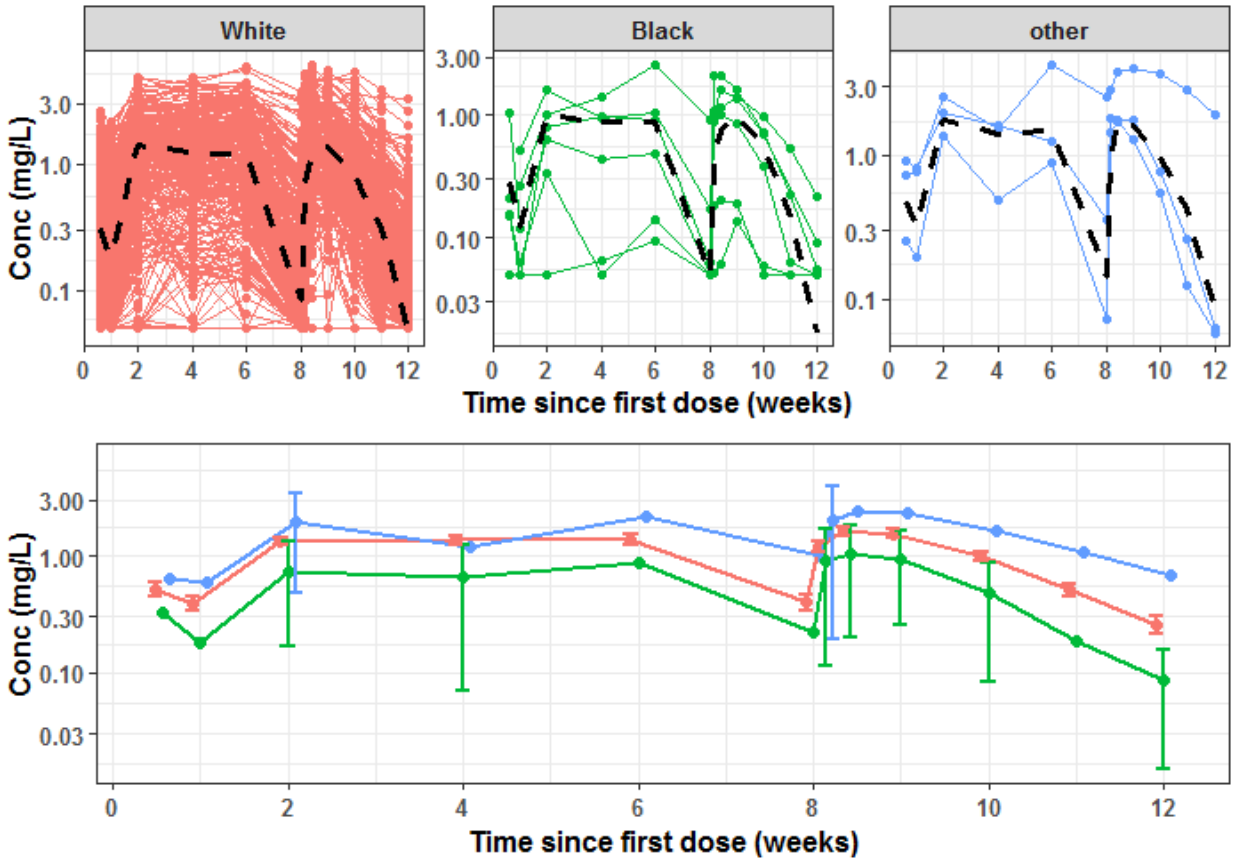
Source: Clinical Overview, Page-56, Figure 4-10.

Race effect

The PK data of 6 Black, 275 White and 3 other subjects dosed with ofatumumab 20 mg were compared and plotted along with the corresponding median population predictions (**Figure 3-7**). Overall, the data was limited to evaluate the impact of race on the PK of ofatumumab. However, the pop PK model was developed from additional studies which has enough subjects across different races (1330 White, 34 Black, 33 Asian and 54

others). The pop PK model did not suggest any clinically relevant impact of race on the PK of ofatumumab.

Figure 3-7: Top row: Individual PK profiles of ofatumumab by race. Black dashed line indicates median population predictions from sponsor's final PK model; Bottom row: Mean PK profiles of ofatumumab by race. Red, green, cyan and blue color indicates White, Black, and others respectively. Error bars indicates 95% confidence intervals.

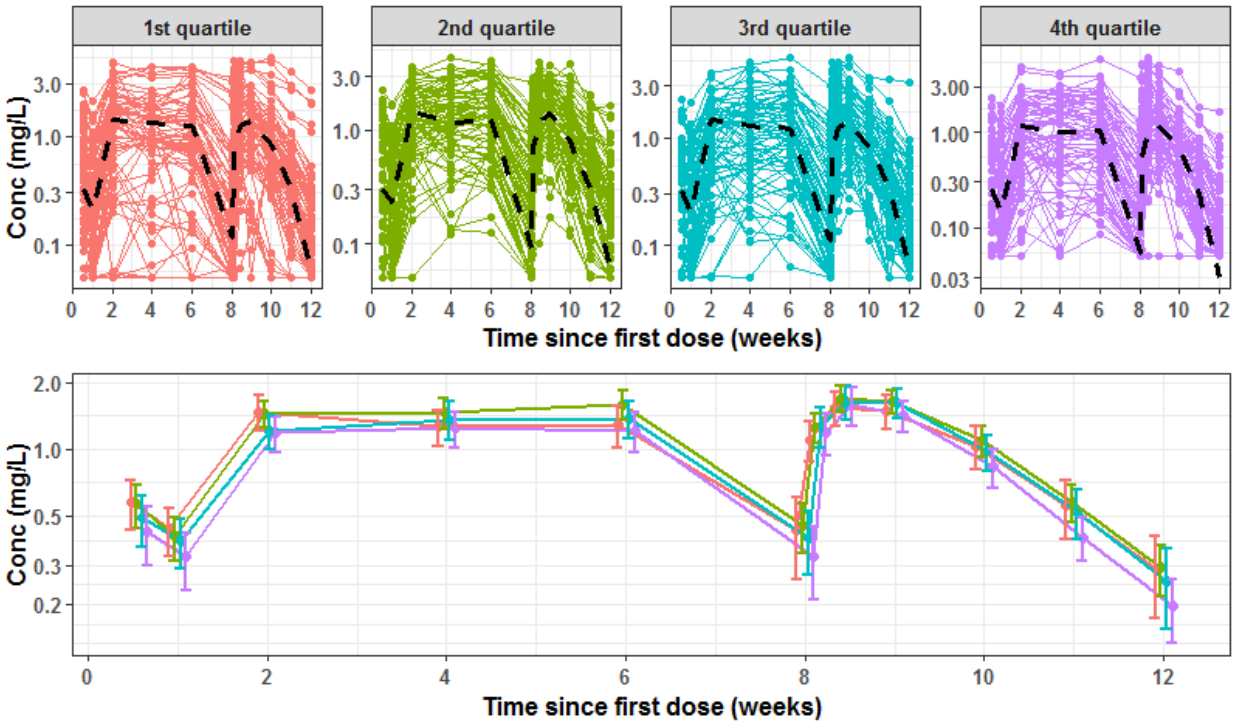


Source: M:\Ofatumumab_BLA125326_VS\Reviewer\Rscripts\pk_analysis_ofatumumab.R

Baseline B-cell effect

The PK data of 284 subjects dosed with ofatumumab 20 mg were distributed into quartiles (i.e. 1st quartile: n=71, 15-154; 2nd quartile: n=71, 154-219; third quartile: n=71, 219-280; and 4th quartile: n=71, 280-859) based on the available baseline B-cell information and plotted along with the corresponding median population predictions (**Figure 3-8**). Overlap of 95% confidence intervals (CI) of the PK profiles by baseline B-cell quartiles suggest lack of clinically relevant impact of baseline B-cell on ofatumumab PK.

Figure 3-8: Top row: Individual PK profiles of ofatumumab by baseline B-cell quartiles. Black dashed line indicates median population predictions from sponsor's final PK model; Bottom row: Mean PK profiles of ofatumumab by baseline B-cell quartiles. Red, green, cyan and purple color indicates 1st, 2nd, 3rd and 4th quartile of B-cell values respectively. Error bar indicates 95% confidence intervals.



Source: M:\Ofatumumab_BLA125326_VS\Reviewer\Rscripts\pk_analysis_ofatumumab.R

LISTING OF ANALYSIS CODES AND OUTPUT FILES

File Name	Description	Location

pk_analysis_ofatumumab.R	Exploratory PK analysis	\\Reviews|Ofatumumab_BLA125326_VS\ Reviewer\Rscripts

REFERENCES

1. Novartis population PK report: Population pharmacokinetics of OMB157 in relapsing multiple sclerosis patients, 25 Nov 2019.
2. Novartis population PD 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, 03 Dec 2019.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAGAN MOHAN R PAREPALLY
06/12/2020 05:07:46 PM

VISHNU D SHARMA
06/15/2020 09:25:43 AM

VENKATESH A BHATTARAM
06/15/2020 09:27:26 AM

YUXIN MEN
06/19/2020 02:14:54 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326Orig1s070

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	August 19, 2020
Reviewer:	Silvia Perez-Vilar, PharmD, PhD Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Deputy Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	KESIMPTA (ofatumumab)
Application Type/Number:	BLA 125326, Supplement 70
Applicant/sponsor:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2020-1422

1. BACKGROUND INFORMATION

1.1. Medical Product

Ofatumumab (KESIMPTA, Novartis Pharmaceuticals Corporation) is a recombinant fully human IgG1 kappa anti-CD20 monoclonal antibody that targets an epitope of the CD20 molecule on the cell membrane.[1,2] The U.S. Food and Drug Administration (FDA) approved ofatumumab (ARZERRA®, currently Novartis Pharmaceuticals Corporation) under accelerated approval regulations for intravenous use for the treatment of patients with chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab in October 2009.[3] The new proposed indication is for the treatment of relapsing forms of multiple sclerosis (RMS).[4] The precise mechanism by which ofatumumab exerts its therapeutic effects in multiple sclerosis (MS) is unknown, but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ofatumumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.[5] Other monoclonal antibodies that target the CD20 molecule are rituximab, commonly used off-label for the treatment of RMS, and ocrelizumab, approved for the treatment of relapsing and progressive forms of MS.[6]

KESIMPTA is administered as a subcutaneous injection. The proposed initial dosing regimen is 20 mg administered at weeks 0, 1, and 2 with subsequent 20 mg-monthly doses starting at week 4.[7] After subcutaneous administration, ofatumumab is believed to be predominantly absorbed via the lymphatic system similarly to other therapeutic monoclonal antibodies. It is eliminated through both a target-independent route as with other IgG molecules and a B cell-mediated route. The half-life at steady state was estimated to be approximately 16 days following subcutaneous administration of repeated KESIMPTA 20 mg dose.[8]

The Supplemental Biological License Application (sBLA) submission included two randomized active comparator-controlled clinical trials—in which 946 adult patients with RMS were treated with KESIMPTA for a median duration of 85 weeks—and three additional studies to support safety.[9] The proposed label (as of August 19, 2020) includes warnings and precautions for infections, injection-related reactions, immunoglobulin levels, and fetal risk.[10]

---

[1] KESIMPTA (ofatumumab). Clinical review dated May 15, 2020. Division of Neurology 2. U.S. Food and Drug Administration.
[2] Proposed KESIMPTA labeling dated August 19, 2020.
[3] ARZERRA (ofatumumab) label dated August 30, 2016. Accessed on July 8, 2020 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125326s063lbl.pdf
[4] The submission for the treatment of relapsing forms of multiple sclerosis is a supplemental Biological License Application with a different proposed trade name (KESIMPTA) to differentiate the therapy's indicated use and because of a different route of administration.
[5] See footnote 2.
[6] See footnote 1.
[7] Ibid.
[8] See footnote 2.
[9] See footnote 1.
[10] See footnote 2.

