Inflammatory Bowel Diseases

What is the Risk of Progressive Multifocal Leukoencephalopathy in Patients with Ulcerative Colitis or Crohn's Disease Treated with Vedolizumab?

--Manuscript Draft--

Manuscript Number:	IBD-D-17-00765R1
Article Type:	Original Research Articles - Clinical
Keywords:	epidemiology; clinical trials; progressive multifocal leukoencephalopathy; Inflammatory bowel disease; vedolizumab.
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Manuscript Region of Origin:	UNITED KINGDOM
Abstract:	Background: Progressive multifocal leukoencephalopathy is a serious condition linked to certain diseases and immunosuppressant therapies, including the α4 integrin antagonist natalizumab. No cases have been reported to date with vedolizumab, a selective antagonist of the α4β7 integrin expressed on gut-homing lymphocytes. This analysis aimed to describe the current and future expected occurrence of progressive multifocal leukoencephalopathy with vedolizumab use, were the risk the same as in other populations in which this disease has been studied. Methods: The expected number of vedolizumab-associated progressive multifocal leukoencephalopathy cases was estimated up to May 19, 2016 and modelled up to 2034. These estimates were based on the cumulative exposure to the drug, assuming an equivalent risk to that of patients treated with natalizumab or those from other reference populations where progressive multifocal leukoencephalopathy has been examined. Future cases were modelled based on similar risks and projected sales. Results: The cumulative vedolizumab exposure was estimated at 54,619 patient-years, with a 95% confidence interval of 0.0-6.75 cases per 100,000 patient-years. An estimated 30.2 (95% confidence interval 19.4-40.9) cases of progressive multifocal leukoencephalopathy would have occurred if vedolizumab had the same risk as that of natalizumab. There would be a 50% chance of the first case occurring by 2018, assuming an equivalent risk to the general population. Conclusions: These analyses indicate the risk of progressive multifocal leukoencephalopathy with vedolizumab is small, and unlikely to be above 6.75 cases per 100,000 patient-years.

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Conflicts of Interest and Source of Funding

Declaration of personal interests: Timothy Card has no active conflicts of interest to declare. Jing Xu is a Takeda employee and holds Takeda stock. Fatima Bhayat is a Takeda employee. Huifang Liang was a Takeda employee at the time of the study and received company stocks, and is currently an employee at AbbVie Inc.

Declaration of funding interests: This work was supported by Takeda Pharmaceuticals International, Inc., which currently employs Jing Xu, and Fatima Bhayat, and which employed Huifang Liang at the time this analysis was carried out. Timothy Card is employed by the University of Nottingham and neither he nor the University received any payment financial or in kind related to this work.

Short title: Is vedolizumab treatment a risk for PML?

Word count: 2975, plus references

ABSTRACT

Background: Progressive multifocal leukoencephalopathy is a serious condition linked to certain diseases and immunosuppressant therapies, including the α_4 integrin antagonist natalizumab. No cases have been reported to date with vedolizumab, a selective antagonist of the $\alpha_4\beta_7$ integrin expressed on gut-homing lymphocytes. This analysis aimed to describe the current and future expected occurrence of progressive multifocal leukoencephalopathy with vedolizumab use, were the risk the same as in other populations in which this disease has been studied.

Methods: The expected number of vedolizumab-associated progressive multifocal leukoencephalopathy cases was estimated up to May 19, 2016 and modelled up to 2034. These estimates were based on the cumulative exposure to the drug, assuming an equivalent risk to that of patients treated with natalizumab or those from other reference populations where progressive multifocal leukoencephalopathy has been examined. Future cases were modelled based on similar risks and projected sales.

Results: The cumulative vedolizumab exposure was estimated at 54,619 patient-years, with a 95% confidence interval of 0.0–6.75 cases per 100,000 patient-years. An estimated 30.2 (95% confidence interval 19.4–40.9) cases of progressive multifocal leukoencephalopathy would have occurred if vedolizumab had the same risk as that of natalizumab. There would be a 50% chance of the first case occurring by 2018, assuming an equivalent risk to the general population.

Conclusions: These analyses indicate the risk of progressive multifocal leukoencephalopathy with vedolizumab is small, and unlikely to be above 6.75 cases per 100,000 patient-years.

Key words: Epidemiology, clinical trials, progressive multifocal leukoencephalopathy, inflammatory bowel disease, vedolizumab

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a disabling and potentially fatal neurological syndrome caused by the John Cunningham virus (JCV) that can occur in the setting of severe immunosuppression.[1, 2] In addition to infection with human immunodeficiency virus (HIV), the use of immunomodulatory therapies – including the α_4 integrin antagonist natalizumab – has been associated with the development of PML.[3-5] Although PML in patients treated with natalizumab is a relatively rare event, the risk increases with duration of use of >2 years, prior use of immunosuppressants, and JCV seropositivity.[3, 6] Currently available data suggest that natalizumab-associated PML is associated with a better survival rate compared with PML in other populations, such as in patients with HIV infection (prior to the availability of highly active antiretroviral therapy) and in transplant recipients.[7-9] Nonetheless, the natalizumab-associated PML mortality rate is approximately 24%, and surviving patients are frequently left with disability.[8, 10]

