UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.
Petitioner,

v.

BIOGEN MA INC.
Patent Owner.

PGR2022-00054
U.S. Patent No. 11,292,845

PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 11,292,845

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1002	Declaration of Dr. Samuel J. Pleasure, M.D., Ph.D.	Declaration
1003	Chaudhuri, Abhijit. "Lessons for clinical trials from natalizumab in multiple sclerosis." Bmj 332.7538 (2006): 416-419.	Chaudhuri
1004	Weber, Thomas, et al. "Immune response in progressive multifocal leukoencephalopathy: an overview." Journal of neurovirology 7.4 (2001): 311-317.	Weber 2001
1005	*Christison v. Biogen IDEC Inc.,* MOTION for Summary Judgment and Memorandum in Support (No. 2:11-cv-01140, filed 12/11/2015)	Biogen MSJ
1006	Alroughani, Raed A., et al. "Natalizumab treatment for multiple sclerosis: Middle East and North Africa regional recommendations for patient selection and monitoring." BMC neurology 14.1 (2014): 1-9.	Alroughani
1007	Tysabri (natalizumab) product label (revised 12/2013)	2013 Tysabri Label
1008	Tysabri (natalizumab) product label (revised 1/2012)	2012 Tysabri Label
1009	CBS News: MS Drug Pulled From Market (https://www.cbsnews.com/news/ms-drug-pulled-from-market/)	
1010	Van Assche, Gert, et al., "Progressive multifocal leukoencephalopathy after natalizumab therapy for	

Exhibit No.	Reference	Referred To As
	Crohn's disease." New England Journal of Medicine 353.4 (2005): 362-368.	
1011	Gorelik, Leonid, et al. "Anti-JC virus antibodies: implications for PML risk stratification." Annals of neurology 68.3 (2010): 295-303.	Gorelik
1012	Olsson, T., et al. "Anti-JCV antibody prevalence in a Swedish cohort of MS patients and non-MS controls." Mult Scler J 16 (2010): S348.	Olsson
1013	Subramanyam, M., et al. "Factors associated with anti-JCV antibody prevalence in a large cohort of natalizumab-treated MS patients." Mult Scler 16 (2010): S38-S39.	Subramanyam
1014	Bozic, Carmen, et al., "Anti-John Cunnigham virus antibody prevalence in multiple sclerosis patients: baseline results of STRATIFY-1." Annals of neurology 70.5 (2011): 742-750.	Bozic
1015	Pepio, Anthony M., et al. "Evaluation of the incidence of anti-JC virus antibodies in a cohort of natalizumab-treated patients." Gastroenterology 5.140 (2011): S-768.	Pepio
1016	Bloomgren, Gary, et al. "Risk of natalizumab-associated progressive multifocal leukoencephalopathy." N Engl J Med 366 (2012):1870–1880.	Bloomgren
1017	Plavina, Tatiana, et al. "Anti–JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy." Annals of neurology 76.6 (2014): 802-812.	Plavina

Exhibit No.	Reference	Referred To As
1018	Tysabri (natalizumab) product label (revised 12/2009)	2009 Tysabri Label
1019	*Christison v. Biogen IDEC Inc.*, Order Granting Defendants' Motion for Summary Judgment (No. 2:11-cv-01140, Aug. 5, 2016)	
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1025	U.S. Application No. 11/711,628 (Publication No. US 2007/0207141)	The '628 Application
1026	U.S. Application No. 10/372,111 (Publication No. U.S. 2004/0009196)	Taylor
1027	Yousry, Tarek A., et al. "Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy." New England Journal of Medicine 354.9 (2006): 924-933.	Yousry
1028	Knowles, Wendy A., et al. "The JC virus antibody response in serum and cerebrospinal fluid in progressive multifocal leucoencephalopathy." Clinical and diagnostic virology 4.2 (1995): 183-194.	Knowles 1995

Exhibit No.	Reference	Referred To As
1029	Tan I.L., et al. "Immune reconstitution inflammatory syndrome in natalizumab-associated PML." Neurology. 2011 Sep 13;77(11):1061-1067.	Tan 2011
1030	Berger, Joseph R. "Too much of a good thing?: IRIS with natalizumab-associated PML." Neurology 77.11 (2011): 1033-1034.	Berger
1031	Kleinschmidt-DeMasters, B.K., et al. "Update on PML and PML-IRIS occurring in multiple sclerosis patients treated with natalizumab." J Neuropathol Exp Neurol. 71(7) (2012 Jul):604-617.	Kleinschmidt
1032	N'gbo N'gbo Ikazabo, Rosy, et al. "Immune-reconstitution Inflammatory Syndrome in Multiple Sclerosis Patients Treated With Natalizumab: A Series of 4 Cases." Clin Ther. 38(3) (2016 Mar): 670-675.	Ikazabo
1033	King, David J. "Applications and engineering of monoclonal antibodies." CRC Press, 1998.	King
1034	Leong, Ka Wai, and Ding, Jeak Ling. "The unexplored roles of human serum IgA." DNA and cell biology 33.12 (2014): 823-829.	Leong
1035	Kinch, Michael S. "An overview of FDA-approved biologics medicines." Drug discovery today 20.4 (2015): 393-398.	Kinch
1036	Mullard, Asher. "FDA approves 100th monoclonal antibody product." Nature reviews. Drug Discovery 20 (2021): 491-495.	Mullard

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1037	Rudick, Richard, et al. "Natalizumab: bench to bedside and beyond." JAMA neurology 70.2 (2013): 172-182.	Rudick
1038	Sospedra, Mireia, and Martin, Roland. "Immunology of multiple sclerosis." Annu. Rev. Immunol. 23 (2005): 683-747.	Sospedra
1039	Goldenberg, Marvin M. "Multiple sclerosis review." Pharmacy and therapeutics 37.3 (2012): 175.	Goldenberg
1040	Mares, Jan, and Hartung, Hans-Peter. "Multiple sclerosis and COVID-19." Biomedical Papers of the Medical Faculty of Palacky University in Olomouc 164.3 (2020).	Maresa
1041	Astrom, K.E., et al. "Progressive multifocal leuko-encephalopathy; a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease." Brain 81 (1958): 93-111.	Åström
1042	Zu Rhein, G. M., and Chou, S.M. "Particles resembling papova viruses in human cerebral demyelinating disease." Science 148.3676 (1965): 1477-1479.	Zu
1043	Padgett, B.L., et al. "Cultivation of papova-like virus from human brain with progressive multifocal leucoencephalopathy." Lancet. 1971 Jun 19;1(7712):1257-60.	Padgett
1044	Knowles, Wendy A., et al. "Population-based study of antibody to the human polyomaviruses BKV and JCV and the simian polyomavirus SV40." Journal of medical virology 71.1 (2003): 115-123.	Knowles 2003

Exhibit No.	Reference	Referred To As
1045	Koralnik, I. J., et al. "JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy." Neurology 52.2 (1999): 253-260.	Koralnik 1999
1046	Berger, Joseph R. "The clinical features of PML." Cleveland Clinic Journal of Medicine 78.2 (2011): S8-S12.	Berger 2011
1047	Koralnik, Igor J. "New insights into progressive multifocal leukoencephalopathy." Current opinion in neurology 17.3 (2004): 365-370.	Koralnik 2004
1048	Geschwind, M. D., et al. "The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS." Journal of neurovirology 7.4 (2001): 353-357.	Geschwind
1049	Berger, Joseph R., et al. "PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section." Neurology 80.15 (2013): 1430-1438.	Berger 2013
1050	Herndon, Robert M. "Natalizumab Returns." International Journal of MS Care 8.1 (2006): 31.	Herndon
1051	Selewski, D. T., et al. "Natalizumab (Tysabri)." American journal of neuroradiology 31.9 (2010): 1588-1590.	Selewski
1052	Kappos, Ludwig, et al. "Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring." The Lancet Neurology 6.5 (2007): 431-441.	Kappos

Exhibit No.	Reference	Referred To As
1053	Pleasure, S.J. *Dangers of stopping natalizumab (Tysabri)* (2011), published at boards.medscape.com/forums?128@432.MhQkdtptHuD@.2a0a4eec!comment=1	
1054	Pleasure, S.J. *Stratifying PML Risk in Multiple Sclerosis* (2015), published at https://www.neurologylive.com/view/stratifying-pml-risk-multiple-sclerosis	
1055	Stavnezer J. "Antibody class switching." Adv Immunol. (1996); 61:79-146.	Stavnezer
1056	Collins, Andrew M., and Jackson, Katherine JL. "A temporal model of human IgE and IgG antibody function." Frontiers in immunology 4 (2013): 235, 1-6.	Collins
1057	Aly, Lilian, et al. "Central role of JC virus-specific CD4+ lymphocytes in progressive multi-focal leucoencephalopathy-immune reconstitution inflammatory syndrome." Brain 134.9 (2011): 2687-2702.	Aly
1058	Durali, Deniz, et al. "B cells and progressive multifocal leukoencephalopathy: search for the missing link." Front Immunol. (2015) May 19;6:241	Durali
1059	Blake, Kim, et al, "JC virus associated meningoencephalitis in an immunocompetent girl." Arch Dis Child. (1992) Jul; 67(7):956-957.	Blake
1060	Khanna, Nina, et al. "JC virus-specific immune responses in human immunodeficiency virus type 1 patients with progressive multifocal	Khanna

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	leukoencephalopathy." J Virol. (2009) May; 83(9):4404-11.	
1061	Tan, Chen Sabrina, et al. "Immune reconstitution after allogeneic hematopoietic stem cell transplantation is associated with selective control of JC virus reactivation." Biology of Blood and Marrow Transplantation 20.7 (2014): 992-999.	Tan
1062	Viscidi, Raphael P, et al. "JC virus antibody and viremia as predictors of progressive multifocal leukoencephalopathy in human immunodeficiency virus-1-infected individuals." Clin Infect Dis. (2011) Oct;53(7):711-715.	Viscidi
1063	Achiron, Anat, et al. "Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies." Ther Adv Neurol Disord 14 (2021): 1-8.	Achiron
1064	Tyler, Kenneth L. "The uninvited guest: JC virus infection of neurons in PML." Neurology 61.6 (2003): 734-735.	Tyler
1065	Ransohoff, Richard M. "Natalizumab and PML." Nature neuroscience 8.10 (2005): 1275.	Ransohoff
1066	Gyang, Tirisham V., et al. "Fingolimod-associated PML in a patient with prior immunosuppression." Neurology 86.19 (2016): 1843-1845.	Gyang
1067	Patel, Arpan, et al. "Progressive multifocal leukoencephalopathy in a patient with progressive multiple sclerosis treated with ocrelizumab	Patel

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	monotherapy." JAMA neurology 78.6 (2021): 736-740.	
1068	van Kester, Marloes S., et al. "PML in Patients Treated with Dimethyl Fumarate." The New England journal of medicine 373.6 (2015): 582-584.	van Kester
1069	Clifford, David B., et al. "Rituximab-associated progressive multifocal leukoencephalopathy in rheumatoid arthritis." Archives of neurology 68.9 (2011): 1156-1164.	Clifford
1070	Berger, Joseph R., and Koralnik, Igor J.. "Progressive multifocal leukoencephalopathy and natalizumab—unforeseen consequences." New England Journal of Medicine 353.4 (2005): 414-416.	Berger 2005
1071	Frisque, Richard J., and White, Frank A.. "The molecular biology of JC virus, causative agent of progressive multifocal leukoencephalopathy." Molecular neurovirology. Humana Press, Totowa, NJ, (1992): 25-158.	Frisque
1072	Koralnik, Igor J., et al. "JC virus-specific cytotoxic T lymphocytes in individuals with progressive multifocal leukoencephalopathy." Journal of virology 75.7 (2001): 3483-3487.	Koralnik 2001
1073	Weber, Thomas, et al. "Analysis of the systemic and intrathecal humoral immune response in progressive multifocal leukoencephalopathy." J Infect. Dis. 176 (1997):250–254.	Weber 1997

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1074	Pucci, Eugenio, et al. "Natalizumab for relapsing remitting multiple sclerosis." Cochrane Database of Systematic Reviews 10 (2011):1-44.	Pucci
1075	Kapoor, Raju, et al. "Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension." The Lancet Neurology 17.5 (2018): 405-415. Published Online March 12, 2018 (http://dx.doi.org/10.1016/S1474-4422(18)30069-3).	Kapoor
1076	Huppke, Peter, et al. "Natalizumab use in pediatric multiple sclerosis." Archives of neurology 65.12 (2008): 1655-1658.	Huppke
1077	Bomprezzi, Roberto, and Pawate, Siddharama. "Extended interval dosing of natalizumab: a two-center, 7-year experience." Therapeutic advances in neurological disorders 7.5 (2014): 227-231.	Bomprezzi
1078	Ryerson, Lana Zhovtis, et al. "Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing." Neurology 93.15 (2019): e1452-e1462.	Ryerson
1079	Riancho, Javier, et al. "Does extended interval dosing natalizumab preserve effectiveness in multiple sclerosis? A 7 year-retrospective observational study." Frontiers in immunology 12 (2021), Article 614715: 1-8.	Riancho
1080	Kelly, Deirdre, et al. "Progressive multifocal leukoencephalopathy secondary to rituximab-induced immunosuppression and the presence of	Kelly

Exhibit No.	Reference	Referred To As
	John Cunningham virus: a case report and literature review." Radiology case reports 11.3 (2016): 251-254.	
1081	Curriculum vitae of Dr. Samuel Pleasure, M.D., Ph.D.	CV

I. INTRODUCTION

Petitioner Sandoz Inc. ("Sandoz") requests post-grant review ("PGR") of Claims 1-16 of U.S. Patent No. 11,292,845 ("the '845 Patent") (Ex. 1001) in accordance with 35 U.S.C. §§ 321-29 and 37 C.F.R. § 42.200 *et seq*.

The '845 Patent represents Biogen's attempt to claim a broad genus of applications of a basic, natural phenomenon—that immunosuppressants can cause life-threatening side effects by hampering the immune response to latent infection—without sufficient disclosure to establish it possessed the breadth of its claims. (Ex. 1002 (Declaration of Dr. Samuel J. Pleasure), ¶¶ 96-97, 117-121.) Here, the latent infection is with the John Cunningham virus ("JCV") and the life-threatening side effect is Progressive Multifocal Leukoencephalopathy ("PML"). (*Id.*) The immunosuppressant is natalizumab, a monoclonal antibody for which Biogen's composition patents have all expired.

The '845 Patent claims result from Biogen's race to capitalize on unfortunate circumstances. On February 28, 2005, in consultation with the FDA, Biogen voluntarily suspended marketing of natalizumab for clinical use because two natalizumab-treated patients had developed PML. (Ex. 1003, 416.) Exactly one year later, on February 28, 2006, Biogen filed the provisional application to which the '845 Patent claims priority. It did so on a very lean disclosure. By 2006, it was already established that JCV infection can cause PML. (Ex. 1001,

20:59-62; Ex. 1002, ¶ 73.) It was also known that antibodies against JCV were found in the blood of PML patients. (Ex. 1004, 312; Ex. 1002, ¶ 122.) Biogen's purported contribution was that JCV antibodies could be monitored in deciding whether to continue administering or to discontinue natalizumab. (Ex. 1001, 3:45-65.) But it did not disclose any methods or support for how to do so that fall within the scope of the '845 Patent's claims. That work occurred years later, and is prior art to the '845 Patent when properly considered.

Biogen's aim with the '845 Patent is plain: covering the field of assays for assessing PML risk before it had even established such an assay. Biogen's attempt to patent the natural relationship between JCV and PML arose from its efforts to market natalizumab before fully assessing the safety of natalizumab. (*See*, *e.g.*, Ex. 1003, 416 (natalizumab was given accelerated FDA approval before obtaining final trial and cumulative safety data); Ex. 1002, ¶¶ 77-79.) The result is a patent specification devoid of any support for a connection between the presence of JCV serum antibodies and the risk of developing PML.

Although the natural relationship between JCV and PML was known, what Biogen claims—that monitoring JCV *antibodies* in the *blood serum* could improve the safety of natalizumab treatment—was not established in 2006. *Most* healthy individuals have detectable JCV serum antibodies, so it was unclear to those of skill in the art whether the presence of these antibodies alone would be diagnostic

for PML risk, and there was no third-party test that established a particular level of antibodies correlated with increased risk of developing PML. (Ex. 1001, 20:62-65, 21:30-22:6.) Nor did Biogen possess this information—by its own admission.[1] The specification of the '845 Patent contains (1) no evidence or data supporting a correlation between levels of JCV serum antibodies and risk of PML, and (2) no working examples that disclose monitoring JCV serum antibodies in patients treated with natalizumab. In its rush to the patent office, Biogen thus failed to show it possessed anything more than an observation of the natural phenomenon that some natalizumab patients were becoming gravely ill and the hypothesis that there must be some way to correlate PML risk with antibodies against JCV. But what the threshold for heightened PML risk was and how to test for it effectively

[1] In litigation on whether the pre-2010 label for Biogen's Tysabri® should have included warnings about JCV antibodies, Biogen submitted to the court as undisputed facts that, in 2006, (1) there was no statistically significant data from which to determine whether the presence of a JCV antibody would assist in assessing whether someone was at a higher or lower risk of getting PML, and (2) there was no consensus on what JCV titers should serve as the clinically relevant cutoff for JCV antibody detection. (Ex. 1005 (Biogen Motion for Summary Judgment), 26, 30-31, 66.)

were not then known, and would not be demonstrated for several more years. (Ex. 1002, ¶¶ 79-86.)