1.2. Describe the Safety Concern

The Division of Neurology 2 (DN2) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of ofatumumab during pregnancy. Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2–4%.[11,12] MS is a chronic inflammatory disease of the central nervous system leading to demyelination and neurodegeneration. The vast majority of patients with MS initially follow a relapsing-remitting course, defined by acute exacerbations from which they typically completely or incompletely recover, with periods of relative clinical stability in between.[13] MS is commonly diagnosed in women of childbearing age and its incidence is two to three times higher in women than men. Women with MS are not less fertile and do not have more difficulty in completing a pregnancy to term compared with healthy controls.[14] However, maternal MS may be associated with an increased rate of caesarean delivery and lower infant birth weight compared with women without MS.[15]

Data on pregnancy exposure during clinical trials are insufficient to inform the risk of maternal, fetal, and infant outcomes associated with the use of ofatumumab. The ofatumumab clinical trials required that sexually active subjects of reproductive potential (both men and women) use an effective form of contraception for the duration of the study. A total of five female participants became pregnant in the ofatumumab long-term group (two randomized active comparator-controlled clinical trials and one of the studies to support safety). Of these, two pregnancies resulted in terminations—one elective (no reason given other than "patient's wish") at approximately eight weeks of gestation, and one therapeutic at eight weeks due to an embryonic pregnancy (blighted ovum). One pregnancy resulted in a normal healthy newborn through vaginal delivery at 39 weeks gestation. The outcomes of the other two pregnancies were unknown (one was ongoing at the time of the report).[16] The nonclinical toxicology package for the original BLA for ofatumumab included an embryofetal development study in monkeys. To support approval for the new indication, the applicant submitted an enhanced pre- and post-natal development study also in monkeys. Both studies showed that exposure to ofatumumab given intravenously during gestation did not cause teratogenicity, but showed increased postnatal mortality, persistently reduced postnatal body weights in females, and

[11] Food and Drug Administration. (2014). "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format. Draft Guidance." Guidance for Industry Retrieved February 3, 2020, from https://www.fda.gov/media/90160/download
[12] Centers for Disease, Control and Prevention (2008). "Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005." MMWR Morb Mortal Wkly Rep 57(1): 1-5
[13] Katz Sand, I. (2015). "Classification, diagnosis, and differential diagnosis of multiple sclerosis." Curr Opin Neurol 28(3): 193-205
[14] Voskuhl, R. and C. Momtazee (2017). "Pregnancy: Effect on Multiple Sclerosis, Treatment Considerations, and Breastfeeding." Neurotherapeutics 14(4): 974-984
[15] Kelly, V. M., L. M. Nelson and E. F. Chakravarty (2009). "Obstetric outcomes in women with multiple sclerosis and epilepsy." Neurology 73(22): 1831-1836
[16] Novartis. OMB157 (ofatumumab). 2.7.4 Addendum 1 to 2.7.4 Summary of Clinical Safety: 120-day Safety Update, dated April 6, 2020.

persistent adverse immune effects in the offspring that were maternally-exposed to the high dose.[17]

The currently proposed labeling, as of August 19, 2020, includes warnings and precautions for fetal risk (Section 5.4). It states that KESIMPTA (b) (4) *cause fetal harm* (b) (4) *Advise females of reproductive potential* (b) (4) *to use* (b) (4) *effective* (b) (4) *contraception* (b) (4) Section 8.1 (Pregnancy) states:

"Risk Summary
There are no adequate data on the developmental risk associated with the use of KESIMPTA in pregnant women. Ofatumumab may cross the placenta and cause fetal B-cell depletion based on findings from animal studies (see Data).
Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to KESIMPTA have not been studied in clinical trials. The potential duration of B-cell depletion in infants exposed to ofatumumab in utero, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown. Avoid administering live vaccines to neonates and infants exposed to KESIMPTA in utero until B-cell recovery occurs [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)].
Following administration of ofatumumab to pregnant monkeys, increased mortality, depletion of B-cell populations, and impaired immune function were observed in the offspring, in the absence of maternal toxicity, at plasma levels substantially higher than that in humans (see Data).
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.
Data
Animal Data
Intravenous administration of ofatumumab (weekly doses of 0, 20, or 100 mg/kg) to pregnant monkeys during the period of organogenesis (gestations days 20 to 50) resulted in no adverse effects on embryofetal development; however, B-cell depletion was observed in fetuses at both doses when assessed on gestation day 100. Plasma exposure (Cave) at the no-effect dose (100 mg/kg) for adverse effects on embryofetal development was greater than 5000 times that in humans at the recommended human maintenance dose of 20 mg. A no-effect dose for effects on B-cells was not identified; plasma exposure (Cave) at the low-effect dose (20 mg/kg) was approximately 780 times that in humans at the recommended human maintenance dose (RHMD) of 20 mg/month.
Intravenous administration of ofatumumab (5 weekly doses of 0, 10, and 100 mg/kg, followed by biweekly doses of 0, 3, and 20 mg/kg) to pregnant monkeys throughout pregnancy resulted in no adverse effects on the development of the offspring. However, postnatal death, B-cell depletion, and impaired immune function were observed in the offspring at the high dose. The deaths at the high dose were considered secondary to B-cell depletion. Plasma exposure (Cave) in dams at the no-effect dose (100/20 mg/kg) for adverse developmental effects was approximately 500 times that in humans at RHMD. A no-effect level for mortality and immune effects in offspring was not established because of the limited number of evaluable offspring at the low dose."

Section 8.3 (Females and Males of Reproductive Potential) states:

[17] KESIMPTA (ofatumumab). Non-clinical primary review dated July 9, 2020. Division of Neurology 2. U.S. Food and Drug Administration.

"Contraception
Females of childbearing potential should use effective contraception while receiving KESIMPTA and for 6 months after the last treatment of KESIMPTA [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]."

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☒ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: Alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to medical records. The pregnancy registry being considered requires that an expert clinical geneticist or dysmorphologist review and classify medical records of all major congenital malformations. Also, although in a first stage, the study using claims or electronic medical data may be algorithm-based, if it shows an imbalance in any of the outcomes being investigated, FDA may consider requiring outcome validation in the selected database(s) or a chart-confirmed analysis.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

2.5. Please include the proposed PMR language in the approval letter.

The following language has been proposed by DN2, as of July 8, 2020, for the PMRs related to pregnancy outcomes:

*"**Pregnancy PMR 3901-2**:*
Prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to KESIMPTA (ofatumumab) during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to KESIMPTA (ofatumumab) before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life."
*"**Pregnancy PMR 3901-3**:*
A pregnancy outcomes study using a different study design than provided for in PMR 3901-2 (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to KESIMPTA (ofatumumab) during pregnancy compared to an unexposed control population."

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SILVIA PEREZ-VILAR
08/19/2020 02:13:22 PM

KIRA N LEISHEAR
08/19/2020 02:17:54 PM

WEI HUA on behalf of SUKHMINDER K SANDHU
08/19/2020 02:20:27 PM

JUDITH W ZANDER
08/19/2020 02:22:15 PM

MICHAEL D NGUYEN
08/19/2020 02:38:04 PM

ROBERT BALL on behalf of GERALD J DALPAN
08/19/2020 03:38:41 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 29, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	BLA 125326/Supplement 70
Product Name and Strength:	Kesimpta [a](ofatumumab) injection, 20 mg/0.4 mL
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2020-84-2
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised Instructions for Use (IFU) and Prescribing Information received on July 28, 2020 for Kesimpta. The Division of Neurology 2 (DN 2) requested that we review the revised IFUs and PI for Kesimpta (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The Applicant implemented our recommendations and we have no additional recommendations at this time.

[a] The proposed proprietary name Kesimpta was found conditionally acceptable on March 26, 2020.
[b] Whaley E. Human Factors Study Report and Label and Labeling Review for Kesimpta (BLA 125326/Supplement 70). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 6. RCM No.: 2020-17 and 2020-84.

APPENDIX A. LABEL AND LABELING RECEIVED ON JULY 28, 2020

Instructions for Use – pen (not pictured)

- See link: \\CDSESUB1\evsprod\bla125326\0288\m1\us\instructions-for-use-pen.docx

Instructions for Use – prefilled syringe (not pictured)

- See link: \\CDSESUB1\evsprod\bla125326\0288\m1\us\instructions-for-use-syringe.docx

Prescribing information (not pictured)

- See link: \\CDSESUB1\evsprod\bla125326\0288\m1\us\proposed-clean.pdf

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EBONY A WHALEY
07/29/2020 03:19:58 PM

LOLITA G WHITE
07/29/2020 04:37:18 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 16, 2020
To:	Candido Alicea, Ph.D. Regulatory Project Manager **Division of Neurology II**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Christine Bradshaw, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	KESIMPTA (ofatumumab)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 125326
Supplement Number:	S-070
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On December 20, 2019, Novartis Pharmaceuticals Corporation submitted for the Agency's review a Prior Approval Supplement-Efficacy for supplemental Biologics License Application (sBLA) 125326 Supplement 070 for KESIMPTA (ofatumumab) injection, for subcutaneous use. The purpose of this sBLA is to propose the addition of a new indication for the treatment of relapsing forms of multiple sclerosis.