Vedolizumab (Entyvio®; Takeda Pharmaceuticals, Deerfield, IL, USA) is licensed to treat adults with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD) who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) antagonist or immunomodulator, or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.[11]

As a humanized monoclonal antibody that antagonizes $\alpha_4\beta_7$ integrin,[11] vedolizumab has some similarity in its mechanism of action to that of natalizumab. Natalizumab is a humanized IgG4 monoclonal antibody that inhibits the α_4-subunit of the $\alpha_4\beta_1$ integrin, preventing it from binding to vascular cell adhesion molecule 1 (VCAM-1).[11-13] This results in decreased immune surveillance within the central nervous system (CNS) and thus increasing the risk of PML development.[4, 14] However, vedolizumab does not inhibit binding

at VCAM-1,[15] and instead selectively targets the $\alpha_4\beta_7$ integrin expressed on gut-homing lymphocytes, with non-gut homing T lymphocytes remaining unaffected.[16, 17]

At the time this paper was submitted for publication, there have been no cases of PML reported in association with vedolizumab use. This, combined with the gastrointestinal selective mechanism of action of vedolizumab, supports the hypothesis that this agent does not predispose to the development of PML.[18-20] However, given the rarity of the condition, the knowledge that the PML risk increases with duration of natalizumab use of >2 years, and the fact that vedolizumab is a relatively novel therapy (United States [US] and European approval was obtained in 2014), we cannot yet have absolute confidence in this supposition.[1, 6, 11, 13] Monitoring for new or worsening neurologic signs or symptoms is therefore recommended with vedolizumab treatment, and continued monitoring has been ongoing since clinical development.[11, 13]

Greater certainty regarding the risk of PML with vedolizumab treatment would be of great benefit to patients and clinicians. Hence, our aim here is to use the totality of available randomized controlled trial (RCT) and observational data to explore how confident we can be that vedolizumab does not predispose to the development of PML.

MATERIALS AND METHODS

Patients and Data Collection

The estimated vedolizumab cumulative exposure to May 19, 2016 was calculated based on data from both the clinical trial program (see Table, Supplemental Digital Content 1, which lists the clinical studies included in the risk modelling analyses) and post-marketing sales (a total of >8 years in the clinical trial program and up to 2 years' post-marketing exposure). For clinical trial data, exposure was calculated as the sum of individual exposure periods for each clinical trial patient. For post-marketing data, it was assumed that each patient was treated with vedolizumab 300 mg (1 vial) every 8 weeks. Exposure was calculated based on sales, and to estimate duration of use we assumed a steady attrition rate between 10–30% per year (based on 7-year long-term observational study data) up to the data cut-off point.

Data on adverse events (AEs) up to May 19, 2016 were obtained from the Takeda Global Safety Database, which contains vedolizumab data from clinical trials and post-marketing reporting, held in accordance with routine pharmacovigilance practices. Vedolizumab AE data were obtained from spontaneous reports submitted to Takeda directly from consumers, manufacturers, healthcare professionals, and regulatory authorities; from Takeda monitoring of the scientific and medical literature; and from solicited reports from clinical trials as well as patient support and market research programs.

From these data (patient-years [PY] of exposure and number of cases of PML), we estimated the risk of PML as cases per 100,000 patient years of exposure; 95% confidence intervals (CIs) around this were calculated assuming a Poisson distribution (the probability of observing at least *k* events was also based on the assumption that events

follow a Poisson distribution). The risk estimates were adjusted to account for the increased risk of PML after 2 years of therapy.

Ethical Considerations

Patients enrolled in clinical trials, post-authorization safety studies, patient support, and market research programs provided informed consent for participation in the studies, including the collection of AE data. Institutional Review Board review and approvals were obtained for these studies.

Expected Number of Vedolizumab-Associated PML Cases Relative to Natalizumab

The total number of expected cases of vedolizumab-associated PML was estimated assuming vedolizumab use conferred a risk equivalent to that associated with natalizumab use. Previously published rates of PML in natalizumab users were utilized, as described in the US prescribing information and published data (0.56/1000 to 13/1000 over 6 years' exposure).[5, 21]

Patients were grouped according to level of exposure to vedolizumab and risk factors (prior immunosuppressant use [same risk assumed for all immunosuppressants including azathioprine, methotrexate, and TNF antagonists] and anti-JCV antibody-positive status) to mirror patient stratification described in the natalizumab US prescribing information. To do this we estimated the levels of prior immunosuppressant use and anti-JCV antibody-positive status. Based on vedolizumab clinical trial data, it was assumed that approximately 80% of patients had prior immunosuppressive use.[22] Because JCV antibody testing was not required by the vedolizumab clinical trial protocols, an estimate was made based on published rates (anti-JCV antibody-positivity was assumed in approximately 50% of patients).[23, 24] Vedolizumab patient counts in each stratum were multiplied by the

corresponding risk estimate for natalizumab and summed to obtain the total number of expected cases; the 95% CI estimate (calculated using the StatXact 9 software) was based on the normal approximation to the Poisson distribution.[25]

Expected Number of Vedolizumab-Associated PML Cases Relative to Other Populations

