CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761053Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA #/Supplement #	761053
Applicant Name	Biogen
Date of Submission	4/28/16
PDUFA Goal Date	3/28/17
Proprietary Name/ Established (USAN) Name	Ocrevus/ocrelizumab
Dosage Forms/Strength	Intravenous infusion/300 mg per 10 mL
Proposed Indication(s)	Treatment of relapsing forms of multiple sclerosis and primary progressive multiple sclerosis
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	Nahleen Lopez, PharmD
Medical Officer Review	Larry Rodichok, MD; Jerry Boehm, MD
Statistical Review	Sharon Yan, PhD
Pharmacology Toxicology Review	Dave Carbone, PhD
CMC/OBP Review	Sarah Kennett, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Jagan Parepally, PhD
OPDP	Aline Moukhtara, RN, MPH
OSI	Cara Alfaro, PharmD
CDTL Review	John Marler, MD
OSE/DMEPA	Ebony Whaley, PharmD
OSE/DDRE	N/A
OSE/DRISK	Laura Zendel, PharmD
OMP/DMPP	Aman Sarai, BSN, RN
PMHS	Tamara Johnson, MD
SEALD	N/A
Other	Katherine Bonson, PhD (CSS); Gwynn Ison, MD (DOP1); Bindu Kanapuru, MD (DHP); Elisa Braver, PhD (OSE)

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
CDRH=Center for Devices and Radiologic Health
PMHS=Pediatric and Maternal Health Staff
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling Development
CSS=Controlled Substance Staff

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The applicant is seeking approval of an application intended to support the inclusion in labeling of a description of effects on two subtypes of multiple sclerosis (MS): 1) relapsing forms of multiple sclerosis (RMS); and 2) primary progressive multiple sclerosis (RRMS).

The applicant has provided substantial evidence of effectiveness for the use of ocrelizumab (OCR) for the treatment of patients with relapsing forms of multiple sclerosis. This conclusion is supported by evidence from two essentially identical adequate and well-controlled studies (Studies WA21092 and WA21093) that evaluated the use of a single dosing regimen of OCR. These studies were generally of typical design and evaluated an often-used primary outcome of annualized relapse rate, comparing OCR to Rebif, an approved therapy for relapsing forms of multiple sclerosis.

As noted, a single dose regimen was evaluated. After an initial dose of two 300 mg infusions given 14 days apart, subsequent doses were single 600 mg infusions every 6 months. The effect on annualized relapse rate in both studies was highly significant with a reduction of 46-47% against Rebif, a drug with an established effect on annualized relapse rate. The effect on accumulation of sustained disability, measured by comparing confirmed disability progression endpoints, was also highly significant in both studies, despite an expected need to assess disability by pooling data from both studies. This pooled analysis was the major secondary endpoint and was highly significant, with an absolute reduction of about 5% compared to Rebif, a drug with an established effect on disability. The effects on relapse and disability were supported by consistent effects on various secondary, subgroup, and sensitivity analyses. The members of the review team all agree that the RMS studies provide substantial evidence of effectiveness for the treatment of RMS.

The review team is in partial agreement (as noted, Dr. Marler dissents) that the applicant has provided substantial evidence of effectiveness for the use of OCR for the treatment of patients with primary progressive multiple sclerosis. This conclusion is primarily supported by evidence from a single study in PPMS (Study WA25046) that evaluated the use of a single dosing regimen of OCR, with additional support from results of the RMS studies described above. This PPMS study evaluated a primary outcome of time to confirmed disability progression, comparing OCR to placebo.

Again, a single dose regimen was evaluated, though it differed slightly from the RMS studies in that all doses in the PPMS study were given as two 300 mg infusions given 14 days apart every 6 months. The effect on confirmed disability progression was significant (p=0.03) with a reduction of 24% compared to placebo. Important secondary outcomes of disability progression sustained for 24 weeks, T25FW, and MRI T2

lesion volume were all significant. Despite concerns regarding an unusual imputation of confirmed disability progression in the absence of an actual measurement (i.e., patients that had an initial event of disability progression but left the study before progression could be confirmed at a second visit 12 weeks later were imputed as confirmed disability progression endpoints), a sensitivity analysis performed by Dr. Yan based on assignment of the imputed endpoints to an event status (i.e., contributing to the count of confirmed disability progression or being censored at the time of withdrawal) based on the actual proportion of confirmed disability progression events in patients that had an initial event of disability progression observed in the study was supportive of primary outcome. Also, a reduction in the occurrence of relapse favoring OCR was seen in the PPMS study. The members of the review team are not unanimous with regard to the evidence that the PPMS study provides, as I noted above. Dr. Yan and Dr. Rodichok support approval for PPMS, while Dr. Marler argues against it. Dr. Marler expresses concern not only about the strength of the PPMS study, but he also doubts the ability of the RMS studies (which showed an effect on disability progression in RMS) to support the PPMS study, leading him to conclude that the PPMS study must be considered on its own. Dr. Rodichok shares concerns about the about the ability of the RMS studies to support the PPMS study, but recommends approval based on the results of the PPMS study and the unmet medical need in this area.

Whether the RMS studies may serve to support the PPMS study deserves some comment in light of the extensive assertions of Dr. Marler and Dr. Rodichok that they cannot.

Substantial evidence of effectiveness is required for approval. There is a need to substantiate any individual finding to avoid reliance on erroneous conclusions, so, in general, two independent studies are typically provided to meet this need. The presumption is that the effect in the second study is related, in some fashion, to the effect in the first, in order to provide mutual support for the findings of the two studies. The two RMS studies, of highly similar design, are an example of this type of evidence, but it is clear from the guidance document on evidence of effectiveness that the clinical endpoints in each study can be different (and can be in different populations, different severities of disease, etc.), as long as they support the overall effectiveness of the drug. An alternative approach is to provide evidence from one study with support from confirmatory evidence. In such a situation, what may constitute confirmatory evidence is left undefined in regulation (wisely so, in my estimation, but many examples are given in the aforementioned guidance document on effectiveness) but the confirmatory evidence serves to substantiate the results of the single study. It is often thought that such an approach (one study plus confirmatory evidence) requires some higher degree of statistical persuasiveness of the clinical study than the conventional (though not absolute) standard of $p=0.05$, but this is not necessarily so. Depending on any number of aspects that may influence the overall confidence one places in the totality of the evidence, a conventional degree of statistical persuasiveness in a single study may well be acceptable when accompanied by confirmatory evidence. In fact, this is really not different conceptually from the typical approach of relying on two adequate and well-controlled studies to support approval, as long as the "confirmatory evidence" is persuasive. In that situation, each study serves as confirmatory evidence to the other. The use of the term confirmatory evidence is generally meant to indicate some evidence other than that resulting from an effect on a clinically meaningful outcome measured in an adequate and well-controlled study. In this situation, we have two clearly positive RMS studies that are intended to serve as

confirmatory evidence, so, if they may do so, the nature of the confirmatory evidence in this application is especially strong, as long .

Although Dr. Rodichok and Dr. Marler argue otherwise, I think it is clear that the results of the RMS studies are relevant to the findings of the PPMS study. RMS is clearly related to PPMS, as both are forms of a single disease, multiple sclerosis. That there are differences between these two forms of MS is not in doubt. If differences could not exist at all, then they would not be different forms and the RMS studies would suffice without any PPMS study. Differences, however, do not preclude the ability of the RMS studies to support the PPMS study. Dr. Rodichok and Dr. Marler argue that differences in the PPMS and RMS populations in demographic and baseline disease characteristics, along with differences in the characteristics of the periods of disability in those populations, is indicative of a lack of relatedness that precludes the ability of one to support the other. This argument is based primarily on assertions that outcome events of interest should have an empiric sameness in order to be related and that the differences in these various characteristics is indicative of differing pathophysiological mechanisms.

It is important to recognize that arguments related to "relatedness" are inherently subjective. Although many individual points are made by Dr. Rodichok and Dr. Marler in an attempt to support the position that the two forms of MS are not related, such an overall position is not suited for point by point refutation, lest one inadvertently establish some type of semi-quantifiable threshold beyond which relatedness is present. Suffice it to say, our considerations of this issue (made pre-submission, not unimportantly) have resulted in our position that these forms of MS are related, and may serve to support each other. Indeed, it might appear almost self-evident that, by definition, they are both MS. It is true that our thinking in the Division regarding the degree of relatedness has evolved from advice given previously that suggested that a conventional independent development program for PPMS was required. Previous advice was based on our perception of the understanding of the scientific community and our own understanding concerning the independence of the pathophysiological mechanisms underlying the forms of MS. We have evolved our thinking from our previous position, consistent with a contemporary understanding of MS. Our judgment is that these forms of MS are related, and the Division is prepared to accept PPMS and RMS populations as mutually supportive.