As a result, Biogen's '845 Patent is infirm for multiple reasons. First, the claims are not entitled to priority to 2006 because they have no written description support in Biogen's 2006 provisional application or its subsequent applications. (*See infra* § VIII.) The absence of any data regarding the correlation between JCV serum antibodies, natalizumab, and PML confirms that Biogen was not in possession of a method that actually improved the safety of the treatment with natalizumab. (Ex. 1002, ¶¶ 94-116.) And despite acknowledging that antibody monitoring depends on the assay utilized, the specification provides no working examples of how to measure seroconversion and/or increasing titer of JCV serum antibodies to predict the risk of continued treatment with natalizumab or to determine when discontinuing administration of natalizumab would improve the safety of the treatment. (*Id*.) The claims also cover monitoring of any class of JCV serum antibodies but lack supporting disclosure for such a broad genus. (*Id*.)

Second, the claims are directed to a patent-ineligible natural phenomenon. 35 U.S.C. § 101. (*See infra* § IX.B.) The claims of the '845 Patent do little more than tell physicians to discontinue treating patients with natalizumab based on the natural relationship between JCV and PML, and the body's natural production of JCV antibodies against the virus. (Ex. 1002, ¶¶ 117-126.) This natural

phenomenon, without an additional inventive contribution, cannot be the basis for the challenged claims.

Third, because the claims are not entitled to any priority date before the filing of the March 2019 application from which they issued, they are obvious based on the intervening 2014 publication by Alroughani *et al*. (Ex. 1006), in view of the intervening 2013 Tysabri label (Ex. 1007). (*See infra* § IX.C; Ex. 1002, ¶¶ 127-179.)

II. GROUNDS FOR STANDING

Pursuant to 37 C.F.R. § 42.204(a), Petitioner certifies that the '845 Patent is available for PGR and that Sandoz is not barred or estopped from requesting PGR on the grounds identified in this Petition. Additionally, (1) neither Petitioner nor any of its privies own the '845 Patent, and (2) neither Petitioner nor any of its privies has filed a U.S. civil action challenging the validity of any claim of the '845 Patent.

Despite claiming priority to applications filed before the effective date of the American Invents Act ("the AIA"), the '845 Patent is eligible for PGR because the granted claims do not find § 112 support in any of the asserted priority applications. (*See infra* § VIII.)

III. GROUNDS FOR UNPATENTABILITY OF CHALLENGED CLAIMS

Petitioner requests review of Claims 1-16 ("challenged claims") of the '845 Patent and cancellation of these claims as unpatentable.

The challenged claims should be canceled as unpatentable on the following grounds:

Ground 1: Claims 1-16 are unpatentable under AIA 35 U.S.C. § 112(a) as failing to satisfy the written description requirement.

Ground 2: Claims 1-16 are unpatentable under AIA 35 U.S.C. § 101 as failing to claim eligible subject matter.

Ground 3: Claims 1-16 are unpatentable under AIA 35 U.S.C. § 103 as being obvious in light of Alroughani, in view of the 2013 Tysabri Product Label.

IV. BACKGROUND OF THE '845 PATENT

A. Technology at Issue

Natalizumab is a humanized monoclonal antibody against the antigen VLA-4. VLA-4 is an integrin, a cell-surface receptor found on the surface of most types of white blood cells. (Ex. 1002, ¶ 67.) VLA-4 facilitates the interaction between immune cells and blood vessel linings and plays a role in guiding the migration of immune cells to inflamed tissues throughout the body. (*Id.*) Because it promotes inflammation, VLA-4 activation coincides with the progression of

numerous inflammatory diseases, such as multiple sclerosis ("MS"), Crohn's disease ("CD"), and rheumatoid arthritis ("RA"). (*Id*., ¶¶ 68-72.)

Natalizumab binds to and inhibits the activation of VLA-4. (*Id.*, ¶ 67) By downregulating VLA-4 activity, natalizumab suppresses the immune response, which can help treat inflammatory and autoimmune diseases. (*Id.*) Although this immune suppression can counteract the harmful effects of prolonged inflammation, the dampening of the immune system by natalizumab can also cause harmful side effects. (*Id.*, ¶ 74.) In a healthy individual, the immune system protects against commonly transmitted bacteria, viruses, and other pathogens. (*Id.*, ¶ 62.) With a suppressed immune system, patients treated with natalizumab are at greater risk of viral infection and disease. (*Id.*, ¶¶ 74, 85-86.)

Natalizumab was first approved by the FDA in November 2004. (*See* Ex. 1008 (2012 Natalizumab Label); Ex. 1002, ¶ 76.) On February 28, 2005, Biogen pulled natalizumab from the market after two patients developed PML. (*See* Ex. 1009; Ex. 1002, ¶ 77.) By the end of 2005, three natalizumab-treated patients had developed PML, and two of them did not survive. (*See* Ex. 1010, Ex. 1001 at 3:29-33; Ex. 1002, ¶ 77.)

PML is caused by JCV, a common virus that usually presents no issue in healthy adults. (Ex. 1002, ¶¶ 73-74.) The presence of JCV in the body can cause the production of anti-JCV antibodies of different classes, including at least IgG,

IgM, and IgA antibodies. (*Id.*, ¶ 114.) A majority of adults in the United States and Europe carry dormant JCV without symptoms. (*Id.*, ¶¶ 46, 119.) But in immune-compromised individuals, JCV can reactivate and cause PML. (*Id.*, ¶ 74.)

To diagnose PML, physicians consider a mixture of clinical, radiological, and serological tests. (*Id.*, ¶ 76.) Patients with PML often exhibit atrophy in specific areas of the brain, which can be measured using magnetic resonance imaging ("MRI"). (*Id.*) PML can also manifest in behavioral changes or loss in vision. (*Id.*) The detection of JCV in patient cerebral spinal fluid ("CSF") can also be an indicator of PML. (*Id.*) Although these measurements can suggest likely PML disease, they are not dispositive. (*Id.*) PML can only be definitively confirmed via post-mortem analysis of the brain. (*Id.*)

B. The '845 Patent

The '845 Patent claims a method of using natalizumab in which monitoring the levels of JCV antibodies in patients improves the safety of administration by indicating when administration of natalizumab should be discontinued. Claim 1 of the '845 Patent, the sole independent claim, recites:

> A method of using natalizumab to treat a patient with an inflammatory or autoimmune disease comprising:
>
> (a) administering a pharmaceutically effective amount of natalizumab to the patient;

> (b) monitoring the patient for indicators of progressive multifocal leukoencephalopathy (PML), wherein the monitoring comprises detecting seroconversion and/or an increasing titer of JC virus (JCV) antibodies in the patient's blood; and
>
> (c) discontinuing the administration of natalizumab in the presence of seroconversion and/or an increasing titer of JCV antibodies;
>
> wherein the monitoring improves the safety of the treatment.

The specification, however, contains only a high-level discussion of the relationship between natalizumab, JCV, and PML without teaching how monitoring JCV antibodies would improve the safety of natalizumab treatment. (Ex. 1002, ¶ 96.) As the specification states, "there is a need in the art for determining the relationship between natalizumab treatment and the occurrence of PML and for safer methods of treating patients with natalizumab that take into account the possibility of contracting PML." (Ex. 1001, 3:34-38.) The scant disclosures in the rest of the specification confirm that Biogen had not fulfilled that need through the disclosures in the '845 Patent and its priority applications. (Ex. 1002, ¶¶ 96-116.)

1. Natalizumab, PML, and JCV

The '845 Patent discloses little regarding the relationship between natalizumab, JCV serum antibodies, and PML. (Ex. 1002, ¶¶ 26-50, 96.) The specification discusses the mechanism of action and efficacy of natalizumab treatment, which do not pertain to natalizumab's effect on JCV or PML. (Ex. 1001, 9:8-47, 16:36-20:57; Ex. 1002, ¶ 43.) The '845 Patent also discusses various safety risks, adverse events, and deaths associated with natalizumab treatment. (Ex. 1001, 9:48-11:20; Ex. 1002, ¶¶ 32-33.)

The '845 Patent notes that, as of February 2006, there were three confirmed cases of natalizumab-treated patients who developed PML, two of which were fatal. (Ex. 1001, 3:29-31, 11:22-32; Ex. 1002, ¶¶ 33-34.) For these three cases, the '845 Patent discusses radiological and behavioral changes that resulted in a diagnosis of PML in these natalizumab-treated patients. (Ex. 1001, 11:21-13:21; Ex. 1002, ¶¶ 34-37.) The '845 Patent does not disclose measuring or monitoring JCV serum antibodies in any of the three patients. (*Id.*)

The patent refers to follow-on studies that looked at whether other MS, CD, or RA patients, a vast majority of which were administered natalizumab, developed PML. (Ex. 1001, 13:41-15:51; Ex. 1002, ¶¶ 38-41.) The "diagnosis of 'confirmed PML' was defined by presence of progressive clinical disease, MRI signs typical of PML, *detection of JCV DNA in CSF*; or pathologic confirmation." (Ex. 1001,

13:31-34 (emphasis added); Ex. 1002, ¶ 38.) While these studies examined patient CSF for the detection of JCV DNA, the studies did not measure JCV antibodies or look at whether there were increases in JCV antibodies over time. (Ex. 1002, ¶ 38.)

The '845 Patent recognizes that it was known long before 2006 that PML is caused by JCV infection of brain cells. (Ex. 1001, 20:59-67; Ex. 1002, ¶ 44.) "JCV infection is usually sub-clinical, is almost universal, occurs in childhood, and persists for life." (Ex. 1001, 25:8-9; Ex. 1002, ¶ 44.) And it was known in the prior art that the presence of JCV can be detected in the CSF, urine, and blood of PML patients. (Ex. 1001, 21:30-22:6, 23:61-24:22; Ex. 1002, ¶¶ 44-45.) Before 2006, the presence of JCV DNA in the CSF had been used to diagnose possible PML disease. (Ex. 1001, 24:19-22; Ex. 1002, ¶ 45.)

The '845 Patent also discusses studies measuring JCV DNA in the plasma of patients with or without natalizumab treatment. (Ex. 1001, 14:52-15:6; Ex. 1002, ¶ 41.) Only five patients had detectable levels of JCV DNA, and three of those patients had never received natalizumab. (*Id.*) None of the patients with detectable JCV DNA in their plasma had clinical features or MRI findings suggestive of PML. (*Id.*) Additionally, serum JCV DNA was detected in only one of the three confirmed PML cases. (Ex. 1001, 15:7-17; Ex. 1002, ¶ 41.) Based on these studies and published literature, the specification states that "[p]lasma testing

[of JCV DNA] proved to be neither predictive nor diagnostic of PML." (Ex. 1001, 15:30-31; Ex. 1002, ¶ 41.) Similarly, the presence of JCV viral load in the blood of PML patients and healthy, immunocompetent individuals is "neither predictive nor diagnostic of PML in these patients; thus the relationship of blood or urine viral load to PML is unclear." (Ex. 1001, 22:4-6; Ex. 1002, ¶ 44.)

While there is some disclosure of using JCV DNA in the CSF to diagnose PML, the '845 Patent provides no disclosure establishing that testing of JCV antibodies would be predictive or diagnostic of PML. (Ex. 1002, ¶¶ 45, 50.) To the contrary, it casts doubt on that hypothesis. (*Id.*, ¶ 50.) The patent recognizes that JCV antibodies are detectable in 20% to 80% of *healthy* patients. (Ex. 1001, 20:62-67; Ex. 1002, ¶ 44.) Thus, it acknowledges that detection of JCV antibodies in the serum alone "will not confirm PML." (Ex. 1001, 23:46-48; Ex. 1002, ¶ 45.)

2. Monitoring JCV Antibodies During Natalizumab Treatment

Despite the lack of supporting disclosure that monitoring the serum or blood of the patient for JCV antibodies would be predictive of PML risk, the '845 Patent specification does briefly mention monitoring the serum or blood of the patient for JCV antibodies. (Ex. 1001, 3:60-65, 3:66-4:8, 5:10-25, 6:24-29, 7:37-43; Ex. 1002, ¶ 28.) The specification refers to measuring IgG JCV antibodies or comparing the levels of IgM JCV antibodies to IgG JCV antibodies from serum.

(Ex. 1001, 3:66-48, 4:56-4:62, 5:7-19, 6:6-12, 6:24-29, 7:15-19, 7:39-56; Ex. 1002, ¶¶ 28-29.) But the specification does not disclose at what intervals antibodies should be measured. (Ex. 1002, ¶¶ 31, 50.) Nor does it disclose what increase in levels of JCV serum antibodies would correlate with PML risk, let alone be diagnostic of PML risk for the patient. (*Id.*) The specification does not even disclose whether to monitor IgA, IgD, or IgE JCV antibodies in patients. (*Id.*) In short, the specification lacks any supporting examples on how to conduct that monitoring, what to measure, and what thresholds to use. (*Id.*)

The specification also mentions informing physicians and patients of the risk of natalizumab treatment, but does not establish that this risk increases if JCV antibodies are detected. (Ex. 1001, 27:34-53; Ex. 1002, ¶ 48.) As discussed above, the specification contains no protocol for assessing risk using JCV antibodies. (Ex. 1002, ¶¶ 48, 50.) Rather, the patent refers to a variety of existing serological tests for detecting JCV antibodies. (Ex. 1001, 25:58-67; Ex. 1002, ¶ 46.) Although these tests can measure specific subtypes of JCV antibodies, such as IgM, IgG, or IgA, the patent acknowledges that "[t]he sensitivity and specificity varies greatly between different techniques." (Ex. 1001, 25:58-67; Ex. 1002, ¶ 46.) None of these tests distinguish the levels of antibodies that would suggest heightened risk of PML. (Ex. 1002, ¶¶ 46, 50.) The patent does not teach or suggest that the mere presence of *any* anti-JCV antibodies should result in

discontinued treatment, because the specification does not disclose any evidence that the mere presence of JCV antibodies correlates with significant risk of PML. (Ex. 1002, ¶¶ 50, 96-98.) If that were the case, it would disqualify the many patients (up to 80%) with prior JCV infection whose infection remains latent and does not present PML risk. (*Id.*, ¶ 98.) Nor does the patent establish what level of JCV antibodies needs to be detected to qualify a patient as "positive" for JCV serum antibodies, or how to exclude false positives, and what threshold of JCV antibodies increases PML risk. (*Id.*, ¶¶ 29, 99-100.) Rather, in 2006, it was thought that the presence of JCV antibodies could decrease the risk of developing PML, as they could be protective against active JCV infection. (*Infra* § IV.E.2.)

3. Working Examples

The '845 Patent includes two working examples. (Ex. 1001, 29:32-31:48; Ex. 1002, ¶ 49.) Example 1, titled "Efficacy of Natalizumab," discusses the efficacy of natalizumab in two Phase 3 clinical trials for patients with MS. (Ex. 1001, 29:32-30:52; Ex. 1002, ¶ 49.) There is no mention of JCV, PML, or monitoring JCV serum antibodies levels in Example 1. (*Id.*) Example 2, titled "Caregiver and Patient Information," describes a general protocol for informing patients and physicians of the risk of PML that comes with natalizumab treatment. (Ex. 1001, 30:54-31:48; Ex. 1002, ¶ 49.) It discusses disclosing the risk of PML to the patient, having the patient acknowledge the risk, and having the patient work

with a physician in a natalizumab risk management program. *(Id.)* There is no mention of JCV or monitoring the levels of serum JCV antibodies in the patients in this example either. (*Id.*)

C. Related Patents and Publications

Biogen has published numerous publications confirming that it had not established the relationship between serum JCV antibodies, risk of developing PML, and natalizumab treatment when it filed its priority application. (Ex. 1002, ¶¶ 79-86.) In fact, it did not begin to make progress in that area until years later. (*Id.*)

In 2010, Biogen published a paper by Gorelik et al. titled "Anti-JC Virus Antibodies: Implications for PML Risk Stratification." (Ex. 1011 (Gorelik)); Ex. 1002, ¶¶ 80-81.). Before 2010, serologic detection of anti-JCV antibodies greatly varied in their sensitivity, ranging in positivity rates between 33% and 91%. (Ex. 1011, p. 295; Ex. 1002, ¶¶ 80-81.) Gorelik provided an assay for classifying MS patients as having detectable or not detectable levels of anti-JCV antibodies in the serum. (Ex. 1002, ¶¶ 80-81.) In patients tested, 17 out of 17 pre-PML patient serum samples exhibited detectable JCV antibodies. (*Id.*) However, the authors noted that "the presence of anti-JCV antibodies alone may not be highly predictive of PML risk." (Ex. 1011, p. 301; Ex. 1002, ¶¶ 80-81.)