The expected occurrence of PML in patients receiving vedolizumab was also calculated, assuming the same PML incidence rate (per 100,000 PY) as in the general population and in populations in which the risk of PML is known to be elevated. These groups include patients with rheumatoid arthritis (RA), HIV-free systemic lupus erythematosus (SLE) patients, HIV-free non-Hodgkin's lymphoma (NHL) patients, HIV-free autoimmune vasculitis patients, HIV-free chronic lymphocytic leukemia patients, bone marrow transplant recipients, patients with HIV, heart and/or lung transplant recipients, and HIV-free rituximab-exposed NHL patients.[9, 26-30] The expected number of PML cases and associated 95% CIs for vedolizumab, if the risk were equivalent to each reference population, were calculated by multiplying the population incidence rate (per 100,000 PY) and 95% CI by the total PY of exposure to vedolizumab. Because data for these populations were not reported in strata of immunosuppression use or JCV positivity, it was not possible to standardize these estimates.

Estimated Probability of Future Vedolizumab-Associated PML Cases

The probability of a future PML case in vedolizumab-treated patients was estimated, assuming the same risk as in three reference populations: the general population, patients with RA, and patients with SLE (without HIV).[26, 27] The current total number of PYs of vedolizumab exposure was estimated as specified above (in the 'Patients and Data Collection' section), and the likely future exposure to vedolizumab from 2016 to 2034 was estimated based on sales projections. The probabilities of a case arising for each year

were estimated using the Poisson approximation to the binomial distribution (frequentist approach), using the expected cumulative PY by that year as the number of trials, and the PML probability in the reference population as the event probability. The probabilities of ≥2 and ≥3 future PML cases in vedolizumab-treated patients were similarly estimated. A sensitivity analysis using a Bayesian approach was also conducted for the general population-based analysis. A conjugate beta distribution was assumed for the prior distribution of the PML probability, with the following two shape parameters: $\alpha = 1 +$ number of PML events in current trials (i.e. zero), and β = the current total PY + the reciprocal of the estimated PML probability of the general population.[31] The predictive probability of ≥1 PML future occurrence for each year was estimated by a beta-binomial distribution based on number of trials equal to the forecasted cumulative PY by that year.

RESULTS

Up to May 19, 2016, the cumulative vedolizumab exposure was approximately 54,619 PY, which comprised 7641 PY (3821 patients) from clinical trials, and an estimated 46,978 PY from post-marketing use (Table 1). To date, no cases of PML have been observed in patients treated with vedolizumab. The CI calculated around the rate of 0 cases of PML per 100,000 PY of exposure was 0–6.75 cases of PML per 100,000 PY of exposure.

Expected Number of Vedolizumab-Associated PML Cases

Based on cumulative exposure to vedolizumab, 30.2 cases of PML (95% CI 19.4–40.9) would be expected if vedolizumab exposure conferred the same risk as that of natalizumab (Table 2). Similarly, given cumulative vedolizumab exposure of approximately 54,619 PY, assuming an equivalent risk to the different reference populations, the number of expected PML cases for vedolizumab-treated patients is lowest in the general population (0.2; 95% CI 0.05–0.3) and patients with RA (0.6; 95% CI 0.2–1.4). Higher numbers would be expected in other disease populations, including bone marrow transplant recipients (19.3; 95% CI 0.5–107.8) and heart and/or lung transplant recipients (67.7; 95% CI 13.7–197.2), with the highest number anticipated in HIV-free rituximab-exposed NHL patients (131.1; 95% CI 54.6–305.9) (Table 3).

Estimated Probability of Future Vedolizumab-Associated PML Cases

If the risk of developing PML with vedolizumab were the same as in the general population, the estimated probability of observing the first PML case in vedolizumab-treated patients would be approximately 50% by 2018, and 90% by 2022 (Figure 1A). An estimated ≥2 or ≥3 cases will occur by 2021 (Figure 1B) and 2023 (Figure 1C), respectively, with a >50% probability.

Assuming the risk of PML with vedolizumab were identical to that in patients with RA or HIV-free SLE, the first PML case would be likely to occur earlier than predicted for the general population (>90% probability of first case by 2019 and 2017, respectively; Figure 1A). Assuming the risk is the same as in RA, ≥2 or ≥3 cases would occur with a >90% probability by 2020 and 2021, respectively, and ≥2 or ≥3 cases would occur with a >90% probability by 2018 and 2019, respectively, assuming an identical risk to that in patients with HIV-free SLE (Figures 1B and 1C).

In the sensitivity analysis, using the Bayesian approach and historical data of the general population as prior information, we estimate that the probability of observing the first PML case in vedolizumab users will occur with 50% probability during 2019, over a year later than in the estimate based on the frequentist approach (Supplemental Digital Content 2).

