CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Office Director Summary Review
BLA #	761053
Applicant Name	Genentech
Date of Submission	April 28, 2016
PDUFA Goal Date	March 28, 2017
Proprietary Name / Established (USAN) Name	Ocrevus /Ocrelizumab
Dosage Forms / Strength	600 mg IV every 24 weeks
Proposed Indication(s)	Relapsing and primary progressive forms of multiple sclerosis
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director	Billy Dunn, MD
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
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/DRISK	Laura Zendel, PharmD
OMP/DMPP	Aman Sarai, BSN, RN
PMHS	Tamara Johnson, MD
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
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
OPQ=Office of Pharmaceutical Quality

I. Benefit-Risk Summary and Assessment

Drs. Dunn, Marler, and Rodichok have presented their overall benefit-risk analyses, and Drs. Boehm and Yasuda have provided similar analyses focused on safety. Ocrelizumab (Ocrevus) is a humanized monoclonal antibody that binds to CD20, a cell surface antigen present on pre-B and mature B lymphocytes, and treatment leads to rapid (by week 2) depletion of CD20 lymphocytes (actually measured as CD-17 lymphocytes). This immunomodulation is thought to be the drug's mechanism of action.

Ocrelizumab has been studied for chronic treatment of two forms of multiple sclerosis (MS), 1) relapsing MS (RMS), and 2) primary progressive MS (PPMS). The RMS indication is fully supported (all reviewers and Dr. Dunn concur) by two adequate and well-controlled studies comparing ocrelizumab to an interferon (Rebif), studies WA 21092 and WA 21093. Each study showed a highly statistically significant advantage of ocrelizumab on relapse rates, progression of disability, and MRI brain lesions, showing a nearly 50% reduction of annualized relapse rates compared to a drug (Rebif) that already produces an approximately 30% reduction in relapses compared to placebo.

The effect on PPMS was supported primarily by a single randomized placebo-controlled study, and the effect, although significant, was not as statistically robust, leading to internal disagreement about whether effectiveness for this use was sufficiently supported to constitute a valid claim., This will be discussed further below, but it should be noted that the controlled study in PPMS is supported by clear effects of ocrelizumab on progression in the RMS studies.

Although there are 13 drugs approved for RMS, and most are also approved for slowing progression of disability in RMS, responses can vary. Ocrelizumab has a distinct and novel mechanism of action, and requires treatment (intravenous) only twice per year. Dr. Boehm's analysis of treatment options in his safety review enumerates the approved drugs' safety problems, which are considerable.

Ocrelizumab has a number of safety concerns:

1. Other CD20 binding antibodies have activated hepatitis B, leading to fulminant hepatitis, hepatic failure, and death, and hepatitis B screening must (according to labeling) be performed before ocrelizumab is used. No cases of activation were seen in the ocrelizumab development program, which included over 5000 patients, nearly 2000 for more than 23 weeks.
2. Vaccination with live or live-attenuated vaccines is not recommended during ocrelizumab treatment, so that all needed vaccinations should be given before it is started.
3. Premedication with methylprednisolone (or other steroid) and antihistamine 30 minutes before each dose of ocrelizumab is recommended to reduce infusion reactions. Previous studies of other anti-CD20 monoclonal antibodies had shown fatal infusion reactions, which led the sponsor to incorporate the use of the pre-medications in studies.
4. There was a small increase in infections in the ocrelizumab patients compared to interferon or placebo-treated patients (58% vs 52% on interferon in RMS and 70% vs 68% on placebo in the PPMS trial). It is difficult to say whether the small differences were really drug-related but the information is included in labeling under Warnings and Precautions; most of the increase was in respiratory infections. There were also small increases in rates of herpes zoster, herpes simplex, oral herpes, and genital herpes that were consistent and reasonably convincing.
5. Other anti-CD20 antibodies, as well as other MS therapies, have caused progressive multi-focal leukoencephalopathy (PML) an often fatal illness caused by activation of JC virus. Although no cases were seen with ocrelizumab, the possibility is noted in labeling.
6. Malignancies
   In controlled trials there were 6 (of 781 exposed) patients who developed breast cancer on ocrelizumab vs O (of 668) on placebo or interferon. This clearly represented a signal,

but the clinical reviewers, with consultation from the oncology groups, did not consider it definitive. It will be noted in Warnings and Precautions and is the subject of a post-marketing monitoring requirement.

