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# Multiple sclerosis: Could Roche's bestselling drug Ocrevus be doing more harm than good in women with primary progressive MS?

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The US Food and Drug Administration (FDA) is reviewing a petition to revoke the approval of ocrelizumab for the treatment of primary progressive multiple sclerosis (PPMS) after allegations that the drug was approved despite internal concerns about its efficacy in women and a potential increased risk of breast cancer.

Costing nearly $80 000 (£59 700; €68 500) a year in the US and approved in markets worldwide, ocrelizumab is the top selling product from the Swiss pharmaceutical giant Roche and is the only treatment specifically approved for PPMS—a form of MS in which symptoms steadily worsen, estimated to affect around 15% of patients.

Sold as Ocrevus in the US, where it is marketed by the Roche subsidiary Genentech, the drug received an expedited review by the FDA. In addition to breakthrough designation (for PPMS), the FDA granted Ocrevus fast track designation and priority review, further speeding up its evaluation.

While ocrelizumab is also approved to treat relapsing MS, the petition challenges only the approval for PPMS, and it echoes experts' concerns that the drug's value in treating PPMS has been oversold.

Joachim Burman, a consultant neurologist who heads the MS clinic at Uppsala University Hospital in Sweden and wasn't involved in the petition, argues that for PPMS, "prolonged treatment is expensive, potentially dangerous, and does not have a strong solid evidence base." Burman, who has studied the research on ocrelizumab,[1] told *The BMJ* that the data for treating PPMS pointed to modest and limited efficacy in a minority of patients—and near zero efficacy in others. A meta-analysis last year, by another group of researchers, reached the same conclusion.[2]

The FDA's review of its original decision has been triggered by Kaylin Bower, a patient advocate focused on MS and other neurodegenerative disorders. Bower, who has a background in financial auditing, told *The BMJ* that what started out as a search for treatment for a loved one had left her "absolutely shocked" from reading lengthy review memorandums written by the FDA scientists who evaluated the manufacturer's application, several of whom recommended against approving ocrelizumab for PPMS.[3] Bower alleges in the petition that the FDA's 2017 licensure violated statutory regulations that require "adequate and well-controlled studies."[4]

She said, "I was always under the impression that the FDA was a very independent regulatory body. They wouldn't be influenced by the pharmaceutical companies. I was disgusted." The FDA has not responded to the allegation.

## FDA reviewers urged rejection of ocrelizumab for PPMS after reviewing the evidence

Before licensure, Roche had tested ocrelizumab's efficacy in treating PPMS in just one trial.[5] But these results were "not persuasive," said Larry Rodichok, one of the FDA doctors who reviewed the study, known as Oratorio.

Rodichok wrote that Oratorio's results weren't statistically significant until missing data were filled in using a statistical method known as imputation, a practice that other reviewers said was unusual for MS trials. Rodichok also commented that the magnitude of purported benefit was small: "The absolute reduction in the proportion of patients with 12 or 24 week confirmed disability is less than 5%."

The FDA's statistical reviewers also noted a lack of benefit for women, where there wasn't even a hint of efficacy. Episodes of increased disability lasting at least three months occurred in 35.5% of women given placebo versus 36.0% who took ocrelizumab. On top of this was an "unusual imbalance" in breast cancer cases across ocrelizumab trials. FDA oncologists reported finding seven cases of breast cancer diagnosed in patients receiving ocrelizumab, across all trials, and zero cases in the placebo or comparator arms.

Concerns weren't limited to data analysis. *The BMJ*'s review of FDA approval memorandums found that agency scientists in divisions evaluating manufacturing quality and toxicology had recommended against approval. Other findings challenged the accuracy of data recorded at some clinical trial sites (box).