DISCUSSION

In this analysis, we provide evidence supporting the hypothesized lower risk of PML in users of vedolizumab versus those of natalizumab. We also estimate the numbers of PML cases that might be expected if vedolizumab users had risk levels equivalent to those of a variety of other population groups. Of these, the risk of PML in the general population or in patients with RA, HIV-free SLE, HIV-free NHL, or autoimmune vasculitis would be consistent with the observed absence of PML cases to date. The current data are, however, not consistent with vedolizumab carrying the elevated risk of PML seen in HIV infection, heart/lung transplantation, or rituximab use. Because there have been no cases of PML observed to date, it is difficult to precisely estimate the true level of risk, although our current analysis suggests it is not likely to be above 6.75 cases per 100,000 PY. Assuming an identical risk to that in the general population, the first PML case with vedolizumab treatment was estimated to occur with a 50% probability in 2019 and 2018, using Bayesian and frequentist approaches, respectively.

The analysis we present here has methodological challenges. Because we do not have access to the health records of the vast majority of patients receiving vedolizumab, we have not reviewed individual patients' medical records to confirm an absence of PML. However, we have gone to great lengths to attempt to ascertain cases through analysis of available RCT and observational data. Bearing in mind the serious nature of PML, it would be expected that all cases occurring in patients receiving vedolizumab in routine clinical practice would be reported. Additionally, direct information regarding prior immunosuppressant use or the presence of JCV in those receiving vedolizumab outside clinical trials is not available. However, there is no reason to believe that those receiving vedolizumab in the post-marketing setting would be less likely to have used immunosuppressants than those in the RCTs. Rather we think it unlikely that many prescribers will yet be using a ‘top-down’ approach starting initial therapy with

vedolizumab, or be using it as rescue therapy in acute flares. Immunosuppressant use might well therefore be almost universal in vedolizumab users, in which case the assumption we have made will be highly conservative (we will have underestimated the likely level of PML if risks were equivalent to those in natalizumab).

A further set of challenges with this analysis relates to the available data on population levels of PML. Ideally, we would standardize for age, sex, and immunosuppressant use for all populations; however, the rarity of the condition means that the population data required to achieve this is unavailable. Our estimates, with the exception of that relating to natalizumab, therefore do not take into account any of these confounding factors.

When considering the limitations of this analysis, however, it is important to consider the alternatives. It could be argued that absolute proof that there is no risk could be demonstrated only through a randomized, placebo-controlled clinical trial, with PML development as the primary outcome measure and with sufficient power to demonstrate equivalence between vedolizumab-treated patients and those receiving placebo. Such a trial would arguably be unethical and would require an unfeasibly large patient population (for example, in the context of zero events and based on the statistical ‘rule of three’, a sample size of 300,000 PY [for each of the vedolizumab and placebo cohorts] would be required to rule out a risk of >1 event per 100,000 PY with 95% confidence). Therefore, targeted observational research such as the current analysis is likely to be the best available option in this scenario. Due to uncertainty in the current estimate of the true risk of PML associated with vedolizumab, we have provided estimates of the probability of observing future PML cases under various risk scenarios.

Despite the limitations of the available data, it is nonetheless useful to consider the conclusions that can confidently be made. To begin with, it is clear that if the risk of PML

were the same as with natalizumab, 30 cases of PML would have been observed by May 19, 2016 in patients treated with vedolizumab, with a 95% CI lower bound of 19 cases. Therefore, we can reasonably conclude that there is a much lower risk of PML with vedolizumab than with natalizumab. Such a conclusion is not surprising because natalizumab is a humanized IgG4 monoclonal antibody that inhibits the α_4 subunit of the $\alpha_4\beta_1$ integrin, preventing it from binding to VCAM-1. By preventing $\alpha_4\beta_1$ binding to VCAM-1 on endothelial cells, extravasation of immune inflammatory cells into the brain is prevented,[4, 14] leading to decreased immune surveillance in the CNS that is hypothesized to predispose to development of PML with natalizumab use.[4, 14] By contrast, vedolizumab is the first available agent that selectively targets the $\alpha_4\beta_7$ integrin heterodimer, specifically preventing extravasation of immune inflammatory cells into the gut, with no evidence of an impact on immune surveillance in the CNS.[15-17] We can also conclude that, if the PML risk does not increase with long-term vedolizumab use, it is unlikely that the true level of risk is above 6.75 cases per 100,000 PY given current exposure estimates.

To put this into context, such a risk should be compared not only to the known risk of PML associated with other treatments (as has been done here), but also with the uncertainty regarding other medications such as corticosteroids and thioguanines, which have both been associated with the development of this condition. A 2009 study of nationwide US inpatient sample data showed that 20% of cases of PML in rheumatic diseases were associated with the use of only very mild immunosuppression with an antimalarial or low-dose prednisolone,[32] and analysis of French pharmacovigilance reports shows that PML has significantly elevated reported odds ratios (in excess of 4) for both prednisolone and azathioprine.[33] Finally, we should consider what other risks patients might run with alternative therapies. In many cases the alternatives to vedolizumab will be either immunosuppression or surgery. Neither of these is risk-free, with a colectomy being

associated with mortality of about 1%[34] and azathioprine with a cumulative lymphoma risk of approximately 0.4–4.0% over 10 years (depending on age).[35]

In conclusion, our calculations have shown that the risk of PML with vedolizumab is likely to be significantly lower than that with natalizumab. With no cases having been reported to date, the eventual level of risk cannot be precisely estimated; however, these analyses indicate the risk is small, and unlikely to be above 6.75 cases per 100,000 PY. Confirmation as to whether the risk is appreciably greater than in the background population remains to be seen as further data is accrued from continued post-marketing surveillance.