Overall, the benefits of ocrelizumab clearly outweigh its risks for both RMS and, as will be explained below, for PPMS as well.

II. Background

Ocrelizumab is a humanized monoclonal antibody that binds to CD20, a B-cell surface antigen, and presumably reduces B-cell activity. It is intended to treat RMS and PPMS, two distinct presentations of MS. There have been a wide range of treatments (13) for relapsing forms of MS (RMS). These are described in Dr. Boehm's review, and some have dramatic effects, 75-80% reductions of relapse rates. Most also diminish the rate of disability progression and show decreased MRI evidence of disease activity. No treatment to date, however, has successfully slowed the rate of disability progression in patients with PPMS. Apart from its substantial effect in RMS, an effect of ocrelizumab on PPMS would represent a response to a substantial unmet need. Reviewers, the CDTL (Dr. Marler), and Dr. Dunn have fully identified areas of incomplete agreement, principally whether ocrelizumab should be approved for treatment of PPMS. In what follows, I will not repeat detailed discussion of the evidence related to ocrelizumab that has been fully considered by reviewers.

III. Product Quality

I have nothing to add to Dr. Dunn's detailed explanation of why he does not consider the manufacturing concerns, valid as they are, a basis for refusing to approve the applications for a drug with a heretofore unattained effect in a devastating progressive disease. As he notes, there will be (b) (4) multiple PMCs directed at product quality.

IV. Non-Clinical Pharm-Tox

I also agree with Drs. Dunn and Freed that concerns about the comparability of product used in reprotox studies and in clinical studies can be resolved post-marketing. Note that labeling already notes adverse fetal effects of pregnancy exposure in monkeys and urges contraception in women of child-bearing potential who will be exposed to ocrelizumab.

V. Clinical/Statistical Effectiveness

As noted, ocrelizumab was studied for both RMS (2 studies) and PPMS (one study). The evidence of effectiveness for RMS is very clear, but evidence for effectiveness PPMS has been a matter for considerable discussion.

A. RMS

Two essentially identical 2-year trials compared ocrelizumab and Rebif in patients aged 18-55 with RMS. As noted above, Rebif is effective in reducing relapse rates and decreasing disability progression. The trials were intended to show superiority of ocrelizumab 600 mg intravenous infusions every 24 weeks (the first dose was given as a 300 mg infusion on days 1 and 15; 600 mg was then given at 6 month intervals) to interferon beta-1a at a dose of 44mcg SC three times per week for the primary endpoint, annualized relapse rate (ARR). Both trials used a randomized double-dummy design.

To enter the trials patients had to have had at least one relapse in the last year or 2 within the past 2 years and had to have an Expanded Disability Status Scale (EDSS) score between 0 and 5.5. Both trials included about 35% of patients form the U.S. and 40-50% from the EU/Switzerland/Norway. Over 90% of patients were white and about 65% were female. Mean

age was 37 years. As Dr. Yan shows (her table 5) populations were balanced for duration of MS, number of relapses during the previous year (mean of 1.3 for all groups in both studies), and extent of disability, with an EDSS mean of 2.8-2.9 for all groups.