Although much literature may be cited that notes a variety of pathophysiological distinctions based on any number of research avenues, the phenotypic categorization of MS into PPMS and other forms (including RMS), a categorization that is the fundamental issue at play, was the result of definitions put forth in 1996 by the US National Multiple Sclerosis Society (NMSS) Advisory Committee on Clinical Trials in Multiple Sclerosis. The distinction was not made on the basis of a fundamental, well-established, and well-understood scientific characterization of the pathophysiology of the various forms of MS. At the time they were proposed, that committee noted that these phenotypic descriptors were consensus subjective views of experts in the field and were not supported by objective biological findings. That same committee recommended that the phenotypic descriptors (MS subtypes) should be re-addressed as the scientific understanding of the disease evolved. In that spirit, The International Advisory Committee on Clinical Trials in Multiple Sclerosis (now a jointly sponsored international entity of the NMSS and The European Committee for Treatment and Research in MS) began in 2011 to explore advances in this area and convened in 2012 to formally review the 1996 classification. This review resulted in the publication in 2013 of revisions to the 1996 definitions. Clearly articulated in these

revisions is the notion that PPMS is related in a fundamental pathophysiological manner to other forms of MS. While many aspects of the revisions relate to the relatedness of MS subtypes, the following quote speaks directly to the issue: "While some evidence suggests that PPMS represents a distinct, noninflammatory or at least less inflammatory pathologic form of MS, abundant clinical, imaging, and genetic data suggest that PPMS is a part of the spectrum of progressive MS phenotypes and that any differences are relative rather than absolute. Analyses of natural history cohorts demonstrate that worsening proceeds at a similar rate in SPMS and PPMS. PPMS should remain a separate clinical course because of the absence of exacerbations prior to clinical progression, but it likely does not have pathophysiologically distinct features from relapsing forms of MS that have entered a progressive course (SPMS)." (Lublin, Fred D., et al. Defining the Clinical Course of Multiple Sclerosis: The 2013 Revisions. Neurology. 2014 Jul 15; 83(3): 278-86.) It is true, of course, that the emphasis of this statement is on the progressive course of the various subtypes, but it illustrates the fact that there is substantial overlap of the subtypes with regard to clinical subtypes and likely pathophysiology, and that there is a reasonable basis to believe that demonstrated benefit in one subtype may increase the expected reliability of a finding of benefit in a study of a related subtype.

An additional comment is needed on the notion of considering this issue of the acceptability of "relatedness" during the review of the application. The Division clearly stated in pre-submission discussions with the sponsor that it was acceptable in principle to support the single PPMS study with the RMS studies (recognizing that the adequacy of the data was, of course, a matter for review, as it is for all applications) and reiterated that statement de facto by filing the application. In fact, the Division, in an effort to ensure streamlined and efficient review, particularly in light of the reported results in PPMS, actively advised the sponsor to submit the PPMS study and RMS studies in a single application, contrary to the sponsor's initial plans to submit the data in two independent applications. Indeed, if the RMS studies were not suitable for support of the PPMS study (i.e., because they were not sufficiently related) then the sponsor should have been (and would have been) advised to conduct another study in PPMS. To delay the conduct of such an additional study in this area by accepting for review an application that could not, on face, be approved because the supportive data are in character fundamentally unacceptable would be deeply troubling. This issue of the "relatedness" of PPMS and RMS is not a typical "matter for review" to be adjudicated during the review process but is primarily a policy "matter for review" that largely took place pre-submission. The Division's comments to the sponsor were clear in this regard, and the Division is cognizant of the problematic issues that would be raised by "moving the goalposts" after accepting the application.

With questions of "relatedness" resolved, the persuasiveness of the PPMS study is the remaining issue. In this regard, the primary clinical review and CDTL review do not take into account the additional sensitivity analysis performed by Dr. Yan that is described above. It is certainly true that the unusual approach to imputation was a significant concern and that eliminating all the imputed data severely weakened the primary result, but we were able to use the data within the study itself to inform a more reasonable approach to the consideration of the patients for whom confirmation of an initial disability progression was not available. That approach indicated that the statistical significance of the primary outcome was a valid representation of the effect of OCR in the PPMS study. This result, supplemented by unequivocal and very strong findings in the RMS studies, is strongly supportive of the effectiveness of OCR for PPMS. Further support is provided by effects on relapse, walking

speed, and MRI findings in the PPMS study itself. Taken together, these various results provide substantial evidence of effectiveness for the use of OCR in PPMS.

It is worth making a brief comment on the previous "failures" in PPMS. Dr. Rodichok and Dr. Marler point out the lack of positive outcomes in trials of other agents in PPMS. Many of those descriptions of failure, however, are simple dichotomous characterizations based on $p>0.05$. Actual clinical findings numerically favored drug in those trials, in general, particularly in the larger trials, and MRI results trended similarly. This relatively consistent trend can be nothing more than hypothesis-generating, of course, whether for any individual drug or for the group of studied drugs as a whole, but it is intriguing. These clinical findings in previous studies concerned various measurements of disability, a notoriously difficult endpoint on which to achieve success. Disability events in MS are more complicated and difficult to study than simple counts of relapse; they occur remarkably infrequently and studies are often underpowered for this outcome. Pooling of sister trials is often necessary to achieve the power to demonstrate statistical significance for disability. Indeed, this was the prespecified plan for the RMS studies of OCR, anticipating an inability to demonstrate a beneficial effect in the individual trials. Despite this expectation, in addition to winning on this planned pooled analysis, OCR actually won in both individual RMS trials. This further reinforces the belief that the disability finding in PPMS is credible. Though purely speculative, it may be that we have hints that drugs effective in RMS may not be as ineffective in PPMS as generally thought, and that the totality of what we see with OCR may suggest that it is actually remarkably effective on disability across clinical phenotypes of MS. The previous apparent inability of other RMS drugs to affect disability in PPMS is undoubtedly noteworthy, but there may have been less failure than meets the eye and only further clinical studies will be able to address the issues involved. Past experience is certainly a reasonable basis for concluding that effectiveness in RMS should not be extrapolated to PPMS and that independent evaluation in PPMS is needed, but the failure of other drugs, often of dissimilar character, is not a basis for rejecting a clear benefit seen in such an independent evaluation.

Subgroup analyses by gender warrant mention. An apparently flat effect on disability in women in the PPMS study is noteworthy (though, it must be kept in mind, such subset analyses are exploratory and not necessarily indicative of an absence of actual benefit on disability in this subgroup). Morevover, somewhat reassuringly (again, keeping well in mind the exploratory nature of such analyses), there are effects on relapse and MRI findings in those same women and there is no gender imbalance for the benefits seen in the RMS studies. Although of limited interpretability, we will describe these findings in labeling to more fully inform both prescriber and patient.

There are no safety concerns, in a database of acceptable size and character, that preclude approval. The most concerning adverse events involve infusion-related reactions, infections, and malignancies, particularly breast cancer. Those will receive Warnings in product labeling and further evaluation in the postmarketing setting. Depression and suicidality, though occurring slightly more frequently than control and recognized as a concern for the active comparator in the RMS studies, were actually less common in OCR-treated patients in the placebo-controlled PPMS study, (b) (4). Overall, the safety profile of OCR is acceptable for its intended use.

Given the presence of substantial evidence of effectiveness and the acceptable safety profile, the risk benefit profile of OCR is favorable and supports approval. RMS is a serious and life-threatening condition, and we know that, given individual patient variability, continued development and approval of drugs for RMS is important. There are no treatments for PPMS, also a serious and life-threatening condition and one in dire need of an approved therapy. The biological activity of OCR is presumed to be mediated through a mechanism not shared with other approved drugs for MS.

For both RMS and PPMS, essentially a single dose was studied, with slight differences in the dosing regimens. Our analyses have indicated that a harmonized dosing regimen is appropriate for both subtypes, so, given the absence of other studied doses, we will describe in labeling the harmonized approach to dosing based on that used in the studies.

Regarding product quality, I must reiterate that identified deficiencies would ordinarily preclude approval, but resolution of remaining product quality issues via initial adjustments to the control strategy, appropriate PMCs, continued process verification by the applicant, and continued implementation of corrective and preventive actions, is an appropriate strategy to support the approval of OCR given the unmet medical need that it will address.

We will not require pediatric studies for PPMS from birth to 17 years of age and for RMS from birth to 10 years of age because the small number of such patients in these age groups make necessary studies impossible or highly impracticable. We will defer submission of a required pediatric safety, tolerability, pharmacokinetic/pharmacodynamic, safety, and efficacy study in RMS for ages 10 through less than 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Postmarketing requirements are needed to assess the incidence and mortality rates of breast cancer and all malignancies associated with use of OCR, to conduct prospective pregnancy exposure registry cohort analyses, to conduct a pregnancy outcomes study, and to conduct an expanded pre-and postnatal development study in nonhuman primate.

Postmarketing commitments are needed for a shipping study, to confirm validation of the Antibody-Dependent Cellular Cytotoxicity assay, to confirm validation of the Capillary Electrophoresis Glycan Analysis assay, to confirm validation of the Reversed-Phase Ultra-High-Performance Liquid Chromatography assay, to confirm validation of the Polysorbate 20 assay, to manufacture, qualify, and implement new primary and secondary reference standards, to perform a leachable study to evaluate the drug product container closure system, and to confirm the acceptability of updates to the drug substance manufacturing process and controls.