ACKNOWLEDGMENT

The authors would like to thank the following: Wei Zhong of Takeda Development Center Americas, Inc. for his assistance with the Bayesian model; Jesse Shick, formerly of Takeda Development Center Americas, USA, for his contribution to the development of this manuscript, including his participation in concept/study discussions, analysis of data, and review of initial drafts; and William Palo, formerly of Takeda Development Center Americas, USA, for his contribution to the development of this manuscript, including providing statistical support, analysis of data, participating in concept/study discussions, and review of initial drafts. This study was supported by Takeda Pharmaceutical Company Ltd. Medical writing support was provided by Khalid Siddiqui of Chameleon Communications International Ltd, UK (a Healthcare Consultancy Group Company) and sponsored by Takeda Pharmaceutical Company Ltd.

AUTHORSHIP

Author contributions: Timothy Card contributed to the study design, data interpretation, writing of the first and all subsequent drafts of the manuscript, and final approval of the manuscript. Jing Xu contributed to the study design, statistical analyses and modelling, data interpretation, writing of the first and all subsequent drafts of the manuscript, and final approval of the manuscript. Huifang Liang contributed to the study design, the literature review of PML incidence rates in different populations, data interpretation, manuscript writing, critical revision for important intellectual content, and final approval of the manuscript. Fatima Bhayat contributed to the study design, data interpretation, writing of the first and all subsequent drafts of the manuscript, and final approval of the manuscript.

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TABLES

TABLE 1. Estimated exposure to vedolizumab (up to May 19, 2016; data cut-off).

Vedolizumab exposure, months	Post-marketing: ~46,978 PY[a]	Clinical trials: ~7641 PY[b]	Total: ~54,619 PY
1–24	46,978	2442	49,420
25–48	0	517	517
49–72	0	862	862
Total patients	46,978	3821	50,799

[a]The number of PY of exposure to vedolizumab in the post-marketing setting is an approximation based on shipping data; it is assumed that each patient received vedolizumab 300 mg (1 vial) every 8 weeks.

[b]The estimated number of PY of vedolizumab exposure in patients who have received at least one dose of vedolizumab in completed and ongoing clinical trials up to May 19, 2016.

PY, patient-years.

TABLE 2. Estimated cumulative incidence of PML with vedolizumab in anti-JCV antibody-positive patients[a] up to May 19 2016[b], assuming a risk equivalent to that associated with natalizumab use (stratified by risk factor).

Vedolizumab exposure, months	**No prior immunosuppressant use, expected cases**	**Prior immunosuppressant use, expected cases[c]**
1–24	2.77	19.77
25–48	0.16	2.48
49–72	0.52	4.48
Total expected cases of PML (95% CI)	30.17 (19.41–40.94)	

[a]Based on previous reports, it was assumed that 50% of patients with Crohn's disease were anti-JCV antibody-positive.[24]

[b]Expected cases based on an estimated 54,619 patient-years of vedolizumab exposure in completed and ongoing clinical trials (n = 3821) and post-marketing (n = 46,978) up to May 19, 2016; for post-marketing data it is assumed that each patient received vedolizumab 300 mg (1 vial) every 8 weeks (see Table 1).

[c]Based on vedolizumab clinical trial data, it was assumed that 80% of patients had prior immunosuppressant use.[22]

CI, confidence interval; JCV, John Cunningham virus; PML, progressive multifocal leukoencephalopathy.

TABLE 3. Expected cases of PML with vedolizumab given current cumulative exposure if the risk were equivalent to that of selected reference populations.

Reference population (country)	Population incidence rate for PML (per 100,000 PY [95% CI])	Expected PML cases (95% CI)[a]
General population (Sweden)[27]	0.3 (0.1–0.6)	0.2 (0.05–0.3)
RA (Sweden)[27]	1.0 (0.3–2.5)	0.6 (0.2–1.4)
HIV-free SLE (USA)[26]	2.4 (0.1–13.2)	1.3 (0.05–7.2)
HIV-free NHL (USA)[26]	8.3 (1.7–24.2)	4.5 (0.9–13.2)
HIV-free autoimmune vasculitis (USA)[26]	10.8 (0.3–60.4)	5.9 (0.2–33.0)
HIV-free chronic lymphocytic leukemia (USA)[26]	11.1 (0.3–61.7)	6.1 (0.2–33.7)
Bone marrow transplant recipients (USA)[26]	35.4 (0.9–197.3)	19.3 (0.5–107.8)
Patients with HIV (Switzerland)[b,29]	60 (40–100)	32.8 (21.9–54.6)
Heart and/or lung transplant recipients (USA, The Netherlands)[9]	124 (25–361)	67.7 (13.7–197.2)
Patients with HIV (Denmark)[c,28]	130 (80–190)	71.0 (43.7–103.8)
HIV-free rituximab-exposed NHL (Italy)[30]	240 (100–560)	131.1 (54.6–305.9)

[a]Based on cumulative exposure of approximately 54,619 PY using May 19, 2016 estimates from clinical trials (7641 PY) and post-marketing data (46,978 PY).