Summarising many of the concerns in a searing note, John Marler, the FDA reviewer overseeing the application, recommended against approval for PPMS. "The application does not provide substantial evidence of safety and effectiveness," he wrote, referencing the FDA's legal requirement. "There was only one efficacy trial. The trial results count events that may not have occurred, are inconsistent among important subgroups, and lack independent confirmation. In addition, there are reasons to suspect the quality of the data [and], in women, there is no evidence of beneficial effect to balance the potential risk of breast cancer."

Marler also appeared suspicious about Roche's late, off-protocol decision to increase the trial's size. He wrote, "Without changing the protocol, the applicant increased the sample size in the PPMS trial by 102 patients from 630 to 732. The trial results would be negative if the analysis uses the first 630 patients (P=0.087)." Marler questioned whether investigators had peeked at the results before making the change.

Roche told *The BMJ*, "The study remained strictly blind, and no bias was introduced as a result of the larger sample size."

**Drug approved despite FDA reviewers' concerns over manufacturing and data integrity**

One FDA reviewer who analysed Roche's manufacturing data, and another responsible for the toxicology review, recommended against approval, noting problems with pharmaceutical quality and concerns that the product manufactured for sale was not sufficiently similar to the product tested in reproductive toxicology studies.

To verify the data submitted in Roche's application, the FDA's Office of Scientific Integrity conducted site inspections. Of the trial's 182 sites, four were inspected. Problems were discovered at two. At one site in Poland, FDA inspectors found that primary endpoint data were not properly recorded for 13 of 19 participants and that "there are no source documents available to verify data integrity."

*The BMJ* has not been able to determine how this issue was resolved. A spokesperson for the FDA said that the agency had included information from the inspections in its review and that "the known and expected benefits outweighed the known and expected risks."

Billy Dunn, the FDA official who signed off on ocrelizumab's approval, acknowledged that the manufacturing problems identified by FDA staff scientists "would ordinarily preclude approval," but he explained that the problems could be ironed out in the postmarketing period. Concerns about the reliability of non-clinical toxicology study data, Dunn wrote, could also be addressed after approval.

Despite disagreements between reviewers and managers on approving ocrelizumab for PPMS, the agency opted against seeking the advice of its external advisory committee. Dunn declined to convene such a meeting "because the safety profile is acceptable," he explained in a memo, "and because the clinical trial design is similar to that of trials of previously approved drugs for the treatment of MS."

## Why did the FDA's top neuroscience drug official overrule advice of expert reviewers?

Senior FDA officials took a markedly different view of the evidence from Marler's, recommending that ocrelizumab be approved for PPMS. In contrast with reviewers reporting to him, Dunn, who was the FDA's top neuroscience drug official at the time, argued that two positive studies in relapsing MS could serve as "confirmatory evidence" of efficacy for PPMS.

As to the atypical methods Roche used to achieve statistical significance in the PPMS trial, Dunn cited an FDA statistical review that he characterised as "supportive of the primary outcome." But *The BMJ* found the review more tempered, concluding that while the data "were indicative of efficacy . . . The evidence of the effectiveness was weakened by the failure of the study to withstand an important sensitivity analysis."

A lack of efficacy in women enrolled in the PPMS trial also didn't seem to worry Dunn, who described the results as "exploratory and not necessarily indicative of an absence of actual benefit." While the agency could have withheld approving the drug for women, Dunn's solution was to approve for both sexes and describe the findings in the drug labelling. However, such findings weren't included in the drug's patient facing medication guide and were buried in the 16 page prescribing information meant for healthcare providers.

Regarding adverse events, Dunn found "no safety concerns . . . that preclude approval" and directed that breast cancer be noted on product labelling and evaluated in an observational study after ocrelizumab's approval. The FDA granted Roche 13 years to report on such a study, due in late 2030.

## Critic questions whether short lived efficacy justifies long term risks

Burman, who is also president of the Neurological Society of Sweden, was puzzled by this long timeline. He told *The BMJ*, "I'm happy that they [Roche] were asked to do a follow-up study, but it's really weird that they are not mandated to report anything until the end of the study. It should be made every year . . . or you know, at some regular time interval. And that's concerning, I think, since there's a biological plausibility that these drugs could cause cancer."