Postmarketing risk management activities will include a request for the applicant to perform postmarketing surveillance and enhanced

pharmacovigilance for pancreatitis, cholecystitis and cholelithiasis, and serious and opportunistic infections, including progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation after exposure to ocrelizumab, with expedited reporting and summarized annual analysis of events.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of ocreclizumab for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis.

For these reasons, I recommend approval of this application, to include the agreed-upon product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Relapsing multiple sclerosis is a condition associated with a risk of short-term disability due to relapses and a risk of gradually increasing longer-term disability due to incomplete recovery from relapses as well as from neurodegenerative changes. • Primary progressive multiple sclerosis is a condition characterized by steady progression of disability from first onset.	Multiple sclerosis is a condition that can result in a significant loss of function over the course of a relapse as well as over the long-term course of the illness. Multiple sclerosis can be a profoundly disabling illness with onset in early adulthood.
Current Treatment Options	• There are multiple treatment options available for RMS. • There are no treatment options available for PPMS. • Current approved therapies consistently reduce the relapse rate but may not have as consistent effects on long-term disability.	There remains a pressing need for additional treatments for RMS and a first treatment for PPMS.
Benefit	• The evidence for a reduction in the rate of relapses and an effect on disability is strong and consistent for RMS. • The evidence for an effect on disability is sufficient for PPMS. It is supported by the RMS results and by similar effects on relapse in PPMS.	The reduction in relapse rate and disability is superior to that of a beta-interferon for RMS, providing an important alternative therapy. The effect on disability and other aspects of the disease for PPMS is sufficiently persuasive and addresses an important unmet need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• There is a clear risk of infusion reactions. • There is a suggestion of an increased risk of breast cancer, and some evidence of increased risk of infections.	Clear and informative labeling is needed.
Risk Management	• Postmarketing pharmacovigilance for breast cancer and other cancers may be effective in clarifying their relationship to the drug. • Postmarketing surveillance will be useful for detection and characterization of known and unknown safety issues.	Safety concerns will require enhanced pharmacovigilance, postmarketing surveillance, and postmarketing requirements, and warnings in labeling.

2. Background

Ocrelizumab (OCR) is not an approved drug product for any indication and has not previously been the subject of any marketing application. It is a new therapeutic biological product intended to be used for the treatment of relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS).

Though numerous medications have been approved for RMS, there can be considerable variability in individual responses to these different medications and patients with multiple sclerosis (MS) may have inadequate control of their disease despite treatment with available therapy. There are no approved therapies for PPMS.

Although the precise mechanism of action of OCR is unknown, OCR is a humanized monoclonal antibody which binds to CD20, a B-cell surface molecule, and it is theorized that OCR may exert its effects by selectively depleting CD20-expressing B cells leading to immunomodulation. This activity appears to be distinct from the varied biological activities of the other drugs approved for the treatment of MS.

The applicant is Genentech. Genentech is an established company in the development of therapeutic biological products, and this is the first application for MS we have received from this applicant. The Division was involved throughout the development of OCR, and Dr. Rodichok has a detailed presentation in his review of the regulatory history and interactions with Genentech. Selected important issues during development included the choice of comparator group, dose selection, trial design, receipt of breakthrough designation (on the basis of the PPMS results), content of the marketing application, and granting of priority review (again, on the basis of the PPMS results).

This application is intended to establish the effectiveness of OCR based primarily on the results of 2 essentially identical studies (WA21092 and WA21093) in RMS, both randomized, double-blind, and active comparator-controlled, and 1 randomized, double-blind, placebo-controlled study (WA25046) in PPMS. Two pre-BLA meetings held on December 8, 2015, and February 4, 2016, led to agreement with the sponsor that data from Studies 301 and 201 could potentially provide substantial evidence of effectiveness.

The application has been reviewed in detail by the review team and I refer to the various primary and supplementary reviews for a detailed presentation and discussion of the application and will not repeat the majority of those reviews in this memo. In particular, with regard to the clinical studies, I will note only briefly the results of the RMS studies. We have many drugs approved for RMS and the approach to studies of drugs for this indication and consideration of the results of those studies is quite consistent. The review team agrees that the effectiveness of OCR for RMS has been established. Similarly, the safety profile of the OCR is not viewed by the review team as an obstacle to approval and I will not repeat in any great detail the findings of the review team in this regard. I will focus the majority of my comments on several important areas of the application that received particular attention during the review process: the acceptability of the manufacturing processes, the acceptability

of the nonclinical data, the approach to harmonized dosing for RMS and PPMS, the suitability for description in labeling of the PPMS results, and concerns regarding the occurrence of breast cancer in association with use of OCR.

In sum, the statistical and clinical review staff unanimously recommend approval of OCR for RMS and largely finds that evidence of effectiveness of OCR for PPMS has been demonstrated with differing opinions about the strength of the PPMS results, with Dr. Yan concluding that the PPMS data were indicative of efficacy, though not strongly so, Dr. Rodichok recommending approval for PPMS in light of the unmet medical need, while noting some uncertainty about the strength of the PPMS results, and Dr. Marler finding insufficient evidence of effectiveness and recommending against approval for PPMS.

I will briefly discuss the major findings of the review team.

3. Product Quality

As noted by Dr. Kennett, she and her colleagues do not recommend approval due to concerns that the manufacture of ocrelizumab is not well controlled and able to consistently produce a product that is pure and has appropriate potency. The nature of these concerns was discussed extensively amongst the review team, and the product quality review notes that if the clinical significance of the efficacy results (i.e., the PPMS results) supported approval, a variety of updates to the control strategy and postmarketing commitments (PMCs) could be implemented to verify resolution of issues that would otherwise preclude approval for a product that does not meet an unmet medical need. After careful discussion with the product quality team and with the applicant, I agree that this approach is reasonable given the efficacy findings in PPMS and we have worked to amend the control strategy and construct an array of PMCs that will acceptably ensure the control of the manufacture of OCR for use in the near term while requiring the sponsor to improve the manufacturing process of OCR to resolve the issues necessitating the need for the PMCs.

Accordingly, while recognizing the importance of the product quality deficiencies and agreeing with Dr. Kennett that such deficiencies would ordinarily preclude approval, I find that resolution of remaining product quality issues via initial adjustments to the control strategy and PMCs for appropriate drug product shipping and leachables studies, to perform method validation for the ADCC potency assay and other product quality assays included in the updated release and stability specifications, to implement more appropriate reference standards, and to validate the updated process, post-approval adjustments by the applicant to control strategy changes that will be submitted as prior approval supplements, continued process verification by the applicant of the marketed product to ensure its quality, and continued investigation by the applicant of product degradation and implementation of corrective and preventive actions, is an appropriate strategy to support the approval of OCR given the unmet medical need that it will address.

Manufacturing site inspections were acceptable. Stability testing supports a drug substance expiry of (b) (4) months at (b) (4) °C and a drug product expiry of 15 months at 2-8°C. The

manufacturing review team has negotiated with the sponsor the PMCs and other issues noted above. There are no other outstanding issues.

4. Nonclinical Pharmacology/Toxicology

As discussed in detail in Dr. Wilcox's review, there are nonclinical concerns about whether the product used in the reproductive toxicology studies is comparable to the product used in the pivotal clinical studies and the product intended for market. Because this issue was unresolved, Dr. Wilcox recommends against approval, noting that some studies may need to be repeated if the products are not comparable.

Dr. Lois Freed, in her supervisory memo, also notes these concerns, as well as the CMC deficiencies which, at the time, were thought to preclude approval. Regarding the nonclinical deficiencies, she notes that if the applicant is able to provide additional data demonstrating sufficient comparability between the nonclinical and clinical products, then the completed embryofetal development study would be adequate, but that it will be necessary to conduct an expanded pre- and postnatal development study in (b) (4) to assess immune function. Given available clinical data, an additional chronic toxicity study was not considered necessary.

I have discussed the issues with Dr. Freed and, given the approach to product quality described above, the nonclinical issues may be addressed post-approval; we have negotiated with the sponsor a PMR for an expanded pre- and postnatal development study.

5. Clinical Pharmacology

I concur with the conclusions reached by Dr. Parepally that there are no outstanding clinical pharmacology issues that preclude approval. There are no needed postmarketing requirements or commitments. His review discusses the usual pharmacokinetic (PK) and pharmacodynamic (PD) considerations. Selected findings include:

- OCR exhibits linear and dose proportional pharmacokinetics between 400 and 2000 mg.
- Elimination half-life is approximately 4 weeks.
- Hepatic metabolism and renal elimination are not expected and no dosing adjustments are required for renal impairment. Weight-based dosing is not required.
- Antidrug antibodies occurred in 12/1311 treated patients, with neutralizing antibodies occurring in 2 of those patients. These 2 patients had more rapid clearance of OCR and more rapid B-cell repletion, but the emergence of antidrug antibodies had no discernable impact on clinical effect.