[b]Study performed before and after the introduction of combination antiretroviral therapy in 1996.

[c]Incidence rate covers period between 2000 and 2006 (late highly active antiretroviral therapy era).

CI, confidence interval; HIV, human immunodeficiency virus; NHL, non-Hodgkin's lymphoma; PML, progressive multifocal leukoencephalopathy; PY, patient-years; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

FIGURE LEGENDS

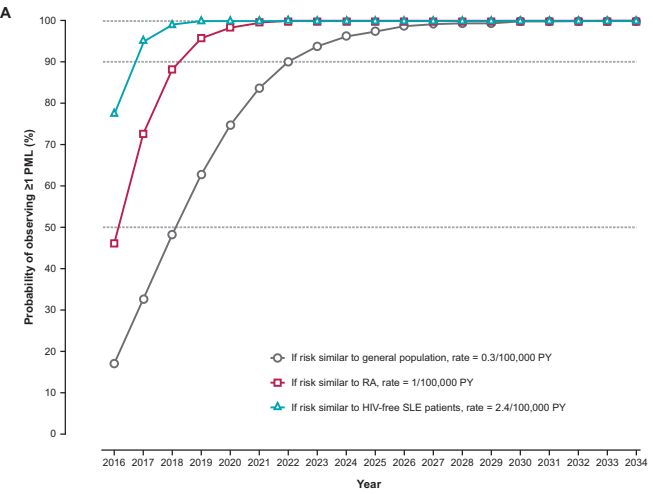
FIGURE 1. Estimated probability of observing **(A)** ≥1 PML case, **(B)** ≥2 PML cases, and **(C)** ≥3 PML cases with vedolizumab over time, assuming equivalent risk to reference populations.

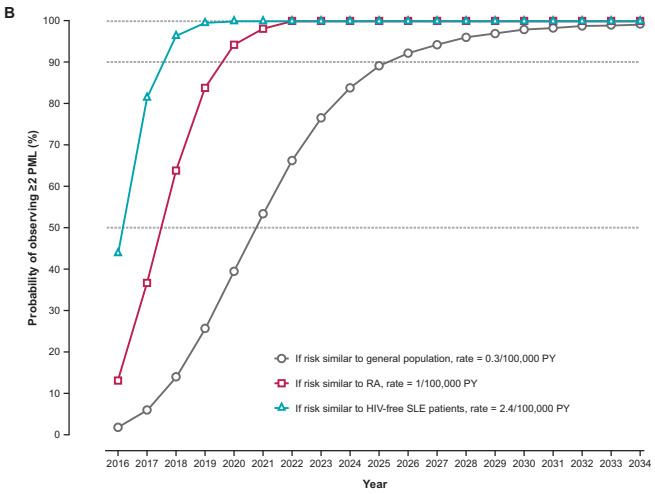
HIV, human immunodeficiency virus; PML, progressive multifocal leukoencephalopathy; PY, patient-years; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

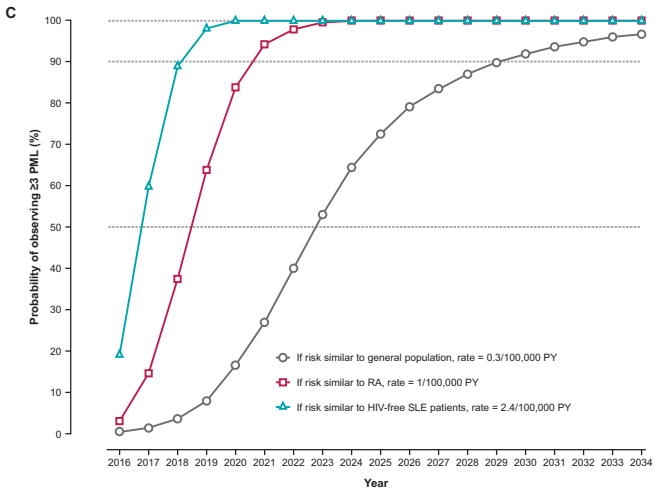
Supplemental Digital Content 1. Table that lists the clinical studies included in the risk modelling analyses.doc

Supplemental Digital Content 2. Figure illustrating the outcomes of the sensitivity analysis for estimation of the probability of observing ≥1 PML case with vedolizumab over time, assuming equivalent risk to the general population (frequentist vs Bayesian approach).