Ofatumumab is currently approved for intravenous use under the tradename ARZERRA for the treatment of Chronic Lymphocytic Leukemia (CLL) and was approved on October 26, 2009.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II on January 17, 2020 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for KESIMPTA (ofatumumab) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft KESIMPTA (ofatumumab) MG and IFUs received on December 20, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 6, 2020.
- Draft KESIMPTA (ofatumumab) Prescribing Information (PI) received on December 20, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 6, 2020.
- DMPPs review of IND 111116 TRADENAME (ofatumumab), injection for subcutaneous use of the pen and prefilled syringe completed on April 23, 2018.
- Medication Guides and Prescribing information for Uplizna BLA 761142 (approved 6/11/2020) and Rituxan BLA 103705 (approved 11/26/1997).

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFUs we:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFUs is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

25 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D JACKSON
07/16/2020 10:48:33 AM

CHRISTINE J BRADSHAW
07/16/2020 12:29:35 PM

MARCIA B WILLIAMS
07/16/2020 12:31:09 PM

LASHAWN M GRIFFITHS
07/16/2020 12:53:45 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 10, 2020

To: Lawrence Rodichok, M.D., Clinical Reviewer
Division of Neurology II (DN2)

Candido Alicea, PhD, Regulatory Project Manager, (DN2)

Tracy Peters, PharmD, Associate Director for Labeling, (DN2)

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for KESIMPTA (ofatumumab) injection, for subcutaneous use

BLA: 125326 / Supplement 70

In response to DN2 consult request dated January 17, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for KESIMPTA (ofatumumab) injection, for subcutaneous use. This supplement (S-70) proposes the addition of a new indication for the treatment of relapsing forms of multiple sclerosis.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN2 (Candido Alicea) on July 6, 2020, and are provided below.

Medication Guide/IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide/IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling downloaded from DN2 SharePoint on July 8, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

23 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DOMENIC G DALESSANDRO
07/10/2020 09:53:20 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 15, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	BLA 125326/Supplement 70
Product Name and Strength:	Kesimpta (ofatumumab) injection, 20 mg/0.4 mL
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2020-84-1
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on May 11, 2020 for Kesimpta. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling for Kesimpta (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented our recommendations and we have no additional recommendations at this time.

7 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

[a] Whaley E. Human Factors Study Report and Label and Labeling Review for Kesimpta (BLA 125326/Supplement 70). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 6. RCM No.: 2020-17 and 2020-84.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EBONY A WHALEY
05/15/2020 12:46:57 PM

LOLITA G WHITE
05/15/2020 12:50:23 PM

Clinical Inspection Summary

Date	5/12/2020
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Susan Daugherty, Regulatory Project Manager Lawrence Rodichok, M.D., Medical Officer Division of Neurology 2 Office of Neuroscience
BLA #	125326 S-70
Applicant	Novartis Pharmaceuticals Corporation
Drug	Ofatumumab (Arzerra®)
NME	No
Proposed Indication	Treatment of relapsing forms of multiple sclerosis
Standard/Priority Review	Priority
Consultation Request Date	1/31/2020
Summary Goal Date	5/20/2020
Action Goal Date	6/20/2020
PDUFA Date	6/20/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical site of Dr. Sundaram was inspected in support of this BLA and covered Protocol COMB157G2302. The study appears to have been conducted adequately, and the data generated by this site generally appear acceptable in support of the respective indication.

OSI received a consult from the Division of Neurology 2 (DN2) on 1/31/2020 that identified the following clinical investigators for Good Clinical Practice (GCP) inspections:

- Dr. Selmaj (Site 4000/Protocol COMB157G2301, Poland)
- Dr. Maciejowski (Site 4001/ Protocol COMB157G2301, Poland)
- Dr. Bosnjak-Pasic (Site 1091/ Protocol COMB157G2302, Croatia)
- Dr. Sundaram (Site 5056/ Protocol COMB157G2302, United States)

An inspection assignment for these four sites was issued on 2/4/2020, and the Office of Regulatory Affairs (ORA) scheduled these inspections. However, at the current time, the COVID-19 global pandemic has significantly limited our ability to conduct on-site GCP inspections. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for these planned inspections in support of BLA 125326 S-70 was reevaluated. At that time, the domestic clinical inspection of Dr. Sundaram was ongoing, so the discussion focused on the need to conduct the remaining inspections at the three foreign sites. Following discussions between OSI and DN2, a decision was made that assessment of the application could proceed without the three foreign GCP inspections. Since

the one completed domestic inspection covered only Protocol COMB157G2302, at this time OSI will be unable to determine if Protocol COMB157G2301 was conducted adequately and whether the study data are reliable in support of the proposed indication.

II. BACKGROUND

Ofatumumab (Arzerra®) injection was approved is 2009 for the treatment of chronic lymphocytic leukemia (BLA 125326). An efficacy supplement (BLA 125326 S-70) was submitted for the treatment of relapsing forms of multiple sclerosis (MS), including relapsing-remitting disease and active secondary progressive disease, in adults.

The sponsor has submitted two Phase 3 studies of identical study design, COMB157G2301 and COMB157G2302, to support the efficacy and safety of ofatumumab in the treatment of relapsing multiple sclerosis in adults.

Protocol COMB157G2301 (ASCLEPIOS I)

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"

Subjects: 927 randomized

Sites: 170 sites in 28 countries; North America (United States 60, Canada 4), Western Europe (48), Eastern Europe (37), Middle East/Central Asia (8), Asia/Pacific (7), Latin America (4), and Australia (2)

Study Initiation and Data Cut-Off Dates: 9/20/2016 – 7/5/2019

This was a randomized, double-blind, double-dummy, active-comparator-controlled study in subjects with a diagnosis of relapsing multiple sclerosis (RMS). Main eligibility criteria included male or female subjects; 18 to 55 years of age; diagnosis of relapsing MS (relapsing-remitting course [RRMS] or secondary progressive course [SPMS] with disease activity), Expanded Disability Status Scale (EDSS) score of 0 to 5.5 (inclusive) at screening; documentation of at least 1 relapse during the previous year, or 2 relapses during the previous two years prior to screening, or a positive Gd-enhancing MRI scan during the year prior to randomization; and neurologically stable within one month prior to randomization. Excluded were subjects with primary progressive MS, SPMS without disease activity, or neuromyelitis optica; disease duration of >10 years in subjects with EDSS score $\leq$2.

This study was comprised on three phases:

Screening/Baseline – up to 45 days

Double-Blind Treatment – continued until the End of Study was declared by the sponsor (based on numbers of events), or 30 months, whichever was sooner.

Subjects were randomized (1:1) to:

- Ofatumumab arm: ofatumumab 20 mg sc injections on Day 1, 7, 14, Week 4 and every 4 weeks thereafter + teriflunomide-matching placebo capsule orally once daily
- Teriflunomide arm: teriflunomide 14 mg capsule orally once daily + ofatumumab-matching placebo injections on Day 1, 7, 14, Week 4 and every 4 weeks thereafter

Randomization was stratified by geographic region and by MS subtype (RRMS, SPMS).

Investigational product was provided in pre-filled syringes for subcutaneous administration containing 20 mg ofatumumab (50 mg/mL) and matching placebo. The control treatment was provided as teriflunomide (Aubagio®) 14 mg over-encapsulated tablets for oral administration and matching placebo.

Safety Follow-up: Subjects who complete the double-blind treatment phase and who do not enroll in the separate open-label extension study will be followed up for safety for a minimum of 9 months. Subjects who have not repleted their B-cells or for whom teriflunomide plasma levels are >0.02mg/L at 9 months will continue in this phase until those targets are met. These assessments were performed centrally to maintain the study blind.

The primary efficacy endpoint was the annualized relapse rate comparing ofatumumab and teriflunomide. The annualized relapse rate was defined as the number of confirmed MS relapses in a year (based on EDSS scores).

Subjects were instructed to immediately report new neurological symptoms, re-occurring, or worsening of previous symptoms to the investigator. If symptoms were consistent with a relapse, an unscheduled visit to the investigator and independent EDSS rater was to occur within 7 days of symptom onset, if possible. The assessment, management, and reporting of MS relapse was made by the investigator. Confirmation of MS relapse and severity grading, based on EDSS score provided by the independent EDSS rater, was done centrally.

The definition of a MS relapse was the 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 or known infection.

The definition of a confirmed MS relapse is one accompanied by a clinically relevant change in the EDSS score, 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). Confirmation of MS relapse based on these definitions was done centrally.

Protocol COMB157G2302 (ASCLEPIOS 2)

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"

Subjects: 955 randomized

Sites: 180 sites in 30 countries; North America (United States 60, Canada 4), Western Europe (60), Eastern Europe (34), Asia/Pacific (8), Latin America (7), Middle East/Central Asia (4), Africa (2) and Australia (1)

Study Initiation and Data Cut-Off Dates: 8/26/2016 – 7/10/2019

The study design was identical to Protocol COMB157G2301.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, site efficacy, numbers of enrolled subjects, and prior inspectional history.

III. RESULTS

Bharathy Sundaram, M.D.
Site #5056
Texas Institute for Neurological Disorders
321 N. Highland Ave, Suite 200
Sherman, TX 75092
Inspection Dates: 3/17/2020 – 3/20/2020

At this site for Protocol COMB157G2302, 12 subjects were screened, 9 subjects were enrolled and randomized, and 6 subjects completed the study. One of the enrolled subjects (b) (6) (b) (6) (b) (6) (b) (6) Three subjects discontinued the study for the following reasons: [noted as physician decision in data listings] (n = 1) and loss to follow-up (n = 2).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (Expanded

Disability Status Score [EDSS]).

At the start of the study, independent EDSS raters recorded EDSS scores on paper forms. In August 2016, approximately 8 months after the sponsor initiated this study, an online, internet-based application (TrialManager) was launched. Independent EDSS raters were instructed to discontinue using the paper forms and to enter EDSS assessments directly into TrialManager. The FDA field investigator was able to review EDSS scores on paper forms as well as having access to TrialManager.