- Dosing adjustments in the presence of concomitant medications that are substrates of CYP isozymes are not required, as this is a monoclonal antibody and such drug-drug interactions are not expected.

- In the RMS studies, the initial dose was administered as two 300 mg infusions given 14 days apart, with subsequent doses administered as single 600 mg infusions every 6 months. In the PPMS study, all doses were given as two 300 mg infusions given 14 days apart every 6 months. The sponsor proposes a single harmonized dosing regimen using the approach of the RMS studies. Based on comparable overall exposure, effects on B-cell depletion and repletion, and safety findings, Dr. Parepally concludes that the sponsor's proposed dosing regimen of two initial 300 mg infusions given 14 days apart with subsequent doses administered as single 600 mg infusions every 6 months is acceptable for both RMS and PPMS. Dr. Rodichok notes that given the uncertain relationship of pharmacokinetic and pharmacodynamic measurements to efficacy, use of this regimen for PPMS patients can introduce uncertainty. Though that is a reasonable point, given the nature of OCR and the high likelihood that its effect is in some way mediated through its observed targeted pharmacodynamic effects, along with the extremely high degree of similarity of the two regimens on various parameters, I agree with Dr. Parepally that the sponsor's proposed regimen is acceptable.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

As discussed by Dr. Yan, Dr. Rodichok, and Dr. Marler, 3 studies provide the primary data intended to support efficacy, Studies WA21092 and WA21093 in RMS, and Study WA25046 in PPMS. I will briefly discuss these studies and refer to the team's reviews for additional detailed discussion.

RMS Studies

As Dr. Marler and other members of the review team note, the RMS studies were essentially identical parallel-group, fixed-dose, randomized, double-blind, double-dummy, active-controlled studies that enrolled patients with relapsing MS. The comparator was Rebif (interferon β-1a), administered according to its approved regimen. Rebif has known effects on relapse rate and disability progression described in approved labeling. OCR dosing is described above. Enrollment criteria are summarized in the various reviews. Patients were adults with relapsing MS; patients with PPMS were excluded from these studies. Similar populations were enrolled in both studies. Both studies included a reasonable number of patients from the United States, about 25% of the total population enrolled in each study. Eligible subjects were enrolled and treated for 2 years. Approximately 400 patients were

enrolled into each arm of each study. The retention rate of patients was 80-85% and slightly more Rebif patients discontinued than did OCR. Discontinuation was generally due to adverse events. Patients in the various arms of the studies were well-matched on demographic and baseline characteristics.

The primary outcome measure in both studies was the annualized relapse rate (ARR) over the time of the study. The ARR was based on relapses defined by protocol, as is usual in these types of studies.

Dr. Yan describes the following secondary outcomes for the RMS studies, in order of hierarchical analysis:

- The time to onset of confirmed disability progression (CDP) for at least 12 weeks (12-week CDP), with the initial event of neurological worsening occurring during the 96-week treatment period
- The total number of T1 Gd-enhancing lesions as detected by brain MRI at Weeks 24, 48, and 96
- The total number of new and/or enlarging T2 hyperintense lesions as detected by brain MRI at Weeks 24, 48, and 96
- The proportion of patients who have confirmed disability improvement (CDI) for at least 12 weeks (12-week CDI), with the initial event of neurological improvement occurring during the 96-week treatment period
- The time to onset of CDP for at least 24 weeks (24-week CDP), with the initial event of neurological worsening occurring during the 96-week treatment period
- The total number of new T1 hypointense lesions at Weeks 24, 48, and 96
- The change in MSFC score from baseline to Week 96
- The percentage change in brain volume as detected by brain MRI from Week 24 to Week 96
- The change in SF-36 PCS Score from baseline to Week 96
- The proportion of patients who have “No evidence of Disease Activity” (NEDA) by Week 96

The following table taken from page 18 of Dr. Marler’s review summarizes the primary outcome findings for the RMS studies, with a highly significant effect on ARR in both.

Primary Outcome for Relapsing MS Trials[15] Annualized Relapse Rate (ARR)				
Trial	**WA21092**		**WA21093**	
Treatment Arm	**Rebif**	**Ocrelizumab**	**Rebif**	**Ocrelizumab**
ITT (n)				
Modified ITT (n)	411	410	418	417
Total number of relapses	166	96	168	98
Total patient years followed	678.1	706.3	661.0	709.5
Unadjusted ARR	0.245	0.136	0.254	0.138
Adjusted ARR*	0.292	0.156	0.290	0.155
(95% CI)**	(0.235, 0.361)	(0.122, 0.200)	(0.234, 0.361)	(0.121, 0.198)
Adjusted rate ratio		0.536		0.532
(95% CI)		(0.400, 0.719)		(0.397, 0.714)
Risk Reduction		46.4%		46.8%
p-value		< 0.0001		< 0.0001

More patients were relapse free on OCR than on Rebif in both trials (81-82% vs. 68-69%).

Dr. Yan presents the results of the secondary outcomes for the RMS studies in this table from page 22 of her review:

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	WA21092		WA21093	
	IFN beta-1a (N=411)	**OCR 600 mg (N=410)**	**IFN beta-1a (N=418)**	**OCR 600 mg (N=417)**
12-week CDP	N=411	N=410	N=418	N=417
N (%) of patients with events	50 (12.17)	31 (7.56)	63 (15.07)	44 (10.55)
Hazard ratio		0.57		0.63
p-value (log-rank)		0.0139		0.0169
12-week CDP Pooled (primary)	**N=829**	**N=827**	**N=829**	**N=827**
% of patients with events	**15.18**	**9.75**	**15.18**	**9.75**
Hazard ratio		**0.60**		**0.60**
p-value (log-rank)		**0.0006**		**0.0006**
T1 Gd-enhancing lesions	N=377	N=388	N=375	N=389
Mean per scan	0.286	0.016	0.416	0.021
Rate ratio		0.058		0.051
p-value		<.0001		<0.0001
New/enlarging T2 lesions	N=378	N=390	N=376	N=390
Mean per scan	0.982	0.323	1.904	0.325
Rate ratio		.229		0.171
p-value		<.0001		<0.0001
12-week CDI	N=306	N=310	N=308	N=318
Proportion of improved	12.42	20.00	18.83	21.38
Relative risk		1.61		1.14
p-value		0.0106		0.4019
12-week CDI pooled	N=614	N=628	N=614	N=628
Proportion of improved	15.64	20.70	15.64	20.70
Relative risk		1.33		1.33
p-value		0.0194		0.0194
24-week CDP	N=411	N=410	N=418	N=417
N (%) of patients with events	39 (9.49)	24 (5.85)	13.63	8.60
Hazard ratio		0.57		0.63
p-value (log-rank)		0.0278		0.0370
24-week CDP pooled	N=829	N=827	N=829	N=827
% of patients with events	12.03	7.58	12.03	7.58
Hazard ratio		0.60		0.60
p-value (log-rank)		0.0025		0.0025
New T1 hypointense lesions	N=377	N=388	N=375	N=389
Mean per scan	0.982	0.420	1.255	0.449
Rate ratio		0.428		0.357
p-value		<0.0001		<0.0001
MSFC	N=308	N=322	N=269	N=308
Mean change from baseline	0.174	0.213	0.169	0.276
Mean difference		0.039		0.107
p-value		0.3261		0.0040
Brain Volume	N=267	N=281	N=259	N=287
Mean % change from week 24	-0.741	-0.572	-0.750	-0.638
Mean difference		0.168		0.112
p-value		0.0042		0.0900

There was a highly significant effect on both independent and pooled disability progression and on MRI lesion counts in both studies.

Various sensitivity analyses of the primary and secondary outcomes were consistent and supportive. Dr. Yan notes that subgroup analyses by demographic and baseline characteristics were relatively consistent with the primary findings, with some suggestion that increased body

mass might be associated with reduced efficacy, though this was not a consistent finding and, as noted above, Dr. Parepally found no reason to adjust dose by body weight. Overall, additional subgroup explorations reported by Dr. Yan and Dr. Rodichok did not suggest substantial differences from the primary and major secondary findings. Dr. Marler agrees with these conclusions.

Overall, Dr. Yan, Dr. Rodichok, and Dr. Marler all agree that the result of the RMS studies provide consistent and strong evidence of the effectiveness of OCR in RMS on ARR, disability progression, and MRI measures, and recommend approval for this population.

PPMS Study

As Dr. Marler and other members of the review team note, the PPMS study was a parallel-group, fixed-dose, randomized (2:1), double-blind, double-dummy, placebo-controlled study that enrolled patients with PPMS. OCR dosing is described above. Enrollment criteria are summarized in the various reviews. Patients were adults with PPMS. About 14% of the total population enrolled in the study was from the US. Eligible subjects were enrolled and treated for a variable duration with the clinical cut-off date occurring after a minimum of 120 weeks and approximately 253 events had been accrued, resulting in at least five treatment doses per patient. Approximately 500 OCR patients and 250 placebo patients were enrolled into the study. The retention rate of patients was about 80% for OCR and about 65% for placebo. Discontinuation was generally due to lack of efficacy (over twice as many for placebo as for OCR) or adverse events. Patients in the various arms of the studies were well-matched on demographic and baseline characteristics.