Image


A
Probability of observing ≥1 PML (%)
0
10
20
30
40
50
60
70
80
90
100
2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030 2031 2032 2033 2034
Year
If risk similar to general population, rate = 0.3/100,000 PY
If risk similar to RA, rate = 1/100,000 PY
If risk similar to HIV-free SLE patients, rate = 2.4/100,000 PY

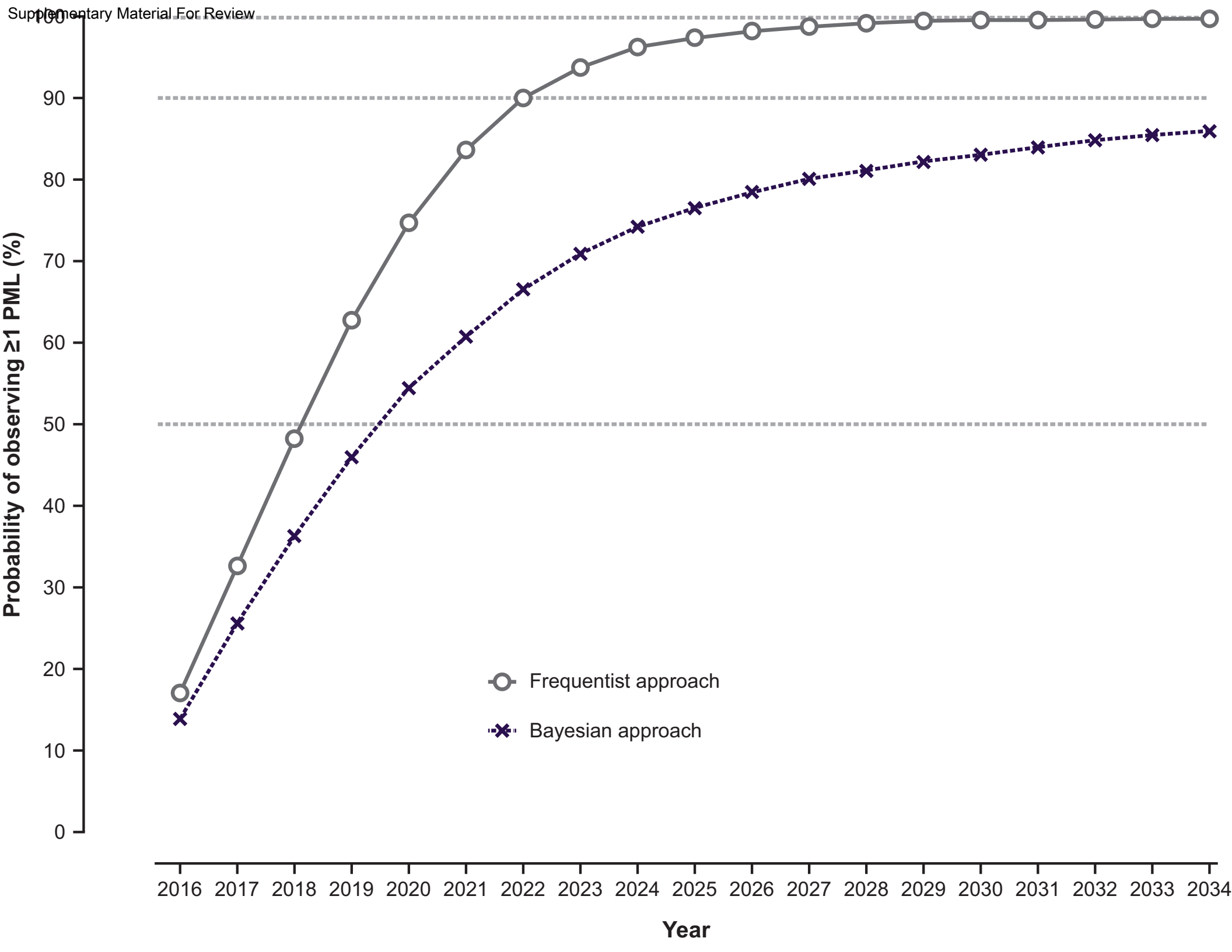

B
Probability of observing ≥2 PML (%)
0
10
20
30
40
50
60
70
80
90
100
2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030 2031 2032 2033 2034
Year
If risk similar to general population, rate = 0.3/100,000 PY
If risk similar to RA, rate = 1/100,000 PY
If risk similar to HIV-free SLE patients, rate = 2.4/100,000 PY


C
Probability of observing ≥3 PML (%)
0
10
20
30
40
50
60
70
80
90
100
2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030 2031 2032 2033 2034
Year
If risk similar to general population, rate = 0.3/100,000 PY
If risk similar to RA, rate = 1/100,000 PY
If risk similar to HIV-free SLE patients, rate = 2.4/100,000 PY

SUPPLEMENTARY TABLE 1. Clinical studies included in the risk modelling analyses.