In an information request, the sponsor was asked to detail the data flow of EDSS data in TrialManager. The sponsor responded that once EDSS examination data were entered into TrialManager, an inbuilt algorithm was used to detect scoring inconsistencies. The independent EDSS rater was required to run this algorithm (noted as "Feedback check" in TrialManager) at least once. There were three further opportunities for the independent EDSS rater to review and change any scores or responses and to run this algorithm. Once the EDSS scores were finalized and submitted, the data was automatically transmitted and a central EDSS expert at (b) (4) reviewed any cases with outstanding inconsistencies or where the EDSS rater had entered comments. The EDSS expert could then perform further data clarification, triggering queries to the independent EDSS rater via TrialManager. The EDSS expert could suggest a different score which the independent EDSS rater could accept or reject.

During the FDA inspection, differences in EDSS scores on paper forms vs. TrialManager data were identified in 2 of 9 enrolled subjects (Subjects (b) (6) and (b) (6) see Table 1). Subject (b) (6) site on (b) (6) Despite the availability of TrialManager, the independent EDSS rater at Site (b) (6) had continued to use the paper forms and transcribe the data, sometimes many months later, into TrialManager. Since all of the EDSS assessments with discrepancies between the paper forms and TrialManager for this subject occurred at Site (b) (6), no further information was available to determine the cause of these discrepancies. However, importantly, there were no data discrepancies for the unscheduled EDSS assessment for the multiple sclerosis relapse performed on (b) (6) for Subject (b) (6) For Subject (b) (6) the independent EDSS rater stated that the score was changed based on communication with the central EDSS expert but that the change was inadvertently not made on the paper form.

Additionally, when EDSS scores in TrialManager were verified against the sponsor data line listings for all subjects, one discrepancy was noted for one baseline EDSS assessment for Subject (b) (6) (see Table 1). There was no evidence of underreporting of adverse events, and no SAEs occurred at this site

Table 1. Data Discrepancies for EDSS Score

Subject	Study Arm	Date of EDSS	EDSS Score		
			EDSS Paper Form	TrialManager Database	Sponsor Data Listing
(b) (6) subject)	Teriflunomide	(b) (6) Screening	1	2.5	2.5
		(b) (6) Baseline	2.5	1.5	1.5
		(b) (6) Month 9	0	1	1
		(b) (6) Month 12	0	1	1
		(b) (6) Month 15	0	1	1
		(b) (6) Month 18	0	1	1
(b) (6)	Ofatumumab	(b) (6) EOS	3.5	3	3
(b) (6)	Teriflunomide	(b) (6) Baseline	3.5	3.5	4

Reviewer's comment: It should be noted that the EDSS data discrepancies noted during the inspection were for EDSS assessments conducted at scheduled visits. No EDSS data discrepancies were noted for the unscheduled EDSS assessments conducted at the time of the multiple sclerosis relapses in the two subjects (Subjects (b) (6) and (b) (6) both randomized to teriflunomide) at this site who had relapses.

Since Subject (b) (6) and the EDSS discrepancies occurred for assessments (b) (6) (Site (b) (6), there was insufficient information available to determine the reason for the discrepancies. The single EDSS discrepancy for Subject (b) (6) was due to an oversight by the independent EDSS rater in which changes to EDSS data in TrialManager were not recorded on the corresponding paper form.

For Subject (b) (6) the single EDSS discrepancy noted was between TrialManager and the sponsor data listings, so this discrepancy would have occurred at a vendor or sponsor level rather than at the site level. Since EDSS scores may be used in analyses of secondary efficacy endpoints, we recommend that the baseline EDSS score for Subject (b) (6) be corrected from 4 to 3.5.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/BLA #125326
Division of Neurology 2/Division Director/Nicholas Kozauer
Division of Neurology 2/Medical Team Leader/Paul Lee
Division of Neurology 2/Medical Officer/Lawrence Rodichok
Division of Neurology 2/Project Manager/Susan Daugherty
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARA L ALFARO
05/12/2020 12:08:47 PM

PHILLIP D KRONSTEIN
05/12/2020 12:18:47 PM

KASSA AYALEW
05/13/2020 07:32:15 AM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 6, 2020
Requesting Office or Division:	Division of Neurology 2 (DN2)
Application Type and Number:	BLA 125326/S-070
Product Type:	Combination product
Drug Constituent Name and Strength	Kesimpta[a] (ofatumumab) injection, 20 mg/0.4 mL
Device Constituent:	Prefilled pen; prefilled syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
Submission Date:	December 20, 2019; December 23, 2019; March 4, 2020; March 17, 2020; March 24, 2020
OSE RCM #:	2020-17; 2020-84
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

[a] The proposed proprietary name Kesimpta was found conditionally acceptable on March 23, 2020.

1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under BLA 125326 Supplement 70 for Kesimpta (ofatumumab) injection. This is a combination product with proposed prefilled pen and prefilled syringe device constituent parts that is intended to treat relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

1.1. PRODUCT DESCRIPTION

Kesimpta (ofatumumab) injection is supplied in two configurations: (1) a single-dose prefilled pen (Sensoready pen) and (2) a single-dose prefilled syringe (b) (4)
Each Kesimpta prefilled pen or prefilled syringe is supplied in a one-count carton.

1.2. REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

Arzerra (ofatumumab) injection BLA 125326 was approved on October 26, 2009 for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. Arzerra is supplied in vials for intravenous infusion and is administered by healthcare providers.

We previously reviewed the Applicant's HF validation study protocol for the proposed RMS indication.[bc] We identified deficiencies in the proposed HF validation study protocol and communicated them to the Applicant. On December 20, 2019, the Applicant submitted Supplement 70.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)

[b] Whaley, E. Human Factors Protocol Review for Ofatumumab injection (IND 111116). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 20. RCM No.: 2018-617.
[c] Karpow, C. Human Factors Protocol Review Memo for Ofatumumab injection (IND 111116). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 8. RCM No.: 2018-617-1.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Tables 2 and 3), and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

The Applicant completed HF validation studies of the prefilled syringe (PFS) and of the prefilled pen (see Appendix D). We note the PFS device platform is used in approved products (i.e. Cosentyx, Zarxio) and the prefilled pen device platform, Sensoready, is also used in an approved product (i.e. Cosentyx).

The HF validation study for the PFS included a total of 33 participants in the following user groups: 15 untrained injection naïve adult patients with RMS and 18 untrained injection experienced adult patients with RMS.

The HF validation study for the prefilled pen included a total of 32 participants in the following user groups: 15 untrained injection naïve adult patients with RMS and 17 untrained injection experienced adult patients with RMS.

In both HF validation studies, participants completed two simulated use sessions. Following the second simulated use session, each participant completed knowledge-based assessment and root cause analysis.

3.2 RESULTS AND ANALYSES

Tables 2 and 3 describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

Table 2. HF validation study results for the prefilled syringe				
Tasks	Number and Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
1A. Store PFS at 2°-8°C (refrigerated) – knowledge-based assessment	*n = 9 failures* • Nine participants did not identify the need for refrigeration. Instead, they stated other places for storage such as: medicine or bathroom cabinet, kitchen counter, kitchen cabinet or drawers, or general cabinet. • Subjective feedback included: do not or did not store their own medication in refrigerator; did not refer to IFU because the short needle length and the simulated environment provided a sense of confidence; reported that the IFU was dense with information; relies on an HCP to train her on how to use PFS (having not identified the information in the IFU); thought that a cabinet or drawer would protect the device from direct sunlight; forgot to mention due to focusing on the mechanics of the injection; and stated they did not notice PFS storage instructions because she was focused on more salient (i.e., bold)	• Previous behaviors used for their own medication (negative transfer) • Not paying attention to the related information in the IFU or not reading the IFU due to study artifact • Focusing on other aspects of the IFU • Expecting to be trained by an HCP	The Applicant stated that in real use, users are also likely to obtain storage information from the pharmacy or would pay more attention to the IFU and/or packaging label if injecting for real. The Applicant also noted that providing storage instructions is also part of routine instructions provided by a pharmacist and/or physician. The Applicant noted the risk of storage error applies to all medications requiring refrigeration prior to use and is not unique to this product. The Applicant indicated that injection-experienced participants frequently assumed they	Based on the Applicant' use-related risk analysis (URRA), failure to store the PFS refrigerated might result in injection of degraded or aggregated drug product and may lead to local and temporary limited pain and/or irritation. We disagree with the Applicant's assertion that users will likely receive storage information as routine instructions from the pharmacist or physician. While we acknowledge this may occur in some cases, it is not guaranteed to occur in all cases. Our review of the study results did not identify subjective feedback indicating confusion with labels and labeling. Our review of the labels and labeling finds that the PFS IFU instructs users to store the product under

	text.		do not need to read the IFU, or not in depth, but the majority of them stated that in real-world use they would have read it. As such, the Applicant attributed some errors to study artifact. The Applicant determined that the conclusion can support that the risk control measures (RCM) in place to mitigate risks related to incorrect storage are sufficiently effective and a small remaining residual risk is acceptable.	refrigeration. We also note the carton labeling includes this storage information. However, we note the information on the carton labeling does not appear on the principal display panel (PDP). As such, we provide PFS carton labeling recommendation #1 in Section 3.5 below to revise the carton labeling to include "REFRIGERATE" on the PDP. In this particular instance, we find this revision can be implemented without the need for submission of additional HF validation data.
4B. Insert needle into skin	*Session 1* *n = 14 use difficulties* • Fourteen participants inserted the needle at steep angle. Subjective feedback was not provided. *Session 2* *n = 17 use difficulties* • Fourteen participants who had use difficulty in Session 1 repeated the	• The Applicant indicated that 1 participant did not notice any IFU content directing him to insert needle at moderate angle and was accustomed to injecting at 90° angle • The Applicant did not complete RCA for the majority of participants who failed this	The Applicant did not recommend revisions to the user interface in response to participant performance on this task.	Based on the Applicant's URRA, failure to correctly insert the needle might result in: (1) underdose, (2) local and temporary limited pain or irritation due to intradermal injection, (3) injection into a blood vessel or muscle, or (4) back spilling of drug product which may lead to underdose.