The primary outcome measure was the time to onset of 12-week CDP, increased disability that persisted for 12 weeks, during the double-blind treatment period, but Dr. Yan's review also shows the effect on overall event rates and event rate over time.

Dr. Yan describes the following secondary outcomes for the PPMS study, in order of hierarchical analysis:

- The time to onset of confirmed disability progression (CDP) for at least 24 weeks
- Change in timed 25 foot walk (T25FW) from baseline to Week 120
- Change in total volume of T2 lesions from baseline to Week 120
- Percent change in total brain volume from Week 24 to Week 120
- The change in SF-36 PCS Score from baseline to Week 120

The following table taken from page 36 of Dr. Yan's review summarizes the primary outcome finding for the PPMS studies, with a significant effect on 12-week CDP. Dr. Yan's review also shows the effect on overall event rates, as is shown below, with a reduction from 39.3% to 32.9%. The reduced event rate is persistent over time, as shown in labeling and in Dr. Yan's analysis.

	Placebo (N=244)	OCR 600mg (N=488)
Patients included in analysis	244 (100.0%)	487 (100.0%)
Patients with event (%)	96 (39.3%)	160 (32.9%)
Patients without event (%)	148 (60.7%)	327 (67.1%)
Time to event (weeks)		
Range	0* to 216*	0* to 217*
Stratified Analysis		
p-value (log-rank)	0.0321	
Hazard Ratio	0.76	
95% CI	(0.59, 0.98)	

There was a significant reduction in 12-week CDP in the OCR group.

Dr. Marler presents the results of the secondary outcomes (they are 5 in number – the notation of a hierarchy of 10 refers to the RMS studies) for the PPMS study in this table from page 34 of his review:

PPMS Secondary Outcomes for Trial WA25046 at 120 Weeks[52]

Hierarchy of Ten Secondary Outcomes 120-week double-blind epoch	Placebo	Ocrelizumab 600	p-value (Applicant)	p-value[53] (Dr. Yan)	Rate Ratio (Ocr/Placebo)[54]	Absolute Difference (NNT)
1. % With Disability progression lasting 24 weeks[55]	32.7%	28.3%	.0365		0.86	4.4%(23)
2. Relative Reduction in Timed 25-Foot Walk (T25FWT)	55.1	38.9	.0404		0.69	
Dr. Yan's T25FWT analysis without imputation Dr. Yan's MMRM analysis				0.0528* or 0.0783**		
3. Change in Total Volume of T2 Lesion Ratio to Baseline[56]	7.426	-3.366	0.0001	na	-1.45	
4. Percent Change Total Brain Volume	-1.093	-0.902	.0206	na	0.82	
5. Change in SF-36 (Physical Component)	-1.108	-0.731	0.6034	na	0.66	

There was a significant effect on 24-week CDP (similar to the primary outcome), on T25FW, and on MRI measurements.

Various sensitivity analyses of the primary and secondary outcomes were performed and provided variable results.

With regard the related endpoints of CDP lasting 12 and 24 weeks, the primary and first secondary outcomes of the trial, the protocol-defined primary analysis allowed initial onset of disability progression for patients who withdrew from the study to be imputed as confirmed without actual confirmation. This approach is unusual as confirmation is generally required in assessment of disability in MS trials. Accordingly, a sensitivity analysis excluding the

imputed data (21 events), consistent with the usual approach for a disability progression endpoint, was performed and failed to achieve a statistically significant treatment effect for CDP of either duration (p=0.1477 for 12 weeks and p=0.1884 for 24 weeks). Other sensitivity analyses of the primary endpoint are presented on pages 38 and 39 of Dr. Yan's review and are largely consistent with the primary analysis. The concern regarding the imputation approach for the primary endpoint is that confirmed disability serves as a proxy for durably persistent disability and is intended to eliminate the contribution of fluctuations in disability to the disability outcome. Although the imputation approach was pre-specified, it was unusual, and, though a simple elimination of the imputed data weakened the result significantly, the trial itself provides a means to estimate the number of patients with imputed disability who would actually have gone on to have confirmation at week 12. We asked Dr. Yan to perform an additional sensitivity analysis based on this estimate. As her review addendum describes, about 23% of patients who had an initial onset of disability did not have it confirmed at 12 weeks. Based on this figure, 5 patients of the 21 who had imputed data could be expected to have an onset that is not confirmed, i.e., to not have an event, while 16 would have had an event. Dr. Yan conducted an analysis that selected 5 of the 21 patients randomly to be unconfirmed, with the remaining 16 contributing confirmed data to the primary analysis. This analysis was repeated 500 times, each with 5 randomly chosen patients to be assigned as unconfirmed. This table from Dr. Yan's supplementary review describes the findings from this exercise.

Descriptive Statistics of 500 p-values	
Mean	0.050
Minimum	0.0177
Maximum	0.0931
90% Range	0.0256 – 0.0701

The results of this analysis indicate that if the 21 imputed patients behaved as suggested by the remainder of the patients in the trial, the primary analysis would be expected, on average, to maintain significance.

Dr. Yan describes the results of her sensitivity analyses of the T25FW on pages 45 and 46 of her review, and while only the sponsor's analysis was significant (p=0.0404), she notes that the results of the sensitivity analyses appeared consistent regardless of which was used with marginally insignificant findings (p-values of 0.05 and 0.08).

Sensitivity analyses of T2 lesion volume remained highly significant.

Sensitivity analyses excluding sites with violations identified during clinical inspections maintained significance.

A sensitivity analysis intended to evaluate the impact of the clinical relapse on the primary outcome by removing disability progression events preceded by relapse resulted in a similar

treatment effect as that seen in the primary analysis, suggesting that OCR has an effect on disability independent of an effect on relapse.

Dr. Yan notes that subgroup analyses by demographic and baseline characteristics were relatively consistent with the primary findings, with the exception of a lack of treatment effect seen in women on the primary outcome (12-week CDP of 35.5% in placebo and 36% in OCR), which represented about half of the enrolled population.

In order to provide further context for this apparent lack of treatment effect in women, I asked Dr. Yan to look for other evidence of treatment effect in women by analyzing clinical relapses and T2 lesion volume and count by sex. She provided the following table.

	Placebo N=244	**Ocrelizumab N=487**
Summary of Relapse		
Number (%) of patients who had relapses	40 (16.4%)	31 (6.4)
Number (%) of the above patients with CDP	19 (47.5%)	16 (51.6%)
Number (%) of patients with relapse prior to CDP	13 (32.5%)	7 (22.6%)
Relapses		
Female		
N	124	236
Number (%) with relapse	17 (13.7%)	16 (6.8%)
Time to 1st relapse - log-rank test		P=0.0168
Hazard Ratio (Cox-model)		0.441 (p=0.0188)
ARR	0.000122	0.000043
Rate Ratio		0.352
Nominal p-value of ARR		0.0216
Male		
N	120	251
Number (%) with relapse	23 (19.2%)	15 (6.0%)
Time to 1st relapse - log-rank test		P<.0001
Hazard Ratio (Cox-model)		0.242 (p<.0001)
ARR	0.000311	0.000066
Rate Ratio		0.212
Nominal p-value of ARR		0.0012
T2 Lesion Volume (change from baseline to Week 120)		
Female		
N	116	226
Mean (medium) Change (LOCF)	0.55 (0.06)	-0.45 (-0.12)
% Change from Baseline (LOCF)	8.03 (1.82)	-3.31 (-3.63)
Nominal p-value		P<.0001
Male		
N	114	235

Mean (medium) Change (LOCF) % Change from Baseline (LOCF) Nominal p-value	0.51 (0.05) 8.26 (1.72)	-0.32 (-0.11) -2.35 (-2.74) P<.0001
T2 New/Enlarging Lesion Count at Week 120 (LOCF) **Female** N Mean (median) Nominal p-value **Male** N Mean (medium) Nominal p-value	 116 3.69 (1.0) 114 4.89 (2.0)	 226 0.39 (0.0) p<.0001 236 0.04 (0.0) P<.0001

Notably, OCR reduces relapses in the overall population and, in women specifically, a consistent effect on incidence of relapse, time to relapse, ARR, and T2 lesion volume and count is seen, all achieving nominal significance.

Overall, the review team endorses somewhat differing opinions.

Dr. Yan concludes that a statistically significant effect was shown on disability, both for the primary endpoint and for the analysis of the timed 25-foot walk, a related major secondary endpoint, and that OCR appears to delay disability progression in PMS patients. She notes that the evidence of effectiveness is weak, citing the loss of significance without imputation of disability events. I note that Dr. Yan came to this conclusion prior to the conduct of the additional sensitivity analysis described above that was informed by the actual pattern of confirmation seen in the study itself, and that maintained significance. I have discussed the result of this additional analysis with Dr. Yan and she agrees that her concerns about the loss of significance without imputation have been mitigated by the additional analysis and that the findings of the PPMS study support approval.