In a subsequent 2010 study, Biogen still had not determined whether testing for anti-JCV antibodies could be used to assess the risk of PML. (Ex. 1002, ¶ 82.) Serological testing in a Swedish cohort of MS and healthy patients confirmed that Biogen's two-step assay could detect JCV antibodies in the serum. (Ex. 1012 (Olsson)), S348; Ex. 1002, ¶ 82.) The paper reported that 61% of MS patients and 67% of non-MS patients had detectable levels of JCV antibody in the serum. (Ex. 1012 (Olsson)), S348; Ex. 1002, ¶ 82.) It stated that large-scale prospective clinical studies were underway to "determine the potential utility of this [test] to stratify PML risk in natalizumab-treated MS patients." (*Id.*) The authors of a paper on another Biogen study made the same statement. (Ex. 1013 (Subramanyam)); Ex. 1002, ¶ 82.) And other, later papers reported that many patients, regardless of prior natalizumab or immunosuppressant use, have anti-JCV antibodies. (Ex. 1014 (Bozic); Ex. 1002, ¶ 83.)

Biogen also published an abstract in 2011 detailing the "Evaluation of the Incidence of Anti-JC Virus Antibodies in a Cohort of Natalizumab-Treated Patients." (Ex. 1015 (Pepio); Ex. 1002, ¶ 84.) Pepio noted that "[c]urrent commercially available techniques for detecting JCV DNA have not proven predictive of the risk of developing PML." (Ex. 1015, p. S-768; Ex. 1002, ¶ 84.) Pepio used an "analytically validated 2-step anti-JCV [antibody]" test to measure JCV antibodies in the plasma and serums samples from MS and CD patients. (*Id.*)

The publication confirmed that natalizumab-treated patients exhibited a similar rate of JCV-positive samples (~56%) compared to previous studies. (*Id.*)

Then, in 2012, Biogen published a paper by Bloomgren et al. titled "Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy." (Ex. 1016 (Bloomgren); Ex. 1002, ¶ 85.) This was one of the first papers to quantify the risk of PML in MS patients treated with natalizumab. (Ex. 1002, ¶ 85.) Prior to Bloomberg, "[d]escriptions of the risk among patients treated with natalizumab have so far been limited and mostly qualitative." (Ex. 1016, 1871; Ex. 1002, ¶ 85.) Bloomgren discussed three main risk factors for PML: (1) the presence of serum JCV antibodies, (2) prior use of immunosuppressants, and (3) increased duration of natalizumab treatment. (Ex. 1016, p. 1870; Ex. 1002, ¶ 85.) Bloomgren did not, however, quantify whether increases in JCV antibody titers correlated with greater risk of PML. (Ex. 1002, ¶ 85.)

Finally, in 2014—*eight years* after the filing of the alleged priority application for the '845 Patent—Biogen published a paper setting forth JCV antibody index values that correlated with increased risk of PML. (Ex. 1017, (Plavina); Ex. 1002, ¶ 86.) Before Plavina, "[a]lthough several publications have commented on the possibility of rising anti-JCV antibody titers being predictive of PML, there are few clinical data to support this hypothesis." (Ex. 1017, 810; Ex. 1002, ¶ 86.) As the paper discusses, there can be patients that are serum-positive

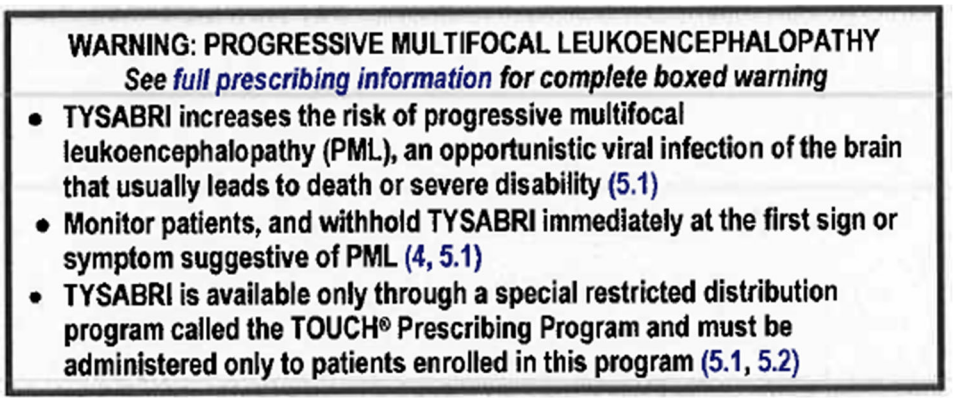
for JCV antibody, but have various degrees of risk for PML depending on the JCV antibody index. (Ex. 1017, Table 2; Ex. 1002, ¶ 86.) For example, in the first 24 months of natalizumab treatment, JCV-positive patients with an index greater than 1.5 and no prior immunosuppressant use had an estimated PML risk of 1.0 per 1,000 patients. (*Id.*) On the other hand, JCV-positive patients with no prior immunosuppressant use with an index between 0.9 and 1.5 had a PML risk of 0.1 per 1,000 patients, which was similar to the PML risk for patients that were JCV antibody-negative. (*Id.*)

D. Tysabri (Natalizumab) Product Labels

Biogen published several revisions of its Tysabri product label between 2009 and 2013. (Ex. 1002, ¶ 87.) These product labels show that Biogen had not established that antibody titers could be used to predict PML incidents until years after 2006. (*Id.*)

In a revised label published in December 2009, the label included a warning for PML, but did not discuss monitoring JCV antibodies. (Ex. 1018, 1; Ex. 1002, ¶ 87.)

December 2009 Tysabri Label



WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

See full prescribing information for complete boxed warning

- **TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability (5.1)**
- **Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML (4, 5.1)**
- **TYSABRI is available only through a special restricted distribution program called the TOUCH® Prescribing Program and must be administered only to patients enrolled in this program (5.1, 5.2)**

Rather, the label's section on PML discusses the known technique of measuring JCV CSF viral DNA levels for diagnosing PML. (Ex. 1018, 4-5 (Section 5.1); Ex. 1002, ¶ 87.)

In January 2012, the section of the label on PML was revised to include the presence of JCV antibody levels as a risk factor for PML. (Ex. 1008, 4-5 (Section 5.1); Ex. 1002, ¶ 87.) Specifically, the label states that "[p]atients who are anti-JCV antibody positive have a higher risk for developing PML." (Ex. 1008, 4 (Section 5.1); Ex. 1002, ¶ 87.) However, the label's "black box warning" for PML still did not include any discussion of JCV antibodies. (Ex. 1002, ¶ 87.)

January 2012 Tysabri Label

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning

- **TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability (5.1)**
- **Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML (4, 5.1)**
- **TYSABRI is available only through a special restricted distribution program called the TOUCH® Prescribing Program and must be administered only to patients enrolled in this program (5.1, 5.2)**

It was not until December 2013 that Biogen revised the label to include the presence of JCV antibodies as a risk factor in its black box warning. (Ex. 1007, 1; Ex. 1002, ¶ 87.)

December 2013 Tysabri Label (highlighting added)

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning

- **TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability (5.1)**
- **Risk factors for the development of PML include duration of therapy, prior use of immunosuppressants, and presence of anti-JCV antibodies. These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI (5.1)**
- **Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML (4, 5.1)**
- **Because of the risk of PML, TYSABRI is available only through a restricted distribution program called the TOUCH® Prescribing Program (5.1, 5.2)**

Yet, even in 2013, the label acknowledged that "[a]nti-JCV antibody testing *should not be used to diagnose PML*" and "*[i]t is not known whether early detection of*

PML and discontinuation of TYSABRI will mitigate the disease." (*Id.*, 5 (Section 5.1) (emphasis added); Ex. 1002, ¶ 87.)

E. Prior Biogen Litigation Regarding JCV Serum Antibody Testing

In 2016, the United States District Court for the District of Utah issued an opinion in a case against Biogen regarding a patient who had passed away from natalizumab treatment-associated PML. (*See* Ex. 1019.) The plaintiff alleged that Biogen had a duty to ensure that Tysabri was safe, but failed to include "warnings about increased risk of developing a brain infection called PML if a patient had previously tested positive for JC Virus antibodies" in the label's black box warning when his wife was on Tysabri in 2012. (*Id.*, 3.) In granting summary judgment, the court provided a list of "Undisputed Material Facts" that it drew from various submitted documents, including Biogen's own undisputed facts and briefing. (*Id.*, 5, n. 17; Ex. 1005, 11-38.) The undisputed material facts listed below show Biogen admitted that it *was not* in possession of the method recited in the challenged claims in the '845 Patent as of Biogen's claimed priority date. The court relied on that position in granting summary judgment. Because the plaintiff did not appeal, its order is now final.[2]

[2] Biogen should be estopped from re-arguing the undisputed material facts that it submitted, and the court relied on, in this prior litigation. *See Daniels v. Merit Sys.*

1. Communications to the FDA Regarding JCV Antibody Testing

- "In evaluating Tysabri prior to its return to the market in 2006, FDA requested that Biogen conduct an assessment for the presence of JCV antibody at baseline for patients entering clinical trials." (Ex. 1005, 20; Ex. 1019, 15.)
- "On March 2, 2006, Biogen submitted to FDA a report on the results of antibody testing conducted at a laboratory at the National Institute of Health ("NIH")—a laboratory led by Plaintiff's expert Eugene Major, Ph.D.—of available serum samples from Tysabri-treated patients who participated in clinical trials. The report concluded '[c]urrently there is no consensus on a clinically relevant cut off for the ELISA assay or JCV antibody detection.'" (Ex. 1005, 20-21; Ex. 1019, 15.)

Prot. Bd., 306 F. App'x 567, 569 (Fed. Cir. 2009) (party did not appeal a prior decision, which "became final by operation of law," and was estopped from litigation in the contested issue).

2. The State of JCV Antibody Testing from 2005 to 2010

- "At the time of the first Tysabri-associated PML cases, it was possible that the presence of JCV antibodies would be found to be protective and thus an indicator of decreased PML risk." (Ex. 1005, 26; Ex. 1019, 22.)
- "When Tysabri was reapproved in June 2006, and in fact without the additional PML cases in 2008 and the ensuing years, and pre-PML serum samples for those patients who developed PML, there was no data from which to determine whether the presence of an antibody would assist in assessing whether someone is at a higher or lower risk of getting PML." (Ex. 1005, 26).
- "When Tysabri was reapproved in June 2006, there was no statistically significant data from which to determine whether the presence of an antibody would assist in assessing whether someone is at higher or lower risk of getting PML." (Ex. 1019, 22).
- "Although a positive finding on a JCV antibody assay would indicate a necessary prerequisite to JCV infection, without data, a *negative* finding could not be used as evidence of decreased PML risk." (Ex. 1005, 27; Ex. 1019, 22.)

- "From 2005 through 2009 there was no published literature correlating the risk of PML with the presence or absence of JCV antibodies circulating in the bloodstream." (Ex. 1005, 30; Ex. 1019, 25.)
- "In late 2009, Biogen scientists developed an 'analytically validated' assay that could reliably detect JCV antibodies in the blood." (Ex. 1005, 30; Ex. 1019, 26.)
- "Using the 'analytically validated' assay, Biogen scientists determined that 53.6% of Tysabri-treated MS patients tested positive for JCV antibodies. (Ex. 1005, 30-31; Ex. 1019, 26.)
- "At an Advisory Board meeting with US regulatory experts on December 9, 2009, the observation that 11 of 11 patients with pre-PML samples had positive JCV antibodies (using an assay with a seroprevalence rate of 54% in the MS population) was discussed and the general consensus from the regulatory experts was the 'data on the assay was too preliminary to be of predictive value' regarding PML at that time." (Ex. 1005, 31-32; Ex. 1019, 27.)
- "On November 18, 2010, FDA again rejected Biogen's proposal concerning the JCV antibody assay and reiterated in the official meeting minutes FDA's

conclusion that '[t]he usefulness of this test in treatment with Tysabri has not been established.'" (Ex. 1005, 34; Ex. 1019, 30.)

F. Prosecution History

In a non-final office action dated February 2, 2021, the Examiner rejected the claims of the '845 Patent under 35 U.S.C. § 112(b) for indefiniteness and under 35 U.S.C. § 103(a) for obviousness. (Ex. 1021, Non-Final Rejection.) The obviousness rejections cited publications predating February 28, 2006, and the 103(a) prior art asserted in this Petition was not discussed in the prosecution history. (Ex. 1021; *see infra* § IX.C.) The Examiner did not reject the claims under 35 U.S.C. § 101 or 112(a). (Ex. 1021.)

V. LEGAL STANDARDS

A. Post-Grant Review Eligibility

A patent is eligible for PGR if it "contains or contained at any time . . . a claim to a claimed invention that has an effective filing date as defined in section 100(i) of title 35, United States Code, that is on or after [March 16, 2013]." AIA §§ 3(n)(1), 6(f)(2)(A). The "effective filing date" of a patent is defined under 35 U.S.C. § 100(i)(1)(B) as "the filing date of the earliest application for which the patent . . . is entitled, as to such invention, to a right of priority under section 119, 365(a), 365(b), 386(a), or 386(b) or to the benefit of an earlier filing date under section 120, 121, 365(c), or 386(c)." In order for a patent application to be entitled

to a "right of priority" or "an earlier filing date" based on an earlier filed application, the earlier filed application must have been disclosed "in the manner provided by section 112(a) (other than the requirement to disclose the best mode)." 35 U.S.C. § 119(e)(1); 35 U.S.C. § 120.

Accordingly, for purposes of determining PGR eligibility, a patent application may rely on the filing date of an earlier filed application under § 100(i)(1)(B) only if it is described in the manner provided by 35 U.S.C. § 112(a), including written description support for the claims. And if § 100(i)(1)(B) does not apply—because there is no entitlement to an earlier filing date—the "effective filing date" is the actual filing date of the patent. 35 U.S.C. § 100(i)(1)(A).

The Board has consistently instituted PGR trials in circumstances where it finds a post-AIA patent unlikely to receive the benefit of its pre-AIA filing date. *See, e.g.*, *Eli Lilly & Co. v. Genentech, Inc.*, PGR2019-00043, Paper 11, 11 (P.T.A.B. Oct. 7, 2019); *Adello Biologics, LLC v. Amgen, Inc.*, No. PGR2019-0001, 2019 WL 1767168, at *6-7 (P.T.A.B. April 19, 2019); *Collegium Pharm., Inc. v. Purdue Pharma L.P.*, No. PGR2018-00048, 2018 WL 5266405, at *4-6 (P.T.A.B. Oct. 4, 2018); *U.S. Endodontics, LLC v. Gold Standard Instruments, LLC*, No. PGR2015-00019, Paper 54, 11–12 (P.T.A.B. Dec. 28, 2016); *Schul Int'l Co. v. Emseal Joint Sys., Ltd.*, No. PGR2017-00053, Paper 10, 12–13 (P.T.A.B.

Apr. 9, 2018); *Inguran, LLC v. Premium Genetics (UK) Ltd.*, No. PGR2015-00017, Paper 8, 17–18 (P.T.A.B. Dec. 22, 2015).

B. Written Description

Under 35 U.S.C. § 112(a), a claim must be supported by sufficient written description of the invention. "[T]he hallmark of written description is disclosure." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "A 'mere wish or plan' for obtaining the claimed invention is not adequate written description." *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (citation omitted). The test for written description support is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date" based on an "objective inquiry into the four corners of the specification." *Ariad*, 598 F.3d at 1351.

It is not sufficient for a description merely to render the claimed invention obvious. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997); *Ariad*, 598 F.3d at 1352. It is also not enough to point to fragmented language in the written description that separately covers each limitation. The test for adequate written description is not about "the presence or absence of literal support in the specification for the claim language," *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983) (citation omitted), but rather whether the specification conveys possession of

the full scope of the "complete and final invention with all its claimed limitations." *Ariad*, 598 F.3d at 1353.

C. Subject Matter Eligibility

Under 35 U.S.C. § 101, "[l]aws of nature, natural phenomena, and abstract ideas are not patentable." *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 589 (2013) (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 70 (2012)). Patent eligibility is assessed under the *Alice/Mayo* two-part test. First, it must be "determine[d] whether the claims at issue are directed to one of those patent-ineligible concepts." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 217 (2014). If the claims are directed to an ineligible concept, then the inquiry is whether any additional elements of the claim "'transform the nature of the claim' into a patent-eligible application." *Id.* (quoting *Mayo*, 566 U.S. at 78).