Without compelling data to support long term treatment, Burman argued, regulatory approval should be narrowed to short term use in patient populations seen to benefit. "From a safety standpoint, that would improve matters so much," he said.

In a 2021 analysis Burman reported that when ocrelizumab works, all the benefit in PPMS occurs in the first year,[1] adding, "After that there's really no treatment effect at all . . . the data actually supports that treatment should be discontinued."

In addition, Burman and others have argued that the drug's benefit in PPMS seems mostly confined to patients with active disease. Such an effect was seen in an individual patient data meta-analysis of six placebo controlled randomised trials.[2]

Roche rejected this characterisation. Citing a post-hoc analysis and extrapolated data on wheelchair use (including a 4.3% absolute risk reduction in patients requiring a wheelchair), as well as open label extension data from Oratorio, a company spokesperson said that "all these data are strong indicators for a sustained benefit of Ocrevus in PPMS beyond the first year of treatment."

The company added that data from a recently completed placebo controlled randomised trial[6] "demonstrated a statistically significant treatment effect in women that exceeded that of men, refuting the previous sex based disparities seen in Oratorio as likely incidental." It said that the still unpublished study, known as "O'Hand," also showed that PPMS patients without active disease at baseline also saw "significant risk reductions on disability progression endpoints." Roche declined *The BMJ*'s request for efficacy results from women and patients without active disease at baseline, as the data have already been submitted to a peer reviewed journal for publication.

Roche has reported steadily increasing sales of ocrelizumab since 2017, reaching 7010 million Swiss francs (£6610m; €7600m; $8875m) in 2025. It is the manufacturer's top selling drug.

While the risk of breast cancer is still not clear, the FDA's postmarketing adverse event reporting system has received more than 2000 reports of cancer after treatment with ocrelizumab, most commonly breast cancer.

Roche told *The BMJ* that it had been closely monitoring cases of malignancy, including breast cancer, and that its analysis "did not reveal any new safety signal or safety concern." The company noted that "the imbalance in malignancies, including breast cancer, observed in Oratorio was not confirmed in the O'Hand study." However, O'Hand investigators reported more malignancies in the ocrelizumab group than with placebo (five versus three), including breast cancer (one versus zero).

A spokesperson for the manufacturer said, "At Roche, patient safety is our highest priority, and we will continue monitoring safety in the ongoing clinical studies, post-approval safety studies, and postmarketing surveillance."

## Regulator behind ocrelizumab approval later oversaw controversial Alzheimer's drug approvals

Ocrelizumab's 2017 approval foreshadowed two more well known controversial approvals overseen by Dunn. In 2021 he championed Biogen's aducanumab for the treatment of Alzheimer's disease while acknowledging "residual uncertainty regarding clinical benefit."[7] He approved the drug against the recommendations of multiple FDA reviewers as well as almost all the agency's external advisory committee, three of whom subsequently resigned in protest. Congressional investigations followed, with one finding that "FDA's approval process was rife with irregularities."[8]

In 2023 Dunn's office approved another Alzheimer's drug, lecanemab, amid concerns over an unacceptable balance of benefits and harms.[9] In 2024 Biogen discontinued aducanumab, saying that it would focus its resources on lecanemab, relieving the company of conducting an FDA required postmarketing study. Dunn left the FDA in 2023 and joined the board of Prothena, a biotech company developing Alzheimer's treatments.

The approvals of ocrelizumab, aducanumab, and lecanemab all benefited from FDA programmes meant for drugs with the potential to tackle an "unmet medical need." But Bower wonders whether the system is working.

"What does it mean to fulfil an unmet medical need?" she asked. "We can all agree there are a number of diseases that have unmet medical needs, and that's a horrible, sad, and tragic situation . . . but is just approving a drug fulfilling that need?"

Competing interests: For full competing interests see www.bmj.com/about-bmj/editorial-staff/peter-doshi


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