Dr. Rodichok concludes that the PPMS study is an adequate and well-controlled study that provides evidence that OCR has a beneficial effect on disability, but, for reasons similar to those of Dr. Yan, feels the evidence is weakened by a lack of statistical persuasiveness. He also expresses concerns about the modest size of treatment effect and about the ability of the RMS studies to support the PPMS study, based on a lack of similarity in patient characteristics and disability findings in the two populations. Notwithstanding these concerns, he recommends approval for this population, in light of the unmet medical need for PPMS and acceptable safety profile of OCR.

Dr. Marler does not recommend approval for the PPMS population. He cites several major concerns. First, he shares the concern of Dr. Yan and Dr. Rodichok regarding the statistical persuasiveness of the study, noting the issues with imputation and the loss of overall significance without imputation. As with Dr. Yan, Dr. Marler came to this conclusion prior to the conduct of the additional sensitivity analysis described above that was informed by the

actual pattern of confirmation seen in the study itself, and that maintained significance. Dr. Marler also expresses concern about the lack of apparent effect on disability seen in the subgroup of women enrolled in the PPMS study, particularly in light of the signal for breast cancer. He does not comment on the notable effect in women (and men, for that matter) on relapses and MRI markers of disease activity in the PPMS population, limiting his assertion of an absence of effect in women to the primary outcome. Dr. Marler is concerned that the rate of events in the two arms of the PPMS study does not appear to differ over the majority of the study, with most of the effect being apparent soon after treatment. He notes that adherence to the protocol was not ideal, with deviations from instructions concerning the need to record baseline scores before randomization. He expresses concern about missing data, an unfortunately common issue. For these reasons, he finds the PPMS study not well-controlled and not persuasive. Like Dr. Rodichok, Dr. Marler also expresses concern about the ability of the RMS studies to support the PPMS study, based on a lack of similarity in patient characteristics and disability findings in the two populations, as well as the inability of other drugs that have succeeded in RMS to show an effect in PPMS.

I agree with Dr. Yan and Dr. Rodichok that the results of the PPMS study support approval. I do not agree with Dr. Marler that the PPMS study does not contribute to substantial evidence of effectiveness. I do not agree with Dr. Rodichok or Dr. Marler that the PPMS study results must be viewed in isolation from the RMS results. I describe my reasoning below.

8. Safety

As discussed in the review of Dr. Boehm, there are no safety issues associated with the use of OCR that would independently preclude approval if effectiveness is demonstrated. In addition to his detailed discussion of safety findings, Dr. Sally Jo Yasuda provides a thorough secondary review of the safety findings and Dr. Marler summarizes the safety findings and issues in his memo. I will briefly consider the major issues they have discussed.

The size of the safety database was adequate. Safety assessments were deemed generally adequate by the review team. Dr. Boehm points out that drug exposure was adequate, was at or above the proposed dose, and the clinical trial subjects reflect the intended population for use. There was substantial exposure in MS patients. A large portion of the exposure comes from the randomized, double-blind, controlled MS studies discussed above, along with their open-label extensions and an earlier dose-finding trial. Other data comes primarily from controlled and open-label studies in rheumatoid arthritis, with limited additional data from studies in patients with systemic lupus erythematosus, lupus nephritis, and non-Hodgkin's lymphoma.

There were 8 deaths in OCR-treated patients in MS studies. Dr. Yasuda notes that there were too few deaths during controlled phases of the MS studies to support conclusions about relative mortality risks. Of those 8, a case of pneumonia and a case of sepsis may be related to OCR. Dr. Boehm does not feel the others are related. One of these death was due to metastatic pancreatic cancer. Dr. Boehm notes that there is no obvious link to OCR, although a possible contribution of OCR cannot be excluded. In the rheumatoid arthritis controlled

studies, the mortality rate for OCR and placebo was comparable, but the OCR group had an excess of infection/sepsis related deaths compared to placebo (5 vs. 0). There were a variety of other deaths that occurred in uncontrolled settings. They are presented and summarized in the various reviews. All review team members agree that there is no evidence to draw any definitive conclusions regarding the role of OCR in the various deaths reported in the application. I have reviewed these cases, also, and I agree with the team.

Dr. Boehm, Dr. Yasuda, and Dr. Marler have discussed safety concerns of interest thoroughly in their comprehensive and summary reviews. Dr. Boehm has included a concise summary of the primary safety findings in her summary framework at the beginning of her review, which have been further summarized with additional commentary by Dr. Yasuda and Dr. Marler. Main findings include:

Infusion-related reactions (IRRs)
35% of patients in the MS studies had IRRs that occurred most frequently after the first dose but continued to occur with subsequent infusions. Patients received required pre-treatment with steroids. Most of the reactions were mild and occurred during the infusion. Some occurred within 24 hours of the infusion.

Infections
Infections were commonly reported (54%) in the MS studies overall and in the controlled trials where they occurred more commonly with OCR than with comparator. Interestingly, SAEs due to infections occurred less frequently with ocrelizumab than with comparator. There were no opportunistic infections OCR-treated MS patients.

Malignancies (most notably breast cancer)
OCR was associated with an approximate 3-fold increase in malignancies vs. comparator in the controlled MS studies. There was an imbalance in the controlled trials for breast cancer associated with OCR (with 6 cases in women exposed to OCR vs. none in comparator). There were 8 cases (8/1,398 females, 0.6%) in the all MS trials. One case of breast cancer in a male occurred in a rheumatoid arthritis trial. Dr. Boehm notes that this was an unexpected occurrence given the background rate of breast cancer in men. Other malignancies tended to be isolated events.

Depression
Depression AEs and depression and suicide-related SAEs occurred more frequently in OCR subjects than in interferon beta-1a subjects. Depression AEs occurred less frequently in ocrelizumab-treated patients than placebo in the PPMS study. Dr. Boehm favors a Warning as interferon beta 1-a product labeling has a Warning statement for Depression and Suicide. As the comparison with placebo is the most interpretable of these findings, (b) (4) .

Pancreatitis
Pancreatitis occurred in 5 OCR patients and none in the comparator subjects in controlled trials, though 3 of the patients with pancreatitis had known risk factors.

Cholecystitis and cholelithiasis
These occurred slightly more frequently with OCR but in very few cases. The team agrees this finding is of unclear significance.

Progressive multifocal leukoencephalopathy
We have become accustomed to seeing cases of progressive multifocal leukoencephalopathy (PML) occur in association with the various immunomodulatory drugs that are approved for MS, and PML is described in the labeling for other approved anti-CD20 antibodies, but no cases of PML were reported in the MS studies. We will include a discussion of PML in the Warning for infections.

Dr. Boehm points out that these adverse reactions have the potential for more serious outcomes in the postmarketing period in which patients are monitored less frequently than in the clinical trial setting.

Dr. Boehm recommends the inclusion in labeling of Warnings and a Medication Guide regarding the risks of IRRs, infections, malignancies, and depression/suicide. Dr. Yasuda notes the need for guidance in labeling for pre-treatment to lessen the risk of IRRs.

Dr. Boehm recommends a postmarketing requirement (PMR) for an observational safety study to evaluate the main safety risks of OCR in the postmarketing setting. Dr. Yasuda recommends enhanced pharmacovigilance for events of serious infections, including opportunistic infections, with a focus on progressive multifocal leukoencephalopathy (PML) and Hepatitis B reactivation; cholecystitis and cholelithiasis; and pancreatitis. She recommends a pregnancy registry as a PMR.

Dr. Yasuda and Dr. Marler have provided summaries of Dr. Boehm's detailed presentation of common adverse event, laboratory, and vital sign data, and I refer to their summaries for further discussion.

There is no foreign marketing experience.

Overall, Dr. Boehm, Dr. Yasuda, and Dr. Marler all find no safety issues that would preclude approval. Postmarketing requirements for an observational safety study and a pregnancy registry are needed. (b) (4).
Enhanced pharmacovigilance for serious infections, including opportunistic infections, with a focus on PML and Hepatitis B reactivation; cholecystitis and cholelithiasis; and pancreatitis will be requested. Dr. Zendel reviewed the need for a REMS and concluded that a REMS is not necessary for this application. The review team concurs with this recommendation.

I concur with the findings of the review team.

9. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of MS and because the clinical trial design is similar to that of trials of previously approved drugs for the treatment of MS.

10. Pediatrics

We will not require pediatric studies for PPMS from birth to 17 years of age and for RMS from birth to 10 years of age because the small number of such patients in these age groups makes necessary studies impossible or highly impracticable. We will defer submission of a required pediatric safety, tolerability, pharmacokinetic/pharmacodynamic, safety, and efficacy study in RMS for ages 10 through less than 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

13. Postmarketing

As noted above, the members of the review team agree that a REMS is not required for this application. I agree.

Postmarketing requirements include a requirement for the pediatric studies noted above.

Postmarketing requirements are needed to assess the incidence and mortality rates of breast cancer and all malignancies associated with use of OCR, to conduct prospective pregnancy exposure registry cohort analyses, to conduct a pregnancy outcomes study, and to conduct an expanded pre-and postnatal development study in nonhuman primate.