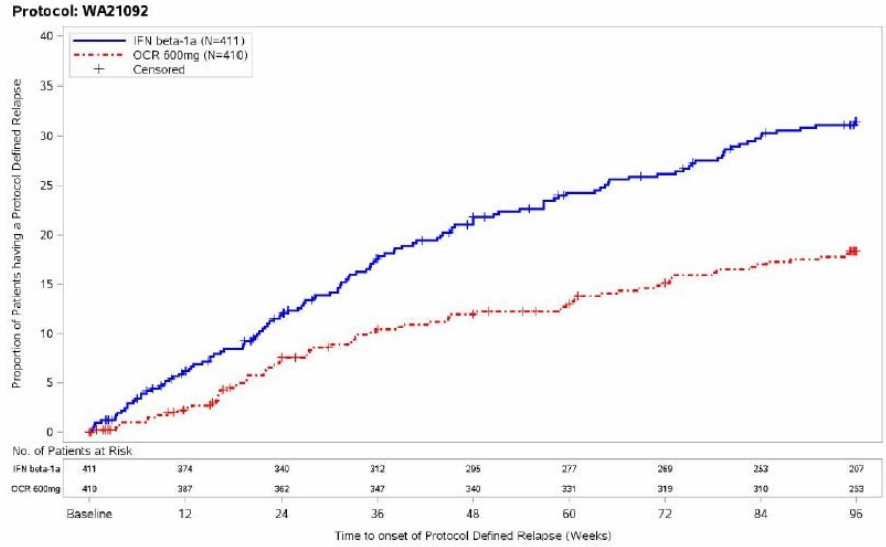
Results
A variety of adjusted and unadjusted analyses of annual relapse events were carried out (See Dr. Yan's review, tables 6 and 7), and all showed clear superiority to Rebif for reductions in relapse rate, with an approximately 46% reduction. The proportion of relapse-free patients was also increased. The planned analysis of confirmed disability progression (CDP), defined as an increase in EDSS of ≥ 1 point if baseline ≥ 2 and ≤ 5.5 and ≥ 0.5 point if baseline score was > 5.5) was a pooled analysis of the 2 studies because, historically, it has been much easier to show an effect on relapse rate than on progression. In fact, each study showed a significant effect on CDP. MRI endpoints were also assessed. The following table of results is taken from labeling. Study 1 is WA21092, and Study 2 is WA21093. The table shows effects on ARR, CDP, and MRI.

Table 4 Key Clinical and MRI Endpoints in RMS Patients from Study 1 and Study 2

Endpoints	Study 1		Study 2	
	OCREVUS 600 mg every 24 weeks N=410	REBIF 44 mcg three times a week N=411	OCREVUS 600 mg every 24 weeks N=417	REBIF 44 mcg three times a week N=418
Clinical Endpoints				
Annualized Relapse Rate (Primary Endpoint)	0.156	0.292	0.155	0.290
Relative Reduction	46% (p<0.0001)		47% (p<0.0001)	
Proportion Relapse-free	83%	71%	82%	72%
Proportion of Patients with 12-week Confirmed Disability Progression[1]	9.8% OCREVUS vs 15.2% REBIF			
Risk Reduction (Pooled Analysis[2])	40%; p=0.0006			
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per	0.016	0.286	0.021	0.416
Relative Reduction	94% (p<0.0001)		95% (p<0.0001)	
Mean number of new and/or enlarging T2 hyperintense lesions per MRI	0.323	1.413	0.325	1.904
Relative Reduction	77% (p<0.0001)		83% (p<0.0001)	

[1] Defined as an increase of 1.0 point or more from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline score of 5.5 or less, or 0.5 or more when the baseline score is greater than 5.5, Kaplan-Meier estimates at Week 96.
[2] Data prospectively pooled from Study 1 and Study 2.

Two figures from Dr. Yan's review show that the reduction in ARR was stable over the 2 year studies.