	same use difficulty in Session 2. Three additional participants also inserted the needle at a steep angle. Subjective feedback was not provided.	task due to study oversight.		Our review of the labels and labeling finds that the PFS IFU Step 10 includes a graphic that depicts an approximately 45-degree injection angle. However, the IFU text does not specify the injection angle. As such, we provide PFS IFU recommendation #1 in Section 3.5 below to revise the IFU specify the injection angle. In this particular instance, we find this revision can be implemented without submission of additional HF validation data.
4D. Wait 5 seconds	*Session 1* *n = 17 failures* • Seventeen participants did not pause after the injection with the needle in the injection site. *Session 2* *n = 16 failures* • Sixteen participants failed this task in Session 2. Fifteen of these 16 participants repeated the same failure in Session 1. The Applicant did not provide subjective feedback.	• Accustomed to removing past devices immediately after fully depressing plunger and/or observed HCPs doing so. • Did not thoroughly read to IFU because they assumed they knew how to perform all steps. • Would have read the IFU if they were to administer an actual injection at home (possible study artifact) • Overlooked IFU Step 12 instruction due to focusing on the figures, the IFU's information density, or	The Applicant did not recommend revisions to the user interface in response to participant performance on this task. Additionally, the Applicant noted that the instruction to "Wait 5 seconds" has been included in the IFU for similar products and was considered to be good practice in order to reduce the risk of a wet injection. The Applicant	Based on the Applicant's URRA, failure to wait 5 seconds after the injection could result in back-spilling of the drug product and further lead to: (1) skin contact with the drug product or (2) eye contact with drug product resulting in local pain and irritation. Our review of the labels and labeling finds that the PFS IFU Step 12 instructs users to hold the PFS in place for 5 seconds. However, we note that this information is not prominent and might be overlooked.

		because the step was not conspicuous. • Assumed injection was complete because all medication was expelled. • Received upward tactile feedback after fully depressing plunger, and interpreted it to mean they could remove the needle	also noted that recently FDA approved labeling for similar products indicates that this instruction is no longer commonly present in the IFU. However, the Applicant indicate they choose to retain the instruction.	Based on our review of the study results and user interface, we recommend the IFU is revised to consolidate IFU Steps 11 and 12 so that Step 12, which instructs users to wait 5 seconds, is not overlooked. As such, the PFS IFU recommendation #2 in Section 3.5. In this particular instance, we find this revision can be implemented without submission of additional HF validation data.

Table 3. HF validation study results for the prefilled pen				
Tasks	Number of, Description of, and Subjective Feedback for Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
1A. Store autoinjector at 2-8°C (KBA)	*n = 4 failures* • Four participants did not identify the need for refrigeration. The participants stated other places for storage: medicine cabinet; a dry location at room temperature; in the cabinet underneath the bathroom sink; and in a cabinet together with other MS medication "unless it must be stored in the refrigerator". Subjective feedback included: overlooked storage information in IFU due to focusing on the IFU's injection administration sections, would store in cabinet not easily accessible by others, were expecting to receive storage instructions from the pharmacy or more clearly printed on the packaging. *n = 2 use difficulties* • Two participants answered correctly but were unable to find the storage information in the IFU.	• Participants focusing on other aspects of the IFU • Partially attributed to study artifact (i.e. if injecting for real, would pay more attention to the IFU and/or packaging label) • Expecting to receive storage information from the pharmacy.	The Applicant states the risks are mitigated by clearly indicating storage conditions in the labeling (carton, IFU and device labelling). The Applicant also states that requiring refrigeration is not unique to the proposed product. The Applicant concludes that given the above assessment of root causes, and that 78.5% (n=28/32) of participants were able to correctly identify and comprehend the required information, the RCMs in place to mitigate risks related to incorrect storage are sufficiently effective and a small remaining residual risk is acceptable.	Based on the Applicant's use-related risk analysis (URRA), failure to store the product refrigerated might result in potential absorption of degraded drug product after injection and injection of aggregated drug product that may lead to local and temporary limited pain and/or irritation. Our review of the study results did not identify subjective feedback indicating confusion with labeling. However, we note one participant expected to see the storage information clearly printed on the packaging. The carton labeling includes the storage information on the back panel and container label includes the storage information on the PDP. We also note this information is listed in the IFU. As such, we provide prefilled pen carton labeling recommendation #1 in Section 3.5 below to revise the carton labeling to include "REFRIGERATE" on the PDP. In this particular instance, we find this revision can be implemented

				without the need for submission of additional HF validation data.

APPEARS THIS WAY ON ORIGINAL

3.3 ANALYSIS OF OTHER CRITICAL TASK ERRORS

The HF validation studies showed use errors (e.g. failures, difficulties, and close calls) with the critical tasks listed below; however, our assessment of these user errors finds the residual risk is acceptable and thus are not the focus of this review. We reviewed the available participants' subjective feedback, the Applicant's root cause analysis, and the Applicant's proposed risk mitigation strategy to determine acceptability. Subsequently, our assessment of the aforementioned considerations in totality finds the residual risk is acceptable for the use tasks below; thus, we find no recommendations to further address the use errors or mitigations are necessary at this time to address the use errors related to the following use tasks:

Prefilled syringe

- Identify appropriate injection site
- Remove rigid needle shield/needle cap
- Depress plunger until the entire solution is injected
- Release plunger to retract the needle guard and remove prefilled syringe from injection site

Prefilled pen

- Identify appropriate injection site
- Remove cap
- Apply the needle end of Delta-04 to the injection site
- Maintain pressure until the injection is completed and monitor injection
- Identify end of injection

3.4 ANALYSIS OF NON-CRITICAL TASKS

The HF validation studies showed use errors, close calls, and use difficulties with the non-critical tasks listed below. We reviewed the available subjective feedback, the Applicant's root cause analysis and Applicant's proposed risk mitigation strategy to determine acceptability. Subsequently, our assessment of the aforementioned considerations in totality finds the residual risk is acceptable for the use tasks below; thus, we find no recommendations to further address the use errors or mitigations are necessary at this time to address the use errors related to the following use tasks:

Prefilled syringe

- Perform safety checks
- Bring drug to room temperature
- Clean injection site with alcohol swab
- Pinch skin
- Dispose of device and packaging

Prefilled pen

- Perform safety checks
- Wash hands
- Clean injection site with alcohol swab
- Dispose of device and packaging

After evaluating the errors pertaining to these use-related events, we agree with the Applicant that no additional mitigation strategies are necessary, and we determined that the residual risk is acceptable.

3.5 LABELS AND LABELING

Tables 4 and 5 below include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

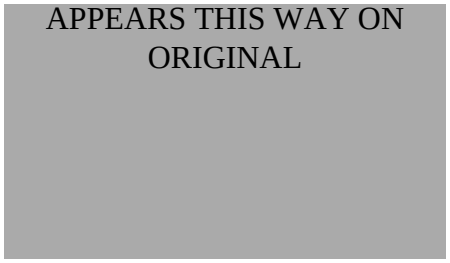


Table 4: Identified Issues and Recommendations for Division of Neurology 2			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information			
1.	The dosing information in Section 2 Dosage and Administration lacks clarity.	Lack of clarity regarding the dosing regimen might contribute to incorrect frequency of administration medication errors.	Revise the statement (b) (6) [redacted] "The recommended dose of PROPRIETARY NAME is: • initial dosing of 20 mg by subcutaneous injection at Weeks 0, 1, and 2, followed by • subsequent dosing of 20 mg by subcutaneous injection once per month starting at Week 4"
2.	In Section 16 How Supplied/Storage and Handling, the NDC numbers are denoted by a placeholder.	We are unable to evaluate this important product identifier for risk of product selection medication error.	We recommend Section 16 is updated to include the actual NDC numbers.

Table 5: Identified Issues and Recommendations for Novartis Pharmaceuticals Corporation (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU) – prefilled syringe			
1.	The IFU does not specify the recommended injection angle.	In the HF validation study, 18 participants had use difficulties in which they inserted the needle of the PFS at a steep angle. Lack of clarity regarding the injection angle might result in wrong technique in drug usage process errors (e.g. administration errors).	Revise the IFU graphic in Step 10 to include text to specify the injection angle.
1.	IFU Step 12 (e.g. wait 5 seconds after injection) might be overlooked due to being decoupled from Step 11.	In the HF validation study, 18 participants did not pause for 5 seconds after the injection. Failure to wait 5 seconds after the injection could result in wet injection or accidental exposure to the drug product.	Revise the IFU such that IFU Steps 11 and 12 are combined into one step.
Container Label – prefilled syringe			
1.	The NDC number is denoted by a placeholder.	We are unable to assess the NDC number.	Revise the labeling to include the intended NDC number.
Container Label – prefilled pen			
1.	See PFS container label recommendation		

	#1 and revise accordingly.		
Carton Labeling – prefilled syringe			
1.	The principal display panel (PDP) does not include key storage information.	In the HF validation study, 9 participants did not identify the need to store the product under refrigeration. User confusion regarding product storage might results in deteriorated drug product errors leading to patient harm and compromised care.	Revise the labeling to include the term "REFRIGERATE" on the PDP.
2.	The NDC number is denoted by a placeholder.	We are unable to assess the NDC number.	Revise the labeling to include the intended NDC number.
Carton Labeling – prefilled pen			
1.	See PFS carton labeling recommendations #1-2 and revise accordingly.		

4. CONCLUSION AND RECOMMENDATIONS

The human factors (HF) validation study results identified use errors, close calls, and use difficulties with critical and non-critical tasks. Upon review of the subjective feedback from study participants and the root cause analyses, we identified some recommendations to revise the Instructions for Use (IFU) and carton labeling to improve prominence, clarity, and understanding of important information. These recommendations are based on our review of the subjective feedback and root cause analysis of the use-related issues as well as our expert review of the proposed product user interface. In this particular instance, we have determined that these changes are a reiteration of information already included in the user interface or are instructions that are not unique to the product. As such, we find these revisions can be implemented without submission of additional HF validation testing data for Agency's review

Additionally, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 4 for the Division and Table 5 for the Applicant. We ask that the Division convey Table 5 in its entirety to the Applicant so that recommendations are implemented prior to approval of this BLA 125326 Supplement 70.