Postmarketing commitments are needed for a shipping study, to confirm validation of the Antibody-Dependent Cellular Cytotoxicity assay, to confirm validation of the Capillary Electrophoresis Glycan Analysis assay, to confirm validation of the Reversed-Phase Ultra-High-Performance Liquid Chromatography assay, to confirm validation of the Polysorbate 20

assay, to manufacture, qualify, and implement new primary and secondary reference standards, to perform a leachable study to evaluate the drug product container closure system, and to confirm the acceptability of updates to the drug substance manufacturing process and controls.

Postmarketing risk management activities will include a request for the applicant to perform postmarketing surveillance and enhanced pharmacovigilance for pancreatitis, cholecystitis and cholelithiasis, and serious and opportunistic infections, including progressive multifocal leukoencephalopathy (PML) and Hepatitis B reactivation after exposure to ocrelizumab, with expedited reporting and summarized annual analysis of events.

14. Decision/Action/Risk Benefit Assessment

The applicant is seeking approval of an application intended to support the inclusion in labeling of a description of effects on two subtypes of multiple sclerosis (MS): 1) relapsing forms of multiple sclerosis (RMS); and 2) primary progressive multiple sclerosis (RRMS).

The applicant has provided substantial evidence of effectiveness for the use of ocrelizumab (OCR) for the treatment of patients with relapsing forms of multiple sclerosis. This conclusion is supported by evidence from two essentially identical adequate and well-controlled studies (Studies WA21092 and WA21093) that evaluated the use of a single dosing regimen of OCR. These studies were generally of typical design and evaluated an often-used primary outcome of annualized relapse rate, comparing OCR to Rebif, an approved therapy for relapsing forms of multiple sclerosis.

As noted, a single dose regimen was evaluated. After an initial dose of two 300 mg infusions given 14 days apart, subsequent doses were single 600 mg infusions every 6 months. The effect on annualized relapse rate in both studies was highly significant with a reduction of 46-47% against Rebif, a drug with an established effect on annualized relapse rate. The effect on accumulation of sustained disability, measured by comparing confirmed disability progression endpoints, was also highly significant in both studies, despite an expected need to assess disability by pooling data from both studies. This pooled analysis was the major secondary endpoint and was highly significant, with an absolute reduction of about 5% compared to Rebif, a drug with an established effect on disability. The effects on relapse and disability were supported by consistent effects on various secondary, subgroup, and sensitivity analyses. The members of the review team all agree that the RMS studies provide substantial evidence of effectiveness for the treatment of RMS.

The review team is in partial agreement (as noted, Dr. Marler dissents) that the applicant has provided substantial evidence of effectiveness for the use of OCR for the treatment of patients with primary progressive multiple sclerosis. This conclusion is primarily supported by evidence from a single study in PPMS (Study WA25046) that evaluated the use of a single dosing regimen of OCR, with additional support from results of the RMS studies described above. This PPMS study evaluated a primary outcome of time to confirmed disability progression, comparing OCR to placebo.

Again, a single dose regimen was evaluated, though it differed slightly from the RMS studies in that all doses in the PPMS study were given as two 300 mg infusions given 14 days apart every 6 months. The effect on confirmed disability progression was significant (p=0.03) with a reduction of 24% compared to placebo. Important secondary outcomes of disability progression sustained for 24 weeks, T25FW, and MRI T2 lesion volume were all significant. Despite concerns regarding an unusual imputation of confirmed disability progression in the absence of an actual measurement (i.e., patients that had an initial event of disability progression but left the study before progression could be confirmed at a second visit 12 weeks later were imputed as confirmed disability progression endpoints), a sensitivity analysis performed by Dr. Yan based on assignment of the imputed endpoints to an event status (i.e., contributing to the count of confirmed disability progression or being censored at the time of withdrawal) based on the actual proportion of confirmed disability progression events in patients that had an initial event of disability progression observed in the study was supportive of primary outcome. Also, a reduction in the occurrence of relapse favoring OCR was seen in the PPMS study. The members of the review team are not unanimous with regard to the evidence that the PPMS study provides, as I noted above. Dr. Yan and Dr. Rodichok support approval for PPMS, while Dr. Marler argues against it. Dr. Marler expresses concern not only about the strength of the PPMS study, but he also doubts the ability of the RMS studies (which showed an effect on disability progression in RMS) to support the PPMS study, leading him to conclude that the PPMS study must be considered on its own. Dr. Rodichok shares concerns about the about the ability of the RMS studies to support the PPMS study, but recommends approval based on the results of the PPMS study and the unmet medical need in this area.

Whether the RMS studies may serve to support the PPMS study deserves some comment in light of the extensive assertions of Dr. Marler and Dr. Rodichok that they cannot.

Substantial evidence of effectiveness is required for approval. There is a need to substantiate any individual finding to avoid reliance on erroneous conclusions, so, in general, two independent studies are typically provided to meet this need. The presumption is that the effect in the second study is related, in some fashion, to the effect in the first, in order to provide mutual support for the findings of the two studies. The two RMS studies, of highly similar design, are an example of this type of evidence, but it is clear from the guidance document on evidence of effectiveness that the clinical endpoints in each study can be different (and can be in different populations, different severities of disease, etc.), as long as they support the overall effectiveness of the drug. An alternative approach is to provide evidence from one study with support from confirmatory evidence. In such a situation, what may constitute confirmatory evidence is left undefined in regulation (wisely so, in my estimation, but many examples are given in the aforementioned guidance document on effectiveness) but the confirmatory evidence serves to substantiate the results of the single study. It is often thought that such an approach (one study plus confirmatory evidence) requires some higher degree of statistical persuasiveness of the clinical study than the conventional (though not absolute) standard of p=0.05, but this is not necessarily so. Depending on any number of aspects that may influence the overall confidence one places in the totality of the evidence, a conventional degree of statistical persuasiveness in a single study may well be acceptable when accompanied by confirmatory evidence. In fact, this is really not different conceptually from the typical approach of relying on two adequate and well-

controlled studies to support approval, as long as the "confirmatory evidence" is persuasive. In that situation, each study serves as confirmatory evidence to the other. The use of the term confirmatory evidence is generally meant to indicate some evidence other than that resulting from an effect on a clinically meaningful outcome measured in an adequate and well-controlled study. In this situation, we have two clearly positive RMS studies that are intended to serve as confirmatory evidence, so, if they may do so, the nature of the confirmatory evidence in this application is especially strong, as long .

Although Dr. Rodichok and Dr. Marler argue otherwise, I think it is clear that the results of the RMS studies are relevant to the findings of the PPMS study. RMS is clearly related to PPMS, as both are forms of a single disease, multiple sclerosis. That there are differences between these two forms of MS is not in doubt. If differences could not exist at all, then they would not be different forms and the RMS studies would suffice without any PPMS study. Differences, however, do not preclude the ability of the RMS studies to support the PPMS study. Dr. Rodichok and Dr. Marler argue that differences in the PPMS and RMS populations in demographic and baseline disease characteristics, along with differences in the characteristics of the periods of disability in those populations, is indicative of a lack of relatedness that precludes the ability of one to support the other. This argument is based primarily on assertions that outcome events of interest should have an empiric sameness in order to be related and that the differences in these various characteristics is indicative of differing pathophysiological mechanisms.

It is important to recognize that arguments related to "relatedness" are inherently subjective. Although many individual points are made by Dr. Rodichok and Dr. Marler in an attempt to support the position that the two forms of MS are not related, such an overall position is not suited for point by point refutation, lest one inadvertently establish some type of semi-quantifiable threshold beyond which relatedness is present. Suffice it to say, our considerations of this issue (made pre-submission, not unimportantly) have resulted in our position that these forms of MS are related, and may serve to support each other. Indeed, it might appear almost self-evident that, by definition, they are both MS. It is true that our thinking in the Division regarding the degree of relatedness has evolved from advice given previously that suggested that a conventional independent development program for PPMS was required. Previous advice was based on our perception of the understanding of the scientific community and our own understanding concerning the independence of the pathophysiological mechanisms underlying the forms of MS. We have evolved our thinking from our previous position, consistent with a contemporary understanding of MS. Our judgment is that these forms of MS are related, and the Division is prepared to accept PPMS and RMS populations as mutually supportive.