The official Patent Office guidance regarding subject matter eligibility analysis mirrors the *Alice/Mayo* test. (Ex. 1020.) Step 1 concerns whether the claimed subject matter falls within a judicial exception, i.e., an unpatentable law of nature, natural phenomena, or abstract idea. (*Id.*, 53-54.) In Step 2, the question is whether the claim is primarily directed to judicial exception, and therefore claims ineligible subject matter. (*Id.*, 53.) A claim is not directed to a judicial exception if the claim as a whole integrates the recited judicial exception into a practical

application of that exception. (*Id.*) However, a claim that is "no more than a drafting effort designed to monopolize the judicial exception" does not integrate the judicial exception into a practical application. (*Id.*)

The Patent Office guidance partitions Step 2 into two steps: Step 2A and 2B. (*Id.*, 53-57.) Step 2A is further divided into two prongs. (*Id.*, 54.) Prong One of Step 2A concerns whether the claim recites a judicial exception, i.e., an abstract idea, a law of nature, or a natural phenomenon. (*Id.*) If the claim does recite a judicial exception, Prong Two then requires a determination whether the claim is directed to the judicial exception or involves integrating the judicial exception into a practical application. (*Id.*) Step 2A does not consider whether the elements are well-understood, routine, or conventional activity. (*Id.*) The judicial exception is not integrated into a practical application if it does not more than generally link the use of a judicial exception to a particular technological environment or field of use. (*Id.*)

If the claim limitations do not integrate the recited judicial exception into a practical application, then the claim is directed to a judicial exception and requires further analysis under Step 2B. (*Id.*, 56.) Under Step 2B, the claims are unpatentable if the additional elements fail to provide "significantly more" than the recited judicial exception, i.e., the additional elements provide an inventive concept. Step 2B takes into consideration what was well-understood, routine, and

conventional activity in the field. (*Id.*) Claim elements that "simply append[] well-understood, routine, conventional activities previously known to the industry and specified at a high level of generality" are "indicative that an inventive concept may not be present." (*Id.*)

D. Obviousness

Under 35 U.S.C. § 103, "[a] patent for a claimed invention may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 401 (2007).

VI. CLAIM CONSTRUCTION

A. "JC virus (JCV) antibodies"

The term "JC virus (JCV) antibodies" should be construed to cover *any* class of a human JCV antibody, including IgA, IgM, IgG, IgD, and IgE antibodies. The term appears in Claim 1, which recites "monitoring the patient for indicators of progressive multifocal leukoencephalopathy (PML), wherein the monitoring

comprises detecting seroconversion and/or an increasing titer of *JC virus (JCV) antibodies* in the patient's blood." (Emphasis added.)

During prosecution, Biogen amended the claims to broaden the scope of the claims to include any class of JCV antibody. (Ex. 1021, 2021-11-13 Claims.) In a November 13, 2020 Amendment, Biogen amended the claims from requiring "serially removing samples of the patient's blood, measuring the amount of *IgG anti-JCV antibodies* in the samples, and comparing the amount of the anti-JCV antibodies in the samples" to "detecting seroconversion and/or an increasing titer of *JC virus (JCV)* in the patient's urine and/or blood." (*Id.* (emphasis added).[3]) *AstraZeneca AB v. Mylan Pharms. Inc.*, 19 F.4th 1325, 1335 (Fed. Cir. 2021) (construing the scope of a claim term based on "the amendments and arguments in the prosecution history"); *Promega Corp. v. Applera Corp.*, No. 01-C-244-C, 2002 WL 32359938, at *4 (W.D. Wis. June 7, 2002) (broadening amendment during prosecution resulted in expanded claim scope).

The '845 Patent specification also discusses monitoring the patient's serum for *both* IgG and IgM JCV antibodies. (S*ee* Ex. 1001, 3:66-4:2 ("In embodiments the method includes measuring the amount of IgM antibodies to JCV in the

[3] To overcome an indefiniteness rejection, the claims were subsequently amended to exclude measuring JCV antibodies in the urine. (Ex. 1021, 2021-08-02 Claims.)

samples, and comparing the amount of the IgM and IgG antibodies in the samples"), 5:16-19, 7:43-46; Ex. 1002, ¶ 91.) The specification further states that "a wide variety of serological tests are available to detect JCV . . . some assays e.g., RIA, EIA, and IF can be designed to detect one specific class, for example, IgM, IgG, or IgA." (Ex. 1001, 25:58-67; Ex. 1002, ¶ 91.) Accordingly, "JC virus (JCV) antibodies" should be construed to include *any* class of a human JCV antibody, because it would be inappropriate to exclude the IgM and IgA antibody embodiments. *See Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276 (Fed. Cir. 2008) ("We normally do not interpret claim terms in a way that excludes embodiments disclosed in the specification").

B. "seroconversion . . . of JCV antibodies"

The term "seroconversion . . . of JCV antibodies" should be construed to require obtaining a reliable "positive" result from a serologic test that excludes false positives. The term "seroconversion" is defined in the specification as "the change of a serologic test from negative to positive, indicating the development of antibodies." (Ex. 1001, 9:3-5; Ex. 1002, ¶ 93.) The specification recognizes that, in 2006, at the time the earliest patent application in the priority chain was filed, "[a] wide variety of serological tests [were] available to detect JCV," and "[t]he sensitivity and specificity varie[d] greatly between different techniques." (*Id.*, 25:58-64; Ex. 1002, ¶ 93.) But there were no established thresholds for JCV

positivity at the time, and without such thresholds, these tests could produce false positives (e.g., by cross-reacting with BK virus) and false negatives. (Ex. 1002, ¶¶ 29, 99-100.) A person of ordinary skill in the art ("POSA") would understand that "seroconversion . . . of JCV antibodies" requires a test "indicating the development of antibodies" that is sufficiently accurate to exclude most false positives and false negatives. (*Id.*)

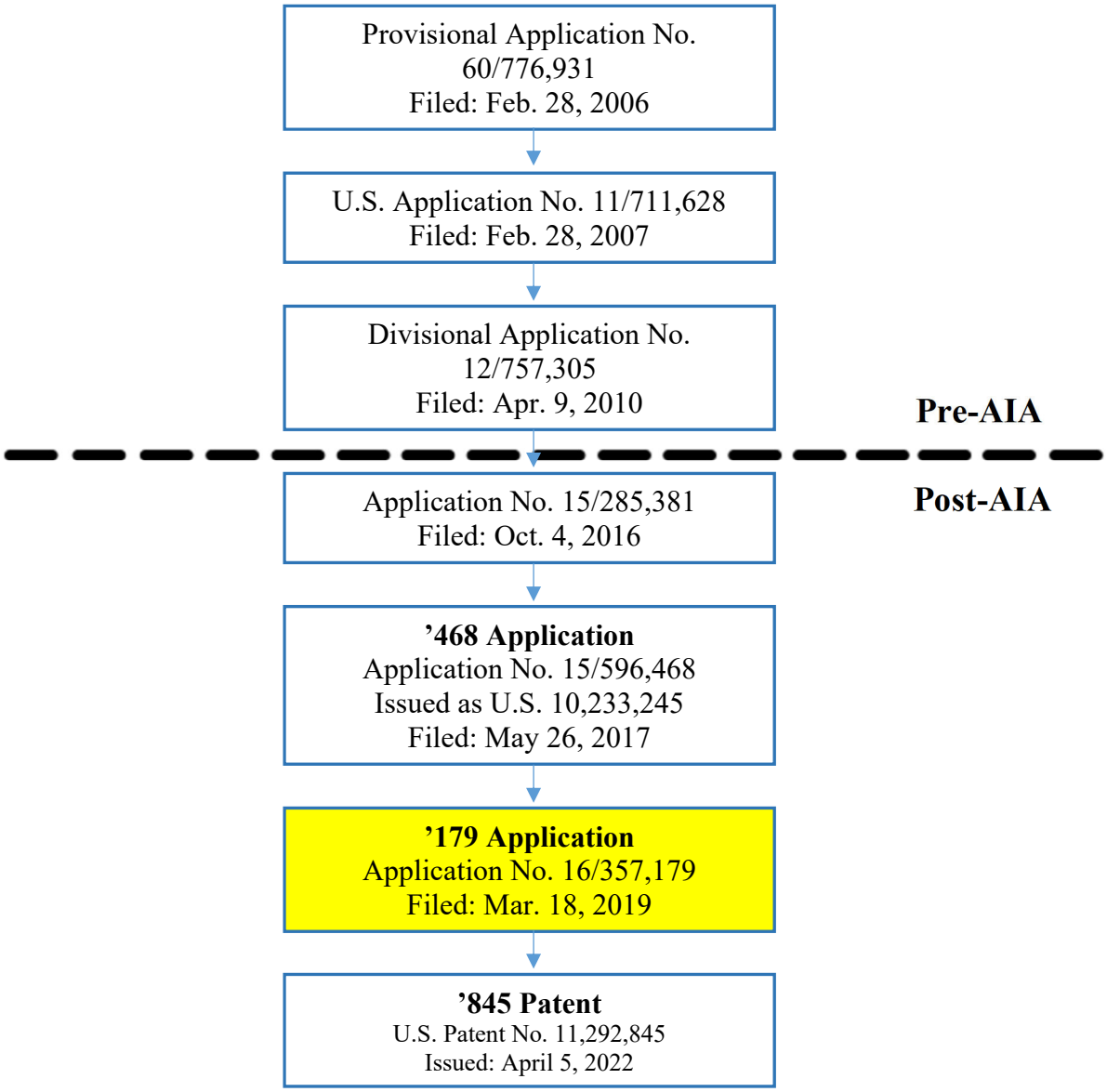
VII. LEVEL OF ORDINARY SKILL IN THE ART

The POSA in the field of the '845 Patent would have had (1) a Ph.D., M.D., or equivalent degree and (2) at least two years of experience with the use of natalizumab to treat patients with inflammatory or autoimmune diseases, including MS, RA, and/or CD. (Ex. 1002, ¶ 88.) More education can supplement practical experience, and vice-versa. (*Id.*) This level of skill in the medical field is applicable as of the filing of the provisional applications through March 2019, the '845 Patent's effective date, as described below. (*Id.*)

VIII. THE '845 PATENT IS ELIGIBLE FOR PGR BECAUSE ITS PRE-AIA PRIORITY APPLICATIONS LACK WRITTEN DESCRIPTION FOR THE CLAIMS

The '845 Patent issued from application 16/357,179 filed on March 18, 2019, and is a continuation of application 15/596,468 filed March 26, 2017. It claims priority to a series of applications filed prior to the effective date of the AIA, including the provisional application No. 60,776,931 ("the '931

Application") and the first non-provisional application No. 11/711,628 ("the '628 Application"), and claims an earliest priority date of February 28, 2006. The purported priority chain is shown below:



The pre-AIA, non-provisional patent applications to which the '845 Patent claims priority share substantially the same specification as the '845 Patent and the

post-AIA patent applications in the priority chain, as the entire non-provisional priority chain consists of continuation applications in which no new matter was added.[4] Thus, like the '845 Patent, they lack disclosure demonstrating possession of the claimed subject matter. Because these priority applications fail to support independent claim 1 and its dependent claims (2-16) under 35 U.S.C. § 112, the patent's effective filing date is March 18, 2019, the filing date of the application from which it issued (*i.e.*, U.S. 16/357,179, or the '179 Application). *PowerOasis, Inc. v. T–Mobile USA, Inc.*, 522 F.3d 1299, 1306 (Fed. Cir. 2008). The patent is thus eligible for PGR.

Claim 1 contains some significant differences from the language that appears in the '845 Patent's specification. (Ex. 1002, ¶ 27.) The table below compares the language of element (c) of claim 1 with the specification, highlighting these differences:

'845 Patent Claim 1	**'845 Patent Specification**
(c) discontinuing the administration of natalizumab in the presence of	discontinuing the administration of natalizumab in the presence of

[4] The specification of Provisional Application 60/776,931 contains less disclosure than the '845 Patent's pre-AIA and post-AIA non-provisional priority applications, but does not differ in ways that affect the written description analysis in this Petition. (*See* Ex. 1022, 1023.)

seroconversion and/or an increasing titer of JCV antibodies;	indicators of progressive multifocal leukoencephalopathy;
	In embodiments the monitoring detects seroconversion and/or an increasing titer of JCV in the patient's urine and/or blood

Notably, the specification's disclosure differs from the language of claim 1 in that discontinuation of natalizumab administration is based on the presence of "seroconversion and/or an increasing titer of JCV antibodies" rather than the more general "indicators of progressive multifocal leukoencephalopathy." The methods for diagnosing PML based on JCV DNA in the CSF known in the prior art and discussed in the specification only support the latter. (Ex. 1001, 23:61-24:22; Ex. 1025 (U.S. Patent Publication US20070207141A1 (the '628 Application)), [0108]; Ex. 1002, ¶ 30.) This portion of the claim attempts to borrow from another section of the specification that refers to monitoring, but there, the specification discloses detecting seroconversion and/or an increasing titer of "JCV" (Ex. 1001, 4:2-4, 5:19-21, 7:46-48; Ex. 1025, [0016], [0020], [0023]) rather than "JCV antibodies" (claim 1). (Ex. 1002, ¶¶ 28-31.) Accordingly, there is no *ipsis verbis* support for the claim in the specification.

Claim 1 and the claims that depend from it (claims 2-16) also lack sufficient written description support in the priority applications for at least three additional reasons.[5] First, the claims lack written description for an improved method of using natalizumab wherein the monitoring of JCV antibodies in the serum improves the safety of the treatment. Second, the claims lack written description for a method of monitoring *increased* JCV antibody titers in the serum. Last, there is insufficient written description support for the broad genus of JCV antibodies covered by these claims.

A. The Pre-AIA Patent Applications Do Not Disclose That Monitoring the Patient's Serum for JCV Antibodies Improves the Safety of Natalizumab Treatment

The challenged claims are PGR-eligible because the specification fails to disclose sufficient written description to show that monitoring for the presence of JCV serum antibodies would improve the safety of natalizumab treatment. *See Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) ("the [written description] test requires an objective inquiry into the four corners of the

[5] The '845 Patent and '628 Application share the same specification. Accordingly, the infirmities present in the challenged '628 Application are also present in the '845 Patent. Citations to both the patent and application have been provided in Section VIII.

specification from the perspective of a person of ordinary skill in the art . . . [to] show that the inventor actually invented the invention claimed."). Claim 1 of the '845 Patent requires monitoring to detect "seroconversion . . . JC virus (JCV) antibodies in the patient's blood" and recites that this can "improve[] the safety of [natalizumab] treatment." Seroconversion is "the change of a serologic test from negative to positive, indicating the development of antibodies." (Ex. 1001, 9:3-5; Ex. 1025, [0036].)

Biogen was not in possession of a method of monitoring JCV serum antibodies to improve the safety of natalizumab treatment as of the date it filed the priority provision and non-provisional applications in 2006 and 2007. (Ex. 1002, ¶¶ 96-116.) The specification includes only two working examples—neither of which mention measuring or monitoring JCV antibodies in the serum, or even JCV antibodies at all. (*See* Ex. 1001, 29:32-31:48; Ex. 1025, [0138]-[0149]; Ex. 1024, [0127]-[0139]; Ex. 1002, ¶ 96.) Nor does the patent elsewhere disclose any actual measurement of JCV antibodies in the serum of PML patients or patients treated with natalizumab. (Ex. 1002, ¶¶ 50, 96-98.) This is no surprise, because Biogen has admitted that it did not possess such a method until years later. It submitted as an undisputed fact in prior litigation that it had not established that the presence of JCV antibodies would predict the risk of developing PML as of 2007, let alone

determined what level of JCV antibodies would serve as a relevant threshold for PML risk. (*Supra* § IV.E.)

Far from providing written description support for what Biogen has acknowledged it had not then established, the '845 Patent specification actually suggests that JCV antibodies in the serum are *not* predictive of PML.[6] It states that JCV antibodies can be examined, but "[a] positive result will not confirm PML." (Ex. 1001, 23:46-48; Ex. 1025, [0107]; Ex. 1024, [0097]; Ex. 1002, ¶¶ 45, 96.) The patent further states that "[t]he presence of JCV in the blood and urine of PML patients and healthy, immunocompetent individuals . . . [is] neither predictive nor diagnostic of PML in these patients; thus the relationship of blood or urine viral load to PML is unclear." (Ex. 1001, 21:30-22:6; Ex. 1025, [0103]; Ex. 1024, [0093]; *see also* Ex. 1001, 15:30-32; Ex. 1025, [0071]; Ex. 1024, [0067] ("Plasma testing proved to be neither predictive nor diagnostic of PML, consistent with the published literature."); Ex. 1002, ¶¶ 41, 97.)

[6] Claim 1 requires monitoring the patient for "indicators" of PML, which can be either diagnostic of the disease or predictive of the risk of developing the disease. (*See*, *e.g.*, Ex. 1001, 21:30-22:6; Ex. 1025, [0103]; Ex. 1024, [0093] (discussing whether blood or urine JCV is "predictive" or "diagnostic" of PML); Ex. 1002, ¶ 97.)