4.1 RECOMMENDATIONS FOR THE NOVARTIS PHARMACEUTICALS CORPORATION

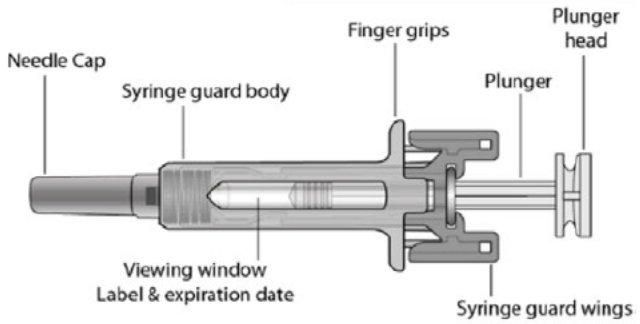
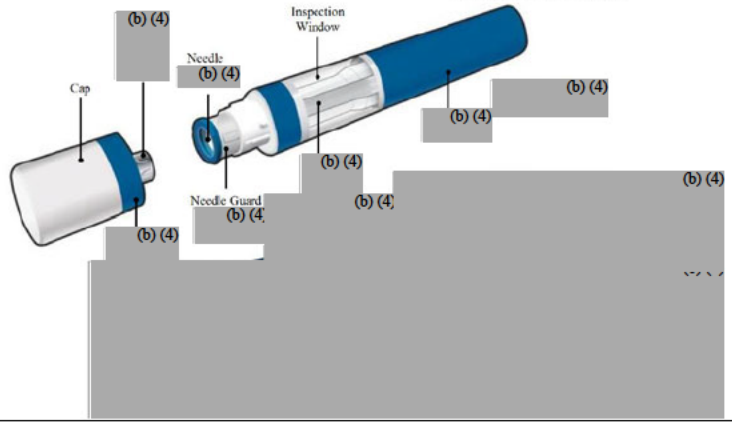
Based on our evaluation of the HF validation study reports and proposed label and labeling, we identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 5 and we recommend that you implement these recommendations.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 6 presents relevant product information for Kesimpta that Novartis Pharmaceuticals Corporation submitted on December 20, 2019.

Table 6. Relevant Product Information	
Initial Approval Date	10/26/2009
Therapeutic Drug Class or New Drug Class	(b) (4) CD20-directed cytolytic antibody
Active Ingredient	ofatumumab
Indication	treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
Route of Administration	Subcutaneous
Dosage Form	Injection solution
Strength	20 mg/0.4 mL
Dose and Frequency	The recommended dose is 20 mg administered by subcutaneous injection with: initial dosing at Weeks 0, 1, and 2 followed by subsequent monthly dosing, starting at Week 4 Missed Doses If an injection is missed, it should be administered as soon as possible without waiting until the next scheduled dose. Subsequent doses should be administered at the recommended intervals. 2.3 Administration Instructions- (b) (4) (b) (4) Intended for patient self-administration by subcutaneous injection. (b) (4) the abdomen, thigh, and outer upper arm. The first injection should be performed under the guidance of a healthcare professional 2.4 Preparation Before administration, remove Sensoready® pen or pre-filled syringe from the refrigerator and allow to reach room temperature for about 15 to 30 minutes. DO NOT remove the needle cover while allowing the pre-filled syringe to reach room temperature.

	Inspect visually for particulate matter (b) (4). Do not use if the liquid contains visible particles or is cloudy.
How Supplied	**Sensoready® pen:** Carton of one 20 mg/0.4 mL single-use Sensoready® pen (injection) NDC 0078-xxxx-xx **Prefilled syringe:** Carton of one 20 mg/0.4 mL single-use pre-filled syringe (injection) NDC 0078-xxxx-xx (b) (4)
Storage	Sensoready pens and pre-filled syringes must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Keep the product in the original carton to protect from light until the time of use. Do not freeze. To avoid foaming do not shake. (b) (4)
Container Closure/Device Constituent	 
Intended Users	Patients, caregivers, HCP
Intended Use Environment	Home, clinical

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On April 7, 2020, we searched the L:drive and AIMS using the terms, ofatumumab and IND 111116, to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified three previous reviews[def], and we confirmed that our previous recommendations were implement or are discussed in this review.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessed in EDR via:
\\cdsesub1\evsprod\bla125326\0262\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ms\5354-other-stud-rep\hfesr\rpt-omb157-hfesr-delta.pdf

\\cdsesub1\evsprod\bla125326\0262\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ms\5354-other-stud-rep\hfesr\rpt-omb157-hfesr-pfs.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results reports can be accessed in EDR via:
\\cdsesub1\evsprod\bla125326\0262\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ms\5354-other-stud-rep\hfesr\rpt-omb157-hfesr-delta.pdf

\\cdsesub1\evsprod\bla125326\0262\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ms\5354-other-stud-rep\hfesr\rpt-omb157-hfesr-pfs.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

In response to the Agency's March 12, 2020 Information Request, the Applicant submitted an updated table of root cause analysis and subjective feedback for both the prefilled syringe and autoinjector data. See EDR links:

\\cdsesub1\evsprod\bla125326\0262\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ms\5354-other-stud-rep\hfesr\rpt-omb157-hfesr-delta.pdf

---

[d] Rider, B. Use-Related Risk Analysis Review for Ofatumumab injection (IND 111116). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 31. RCM No.: 2017-1775-1.
[e] Whaley, E. Human Factors Protocol Review for Ofatumumab injection (IND 111116). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 20. RCM No.: 2018-617.
[f] Karpow, C. Human Factors Protocol Review Memo for Ofatumumab injection (IND 111116). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 8. RCM No.: 2018-617-1.

\\cdsesub1\evsprod\bla125326\0262\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ms\5354-other-stud-rep\hfesr\rpt-omb157-hfesr-pfs.pdf

In response to the Agency's March 20, 2020 Information Request, the Applicant submitted information to justify that the education demographics of the HF validation study participants are reflective of the intended users of the proposed product. The Applicant indicated that the results of the REALM-SF[g] test of study indicated that 12% of the study participants had had a health literacy score equivalent to a seventh to eighth grade educational level. The Applicant also noted that 5 out of 30 injection naïve participants (17%) and 3 out of 35 injection experienced participants (9%) had a health literacy score equivalent to a seventh to eighth grade educational level, which per the Applicant is greater than the US adult population rates (i.e. the Applicant noted that US Census Bureau results for the 'Educational Attainment in the United States: 2018' showed that less than 4% of the US adult population have an educational level of 8th grade or below). As such, the Applicant determined that the education demographics of the participants in the HF validation studies are reflective of the intended user population. The Applicant provided their response on March 24, 2020. See EDR link:

\\cdsesub1\evsprod\bla125326\0266\m1\us\fda-response-clinical-03242020.pdf

[g] The Rapid Estimate of Adult Literacy in Medicine—Short Form (REALM-SF) is a 7-item word recognition test to provide clinicians with an assessment of patient health literacy. Source: https://www.ahrq.gov/health-literacy/quality-resources/tools/literacy/index.html.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following Kesimpta (ofatumumab) labels and labeling submitted by Novartis Pharmaceuticals Corporation.

- Container label received on December 20, 2019
- Carton labeling received on December 20, 2019
- Professional Sample container label received on December 20, 2019
- Professional Sample carton labeling received on December 20, 2019
- Instructions for Use (Image not shown) received on December 23, 2019
    - EDR link: \\cdsesub1\evsprod\bla125326\0249\m1\us\proposed.pdf
- Prescribing Information (Image not shown) received on December 23, 2019
    - EDR link: \\cdsesub1\evsprod\bla125326\0249\m1\us\proposed.pdf

6 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

[h] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EBONY A WHALEY
05/06/2020 03:29:58 PM

LOLITA G WHITE
05/06/2020 04:48:53 PM

QUYNHNHU T NGUYEN
05/06/2020 04:53:03 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326Orig1s070

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 23, 2020
Application Type and Number:	BLA 125326/S-070
Product Name and Strength:	Kesimpta (ofatumumab) Injection [pre-filled syringe], 20 mg/0.4 mL Kesimpta Sensoready Pen (ofatumumab) Injection [pen autoinjector], 20 mg/0.4 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceutical Corporation (Novartis)
Panorama #:	2020-36962958 (Kesimpta); 2020-36970293 (Kesimpta Sensoready Pen)
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary names, Kesimpta and Kesimpta Sensoready Pen, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A respectively. Novartis did not submit an external name study for these proposed proprietary names.

1.1 REGULATORY HISTORY

Novartis currently markets ofatumumab under the proprietary name Arzerra for BLA 125326 which was approved October 26, 2009. Arzerra is indicated for the treatment of chronic lymphocytic leukemia.

On December 20, 2019, Novartis submitted efficacy supplement (070) to seek approval of ofatumumab for the treatment of relapsing forms of multiple sclerosis under a different proprietary name, with separate and distinct labeling and presentations (i.e., prefilled syringe and auto-injector).

Thus, Novartis submitted the names, Kesimpta and Kesimpta Sensoready Pen, for a dual proprietary name review on January 6, 2020.

1.2 PRODUCT INFORMATION

The following product information for Kesimpta and Kesimpta Sensoready Pen is provided in the proprietary name submission received on January 6, 2020.

- Intended Pronunciation: Ke-SIMP-ta and Ke-SIMP-ta SEN-so-re-di pen
- Nonproprietary Name: ofatumumab
- Indication of Use: Treatment of relapsing forms of multiple sclerosis
- Route of Administration: subcutaneous
- Dosage Form: injection
- Strength: 20 mg/0.4 mL
- Dose and Frequency: 20 mg at week 0, 1, and 2, then every month beginning with week 4
- How Supplied: carton of one 20 mg/0.4 mL prefilled syringe (Kesimpta); carton of one 20 mg/0.4 mL auto-injector (Kesimpta Sensoready Pen)
- Storage: Refrigerate between 2˚C to 8˚C (36˚F to 46˚F). Keep in original container to protect from light until time of use. Do not freeze. To avoid foaming, do not shake. (b) (4) (b) (4)

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary names.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed names would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Neurology 2 (DN 2) concurred with the findings of OPDP's assessment of the proposed names.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary names[a].

2.2.2 Components of the Proposed Proprietary Names and Analysis of Modifier "Sensoready Pen"

Novartis did not provide a derivation or intended meaning for the proposed proprietary names, Kesimpta and Kesimpta Sensoready Pen, in their submission.

Kesimpta

The proprietary name, Kesimpta, is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

Kesimpta Sensoready Pen

The proprietary name Kesimpta Sensoready Pen is comprised of the root name, Kesimpta and the modifier, 'Sensoready Pen'. The Applicant states that 'Sensoready Pen' refers to the name of the autoinjector device and is the same device used to deliver two other Novartis products, Cosentyx (BLA 125504) and Erelzi (BLA 761042). We note that the naming convention of adding a modifier to represent a specific device has been used before to differentiate the autoinjector presentation from other presentations (e.g., vial, prefilled syringe).

We acknowledge that modifiers may sometimes be omitted. If the modifiers, Sensoready Pen, are omitted, the pharmacist should call the prescriber to seek clarification, or the patient may receive the prefilled syringe presentation. However, since the 20 mg/0.4 mL strength will be available in both the prefilled syringe and autoinjector presentations, the patient will still be receiving the correct product and dose. Furthermore, as with any product that is available in multiple dosage forms or packaging presentations, the prescriber will need to indicate the intended product on the prescription.