Although much literature may be cited that notes a variety of pathophysiological distinctions based on any number of research avenues, the phenotypic categorization of MS into PPMS and other forms (including RMS), a categorization that is the fundamental issue at play, was the result of definitions put forth in 1996 by the US National Multiple Sclerosis Society (NMSS) Advisory Committee on Clinical Trials in Multiple Sclerosis. The distinction was not made on the basis of a fundamental, well-established, and well-understood scientific characterization of the pathophysiology of the various forms of MS. At the time they were proposed, that

committee noted that these phenotypic descriptors were consensus subjective views of experts in the field and were not supported by objective biological findings. That same committee recommended that the phenotypic descriptors (MS subtypes) should be re-addressed as the scientific understanding of the disease evolved. In that spirit, The International Advisory Committee on Clinical Trials in Multiple Sclerosis (now a jointly sponsored international entity of the NMSS and The European Committee for Treatment and Research in MS) began in 2011 to explore advances in this area and convened in 2012 to formally review the 1996 classification. This review resulted in the publication in 2013 of revisions to the 1996 definitions. Clearly articulated in these revisions is the notion that PPMS is related in a fundamental pathophysiological manner to other forms of MS. While many aspects of the revisions relate to the relatedness of MS subtypes, the following quote speaks directly to the issue: "While some evidence suggests that PPMS represents a distinct, noninflammatory or at least less inflammatory pathologic form of MS, abundant clinical, imaging, and genetic data suggest that PPMS is a part of the spectrum of progressive MS phenotypes and that any differences are relative rather than absolute. Analyses of natural history cohorts demonstrate that worsening proceeds at a similar rate in SPMS and PPMS. PPMS should remain a separate clinical course because of the absence of exacerbations prior to clinical progression, but it likely does not have pathophysiologically distinct features from relapsing forms of MS that have entered a progressive course (SPMS)." (Lublin, Fred D., et al. Defining the Clinical Course of Multiple Sclerosis: The 2013 Revisions. Neurology. 2014 Jul 15; 83(3): 278-86.) It is true, of course, that the emphasis of this statement is on the progressive course of the various subtypes, but it illustrates the fact that there is substantial overlap of the subtypes with regard to clinical subtypes and likely pathophysiology, and that there is a reasonable basis to believe that demonstrated benefit in one subtype may increase the expected reliability of a finding of benefit in a study of a related subtype.

An additional comment is needed on the notion of considering this issue of the acceptability of "relatedness" during the review of the application. The Division clearly stated in pre-submission discussions with the sponsor that it was acceptable in principle to support the single PPMS study with the RMS studies (recognizing that the adequacy of the data was, of course, a matter for review, as it is for all applications) and reiterated that statement de facto by filing the application. In fact, the Division, in an effort to ensure streamlined and efficient review, particularly in light of the reported results in PPMS, actively advised the sponsor to submit the PPMS study and RMS studies in a single application, contrary to the sponsor's initial plans to submit the data in two independent applications. Indeed, if the RMS studies were not suitable for support of the PPMS study (i.e., because they were not sufficiently related) then the sponsor should have been (and would have been) advised to conduct another study in PPMS. To delay the conduct of such an additional study in this area by accepting for review an application that could not, on face, be approved because the supportive data are in character fundamentally unacceptable would be deeply troubling. This issue of the "relatedness" of PPMS and RMS is not a typical "matter for review" to be adjudicated during the review process but is primarily a policy "matter for review" that largely took place pre-submission. The Division's comments to the sponsor were clear in this regard, and the Division is cognizant of the problematic issues that would be raised by "moving the goalposts" after accepting the application.

With questions of "relatedness" resolved, the persuasiveness of the PPMS study is the remaining issue. In this regard, the primary clinical review and CDTL review do not take into account the additional sensitivity analysis performed by Dr. Yan that is described above. It is certainly true that the unusual approach to imputation was a significant concern and that eliminating all the imputed data severely weakened the primary result, but we were able to use the data within the study itself to inform a more reasonable approach to the consideration of the patients for whom confirmation of an initial disability progression was not available. That approach indicated that the statistical significance of the primary outcome was a valid representation of the effect of OCR in the PPMS study. This result, supplemented by unequivocal and very strong findings in the RMS studies, is strongly supportive of the effectiveness of OCR for PPMS. Further support is provided by effects on relapse, walking speed, and MRI findings in the PPMS study itself. Taken together, these various results provide substantial evidence of effectiveness for the use of OCR in PPMS.

It is worth making a brief comment on the previous "failures" in PPMS. Dr. Rodichok and Dr. Marler point out the lack of positive outcomes in trials of other agents in PPMS. Many of those descriptions of failure, however, are simple dichotomous characterizations based on $p>0.05$. Actual clinical findings numerically favored drug in those trials, in general, particularly in the larger trials, and MRI results trended similarly. This relatively consistent trend can be nothing more than hypothesis-generating, of course, whether for any individual drug or for the group of studied drugs as a whole, but it is intriguing. These clinical findings in previous studies concerned various measurements of disability, a notoriously difficult endpoint on which to achieve success. Disability events in MS are more complicated and difficult to study than simple counts of relapse; they occur remarkably infrequently and studies are often underpowered for this outcome. Pooling of sister trials is often necessary to achieve the power to demonstrate statistical significance for disability. Indeed, this was the prespecified plan for the RMS studies of OCR, anticipating an inability to demonstrate a beneficial effect in the individual trials. Despite this expectation, in addition to winning on this planned pooled analysis, OCR actually won in both individual RMS trials. This further reinforces the belief that the disability finding in PPMS is credible. Though purely speculative, it may be that we have hints that drugs effective in RMS may not be as ineffective in PPMS as generally thought, and that the totality of what we see with OCR may suggest that it is actually remarkably effective on disability across clinical phenotypes of MS. The previous apparent inability of other RMS drugs to affect disability in PPMS is undoubtedly noteworthy, but there may have been less failure than meets the eye and only further clinical studies will be able to address the issues involved. Past experience is certainly a reasonable basis for concluding that effectiveness in RMS should not be extrapolated to PPMS and that independent evaluation in PPMS is needed, but the failure of other drugs, often of dissimilar character, is not a basis for rejecting a clear benefit seen in such an independent evaluation.

Subgroup analyses by gender warrant mention. An apparently flat effect on disability in women in the PPMS study is noteworthy (though, it must be kept in mind, such subset analyses are exploratory and not necessarily indicative of an absence of actual benefit on disability in this subgroup). Morevover, somewhat reassuringly (again, keeping well in mind the exploratory nature of such analyses), there are effects on relapse and MRI findings in those same women and there is no gender imbalance for the benefits seen in the RMS studies.

Although of limited interpretability, we will describe these findings in labeling to more fully inform both prescriber and patient.

There are no safety concerns, in a database of acceptable size and character, that preclude approval. The most concerning adverse events involve infusion-related reactions, infections, and malignancies, particularly breast cancer. Those will receive Warnings in product labeling and further evaluation in the postmarketing setting. Depression and suicidality, though occurring slightly more frequently than control and recognized as a concern for the active comparator in the RMS studies, were actually less common in OCR-treated patients in the placebo-controlled PPMS study, (b) (4) . Overall, the safety profile of OCR is acceptable for its intended use.

Given the presence of substantial evidence of effectiveness and the acceptable safety profile, the risk benefit profile of OCR is favorable and supports approval. RMS is a serious and life-threatening condition, and we know that, given individual patient variability, continued development and approval of drugs for RMS is important. There are no treatments for PPMS, also a serious and life-threatening condition and one in dire need of an approved therapy. The biological activity of OCR is presumed to be mediated through a mechanism not shared with other approved drugs for MS.

For both RMS and PPMS, essentially a single dose was studied, with slight differences in the dosing regimens. Our analyses have indicated that a harmonized dosing regimen is appropriate for both subtypes, so, given the absence of other studied doses, we will describe in labeling the harmonized approach to dosing based on that used in the studies.

Regarding product quality, I must reiterate that identified deficiencies would ordinarily preclude approval, but resolution of remaining product quality issues via initial adjustments to the control strategy, appropriate PMCs, continued process verification by the applicant, and continued implementation of corrective and preventive actions, is an appropriate strategy to support the approval of OCR given the unmet medical need that it will address.

We will not require pediatric studies for PPMS from birth to 17 years of age and for RMS from birth to 10 years of age because the small number of such patients in these age groups make necessary studies impossible or highly impracticable. We will defer submission of a required pediatric safety, tolerability, pharmacokinetic/pharmacodynamic, safety, and efficacy study in RMS for ages 10 through less than 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Postmarketing requirements are needed to assess the incidence and mortality rates of breast cancer and all malignancies associated with use of OCR, to conduct prospective pregnancy exposure registry cohort analyses, to conduct a pregnancy outcomes study, and to conduct an expanded pre-and postnatal development study in nonhuman primate.

Postmarketing commitments are needed for a shipping study, to confirm validation of the Antibody-Dependent Cellular Cytotoxicity assay, to confirm validation of the Capillary Electrophoresis Glycan Analysis assay, to confirm validation of the Reversed-Phase Ultra-

High-Performance Liquid Chromatography assay, to confirm validation of the Polysorbate 20 assay, to manufacture, qualify, and implement new primary and secondary reference standards, to perform a leachable study to evaluate the drug product container closure system, and to confirm the acceptability of updates to the drug substance manufacturing process and controls.

Postmarketing risk management activities will include a request for the applicant to perform postmarketing surveillance and enhanced pharmacovigilance for pancreatitis, cholecystitis and cholelithiasis, and serious and opportunistic infections, including progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation after exposure to ocrelizumab, with expedited reporting and summarized annual analysis of events.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of ocreclizumab for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis.

For these reasons, I recommend approval of this application, to include the agreed-upon product labeling.

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/s/

WILLIAM H Dunn
03/28/2017