Study number	Title	References
C13001	A phase 1, single ascending dose, randomized, placebo-controlled, double-blind study to determine the safety, tolerability, pharmacokinetics, and pharmacodynamics of MLN0002 in healthy subjects	Wyant T et al. *Cytometry Part B* 2016;90:168
C13002	A phase 2, randomized, placebo-controlled, double-blind study to determine the safety, tolerability, pharmacokinetics, and pharmacodynamics of MLN0002 following multiple intravenous doses in patients with ulcerative colitis	https://clinicaltrials.gov/ct2/show/NCT01177228 (accessed August 22, 2017); Rosario M et al. *Aliment Pharmacol Ther* 2015;42:188 Wyant T et al. *Cytometry Part B* 2016;90:168
C13004	A phase 2, multiple dose, open-label study to determine the long-term safety of MLN0002 in patients with ulcerative colitis and Crohn's disease	https://clinicaltrials.gov/ct2/show/NCT00619489 (accessed August 22, 2017)
C13005	A phase 1, single dose, open-label study to determine the pharmacokinetics, safety, and tolerability of MLN0002 in healthy subjects across a range of low and high body weights	https://www.takedaclinicaltrials.com/files2/C13005-RDS-2008-10-14.pdf (accessed August 22, 2017)
C13006	A phase 3, randomized. placebo-controlled, blinded, multicenter study of the induction and maintenance of clinical response and remission by MLN0002 in patients with moderate to severe ulcerative colitis	https://clinicaltrials.gov/ct2/show/NCT00783718 (accessed August 22, 2017); Feagan BG et al. *N Engl J Med* 2013;369:699
C13007	A phase 3, randomized, placebo-controlled, blinded, multicenter study of the induction and maintenance of clinical response and remission by MLN0002 in patients with moderate to severe Crohn's disease	https://clinicaltrials.gov/ct2/show/NCT00783692 (accessed August 22, 2017); Sandborn WJ et al. *N Engl J Med* 2013;369:711
C13008	A phase 3, open-label study to determine the long-term safety and efficacy of vedolizumab in subjects with ulcerative colitis and Crohn's disease	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-002784-14 (ongoing) (accessed August 22, 2017)
C13009	A phase 1 single dose study to determine the pharmacokinetics, pharmacodynamics, safety, and tolerability of a lyophilized formulation (Process C drug product) of MLN0002 in healthy subjects	Wyant T et al. *Cytometry Part B* 2016;90:168
C13010	A phase 1 study of the bioavailability of MLN0002 administered by subcutaneous and intramuscular injection to healthy male subjects	https://www.takedaclinicaltrials.com/files2/C13010-RDS-2010-04-08.pdf (accessed August 22, 2017)
C13011	A phase 3, randomized, placebo-controlled, blinded, multicenter study of the induction of clinical response and remission by vedolizumab in patients with moderate to severe Crohn's disease	https://clinicaltrials.gov/ct2/show/NCT01224171 (accessed August 22, 2017); Sands BE et al. *Gastroenterology* 2014;147:618
C13012	A phase 1 single-arm study to evaluate the effects of a single intravenous dose of vedolizumab (MLN0002) on the CD4+:CD8+ lymphocyte ratio in the cerebrospinal fluid of healthy subjects	https://www.takedaclinicaltrials.com/files2/C13012-RDS-2011-12-12.pdf (accessed August 22, 2017)
C13013	A phase 1, randomized, double-blinded, placebo-controlled single dose study in healthy subjects to determine the immune response to systemic and gut antigenic challenge in the presence of vedolizumab	https://clinicaltrials.gov/ct2/show/NCT01981616 (accessed August 22, 2017); Wyant T et al. *Gut* 2015;64:77
MLN0002_401	Entyvio (vedolizumab) long-term safety study: an international observational prospective cohort study comparing vedolizumab to other biologic agents in patients with ulcerative colitis or Crohn's disease	https://clinicaltrials.gov/ct2/show/NCT02674308 (accessed August 22, 2017)
MLN0002-3026	A randomized, double-blind, double-dummy, multicenter, active-controlled study to evaluate the efficacy and safety of vedolizumab iv compared to adalimumab SC in subjects with ulcerative colitis	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-000939-33 (accessed August 22, 2017)
MLN0002-3027	A phase 3 randomized, double-blind, placebo-controlled study, with a vedolizumab iv reference arm, to evaluate the efficacy and safety of vedolizumab subcutaneous as maintenance therapy in subjects with moderately to severely active ulcerative colitis who achieved clinical response following open-label vedolizumab intravenous therapy	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-000480-14 (accessed August 22, 2017)

MLN0002-3031	A phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vedolizumab subcutaneous as maintenance therapy in subjects with moderately to severely active Crohn's disease who achieved clinical response following open-label vedolizumab intravenous therapy	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-000481-58 (accessed August 22, 2017)


Probability of observing ≥1 PML (%)
0
10
20
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2016
2017
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2020
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Year
Frequentist approach
Bayesian approach

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Bret Lashner, M.D. and Fabio Cominelli , M.D., Ph.D.
Editors in Chief
Inflammatory Bowel Diseases

September 28, 2017

Dear Dr Lashner and Dr Cominelli

Re: IBD-D-17-00765 ***What is the risk of progressive multifocal leukoencephalopathy in patients with ulcerative colitis or Crohn's disease treated with vedolizumab?***

Thank you for confirming your tentative acceptance of our manuscript "*What is the risk of progressive multifocal leukoencephalopathy in patients with ulcerative colitis or Crohn's disease treated with vedolizumab?"* for publication in *Inflammatory Bowel Diseases.*

On behalf of my coauthors, I would like to thank the reviewers for their thoughtful and positive feedback. As requested by Reviewer 1, we have reassigned Figure 2 as a Supplementary figure mentioned on pages 11 and the legend on page 22 of the revised manuscript draft. We hereby submit this revised version for your final consideration as we understand that no further revisions are required at this stage.

We look forward to working with you to bring our research to the public domain.

Kind regards

Dr Fatima Bhayat, *MBChB, MPH, PhD, MFPM*
Executive Medical Director - GI TA Lead
Global Patient Safety