The ’845 Patent also fails to disclose any data showing that the presence of JCV antibodies in patient serum affects development or risk of PML. (Ex. 1002, ¶¶ 96-98.) The patent purports to establish a causal relationship between natalizumab treatment, JCV serum antibodies, and PML based on three confirmed cases of PML in patients treated with natalizumab. (Ex. 1001, 3:29-31, 11:22-32; Ex. 1025, [0012], [0054]; Ex. 1024, [0012], [0050]; Ex. 1002, ¶¶ 96-97.) However, while the specification discusses measuring *JCV viral DNA* in the *CSF* of those patients, the specification does not mention measuring *JCV antibodies* in the *serum* of any of those patients. (Ex. 1001, 11:62-12:16, 12:29-51, 14:37-51; Ex. 1025, [0057], [0059], [0068]; Ex. 1024, [0053], [0055], [0064]; Ex. 1002, ¶¶ 50, 97.)

The specification’s discussion of additional follow-on studies for natalizumab-treated patients also fails to disclose a relationship between JCV antibodies in the serum and risk of PML for those receiving natalizumab treatment. (Ex. 1002, ¶ 98.) In these follow-on studies, the criteria for diagnosing a “confirmed PML” case included “detection of JCV DNA in CSF,” but did not include measuring JCV antibodies either in the serum or CSF. (Ex. 1001, 13:29-40; Ex. 1025, [0063]; Ex. 1024, [0059]; Ex. 1002, ¶ 98.) In one follow-up study, of the 41 patients recommended for further evaluation of PML, only a single patient was recommended based on high plasma JCV viral load. (Ex. 1001, 13:55-

14:23; Ex. 1025, [0065]-[0066]; Ex. 1024, [0061]-[0062]; Ex. 1002, ¶ 98.) This makes sense because plasma-testing studies have found that detecting JCV DNA in the plasma was ultimately not predictive of PML risk. (Ex. 1001, 14:52-15:6; Ex. 1025, [0069]; Ex. 1024, [0065]-[0066]; Ex. 1002, ¶ 98.)

The patent's disclosure of JCV DNA in the CSF fails to support the claims of the '845 Patent. (Ex. 1002, ¶¶ 97-98.) The patent states that "PCR analysis of the CSF for JC viral DNA is a highly sensitive and specific test for the diagnosis of PML." (Ex. 1001, 23:61-62; Ex. 1025, [0108]; Ex. 1024, [0098].) But the purported relationship between PML and *JCV DNA* in the *CSF* cannot be applied to *JCV antibodies* in the *serum*. (Ex. 1002, ¶ 97.) The '845 Patent repeatedly states that JCV DNA in the *serum* is not predictive of diagnostic of PML. (Ex. 1001, 15:13-17, 15:30-32, 15:44-46, 22:4-6; Ex. 1025, [0070], [0071], [0103]; Ex. 1024, [0065]-[0067], [0093]; Ex. 1002, ¶ 97.) Only one of the three confirmed PML cases had detectable levels of JCV DNA in the serum. (Ex. 1001, 15:7-11; Ex. 1025, [0070]; Ex. 1024, [0066]; Ex. 1002, ¶ 98.)

The specification's lack of data supporting a relationship between PML and JCV antibodies in serum, combined with its statement that JCV antibodies in the serum are detectable in 20% to 80% of healthy individuals, shows that Biogen did not know whether JCV serum antibodies would be predictive of PML risk, let alone possess a method of improving the safety of natalizumab treatment by

measuring them. (Ex. 1001, 20:62-67; Ex. 1025, [0100]; Ex. 1024, [0090]; Ex. 1002, ¶¶ 96-98.) Nor would a POSA have thought that the presence of JCV serum antibodies would indicate an increased or significant PML risk. (Ex. 1002, ¶ 97.) Instead, "[a]t the time of the first Tysabri-associated PML cases, it was possible that the presence of JCV antibodies would be found to be protective and thus an indicator of decreased PML risk." (Ex. 1019, 22; *see also* Ex. 1002 ¶ 29.)

As in *Syngenta*, this means the '845 Patent claims do not have sufficient written description support. *See Syngenta Crop Protection AG v. FMC Corp.*, No. PGR2020-00028, 2020 WL 5539136, at *16-17 (P.T.A.B. Sept. 15, 2020). There, the Board concluded that claims directed to a method of using herbicidal compounds with a requisite herbicidal activity lacked adequate written description, because the specification failed to provide "any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the [herbicidal activity]." *Id.* at *17, quoting *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019), cert. denied, 141 S.Ct. 1234 (2021). Similarly, here, the specification fails to explain how JCV serum antibodies would affect the risk of developing PML or how JCV antibodies can be used to achieve the requisite improvement in the safety of natalizumab treatment. (Ex. 1002, ¶¶ 96-98.)

This case is also similar to *Collegium*, where the Board found claims directed to a method of preparing a controlled released oral dosage form to be PGR-eligible due to a lack of sufficient written description. *See Collegium Pharm., Inc. v. Pharma*, No. PGR2018-00048, 2021 WL 6340198, at **15, 18 (P.T.A.B. Nov. 19, 2021). The challenged claims there required using a combination of pharmaceutical ingredients to achieve the recited prolonged therapeutic effect. *Id.* While the specification listed these pharmaceutical ingredients, it failed to teach how to use them to achieve the claimed effect. *Id.* at *14-15. The '845 Patent's claims similarly requires an effect—improving the safety of natalizumab treatment (*i.e.*, by reducing the risk of PML). (Ex. 1002, ¶ 96.) Yet, as was the case in *Collegium*, the '845 Patent specification does not disclose how the combination of claimed steps, including monitoring JCV serum antibodies, would predict the risk or development of PML.

Galderma also supports finding the '845 Patent fails to adequately disclose the claimed invention. *See Galderma S.A. v. Medy-Tox, Inc.*, No. PGR2019-00062, 2020 WL 1486770, at *7 (P.T.A.B. Mar. 19, 2020). There, the claims required administering a therapeutically effective amount of a compound that exhibits a "longer lasting effect." *Id.* The specification did not provide any evidence that the claimed compound would achieve the requisite "longer lasting effect," and it was known in the prior art that the compound was known to be

"inactive and ineffective in humans." *Id.* Here, the '845 Patent specification also does not provide any support that monitoring JCV serum antibodies would provide the claimed effect of improved safety. (Ex. 1002, ¶¶ 96-98.) To the contrary, the specification acknowledges that JCV serum antibodies are present in healthy adults and that monitoring JCV serum DNA is ineffective at assessing the risk of PML. (*See* Ex. 1001, 20:62-67, 15:30-31; Ex. 1025, [0100], [0071]; Ex. 1002, ¶ 97.)

That the specification does not show possession of a method of monitoring JCV serum antibodies that improves the safety of the treatment would be true even if Biogen could establish that methods for detecting the presence of anti-JCV antibodies would have been well-known in the art. The '845 Patent specification recognized that although "serological tests are available to detect JCV," "[t]he sensitivity and specificity varies greatly between different tests." (Ex. 1001, 25:58-64; Ex. 1025, [0116]; Ex. 1002, ¶ 99.) In fact, the rate of detection for JCV antibodies amongst healthy individuals varied from "20% to 80% depending upon the testing methodology." (Ex. 1001, 20:62-67; Ex. 1025, [0100]; Ex. 1002, ¶ 98.) Moreover, the serologic assays available in the art struggled to conclusively determine a positive or negative JCV antibody result for at least some patient serum samples. (Ex. 1002, ¶¶ 29, 99-100.) JCV serological assays, such as the STRATIFY test, use a range of JCV antibody index values to determine whether a patient sample is negative or positive for JCV antibodies. (*Id.*) Some patient

samples, however, exhibit JCV index values within an indeterminate range that requires further testing to reliably determine whether the sample is positive or negative for JCV antibodies. (*Id.*) These indeterminate samples are especially vulnerable to false positive or false negative measurements. (*Id.*) Despite the technical challenges associated with detecting a true positive or negative result, the '845 Patent specification fails to provide any guidance regarding which serological techniques could reliably detect seroconversion of JCV antibodies and reduce the occurrence of false-positive or false-negative results. (*Id*.)

As Biogen admitted in its prior litigation, "[f]rom 2005 through 2009 there was no published literature correlating the risk of PML with the presence or absence of JCV antibodies circulating in the bloodstream." (Ex. 1005, 30; Ex. 1019, p. 25; *supra* § IV.E.) In 2006, Biogen also reported to the FDA that it had "no statistically significant data from which to determine whether the presence of an antibody would assist in assessing whether someone is at a higher or lower risk of getting PML." (Ex. 1019, p. 22; *supra* § IV.E.) It was not until 2012 that Biogen published work showing that a serological assay for JCV antibodies could be used as an indicator for PML risk. (*See* Ex. 1016, (Bloomgren); Ex. 1002, ¶¶ 85, 102.) And it was not until 2014 that Biogen finally published a paper using an established serological assay to quantify the risk of PML provided by specific JCV antibody titers. (*See*, Ex. 1017 (Plavina); Ex. 1002, ¶¶ 86, 102.)

The absence of data required to support a correlation between JCV antibodies and risk of PML during this timeframe is evident not only from Biogen's scientific publications, but also from its product labels. The Tysabri label was first updated to suggest measuring JCV serum antibodies in natalizumab-treated patients in 2012. (*See* Ex. 1008, pp. 4-5; Ex. 1002, ¶ 87.) And even in its 2013 Tysabri product label, Biogen acknowledged that "[a]nti-JCV antibody testing *should not be used to diagnose PML*" and "[i]t is not known whether early detection of PML and discontinuation of TYSABRI will mitigate the disease." (Ex. 1007, 5 (Section 5.1); Ex. 1002, ¶ 102.)

This evidence is relevant to establishing that the claims lack written description support as of Biogen's pre-AIA priority dates. *See Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003) ("Report of a first success after [a claimed priority date] indicates failure or difficulty in or before [the claimed priority date]."); *see also* C*hiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1255 (Fed. Cir. 2004) (evidence that technology did not exist at the time of invention contributed to the finding that the patentee did not possess the technology).

B. The Pre-AIA Patent Applications Do Not Disclose a Method for Monitoring Increasing Titers of JCV Antibodies to Improve the Safety of Natalizumab Treatment

The challenged claims also lack written description support that monitoring *increasing titer* of JCV antibodies in the serum can improve the safety of natalizumab treatment. (Ex. 1002, ¶¶ 104-109.) Specifically, Claim 1 of the '845 Patent requires monitoring for "*an increasing titer of JC virus (JCV) antibodies* in the patient's blood." (Emphasis added). An increasing titer of JCV antibodies is the increasing "concentration of [JCV] antibody in solution." (Ex. 1001, 9:6-7; Ex. 1025, [0037]; Ex. 1002 ¶ 104.)

The specification does not cite any data or studies establishing that JCV serum antibodies increased over time in PML patients or patients treated with natalizumab. (*Id.*, ¶ 105.) As discussed above, the three confirmed PML cases looked at whether JCV DNA (not antibodies) was present in the CSF (not the serum). (*Supra* § VIII.B; Ex. 1002, ¶ 105.) For one of the confirmed PML cases, the specification discloses that JC viral load *decreased* in the plasma over time as the patient deteriorated, which indicates that the increasing presence of JCV in the serum is not necessarily predictive of PML. (Ex. 1001, 12:34-45; Ex. 1025, [0059]; Ex. 1024, [0055]; Ex. 1002, ¶ 105.) In addition, the follow-on studies discussed in the specification measured only whether JCV DNA was detectable,

not whether there were increasing levels of JCV antibodies over time. (Ex. 1001, 13:29-15:51; Ex. 1025, [0063]-[0071]; Ex. 1024, [0059]-[0064]; Ex. 1002, ¶ 105.)

The specification also does not disclose how to measure increases in JCV antibody levels, and what increases would correspond with the risk of PML. (Ex. 1002, ¶¶ 104-106.) Biogen may point to the brief statement about "serially removing samples of the patient's blood, measuring the amount of IgG antibodies to JCV in the samples, and comparing the amount of the antibodies in the samples." (Ex. 1001, 5:12-16; Ex. 1025, [0020]; Ex. 1024, [0015].) But the specification does not specify how often or when serum samples should be taken. (Ex. 1002, ¶¶ 105-106.) It does not specify what serological test should be used to measure JCV serum antibodies. (*Id.*) It does not disclose what increased JCV antibody levels are correlated with a greater risk of PML. (*Id.*) It does not disclose any quantifiable measurements of increases in JCV serum antibodies over time for PML patients, patients treated with natalizumab, or healthy individuals. (*Id.*) To the contrary, the specification acknowledges that "[a] wide variety of serological tests are available to detect JCV" and "[t]he sensitivity and specificity varies greatly between different techniques." (Ex. 1001, 25:58-67; Ex. 1025, [0116]; Ex. 1024, [0106]; Ex. 1002 ¶ 105.)

Accordingly, the priority applications do not provide sufficient written description support for the claims. *See Advanced Accelerator Applications USA,*

Inc. v. Molecular Insight Pharms., Inc., No. PGR2021-00048, 2021 WL 3265090, at *9 (P.T.A.B. July 29, 2021) (instituting PGR and finding that claims directed to compounds with a certain therapeutic efficacy more likely than not lacked written description).

C. The Pre-AIA Priority Applications Lack Sufficient Written Description Support for the Broad Genus of JCV Antibodies of the Claims

The challenged claims also lack written description support, because they cover the broad, unsupported genus of all classes of JCV antibodies. (Ex. 1002, ¶¶ 110-116.) Claim 1 of the '845 Patent requires monitoring a genus of antibodies that are functionally defined by their ability to bind to JCV. (*Id.*, ¶ 110.) To support genus claims of this type, the specification must disclose either "a representative number of species falling within the scope of the genus or structural features common to the members of the genus." *Ariad*, 598 F.3d at 1349-50. The "representative species/common structural features" framework applies not only to claims directed to a genus of compositions, but also to methods of a genus. *See Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019) (applying representative species/common structural features framework to invalidate a method claim using a genus of nucleoside compounds defined by the function of treating hepatitis C), cert. denied, 141 S.Ct. 1234 (2021); *In re*

Alonso, 545 F.3d 1015, 1018-22 (Fed. Cir. 2008) (same, for method of treatment claim using an antibody defined by its function of binding to a particular target).

Biogen cannot satisfy the requirement to disclose a representative number of species because there are *no examples* of monitoring any specific JCV antibodies in the '845 Patent specification. (Ex. 1002, ¶ 112.) *Univ. of Rochester v. G.D. Searle Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004) (the patent failed to disclose "any compounds that can be used in its claimed methods"); *Alonso*, 545 F.3d at 1020-22 (the specification did not disclose any examples teaching "the structure, epitope characterization, binding affinity specificity, or pharmacological properties common to the large family of antibodies implicated by the method"). At best, Biogen mentions two antibody classes (IgG and IgM), but does not establish that these can be detected reliably in patients receiving natalizumab who are at risk of developing PML. (Ex. 1002, ¶¶ 111-112.) It merely proposes such monitoring without any support. (*Id.*) Its passing reference to these two of the many classes of antibodies, without establishing it possessed a method of monitoring for species of antibodies that fall within these classes, fails to show adequate written description. (*Id.*)

If a patent does not describe a representative number of species of a claimed genus, it must disclose an "identification of structural features . . . possessed by members of the genus that distinguish them from others," sufficient to allow a

POSA to "visualize or recognize the identity of the members of the genus"; the features must also be "common" insofar as they constitute a "substantial portion" of the genus. *Glaxosmithkline LLC v. Banner Pharmacaps, Inc.*, 744 F. 3d 725, 730 (Fed. Cir. 2014) (internal quotation marks and citations omitted). Claims with functional limitations, as here, are particularly problematic, because they "simply claim a desired result, and may do so without describing species that achieve that result." *Ariad*, 598 F.3d at 1349; *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1125 (Fed. Cir. 2008).