[a] USAN stem search conducted on January 21, 2020.

We do not anticipate that the modifiers "Sensoready Pen" will be written on their own on a prescription without the root name. Additionally, we do not anticipate any confusion between Cosentyx Sensoready Pen, Erelzi Sensoready Pen, and Kesimpta Sensoready Pen, given the root names are different. Also, we are not aware of any errors relating to the misinterpretation of the modifiers "Sensoready Pen" through our routine post-marketing surveillance.

In summary, we acknowledge that the proposed modifier, "Sensoready Pen", is consistent with the device platform of the proposed product and with the naming strategy used for other products, including Cosentyx and Erelzi. Furthermore, use of a modifier such as "Sensoready Pen" provides a safe means to differentiate the pen autoinjector from the prefilled syringe presentation of ofatumumab. Thus, we find the use of the modifiers, Sensoready Pen, appropriate for this product.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE, January 16, 2020 e-mail, the Division of Neurology 2 (DN 2) did not forward any comments or concerns relating to Kesimpta at the initial phase of the review.

2.2.4 FDA Name Simulation Studies

Kesimpta

Ninety-nine practitioners participated in DMEPA's prescription studies for Kesimpta. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. However, one respondent in the CPOE simulation study interpreted Kesimpta as the discontinued product, Kemstro. We evaluated the name pair, Kesimpta and Kemstro, further and find that Kemstro (NDA 021589) was withdrawn FR effective July 21, 2017 and there are no generic equivalents available. Thus, we find there is no risk of name confusion (See Appendix G).

Kesimpta Sensoready Pen

Eighty-eight practitioners participated in DMEPA's prescription studies for Kesimpta Sensoready Pen. The responses did not directly overlap with any currently marketed products or any products in the pipeline.

One respondent in the voice study interpreted the proposed proprietary name as "Casentra Sensa Ready Pen", which sound similar to the marketed product Kcentra. We evaluated the name pair, Kesimpta and Kcentra, further and find that there are sufficient orthographic and product characteristic differences.

> Orthographically, the suffixes (pta vs. tra) look sufficiently different. Kesimpta contains the downstroke letter 'p', which gives the names different shapes when scripted.
>
> Additionally, the modifier "Sensoready Pen" may provide additional orthographic and phonetic differentiation, if included.
>
> Furthermore, there is no direct overlap in strength (20 mg/0.4 mL vs. 500 U range), dosage form (injection vs. lyophilized concentrate), route of administration (subcutaneous vs. intravenous), or frequency of administration (week 0, 1, and 2, then every month beginning with week 4 vs. as needed for urgent reversal of acquired coagulation factor deficiency), which may provide additional differentiation if included.

When all of the aforementioned mitigations are considered in totality, we find the risk of name confusion is mitigated to an acceptable level (See Appendix E).

Appendix B contains the results from the prescription simulation studies.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Our POCA search[b] identified 55 names with a combined phonetic and orthographic score of ≥55% or an individual phonetic or orthographic score ≥70%. These names are included in Table 1 below.

2.2.6 Names Retrieved for Review Organized by Name Pair Similarity

Table 1 lists the number of names retrieved from our POCA search. These name pairs are organized as highly similar, moderately similar or low similarity for further evaluation.

Table 1. Names Retrieved for Review Organized by Name Pair Similarity

Similarity Category	Number of Names
Highly similar name pair: combined match percentage score ≥70%	1
Moderately similar name pair: combined match percentage score ≥55% to ≤ 69%	53
Low similarity name pair: combined match percentage score ≤54%	1

2.2.7 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the 55 names contained in Table 1 determined none of the names will pose a risk for confusion as described in Appendices C through H.

2.2.8 Evaluation of Dual Proprietary Names

Novartis currently markets ofatumumab injection under the proprietary name, Arzerra, for the treatment of chronic lymphocytic leukemia under BLA 125326 (See Section 1.1 above), and now seeks the dual proprietary names, Kesimpta and Kesimpta Sensoready Pen, for the new indication of treatment of relapsing forms of multiple sclerosis. Table 2 provides a side-by-side comparison of the two proprietary names and their respective product characteristics.

[b] POCA search conducted on February 26, 2020 in version 4.3.

Table 2. Relevant Product Information for Arzerra and Kesimpta		
	Arzerra	**Kesimpta**
Approval date	October 26, 2009	Not applicable
Intended pronunciation	ahr-zer´-a	Ke-SIMP-ta
Indication	Treatment of chronic lymphocytic leukemia	Treatment of relapsing forms of multiple sclerosis
Route of administration	Intravenous infusion	subcutaneous
Dosage Form	injection	injection
Strength	100 mg/5 mL and 1000 mg/50 mL	20 mg/0.4 mL
Dose and Frequency	300 mg on Day 1 followed by 1000 mg to 2000 mg depending upon the CLL indication	20 mg at week 0, 1, and 2, then every month beginning with week 4
How Supplied	Carton of three single use glass vials, 100 mg/5 mL in a carton; Carton of one single use glass vial, 1000 mg/50 mL in a carton	Carton of one 20 mg/0.4 mL single use pre-filled syringe (Kesimpta); Carton of one 20 mg/0.4 mL single use auto-injector (Kesimpta Sensoready Pen)
Storage	Refrigerate between 2˚C to 8˚C (36˚F to 46˚F). Do not freeze. Vials should be protected from light.	Refrigerate between 2˚C to 8˚C (36˚F to 46˚F). Keep in original container to protect from light until time of use. Do not freeze. To avoid foaming, do not shake. (b) (4) (b) (4)

We have evaluated the risks associated with this naming strategy and do not object to the use of a dual proprietary name in this case.

2.2.9 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Neurology 2 (DN 2) via e-mail on March 17, 2020. At that time, we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Neurology 2 (DN 2) on March 23, 2020, they stated no additional concerns with the proposed proprietary names, Kesimpta and Kesimpta Sensoready Pen.

3 CONCLUSION

The proposed proprietary names Kesimpta and Kesimpta Sensoready Pen, are acceptable.

If you have any questions or need clarifications, please contact Monique Killen, OSE project manager, at 240-402-1985.

3.1 COMMENTS TO NOVARTIS

We have completed our review of the proposed proprietary names, Kesimpta and Kesimpta Sensoready Pen and have concluded that the names are acceptable.

If any of the proposed product characteristics as stated in your submission, received on January 6, 2020, are altered prior to approval of the marketing application, the names must be resubmitted for review.

4 REFERENCES

1. USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)

USAN Stems List contains all the recognized USAN stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [c]

[c] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.
- Low similarity: combined match percentage score ≤54%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names[d]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).

- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

[d] Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   Four separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions, verbal pronunciation of the drug name or during computerized provider order entry. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify vulnerability of the proposed name to be misinterpreted by healthcare practitioners during written, verbal, or electronic prescribing.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name during written, verbal, or electronic prescribing of the name, written inpatient medication orders, written outpatient prescriptions, verbal orders, and electronic orders are simulated, each consisting of a combination of marketed and unapproved drug products, including the proposed name.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

   When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	**Y/N**	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	**Y/N**	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥55% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

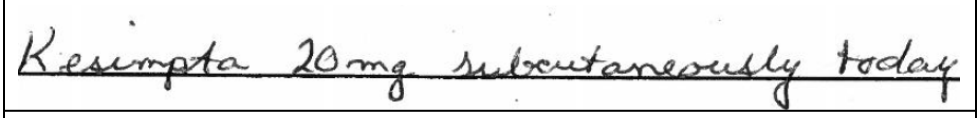
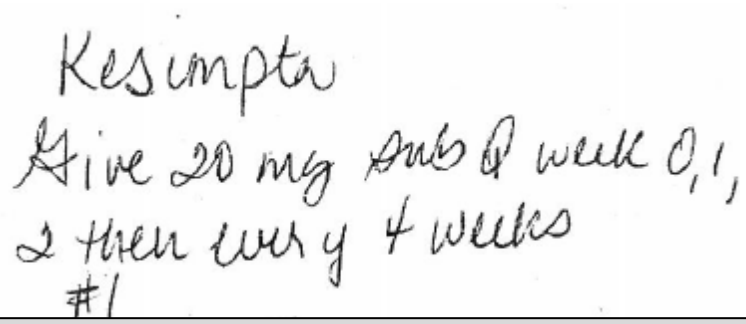
	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤54%).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Kesimpta Study (Conducted on January 31, 2020)

Handwritten Medication Order/Prescription	**Verbal Prescription**
Medication Order: K  	Kesimpta – give 20 mg subcutaneously on weeks 0, 1, 2 and every 4 weeks. Dispense # 1
Outpatient Prescription:  	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Kesimpta	

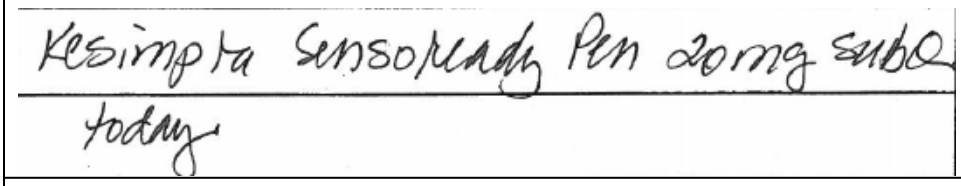
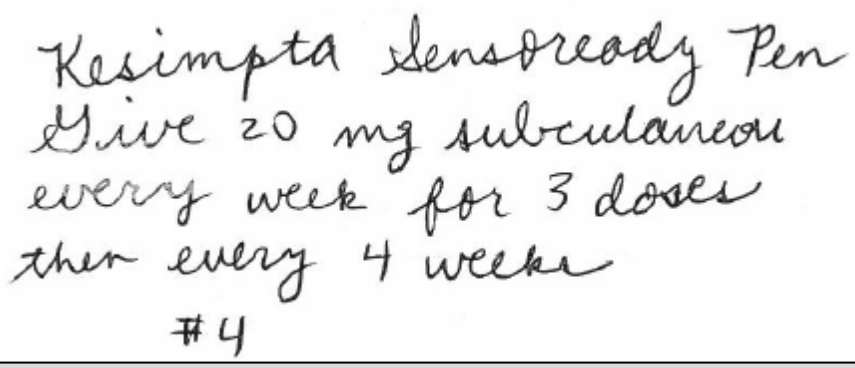
FDA Prescription Simulation Responses (Aggregate Report)