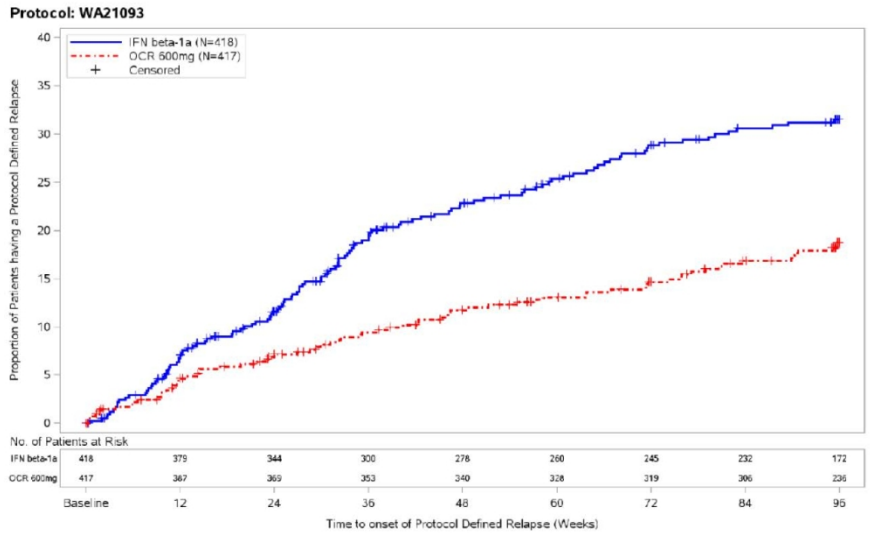


Figure 3 Kaplan-Meier Plot for Time to First protocol Defined Relapse for Studies WA21092 and WA21093

The pooled disability progression results over time, also taken from the labeling, are shown below for the pooled studies (the planned analysis).

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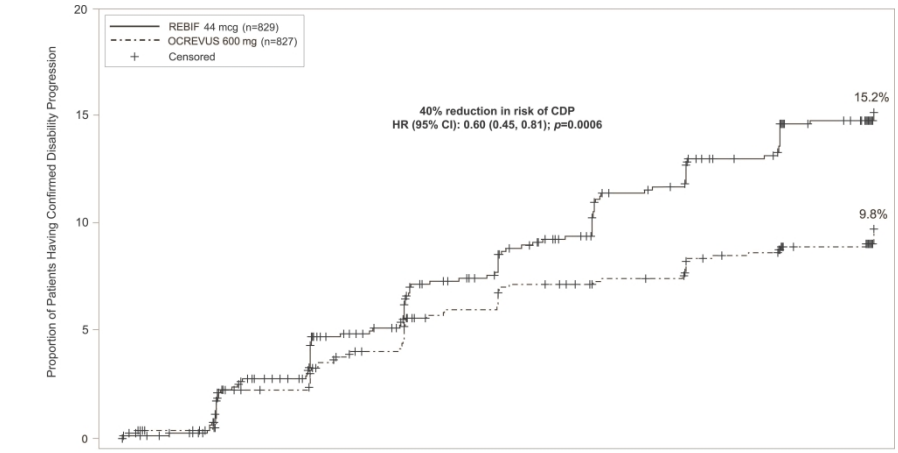
Figure 1 Kaplan-Meier Plot* of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks with the Initial Event of Neurological Worsening Occurring During the Double-blind Treatment Period in Pooled Studies 1 and 2 in Patients with RMS (Pooled ITT Population)



No. of Patients at Risk

REBIF 44 mcg	828	784	741	696	665	632	608	583	449
OCREVUS 600 mg	827	795	765	737	716	702	688	672	526
Baseline	12	24	36	48	60	72	84	96	

*Pre-specified pooled analysis of Study 1 and 2

Analyses of effects on ARR and CDP by gender and age subgroups (Dr. Yan's tables 26, 27) showed similar effects in patients <40 and ≥ 40, and in men and women.

B. PPMS, Study WA 25046

For PPMS there was a single randomized placebo-controlled double-blind trial intended to show delayed onset of 12-week CDP (confirmed disability progression) with 2:1 randomization to ocrelizumab or placebo. Ocrelizumab was given as 300 mg infusions 2 weeks apart every 24 weeks for at least 120 weeks.