The '845 Patent specification does not disclose any common structural features for the claimed antibodies other than that they should bind to JCV. (Ex. 1002, ¶ 112.) The specification contains no discussion of antibody structures that could be used to identify the types of JCV antibodies that may fall within the scope of the claimed genus of antibodies. (*Id.*) On the contrary, claim 1 of the '845 Patent is directed to "JC virus (JCV) antibodies in the patient's blood" without limiting the genus to any specific class of antibodies, let alone a class of antibodies with a specified complementarity-determining region (CDR) motif or sequence. (*Id.*) During prosecution of the '845 Patent, Biogen broadened the claims from "measuring the amount of *IgG* anti-JCV antibodies in the samples" to "detecting seroconversion and/or an increasing titer of *JC virus (JCV) antibodies*." (Ex. 1021, 2020-11-13 Claims, 2021-08-02 Claims, Amended Claim 1 (emphasis

added); Ex. 1002, ¶ 92.) The '845 Patent specification similarly does not limit the genus of antibodies to IgG. (Ex. 1002, ¶¶ 90-92, 110.) For example, the specification expressly recognizes that different serological tests "can be designed to detect one specific class [of JCV antibodies], for example, IgM, IgG, or IgA," although it does not provide any test designs. (Ex. 1001, 25:58-67; Ex. 1025, [0116]; Ex. 1024, [0106]; Ex. 1002, ¶¶ 46, 91, 110-112.) The specification also mentions comparing the levels of IgM to IgG JCV antibodies, again without providing a test or any supporting data. (Ex. 1001, 3:66-4:2, 5:16-19, 7:43-46; Ex. 1025, [0016], [0020], [0026]; Ex. 1024, [0016], [0020], [0026]; Ex. 1002, ¶¶ 110-111.) The genus of JCV antibodies that claim 1 of the '845 Patent encompasses thus includes all classes of human antibodies, including IgG, IgA, IgM, IgE, and IgD antibodies. (*Id.*)

Despite the broad scope of the claims, the '845 Patent specification provides no support for how to monitor any of the JCV antibody classes. (Ex. 1002, ¶ 112.) Nor does it disclose any working examples of monitoring JCV serum antibody levels to improve the safety of natalizumab treatment. (*Supra* § IV.B.3; Ex. 1002, ¶ 112.) There is zero discussion regarding IgE or IgD JCV antibodies. (Ex. 1002, ¶ 112.) The specification only provides passing reference to IgA. (*Id.*, 25:64-67; Ex. 1024, [0106]; Ex. 1002, ¶ 112.) And even as to IgG and IgM, the specification suggests comparing them, but does not say how to compare them or what that

comparison would show. (Exhibit 1001, 3:66-4:2, 5:16-19, 7:43-46; Ex. 1025, [0016], [0020], [0026]; Ex. 1024, [0016], [0020], [0026]; Ex. 1002, ¶ 112.)

These failures of disclosure render the challenged claims unpatentable. The various classes of JCV antibodies have both structural and functional differences that materially affect how JCV serum antibodies are monitored. (Ex. 1002, ¶¶ 112-114.) First, the differences in sensitivity and specificity between different serological techniques require that the serological assay be tailored towards the specific JCV antibody class or classes that are being monitored. (*Id.*, ¶ 112.) But neither the specification nor the claims of the '845 Patent provide any guidance for what assay to use with which antibody. (*Id.*, ¶ 112.) Second, different classes of antibodies will be detected at different levels within the body depending on when the patient serum sample is collected. (*Id.*, ¶ 113.) For example, if the patient samples are collected at the early stages of a JCV infection, IgM antibody levels may be higher while IgG antibodies may not be detectable. (*Id.*) On the other hand, if the patient samples are collected at the later stages of a JCV infection, IgM antibody levels may be lower than IgG antibody levels. (*Id.*) The specification provides no guidance on these points, nor does it identify antibody structures shared by the various classes of antibodies predictive of PML risk. (*Id.*, ¶¶ 112-113.)

The failure to include this information confirms that Biogen was not in possession of the claimed invention. The Federal Circuit has repeatedly held that genus claims with unsupported, functional genus limitations fail to satisfy the written description requirement. *See, e.g.*, *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1339-40 (Fed. Cir. 2021) (invalidating broad genus claims directed to antibody fragments that bind to any target for lack of written description), cert. filed (Jun. 15, 2022); *Idenix*, 941 F.3d at 1164 (invalidating broad genus claims directed to nucleosides that are effective at treating a disease for lack of written description). And at least one district court has confirmed that claims that broadly encompass all classes of antibodies without supporting examples failed to satisfy § 112. *See Baxalta Inc. v. Genentech, Inc.*, No. CV 17-509-TBD, 2022 WL 420479, at *2 (D. Del. Jan. 13, 2022), appeal filed, No. 22-1461 (Fed. Cir. Feb. 10, 2022).

In *Baxalta*, the court held invalid a claim directed to "an isolated antibody or antibody fragment thereof that binds" a specific protein, because the specification included working examples of IgG and IgM antibodies, but no working examples of IgE, IgA, or IgD antibodies. *See id.* The court concluded that there was insufficient disclosure of each type of antibody class to support the broad structural limitations of the claims. *Id.* at *19-20 (pointing out that the specification did not include working examples of IgE or IgA antibodies). Here, there is even less

written description support for the broad structural limitations of the '845 Patent claims, because the '845 Patent specification includes no working examples of monitoring for *any* specific class of JCV serum antibody. (Ex. 1002, ¶¶ 110-116.) Accordingly, the pre-AIA patent applications fail to provide sufficient written description support for the claimed genus of JCV antibodies, and the challenged claims are PGR-eligible.

IX. THE CHALLENGED CLAIMS ARE UNPATENTABLE

Claims 1-16 of the '845 Patent are not patentable on at least three grounds: (1) lack of written description under 35 U.S.C. § 112; (2) ineligible subject matter under 35 U.S.C. § 101; and (3) obviousness under 35 U.S.C. § 103.

First, as discussed above, the challenged claims are not supported by adequate written description in the specification of the '845 Patent. (*Supra* § VII.) This ground alone is sufficient to render all challenged claims of the '845 Patent unpatentable.

Second, the challenged claims are unpatentable because they are directed to ineligible subject matter. The claims are directed to the naturally occurring relationship between JCV, PML, and the body's production of JCV antibodies after being treated with natalizumab. The claimed method requires stopping treatment with natalizumab rather than continuing treatment at a specified or changed dosage. Thus, the claims simply ask physicians to apply the known natural

relationship between JCV and PML to the decision of whether to continue therapy. Moreover, the challenged claims only generally require an improvement in safety, rather than specify that the monitoring of JCV antibodies should achieve a quantifiable or specific result.

Finally, because the challenged claims have an effective filing date of March 18, 2019, pre-existing public disclosures of a method of improving the safety of natalizumab treatment by measuring JCV serum antibodies and determining whether to continue treatment of natalizumab render obvious the claims of the '845 Patent. Specifically, Alroughani, a scientific article published in 2014, and the 2013 Tysabri Label render claims 1-16 of the '845 Patent obvious.

A. Ground 1: The '845 Patent's Claimed Method Lacks Adequate Written Description Support

As previously established, the challenged claims of the '845 Patent are unpatentable for lack of written description. (*Supra* § VIII.) The '845 Patent and post-AIA applications share the same specification as the pre-AIA applications in the priority chain. (*Id.*) Thus, the written description deficiencies present in the shared specification that make the challenged claims PGR eligible also cause the claims to be unpatentable. (*Id.*) The '845 Patent's lack of adequate written description for the challenged claims is alone sufficient to institute review on this Petition.

B. Ground 2: The '845 Patent's Claimed Method Is Ineligible Subject Matter

The '845 Patent is directed to an observed, natural phenomenon—that an immunosuppressant (natalizumab) can cause life-threatening side effects (PML) by hampering the immune response to latent disease (infection with JCV)—and claims the conventional conclusion a POSA would draw when this occurs: that therapy should be discontinued. (Ex. 1002, ¶¶ 117-121.) Biogen did not provide an inventive contribution that improved the safety of natalizumab treatment to transform the nature of the claims beyond simply claiming this natural phenomenon. (*Id.*, ¶¶ 122-126.) The challenged claims thus cover ineligible subject matter.

1. Step 1: The Claims Are Directed to a Natural Phenomenon

The crux of the invention claimed by the '845 Patent pertains to the natural phenomenon that active JCV infection correlates with the risk of developing PML in patients, and an immunosuppressant such as natalizumab can cause a latent JCV infection to become active. (Ex. 1002, ¶ 118.) Biogen did not add anything beyond that. (*Id.*) It was well known before the filing of the '845 Patent that PML is caused by JCV. (*See* Ex. 1001, 3:23-25 ("JC virus (JCV) is the etiological agent of PML and may result from a primary infection or follow reactivation of latent virus"), 20:59-60 ("PML is an infectious disease of the central nervous system

caused by JCV infection of oligodendrocytes"); Ex. 1002, ¶ 119.) Nor is the claimed monitoring for JCV the result of any inventive diagnostic, monitoring, or testing method. (*See* Ex. 1001, 13:29-51 (third-party investigators or physicians were asked to perform the testing for JCV); Ex. 1002, ¶ 118.)

The '845 Patent claims are therefore similar to claims that the Supreme Court has found patent-ineligible because they were directed to natural phenomena. *See Mayo*, 566 U.S. at 77. In *Mayo*, for example, the claims were directed to measuring the concentrations of certain metabolites in the blood and correlating them to the likelihood that a dosage of a drug would cause harm and produce toxic side effects. *Id.* The Supreme Court noted that "[w]hile it takes human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in principle apart from any human action." *Id.* Here, the '845 Patent claims are directed to monitoring for JCV infection because active JCV infection was a known PML risk factor. (*See* Ex. 1001, 14:47-49 ("Each of the three patients with confirmed PML had detectable JCV DNA"); Ex. 1002, ¶ 119.) That an immunosuppressant can activate latent disease is a naturally occurring phenomenon. (Ex. 1002, ¶ 118.) And the natural relationship between JCV infection and PML exists in principle apart from the administration of any human action. (*Id.*) Just as in *Mayo*, they are thus directed to a natural phenomenon.

Other Federal Circuit cases confirm that the '845 Patent claims are directed to a patent-ineligible natural phenomenon. In *Cleveland Clinic*, the Federal Circuit found that claims directed to assessing the levels of an enzyme (MPO) in a patient and correlating that to the patient's risk of developing a cardiovascular disease had an ineligible natural phenomenon as their focus. *See Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352, 1360–61 (Fed. Cir. 2017) (finding the claims "employ[ed] the natural relationship between those MPO values and predetermined or control values to predict a patient's risk of developing or having cardiovascular disease"). More recently, in *CareDx*, the Federal Circuit found patent claims directed to ineligible subject matter because they involved "collecting a bodily sample, analyzing the cfDNA using conventional techniques, including PCR, identifying naturally occurring DNA from the donor organ, and then using the natural correlation between heightened cfDNA levels and transplant health to identify a potential rejection." *CareDx, Inc. v. Natera, Inc.*, No. 2022-1027, 2022 WL 2793597, at *6 (Fed. Cir. July 18, 2022). Here, the claims are similarly directed to the natural relationship between JCV antibody levels and JCV infection to identify the potential risk of developing PML in natalizumab-treated patients. (Ex. 1002, ¶¶ 118-121.) That the claims mention treatment does not change the analysis. In *INO*, the Federal Circuit found claims directed to *not treating a patient* based on a natural phenomenon to be patent-ineligible. *INO*

Therapeutics LLC v. Praxair Distribution Inc., 782 F. App'x 1001, 1005-06 (Fed. Cir. 2019). The claims here likewise are directed to *discontinuing* treatment.

2. Step 2A: The Claims Do Not Incorporate the Natural Phenomenon into a Practical Application

The challenged claims of the '845 Patent fail to incorporate the natural phenomenon pertaining to JCV, PML, and JCV antibodies into a practical application.

The Federal Circuit has been clear that to incorporate the natural phenomenon in a practical application for a method of treatment claim, the claim must include additional, affirmative treatment steps based on the natural phenomenon. The challenged claims do not and are thus distinct from the claims the Federal Circuit found eligible in *Vanda*. *See Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1134-36 (Fed. Cir. 2018), cert. denied, 140 S.Ct. 911 (2020). There, the claims were directed to a method of treatment, rather than limiting the chances of side effects, as was the case in *Mayo* and is the case here. To distinguish *Mayo*, the Federal Circuit noted that the method there "as a whole was not directed to the application of a drug to treat a particular disease." *Id.* at 1134. But neither are the claims at issue here. The '845 Patent claims do not recite an affirmative treatment plan that varies the dosages of natalizumab depending on whether seroconversion and/or increasing titer of JCV antibodies are

detected in the patient. (Ex. 1002, ¶ 123.) Rather, they merely require that the physician discontinue administering the drug. (*Id.*)

This is akin to the patent-ineligible claims in *INO*, where the Court noted that the increased risks that could warrant suspending treatment were a consequence of the "the body's natural processes" if they "are simply allowed to take place." *INO*, 782 F. App'x at 1005. Like the claims in *INO*, the '845 Patent claims do not recite any additional affirmative treatment steps in response to monitoring the natural phenomenon. *See INO*, 782 F. App'x at 1005 ("The patent claim does no more than add an instruction to withhold iNO treatment from the identified patients; it does not recite giving any affirmative treatment for the iNO-excluded group"); Ex. 1002, ¶ 123. Rather, the claims only instruct that treatment with natalizumab be discontinued. (Ex. 1002, ¶¶ 123-124.) This, according to the Federal Circuit, does not make the claims patent-eligible because claims directing physicians "not to treat—i.e., not to disturb these naturally-occurring physiological processes within the . . . patient's body—risks monopolizing the natural processes themselves," and "[do] not propose a new way of treating . . . patients." *INO*, 782 F. App'x at 1006.

The claims here are also like the claims found patent-ineligible in *Cleveland Clinic*, as they do not purport to alter the JCV antibody titer in any way, and merely involves "seeing" the antibodies "already present in a bodily sample and

correlating that to" the risk of developing PML. *Cleveland*, 859 F.3d at 1361. (Ex. 1002, ¶ 124.) Moreover, the claims are not directed to any novel laboratory technique for detecting this naturally-occurring relationship and only recite "monitoring" for JCV antibodies. (Ex. 1002, ¶¶ 123-124.) Because the claims are based on the relationship between risk for developing PML and seroconversion or heightened JCV antibody titer levels that "exists in principle apart from human action," they do not incorporate the natural phenomenon into a practical application. *Cleveland*, 859 F.3d at 1361 (quoting *Mayo*, 566 U.S. at 77).

3. Step 2B: The Claims Fail to Provide an Inventive Concept and Do Not Transform the Nature of the Claim into Eligible Subject Matter

The challenged claims of the '845 Patent fail to provide an inventive concept under Step 2B of the *Alice/Mayo* test. As previously discussed, the challenged claims contain a single "monitoring" step that requires analyzing JCV antibody titer with any known techniques. The first "wherein" clause limits the monitoring of PML indicators to detecting for seroconversion or increasing titers of JCV serum antibodies, and the second "wherein" clause generally requires that the monitoring improve the safety of the treatment without providing any criteria to evaluate the change in safety. The claims do not specify whether the "change in safety" pertains to a change in the risk of PML, a change in JCV serum antibody titer, or a decrease in the adverse side effects of the treatment. (Ex. 1002, ¶ 123.)

This "merely tell[s] those 'interested in the subject about the correlations that the researchers discovered.'" *Cleveland Clinic*, 859 F.3d at 1362 (quoting *Mayo*, 566 U.S. at 78).

Nor does the '845 Patent specification provide any evidence that monitoring JCV serum antibodies actually improves the safety of natalizumab treatment. (Ex. 1002, ¶ 123.) It does not provide a working example of how natalizumab-treated patients would be monitored for seroconversion or increasing titer of JCV serum antibodies. (*Id.*) It also does not provide any guidance regarding how physicians and patients would factor seroconversion or increasing titer of JCV serum antibodies into the risk/benefit analysis involved in deciding whether to discontinue treatment of natalizumab. (*Id.*)

None of the elements of challenged claims, either in isolation or in combination, transform the nature of the claim into eligible subject matter. (Ex. 1002, ¶¶ 122-126.) Each element was already well-known in the art and established before the '845 Patent. For example, treating a patient with an inflammatory or autoimmune disease with natalizumab was known. (*See, e.g.*, Ex. 1001, 3:26-29 ("Natalizumab, an α4-integrin antagonist, has been used successfully to treat diseases with inflammatory and/or autoimmune components, for example, MS, Crohn's Disease, and rheumatoid arthritis."); Ex. 1026 (Taylor) (claiming treating patients with pathological inflammation including multiple

sclerosis and Crohn's disease with natalizumab); Ex. 1002, ¶ 124). It was known that "JC virus (JCV) is the etiological agent of PML" (Ex. 1001, 3:23-25) and that bodily samples from natalizumab-treated patients with confirmed PML tested positive for JCV. (*See* Ex. 1001, 14:47-49 ("Each of the three patients with confirmed PML had detectable JCV DNA"); Ex. 1027 (Yousry) at Table 2; Ex. 1002, ¶ 124.) It was also known that PML patients can have JCV serum antibodies. (*See* Ex. 1028 (Knowles 1995); Ex. 1002, ¶ 124.) In addition, it was and is conventional practice to discontinue administration of a drug if the patient is at serious risk of developing harmful side effects. (*Id*.) Accordingly, the claims "amount[] to little more than an instruction to doctors to 'apply' the applicable law when treating their patients." *INO*, 782 F. App'x at 1012; *see also CareDx*, 2022 WL 2793597 at *5-7 (patent claims were invalid where the inventors "did not invent or discover the [natural phenomenon]" and the claims did not involve "a new measurement technique," but rather "recited standard, well-known techniques in a logical combination to detect natural phenomena"). They therefore fail Step 2 of the *Alice/Mayo* test.