212 People Received Study

99 People Responded

Total	**19**	**41**	**19**	**20**	
INTERPRETATION	**OUTPATIENT**	**CPOE**	**VOICE**	**INPATIENT**	**TOTAL**
CASEMPTA	0	0	1	0	1
CASIMPTA	0	0	2	0	2
CASIMTA	0	0	3	0	3
CASYMPTA	0	0	2	0	2
COSEMPTA	0	0	1	0	1
COSIMPTA	0	0	1	0	1
CUSIMPTA	0	0	1	0	1
KASIMPTA	0	0	3	0	3
KASIMTA	0	0	2	0	2
KASYMPTA	0	0	1	0	1
KAZIMTA	0	0	1	0	1
KEMSTRO	0	1	0	0	1
KESIMPTA	16	40	0	19	75
KESIMPTA INJECTION	1	0	0	0	1
KESIMPTAI	1	0	0	0	1
KESIMPTOR	1	0	0	0	1
KESIPTA	0	0	0	1	1
QUESIMTA	0	0	1	0	1

Figure 1. Kesimpta Sensoready Pen Study (Conducted on February 4, 2020)

Handwritten Medication Order/Prescription	**Verbal Prescription**
Medication Order:  	"Kesimpta Sensoready Pen - give 20 mg subcutaneously every week for 3 doses, then every 4 weeks Dispense 4"
Outpatient Prescription:  	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Kesimpta Sensoready Pen	

FDA Prescription Simulation Responses (Aggregate Report)

212 People Received Study
88 People Responded

Study Name: Kesimpta Sensoready Pen

Total	21	17	32	18	
INTERPRETATION	**OUTPATIENT**	**CPOE**	**VOICE**	**INPATIENT**	**TOTAL**
CASEMPTA PEN	0	0	1	0	1
CASENTRA SENSA READY PEN	0	0	1	0	1
CASIMPTA SENSOR READY PEN	0	0	1	0	1
CASIMTA	0	0	1	0	1
DESIMPTA SENSOREADY PEN	0	0	0	1	1
KACEMPTA SENSORETTI PEN	0	0	1	0	1
KASEMPTA SENSOR READY PEN	0	0	1	0	1
KASIMPSA	0	0	1	0	1
KASIMPTA	0	0	1	0	1
KASIMPTA PEN	0	0	1	0	1
KASIMPTA SENSA READY PEN	0	0	2	0	2
KASIMPTA SENSAREDI PEN	0	0	1	0	1
KASIMPTA SENSIREADY PEN	0	0	1	0	1
KASIMPTA SENSOR READY PEN	0	0	1	0	1
KASIMPTA SENSOREADY PEN	0	0	1	0	1
KASIMPTA SENSORREDI PEN	0	0	1	0	1
KASIMPTASENSAREADIPEN	0	0	1	0	1
KASIMPTO SENSOREADY PEN	0	0	1	0	1

KASINTHA SENSORETTI PEN	0	0	1	0	1
KASYMPTA	0	0	1	0	1
KASYMPTA PEN	0	0	1	0	1
KASYMPTA SENSAREADY PEN	0	0	1	0	1
KASYMPTA SENSOREADY PEN	0	0	1	0	1
KAZIPTAM SENSOREDI PEN	0	0	1	0	1
KERSIMPTA	0	0	1	0	1
KESIMPRA SENSOREADY	0	0	0	1	1
KESIMPRA SENSOREADY PEN	0	0	0	1	1
KESIMPTA	2	0	1	2	5
KESIMPTA PEN	0	0	1	0	1
KESIMPTA SENORREADY PEN	0	0	0	1	1
KESIMPTA SENSORADY PEN	1	0	0	0	1
KESIMPTA SENSOREADY PEN	14	17	0	11	42
KESIMPTA SENSOREADY PM	0	0	0	1	1
KESIMPTA SENSORREADY	1	0	0	0	1
KESIMPTA SENSORREADY PEN	1	0	0	0	1
KESIMPTA SENSOR-READY PEN	0	0	1	0	1
KESIMPTA SESNOREADY PEN	1	0	0	0	1
KESIMPTA SESOREADY PEN	1	0	0	0	1
KESIMTA SENIREADY PEN	0	0	1	0	1
TASEMPTA PEN	0	0	1	0	1
TECINTA	0	0	1	0	1

TESIMTA SENSA READY PEN	0	0	1	0	1

APPEARS THIS WAY ON ORIGINAL

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	**Proposed name:** Kesimpta **Established name:** ofatumumab **Dosage form:** injection **Strength(s):** 20 mg/0.4 mL **Usual Dose:** 20 mg at week 0, 1, and 2, then every month beginning with week 4	POCA Score (%)	**Orthographic and/or phonetic differences in the names sufficient to prevent confusion** **Other prevention of failure mode expected to minimize the risk of confusion between these two names.**
1.	Kesimpta	100	Name is the focus of this review.

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Name	POCA Score (%)
2.	Septa	58

Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	**Proposed name:** Kesimpta **Established name:** ofatumumab **Dosage form:** injection **Strength(s):** 20 mg/0.4 mL **Usual Dose:** 20 mg at week 0, 1, and 2, then every month beginning with week 4	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
3.	Cotempla	64	This name pair has sufficient orthographic and phonetic differences. Orthographically, the prefixes (Kes vs. Cot) look different. The names begin with different first letters (K vs. C) that look different and Cotempla contains the cross-stroke letter ‘t’ in the prefix, whereas Kesimpta does not contain any cross-stroke letters in the prefix, which gives the names different shapes when scripted. Phonetically, the first syllables (ke vs. koh), second syllables (SIMP vs. TEM)

No.	**Proposed name:** Kesimpta **Established name:** ofatumumab **Dosage form:** injection **Strength(s):** 20 mg/0.4 mL **Usual Dose:** 20 mg at week 0, 1, and 2, then every month beginning with week 4	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
			and third syllables (ta vs. pluh) sound different. Additionally, there is no direct overlap in strength (20 mg/0.4 mL vs. 8.6 mg, 17.3 mg, 25.9 mg), dose (20 mg vs. 17.3 mg to 51.8 mg in increments of 8.6 mg to 17.3 mg), dosage form (injection vs. orally disintegrating tablet), route of administration (subcutaneous vs. oral), or frequency of administration (week 0, 1, and 2, then every month beginning with week 4 vs. once daily in the morning), which may provide additional differentiation if included.
4.	Tevimbra***	60	This name pair has sufficient orthographic and phonetic differences.
5.	Kitabis Pak	59	This name pair has sufficient orthographic and phonetic differences.
6.	Cassipa	58	This name pair has sufficient orthographic and phonetic differences. Additionally, there is no direct overlap in strength (20 mg/0.4 mL vs. 16 mg/4 mg), dosage form (injection vs. film), route of administration (subcutaneous vs. sublingual), or frequency of administration (week 0, 1, and 2, then every month beginning with week 4 vs. once daily), which may provide additional differentiation if included.
7.	(b) (4)	58	This name pair has sufficient orthographic and phonetic differences.
8.	Kcentra	58	This name pair has sufficient orthographic and product characteristic differences.

No.	**Proposed name:** Kesimpta **Established name:** ofatumumab **Dosage form:** injection **Strength(s):** 20 mg/0.4 mL **Usual Dose:** 20 mg at week 0, 1, and 2, then every month beginning with week 4	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
			Orthographically, the suffixes (pta vs. tra) look sufficiently different. Kesimpta contains the downstroke letter 'p', which gives the names different shapes when scripted. Additionally, there is no direct overlap in strength (20 mg/0.4 mL vs. 500 U range), dosage form (injection vs. lyophilized concentrate), route of administration (subcutaneous vs. intravenous), or frequency of administration (week 0, 1, and 2, then every month beginning with week 4 vs. as needed for urgent reversal of acquired coagulation factor deficiency), which may provide additional differentiation if included. When all of the aforementioned mitigations are considered in totality, we find the risk of name confusion is mitigated to an acceptable level.
9.	K-Vescent	56	This name pair has sufficient orthographic and phonetic differences.
10.	Vimpat	55	This name pair has sufficient orthographic and phonetic differences.
11.	(b) (4) ***	55	This name pair has sufficient orthographic and phonetic differences.
12.	Ketamine	55	This name pair has sufficient orthographic and phonetic differences.

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤54%)

No.	Name	POCA Score (%)
13.	Stimate	52

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described**.**

No.	Name	POCA Score (%)	Failure preventions
14.	Simplet	60	Name identified in RxNorm database. Product is deactivated and no generic equivalents are available.
15.	Ketoseb Ps	60	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
16.	Ketaset	58	Veterinary product.
17.	Tussin Pe	58	Name identified in RxNorm. Product is deactivated and no generic equivalents are available.
18.	Sensipak	58	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
19.	Desihist SA	56	Name identified in RxNorm database. Product is deactivated and no generic equivalents are available.
20.	Campto	56	International product marketed in various countries outside of the U.S.
21.	K Tussin DM	56	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
22.	Kemstro	56	Brand discontinued with no generic equivalents available. NDA 021589 withdrawn FR effective 07/21/2017.
23.	Ketathesia	55	Veterinary product.
24.	Keta-Thesia	55	Veterinary product.
25.	(b) (4) ***	55	Proposed proprietary name found to be acceptable (OSE # 2016-7963411 dated August 1, 2016) for BLA 125544. However, the Applicant withdrew the name on September 6, 2016. BLA 125544 approved under the proprietary name Inflectra.

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion[e].

No.	Name	POCA Score (%)
26.	Ixempra	62
27.	Cresemba	61
28.	Tisept	61
29.	Desempacho	60
30.	Pediamist	59
31.	Prezista	59
32.	Femstat	58
33.	Femstat 3	58
34.	Peptimax 200	58
35.	Peptimax 400	58
36.	Peptimax 800	58
37.	Tepmetko***	58
38.	(b) (4)***	58
39.	T-Tussin Pe	58
40.	Cesamet	57
41.	Medi-Paste	57
42.	Q-Tussin Pe	57
43.	Antisept	56
44.	Betasept	56
45.	(b) (4)***	56
46.	Padimate A	56
47.	Pytest Kit	56
48.	(b) (4)***	56
49.	(b) (4)***	56
50.	Semintra	56
51.	Sensipar	56
52.	Tavist Da	56
53.	Cepastat	55
54.	Gemtesa***	55
55.	(b) (4)***	55

[e] Shah, M, Merchant, L, Chan, I, and Taylor, K. Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DENISE V BAUGH
03/23/2020 03:17:36 PM

BRIANA B RIDER
03/23/2020 03:21:34 PM