To enter the trial, patients had to be age 18-55 with an EDSS of 3.0-6.5 and disease duration < 10 years if EDSS ≤ 5 or duration < 15 years if EDSS > 5 at screening. The study primary endpoint was time to onset of a 12-week duration CDP, i.e., CDP that lasted at least 12 weeks. Disability progression (CDP) was defined as

- Increase in EDSS from baseline of ≥ 1.0 point, if baseline EDSS was ≤ 5.5 points, or
- Increase in EDSS from baseline of ≥ 0.5, point, if baseline EDSS in > 5.5 points.

The changes had to occur > 30 days after a relapse. As noted, the change in disability had to be present at the next neurological assessment 12 weeks later. If the change was not present, the case was not considered a CDP. If, however, the patient left the study before the next assessment, the case was considered CDP. This approach was clearly protocol-specified, but it has been a source of controversy.

The study primary endpoint was time to the onset of disability progression that was confirmed 12 weeks later (with the exception noted for patients who left the study before the 12 week assessment). The primary endpoint was thus similar to the time to event analyses typical of cardiovascular outcome trials. A more intuitive endpoint (to me at least) would have been total number of disability progressions (CDP's) over the course of the study, but the approach used may work better when there are many dropouts. In any event, the results, shown in Dr. Yan's table 17 were similar for both endpoints: total events (39.3% on placebo; 32.9% on dacluzimab) and on time to event (a reduction shown at 48 weeks, 96 weeks, and 120 weeks and in a Kaplan-Meier plot, showing a 24% risk reduction.

Table 17 Time to Onset of 12-week CDP during the Treatment Period with Imputation

	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)	
Time Point Analysis			
48 Weeks			
Patients at risk	189		414
Event rate (%)	16.96		11.05
95% CI	(12.17, 21.76)		(8.22, 13.88)
96 Weeks			
Patients at risk	153		338
Event rate (%)	28.28		24.75
95% CI	(22.43, 34.13)		(20.80, 28.70)
120 Weeks			
Patients at risk	136		304
Event rate (%)	33.98		30.23
95% CI	(27.77, 40.18)		(26.00, 34.45)

Time to CDP (weeks) - Censoring: Event (1=censored, 0=event)
<* Censored observation>
Stratified by Geographical Region (US vs. ROW) and Age (<= 45, >45 years).
Hazard ratios were estimated by stratified Cox regression.
Patient with missing baseline EDSS excluded from analysis. Patients with an initial disability progression during the blinded treatment period who discontinue the treatment early and do not have a subsequent visit with EDSS measurement are imputed as having a CDP event.

Source: CSR

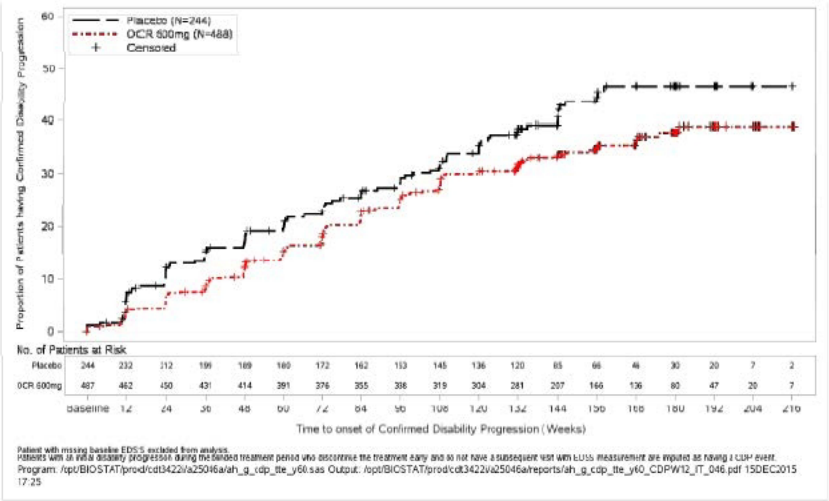


Figure 7 Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression for At Least 12 Weeks during the Double-blind Treatment Period

Source: CSR

Study WA 25046 thus showed an effect, as analyzed by the sponsor (and as planned in the protocol), but two major concerns have arisen.