As discussed above, the claims of the '845 Patent are not directed to patent-eligible subject matter simply because the preamble refers to treatment. Unlike *Vanda*, the claims do not refer to "a specific compound at specific doses to achieve a specific outcome." *Vanda*, 887 F.3d at 1136. This distinguishes the claims from

other treatment claims found patent-eligible. *Id.*; *Endo Pharms. Inc. v. Teva Pharms. USA, Inc.*, 919 F.3d 1347, 1353 (Fed. Cir. 2019) (claims directed to "specific dosage regimen" to achieve a specific therapeutic range).

Accordingly, the claims of the '845 Patent are directed to ineligible subject matter and are invalid under 35 U.S.C. § 101.

C. Ground 3: The Method Claimed by the '845 Patent Is Obvious in Light of Alroughani and the 2013 Tysabri Label

Pursuant to 35 U.S.C. § 103, the claims of the '845 Patent are obvious in view of Alroughani (Ex. 1006) and the 2013 Tysabri Label (Ex. 1007). (Ex. 1002, ¶¶ 127-179.) As discussed above, the '845 Patent has an effective filing date of March 18, 2019, because it is not entitled to priority to any of the earlier applications in the same family. (*See supra* §§ VIII, IX.A.) Thus, the 2014 Alroughani publication and 2013 Tysbari Label qualify as prior art under post-AIA § 102(b)(1). The Examiner did not cite either reference during the prosecution of the '845 Patent.

The summary of results in Alroughani makes clear that the reference renders the challenged claims obvious because it is directed to nearly identical subject matter—a method of improving the safety of natalizumab treatment based on monitoring of JCV serum antibodies during treatment (Ex. 1002, ¶ 129):

> Several factors including prior immunosuppressant therapy, *anti-John Cunningham virus (JCV) antibody status* and patient choice will affect the selection of natalizumab. In highly active MS, natalizumab is considered as a first-line therapy for naive patients with disabling relapses in association with MRI activity. *The anti-JCV antibody test is used to assess anti-JCV antibody status and identify the risk of PML*. While seronegative patients should continue treatment with natalizumab, anti-JCV antibody testing every 6 months and annual MRI scans are recommended as part of patient monitoring. *In seropositive patients, the expected benefits of natalizumab treatment have to be weighed against the risks of PML.*

(Ex. 1006, 1 (emphasis added).)

The 2013 Tysabri label also discloses that JCV serum antibody levels in patients treated with natalizumab should be monitored and considered for determining whether to discontinue treatment. (Ex. 1002, ¶¶ 132-134.) The label discloses a black box warning for PML that states that the "presence of anti-JCV antibodies" is one of the "[r]isk factors for the development of PML." (Ex. 1007, p. 1; Ex. 1002 ¶ 132.) The label further discloses that the presence of anti-JCV antibodies "should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI." (*Id.*, pp. 2, 5; Ex. 1002, ¶ 134.)

A POSA would have been motivated to combine the teachings of Alroughani and the 2013 Tysabri Label to practice the claims of the '845 Patent,

because both describe PML risk management for patients undergoing natalizumab treatment. (Ex. 1002, ¶ 135.)

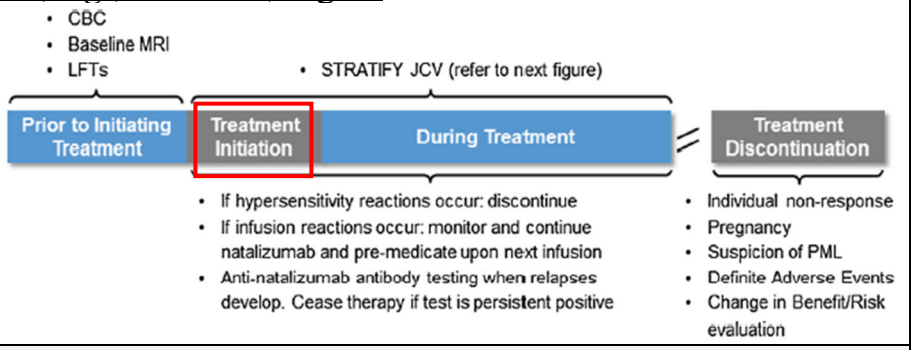
1. Independent Claim 1 Is Obvious

As shown in the chart below, Claim 1 is obvious in light of Alroughani and in view of the 2013 Tysabri Label.

<table>
<tr><th colspan="2">’845 Patent Claim 1</th></tr>
<tr><td rowspan="4">1. A method of using natalizumab to treat a patient with an inflammatory or autoimmune disease comprising:</td><td>Alroughani (Ex. 1006)</td></tr>
<tr><td>Alroughani discloses using natalizumab to treat patients with MS, an inflammatory disease (see Ex. 1006, pp. 1-8; Ex. 1002, ¶ 136):

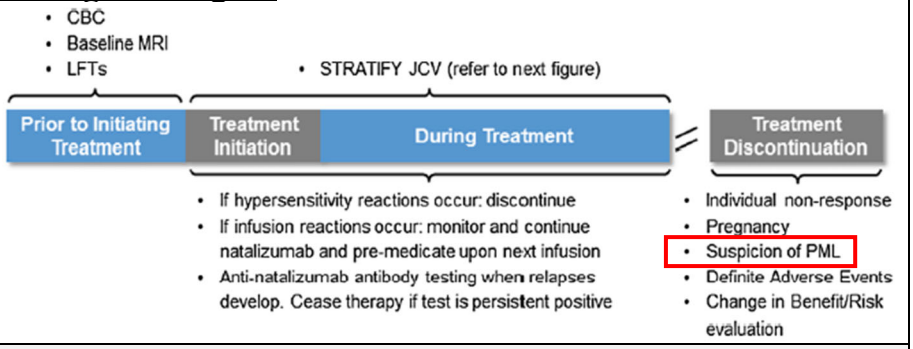
See, e.g., Ex. 1006, p. 2 (“Multiple sclerosis (MS) is an inflammatory demyelinating disorder affecting the central nervous system . . . . Interferon-beta is generally regarded as the first-line treatment for MS, with natalizumab and fingolimod used as second-line agents in the case of treatment failure with interferon-beta . . . . or for those who have rapidly evolving, severe relapsing-remitting MS . . . . Our aim is to guide local neurological societies in the MENA region by developing recommendations for the selection and monitoring of MS patients to be treated with natalizumab”) (emphasis added).</td></tr>
<tr><td>2013 Tysabri Label (Ex. 1007)</td></tr>
<tr><td>The 2013 Tysabri Product Label discloses that Tysabri (i.e. natalizumab) should be used to treat patients with MS or CD, both inflammatory diseases (see Ex. 1007, pp. 1-3, 10-26; Ex. 1002, ¶ 136):

See, e.g., Ex. 1007, p. 1 (“TYSABRI is an integrin receptor antagonist indicated for the treatment of: Multiple Sclerosis (MS) . . . Crohn’s Disease (CD)”).</td></tr>
</table>

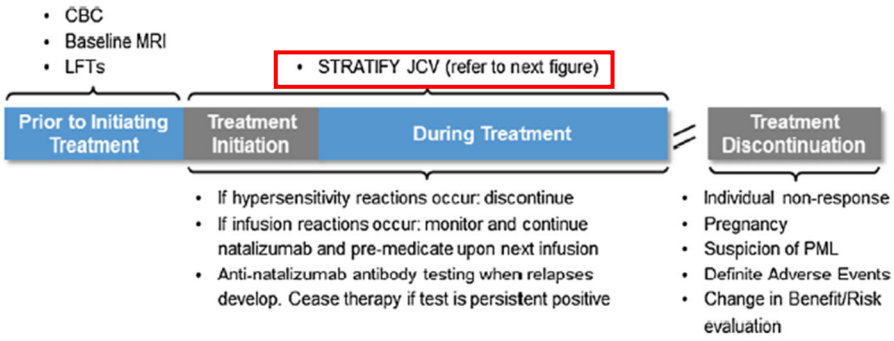
(a) administering a pharmaceutically effective amount of natalizumab to the patient;	Alroughani (Ex. 1006) Alroughani discloses treating patients with natalizumab, which requires administering a pharmaceutically effective amount of natalizumab to the patient (*see* pp. 1-8; Ex. 1002 ¶ 137): *See*, *e.g.*, Ex. 1006, p. 6 ("Natalizumab is recommended as an escalation therapy in patients with breakthrough disease on the basis of its established efficacy in Phase III studies. In highly active MS, natalizumab is considered as a first-line therapy for naïve patients with disabling relapses in association with MRI activity"). Alroughani discloses initiating treatment of MS patients with natalizumab. (Ex. 1002, ¶ 137.) *See*, *e.g.*, Ex. 1006, Fig. 3:  2013 Tysabri Label (Ex. 1007) The 2013 Tysabri Product Label discloses administering a therapeutically effective amount (300 mg) of Tysabri (i.e. natalizumab) to patients with MS or CD (*see* pp. 1-3, 10-26; Ex. 1002, ¶ 137): A POSA would recognize that a "recommended dose" is a "pharmaceutically effective amount," because the product label would disclose an amount effective for treating the patient. (Ex. 1002, ¶ 137.) *See*, *e.g.*, Ex. 1007, p. 3 ("The recommended dose of TYSABRI for multiple sclerosis is 300 mg intravenous infusion over one hour every four

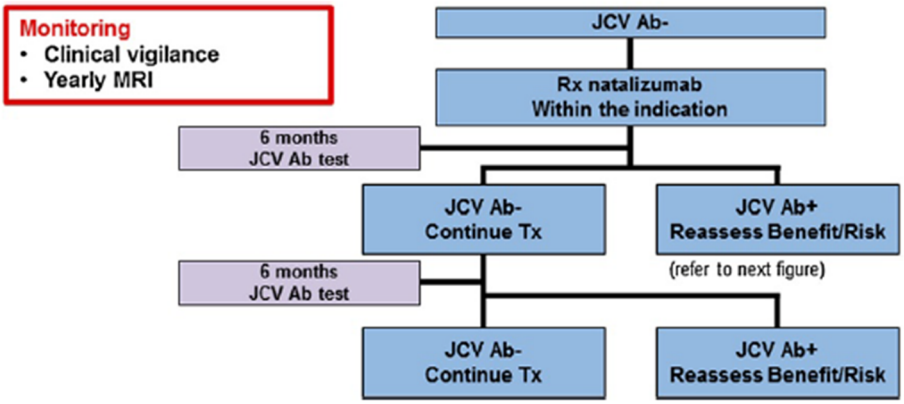
<table>
<tr><td></td><td>weeks . . . . The recommended dose of TYSABRI for Crohn's disease is 300 mg intravenous infusion over one hour every four weeks").</td></tr>
<tr><td rowspan="3">(b) monitoring the patient for indicators of progressive multifocal leukoencephalopathy (PML),</td><td>Alroughani (Ex. 1006)</td></tr>
<tr><td>Alroughani discloses monitoring natalizumab-treated patients for PML to evaluate whether to continue treatment (see pp. 1-8; Ex. 1002, ¶ 138):

See, e.g., Ex. 1006, pp. 4 ("Neurologists need to exercise clinical vigilance for the signs and symptoms of PML"), 6 ("Treatment is discontinued in the event of non-response, pregnancy, suspicion of PML, definite adverse events or a change in the benefit-risk evaluation") (emphasis added).

<u>See, e.g., id, Fig. 3:</u>
 
</td></tr>
<tr><td>2013 Tysabri Label (Ex. 1007)</td></tr>
<tr><td></td><td>The 2013 Tysabri Product Label discloses that patients on Tysabri (i.e., natalizumab) should be monitored for PML (see pp. 1-2, 4-7, 14-15, 27-28, Medication Guide; Ex. 1002, ¶ 138):

See, e.g., Ex. 1007, pp. 1 ("TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability . . . . Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML"), 6 ("Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom suggestive of PML").</td></tr>
</table>

	Alroughani (Ex. 1006)
wherein the monitoring comprises detecting seroconversion and/or an increasing titer of JC virus (JCV) antibodies in the patient's blood; and	Alroughani discloses monitoring natalizumab-treated patients by measuring for JCV antibodies and evaluating whether JCV serum antibody-negative patients turn JCV serum antibody-positive (i.e., seroconversion of JCV antibodies) (*see* pp. 1-8; Ex. 1002, ¶ 139): *See*, *e.g.*, Ex. 1006, pp. 6-7 ("Several factors including prior immunosuppressant therapy, anti-JCV antibody status and patient choice may contribute to the selection of natalizumab . . . . The anti-JCV antibody test is used to **assess anti-JCV antibody** status. It is recommended to obtain the test at treatment initiation or during treatment with natalizumab . . . **Seronegative** patients should continue treatment with natalizumab. In **seropositive** patients, the expected benefits of natalizumab treatment have to be weighed against the risks") (emphasis added). *See*, *e.g.*, *id.*, Fig. 3:  "STRATIFY JCV" refers to monitoring natalizumab-treated patients for JCV serum antibodies. (Ex. 1002, ¶ 139.) *See*, *e.g.*, Ex. 1006, Fig. 4:



"JCV Ab-" below means patients that test negative for JCV serum antibodies. "JCV Ab+" below means patients that test positive for JCV serum antibodies. Patients that are initially JCV Ab- and then become JCV Ab+ have seroconversion of JCV serum antibodies. (Ex. 1002, ¶ 139.)

2013 Tysabri Label (Ex. 1007)

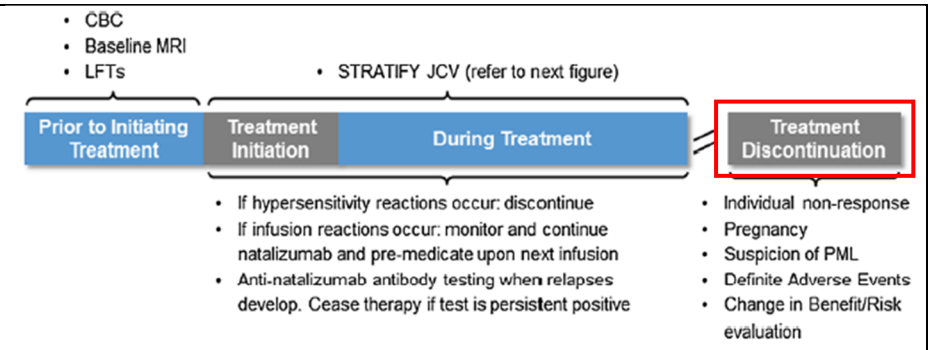
The 2013 Tysabri Product Label discloses that the presence of anti-JCV antibodies (i.e., seroconversion) is a risk factor for the development of PML (*see* pp. 1-2, 4-7, 14-15, 27-28, Medication Guide; Ex. 1002, ¶ 140):

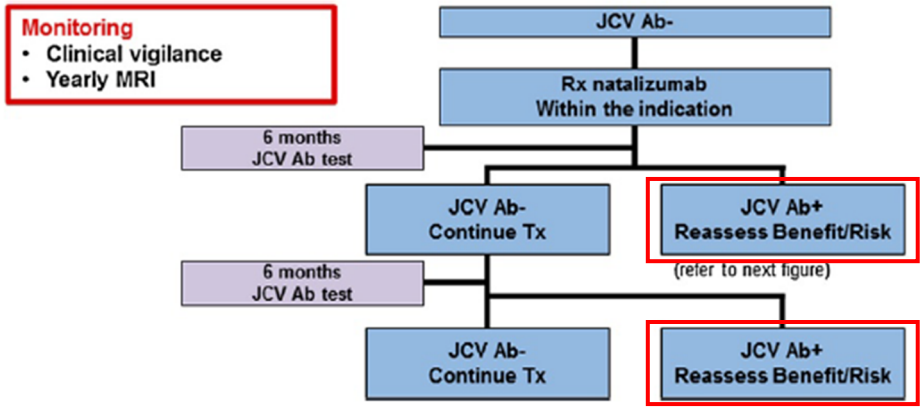
See, *e.g.*, Ex. 1007, p. 1 ("Risk factors for the development of PML include. . . presence of anti-JCV antibodies. These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI (5.1)").

See, *e.g.*, *id.*, pp. 4-5 ("Three factors that are known to increase the risk of PML in TYSABRI-treated patients have been identified: . . . The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML. These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI").