The first concern, well described by Dr. Marler, arose over the planned imputation used for patients who did not have confirmation at 12 weeks of their disability. That was clearly part of the planned analysis, nor does it introduce any obvious bias, but the unverified patients had an important effect on the outcome. There were 21 such patients, i.e., with imputed data, and removal of these led to a non-significant result. As described in the amendment to her review, Dr. Yan used available data

from the study on the proportion of patients, with an initial finding a disability, who were seen 12 weeks later but had no disability. This happened in 23% of patients with initial disability. If 23% of initial positives would not be confirmed, that could mean 5 of the 21 unverified patients could have been "false positives," and results would be affected by their distribution. Using a randomized distribution of the 5 patients with expected positive results, with 500 repetitions, Dr. Yan found that the results of the study would remain nominally significant.

Apart from the imputation issue, there was a view by Dr. Marler that a single study in a novel MS setting, even if nominally statistically significant at p about 0.05, was not strong enough, well short of the usual 2 study standard. A critical question here is whether the two very persuasive studies in RMS, which showed strong effects on disability in each study, provide what can be considered "confirmatory evidence" for the single positive (at about p=0.05) study in PPMS. Confirmatory evidence under law and guidance can certainly be a legal basis for relying on a single positive study. In our evidence guidance, most of the illustrations of confirmatory evidence are in fact studies in closely related diseases, as would be the case here. Dr. Dunn has explained in full detail, with extensive expert group citations, why he thinks the RMS studies support the single positive PPMS study and, although he has far more experience than I do in MS, I add my agreement and find his explanation persuasive. It is hard to prove such things but the consistent effects of the many drugs that treat MS recurrence on progressive disability as well makes PPMS and RMS seem more related than wholly different diseases. It is also pertinent that in pre-submission discussions we did not tell the sponsor to conduct two PPMS studies and accepted the sponsor's application as discussed by Dr. Dunn.

A further concern was the lack of effect of ocrelizumab on CDP in women with PPMS (see Dr. Yan's Table 28). Given the modest effect, this is not wholly surprising (patients > 45 also had a small effect).I believe the strong findings in women in the RMS studies and on some endpoints in the PPMS study reduce concern with the lack of effect in women on progression in the PPMS study. The lack of effect will be noted in the description of the PPMS results; other effects will also be described.

VI. Safety

Safety issues are fully described by Drs. Boehm, Yasuda, Marler, Rodichok, and Dunn and I have little to add.

Labeling will note the risk of infusion reactions and how to attempt to minimize reactions with a steroid and antihistamine. It also notes the modest increased risk of infections, especially respiratory. Whether this modest difference from control groups really merits a W/P could be debated, I think, but close observation will do no harm. The small but quite consistent increase in herpes infections seems real.

The risk of PML with ocrelizumab seems a valid concern, given the history of other MS drugs and close observations is warranted.

Ocrelizumab clearly can activate hepatitis B and patients should be screened.

VII. Action

Ocrelizumab should be approved for treatment of RMS and PPMS. There is substantial evidence of effectiveness in both conditions and the drug is reasonably safe. There will be post-marketing requirements to assess the incidence and mortality of breast cancer and other malignancies, and the outcomes of pregnancy, and to perform post-marketing surveillance for pancreatitis, cholecystitis, serious and opportunistic infections, PML, and hepatics B reactivation.

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/s/

ROBERT TEMPLE
03/28/2017