See, *e.g.*, p. 5 ("Infection by the JC virus is required for the development of PML . . . . Therefore, patients with a

	negative anti-JCV antibody test result should be retested periodically. For purposes of risk assessment, a patient with a positive anti-JCV antibody test at any time is considered anti-JCV antibody positive regardless of the results of any prior or subsequent anti-JCV antibody testing").
(c) discontinuing the administration of natalizumab in the presence of seroconversion and/or an increasing titer of JCV antibodies;	Alroughani (Ex. 1006)
	Alroughani discloses discontinuing the administration of natalizumab in the presence of seroconversion of JCV antibodies where the seroconversion changes the benefit/risk evaluation of administering natalizumab (*see* pp. 1-8; Ex. 1002, ¶ 142): *See*, *e.g.*, Ex. 1006, p. 3 ("When considering the withdrawal of natalizumab therapy, the physician should consult with patients on an individual basis, reassess the benefit/risk of natalizumab versus burden of disease and alternative therapies, and increase alertness and monitoring"). *See*, *e.g.*, *id.*, p. 6 ("Several factors including prior immunosuppressant therapy, anti-JCV antibody status and patient choice may contribute to the selection of natalizumab . . . . **Treatment is discontinued** in the event of non-response, pregnancy, suspicion of PML, definite adverse events or a **change in the benefit-risk evaluation**") (emphasis added). *See*, *e.g.*, *id.*, p. 1 ("In seropositive patients, the expected benefits of natalizumab treatment have to be weighed against the risks of PML"). *See*, *e.g., id.*, p. 8 (Fig. 3):

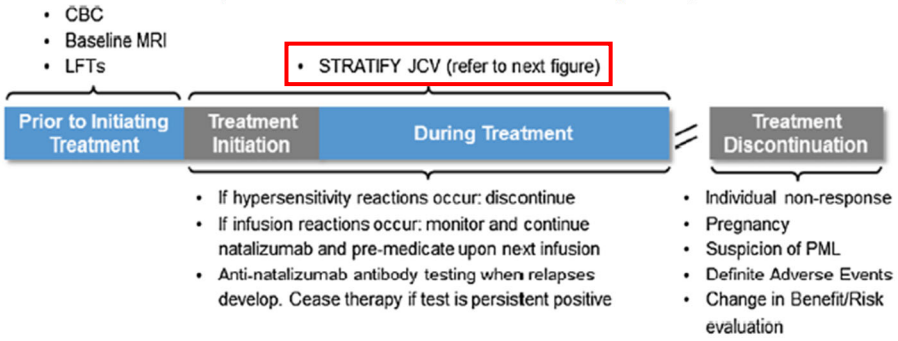
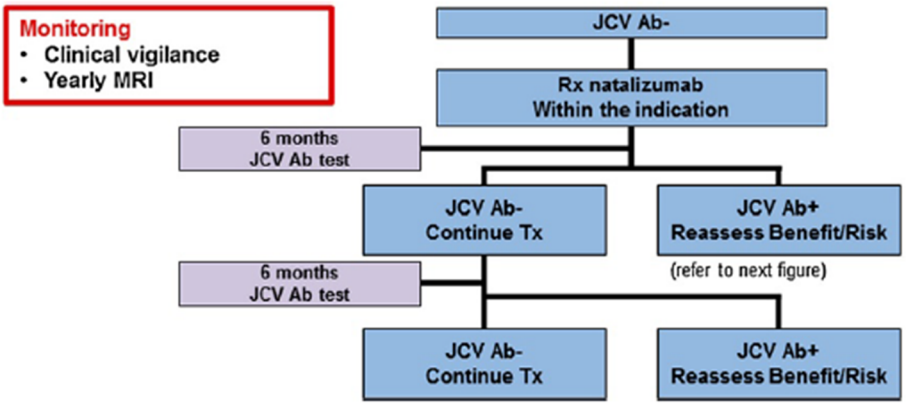
<table>
<tr><td></td><td>


<u>*See*, *e.g.*, *id.*, Fig. 4:</u>


</td></tr>
<tr><td></td><td>2013 Tysabri Label (Ex. 1007)</td></tr>
<tr><td></td><td>JCV serum antibody levels contribute to the risk of PML, and the 2013 Tysabri Product Label discloses that patients with PML should not be treated with Tysabri (i.e., natalizumab) (*see* pp. 1-2, 4-7, 14-15, 27-28, Medication Guide; Ex. 1002, ¶ 143):

See, *e.g.*, Ex. 1007, p. 4 (“TYSABRI is contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML) [*see Warnings and Precautions (5.1)*]”).

See, *e.g.*, *id.*, p. 1 (“Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML (4, 5.1)”).</td></tr>
<tr><td>wherein the monitoring improves the</td><td>Alroughani (Ex. 1006)</td></tr>
<tr><td></td><td>Alroughani discloses that monitoring natalizumab-treated patients for JCV antibodies will maximize the safety of</td></tr>
</table>

safety of the treatment.	natalizumab and improve the safety of the treatment (*see* pp. 1-8; Ex. 1002, ¶ 145): *See, e.g., id.*, Fig. 3: Fig. 3 dicloses "Regional recommendations for **maximising safety of natalizumab**" (emphasis added); "Figure 3 shows recommendations for maximising the safety of natalizumab." (Ex. 1006, p. 6; Ex. 1002, ¶ 145)  The monitoring comprises "STRATIFY JCV," which involves monitoring for JCV serum antibody seroconversion, as shown in Fig. 4 (Ex. 1006, p. 7) below. (Ex. 1002, ¶ 145.) 
	2013 Tysabri Label (Ex. 1007)
	The 2013 Tysabri Product Label discloses that patients should be monitored for JCV antibody presence, patients that show signs or symptoms of PML should not take TYSABRI, and monitoring of PML risk through the TOUCH patient program assesses the risk of PML and improves the safety of the treatment (*see* pp. 1-2, 4-7, 14-15, 27-28, Medication Guide; Ex. 1002, ¶ 146):

	See, *e.g.*, Ex. 1007, p. 1 ("Risk factors for the development of PML include. . . presence of anti-JCV antibodies . . . . Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML . . . Because of the risk of PML, TYSBARI is available only through a restricted distribution program called the TOUCH Prescribing Program"). *See*, *e.g., id.*, p. 30, first page of the MEDICATION GUIDE ("Your risk of getting PML is higher if you: . . . have been exposed to John Cunningham Virus (JCV)"). *See*, *e.g., id.*, p. 31, second page of the MEDICATION GUIDE ("Because of your risk of getting PML while you receive TYSABRI, TYSABRI is available only through a restricted distribution program called the TOUCH Prescribing Program. To receive TYSABRI, you must talk to your doctor and understand the risks and benefits of TYSABRI and agree to follow all of the instructions in the TOUCH Prescribing Program").

Accordingly, Claim 1 of the '845 Patent is obvious in view of Alroughani and the 2013 Tysabri Product Label.

2. Dependent Claims 2-16 Are Obvious

Dependent Claims 2-16 of the '845 Patent are also obvious because they simply add other elements that were well known in the art.

Claim 2 through 4 pertain to treating MS patients with natalizumab. (Ex. 1002, ¶¶ 148-152.) Claim 2 requires that the treated disease is MS. (*Id.*, ¶ 149.) Claim 3 requires that the treated MS is selected from relapsing remitting, secondary progressive, primary progressive, and chronic progressive MS. (*Id.*,

¶ 150.) Claim 4 requires that the treated MS is relapsing remitting MS. (*Id.*, ¶ 151.) All of these claims are obvious in light of Ex. 1006 (Alroughani), Ex. 1007 (the 2013 Tysabri Label), and the knowledge of a POSA. (*Id.*, ¶¶ 150-151.) Alroughani and the 2013 Tysabri Label disclose treating MS patients (for e.g., relapsing remitting MS) with natalizumab. (Ex. 1006 (Alroughani), Fig. 3., pp. 1-2; Ex. 1007 (2013 Tysabri Label), pp. 1-2; Ex. 1002, ¶ 149-151.) When physicians treat patients with MS, they would know that MS can come in different forms, including relapsing remitting, secondary progressive, primary progressive, or chronic progressive MS. (Ex. 1002, ¶¶ 149-151.)

Claims 5 and 6 pertain to treating CD patients with natalizumab. (*Id.*, ¶¶ 153-155.) Claim 5 requires that the treated disease is inflammatory bowel disease. (*Id.*, ¶ 154.) Claim 6 requires that the treated inflammatory bowel disease is CD. (*Id.*) Both of these claims are obvious in light of Alroughani, the 2013 Tysabri Label, and the knowledge of a POSA. (*Id.*) Tysabri had been used to treat inflammatory bowel disease, such as CD, prior to 2019. (*Id.*) The 2013 Tysabri Label even specifically discloses treating CD patients with natalizumab. (Ex. 1007 (2013 Tysabri Label), pp. 1-2; Ex. 1002, ¶ 154.)

Claim 7 through 10 pertain to using clinical (neurological) or radiological (MRI) symptoms to monitor for PML. (Ex. 1002, ¶¶ 157-161.) Claim 7 requires that the monitoring for indicators of PML comprise testing for clinical and/or

radiologic symptoms of PML. (*Id.*, ¶ 157.) Claim 8 requires that the clinical testing for PML comprise testing for new or worsening neurological symptoms. (*Id.*, ¶ 158.) Claim 9 requires that the testing for new or worsening neurological symptoms comprise testing for central blindness, mental confusion, personality change, and/or dyskinesia. (*Id.*, ¶ 159.) Claim 10 requires that the radiological testing comprise performing a Gd-enhanced MRI scan. (*Id.*, ¶ 160.) These claims are also obvious in light of Alroughani, the 2013 Tysabri Label, and the knowledge of a POSA. (*Id.*, ¶¶ 157-161.) Even before 2006, it was common practice to use clinical or radiological measures to assess PML in patients. (*Id.*, ¶ 157.) Alroughani and the 2013 Tysabri label disclose using clinical symptoms to monitor for PML. (Ex. 1006 (Alroughani), pp. 1, 4, 7; Ex. 1007 (2013 Tysabri Label), p. 6; Ex. 1002, ¶¶ 157-159.) They also disclose using radiological symptoms to monitor for PML. (Ex. 1006 (Alroughani), pp. 1, 4, 6-7; Ex. 1007 (2013 Tysabri Label), p. 6; Ex. 1002, ¶¶ 157, 160.)

Claims 11 and 12 pertain to pharmaceutically effective amounts of natalizumab. (Ex. 1002, ¶¶ 162-165.) Claim 11 requires that the pharmaceutically effective amount is from 1 to 5 mg antibody per kilogram of body weight. (*Id.*, ¶ 163.) Claim 12 requires that the pharmaceutically effective amount is 300 mg. (*Id.*, ¶ 164.) Both claims are obvious in light of Alroughani, the 2013 Tysabri Label, and the knowledge of a POSA. (*Id.*, ¶¶ 163-165.) It was known that

natalizumab was used to treat patients at a pharmaceutically effective amount of 1 to 5 milligrams per kilogram of body weight or at 300 milligrams. (*Id.*, ¶¶ 163-165.) The 2013 Tysabri Label discloses administering specific pharmaceutically effective amounts of natalizumab (300 mg) to MS and CD patients. (Ex. 1007 (2013 Tysabri Label), pp. 1, 3; Ex. 1002, ¶ 164.) At common body weights, this would be 1 to 5 milligrams per kilogram. (Ex. 1002, ¶ 164.)

Claim 13 requires that the natalizumab is administered repeatedly at intervals from two to eight weeks, and is obvious in light of Alroughani, the 2013 Tysabri Label, and the knowledge of a POSA. (*Id.*, ¶¶ 166-168.) Natalizumab had been previously administered to patients at an interval between two to eight weeks. (*Id.*, ¶ 167.) For example, the 2013 Tysabri Label discloses administering natalizumab to patients at a four week interval. (Ex. 1007 (2013 Tysabri Label), pp. 1, 3; Ex. 1002, ¶ 167.)

Claim 14 requires that the monitoring of patients for PML comprises detecting the presence of JCV in the patient's CSF, and is obvious in light of Alroughani, the 2013 Tysabri Label, and the knowledge of a POSA. (Ex. 1002, ¶¶ 169-171.) Patients had been monitored for PML through the detection of JCV in the CSF, either via measuring JCV CSF DNA or antibodies, long before 2019. (*Id.*, ¶ 170.) Alroughani and the 2013 Tysabri Label both disclose testing for JCV

in CSF patient samples. (Ex. 1006 (Alroughani), p. 4; Ex. 1007 (2013 Tysabri Label), pp. 2, 6; Ex. 1002, ¶ 170.)

Claim 15 requires detecting the seroconversion and/or increasing titer of JCV antibodies in the patient's blood by measuring and comparing the amount of IgG JCV antibodies from multiple, serially-removed patient samples. (Ex. 1002, ¶¶ 172-174.) This claim, too, is obvious in light of Alroughani, the 2013 Tysabri Label, and the knowledge of a POSA. (*Id.*) Monitoring seroconversion or increasing levels of antibody titers was known to require comparing serum samples that were serially removed from the patient's blood, and IgG antibodies were an obvious class of antibodies to monitor. (*Id.*, ¶ 173.) Alroughani and the 2013 Tysabri Label disclose measuring JCV serum antibodies in patients periodically over time. (Ex. 1006 (Alroughani), pp. 4, 7, Fig. 4; Ex. 1007 (2013 Tysabri Label), p. 5; Ex. 1002, ¶ 173.)

Claim 16 requires that patients that test positive for seroconversion and/or increasing JCV antibodies and discontinue treatment with natalizumab be further treated by intravenous immunoglobulin therapy, plasmapheresis, and/or antiviral therapy. (Ex. 1002, ¶¶ 175-179.) This claim is also obvious. (*Id.*) Alroughani and the 2013 Tysabri Label disclose using plasma exchange (i.e., plasmapheresis) to treat patients previously administered with natalizumab. (Ex. 1006 (Alroughani), p. 4; Ex. 1007 (2013 Tysabri Label), p. 6; Ex. 1002, ¶ 177.)

Accordingly, the dependent claims of the '845 Patent are all obvious in view of the prior art.

X. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Parties-in-Interest

Pursuant to 37 C.F.R. § 42.8(b)(1), the real party-in-interest in this proceeding is Sandoz Inc. Polpharma SA is a privy of Sandoz Inc.

B. Related Matters

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner identifies the following related matters.

- None applicable

C. Lead and Back-Up Counsel and Service Information

Pursuant to 37 C.F.R. § 42.8(b)(3), Petitioner identifies the following Counsel (and a power of attorney accompanies this Petition).

Lead Counsel for Petitioner	Back-up Counsel for Petitioner
Matthew A. Chivvis Registration No.: 61,256 MORRISON & FOERSTER LLP 425 Market Street San Francisco, CA 94105-2482 Email: MChivvis@mofo.com Tel.: (415) 268-7000 Fax: (415) 268-7522	**Erik J. Olson** *pro hac vice* to be submitted MORRISON & FOERSTER LLP 755 Page Mill Road Palo Alto, CA 94304-1018 Email: EJOlson@mofo.com Tel.: (650) 813-5600 Fax: (650) 494-0792 **Eric C. Pai** *pro hac vice* to be submitted

	MORRISON & FOERSTER LLP 755 Page Mill Road Palo Alto, CA 94304-1018 Email: EPai@mofo.com Tel.: (650) 813-5600 Fax: (650) 494-0792

Pursuant to 37 C.F.R. § 42.8(b)(4), service information for lead and back-up Counsel is provided above. Petitioner consents to electronic service by email to Sandoz-Biogen-PGR@mofo.com.

The USPTO is authorized to charge any required fees, including the fee as set forth in 37 C.F.R. §42.15(a) and any excess claim fees, to Deposit Account No. **03-1952** referencing Docket No. **12935-00001.00**.

XI. CONCLUSION

Because there is a reasonable likelihood that Sandoz will prevail on its asserted grounds with respect to at least one claim, Sandoz requests that the Board institute PGR of claims 1-16 of the ’845 Patent.

Dated: July 29, 2022

Respectfully submitted,

/s/ Matthew A. Chivvis

Matthew A. Chivvis
Registration No.: 61,256
MORRISON & FOERSTER LLP
425 Market Street
San Francisco, CA 94105-2482
Email: MChivvis@mofo.com
Tel.: (415) 268-7000
Fax: (415) 268-7522

CERTIFICATION OF WORD COUNT (37 C.F.R. §42.24)

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for Post-Grant Review of U.S. Patent No. 11,292,845 contains, as measured by the word processing system used to prepare this paper, 18,009 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: July 29, 2022

By: */s/ Matthew A. Chivvis*
Matthew A. Chivvis
Registration No.: 61,256

CERTIFICATE OF SERVICE (37 C.F.R. §42.6(e)(4) and 42.205(a))

I hereby certify that a true and correct copy of the foregoing Petition for Post Grant Review of U.S. Patent No. 11,292,845 and supporting materials were served as of the below date by UPS, which is a means at least as fast and reliable as U.S. Express Mail, on the Patent Owner at the following correspondence address of record as listed on PAIR:

SQUIRE PB (Biogen Ma Inc.)
475 Sansome Street
Suite 1600
San Francisco, CA 94111-3356

Dated: July 29, 2022

By: */s/ Matthew A. Chivvis*

Matthew A. Chivvis
Registration No.: 61,256
MORRISON & FOERSTER LLP
425 Market Street
San Francisco, CA 94105-2482
Email: MChivvis@mofo.com
Tel.: (415) 268-7000
Fax: (415) 268-7522