Annex A

1. A method of evaluating a patient's risk of developing Progressive Multifocal Leukoencephalopathy (PML), the method comprising:

   i) determining, in a serum or plasma sample of the patient, an anti-JC Virus (JCV) antibody titer, wherein the anti-JCV antibody titer is determined by an ELISA assay comprising the following steps:

      a) forming a reaction mixture comprising an aliquot of sample and a substrate on which is disposed Highly Purified Viral-Like Particles (HPVLPs), and

      b) detecting the level of anti-JCV antibody bound to said substrate on which is disposed HPVLPs;

      wherein the anti-JCV antibody titer is expressed as an index value, wherein the index value is determined by normalizing an optical density (OD) value of the sample to a cut-off calibrator adjusted to have an nOD of 1, and a positive control is adjusted to have an nOD of 1.3; wherein the cut-off calibrator and positive control comprise a mixture of serum positive for anti-JCV antibodies and serum negative for anti-JCV antibodies, and wherein a negative control comprises anti-JCV antibody negative serum and has an nOD of 0.1; and

   ii) determining the patient to be at high risk of developing PML if the anti-JCV antibody index value is determined to be ⟩ 1.5.

~~2. The method of claim 1, wherein~~

~~the anti-JCV antibody titer is expressed as an index value for a first reaction mixture comprising a first aliquot of the serum or plasma sample of the patient and a substrate on which is disposed HPVLP; and~~

~~in a second step, a % inhibition indicative of a degree to which incubation with soluble-phase HPVLP reduces a level of unbound anti-JCV antibody that binds to HPVLP disposed on a substrate as compared to the first reaction mixture, is determined in a second reaction mixture comprising a second aliquot of the serum or plasma sample of the patient and a substrate on which is disposed HPVLP; and~~

~~determining the patient to be at high risk of developing PML if the anti-JCV antibody index value is determined to be ⟩ 1.5 and % inhibition is determined to be ⟩ 70%.~~

~~3.~~2. The method according to claim 1 ~~or claim 2~~, wherein the anti-JCV antibody titer ~~or % inhibition~~ is determined prior to an administration of natalizumab.

~~4.~~3. The method according to ~~any one of~~ claim~~s~~ 1 ~~to 3~~ or claim 2, wherein the anti-JCV antibody titer ~~or % inhibition~~ is determined after the patient has initiated a treatment with natalizumab.

~~5.~~4. The method according to any one of claims 1 to ~~4~~ 3, further comprising:

   a) determining if the patient has received treatment with natalizumab for longer than 24 months; or

b) determining if the patient has received a non-anti-VLA-4 immunosuppressant therapy, wherein the non-anti-VLA-4 immunosuppressant therapy is selected from mitoxantrone, methotrexate, azathioprine, cyclophosphamide, mycophenolate, anti-CD20 therapy, anti-CD11a therapy, and mycophenolate mofetil.

~~6.~~5. The method according to any one of claims 1 to ~~5~~ 4, wherein the anti-JCV antibody titer ~~or % inhibition~~ is retested at 6 month or 12 month intervals.

~~7.~~6. The method according to claim ~~6~~ 5, wherein an increase in anti-JCV antibody titer ~~or % inhibition~~ indicates an increase in the patient's risk of developing PML.

~~8.~~7. The method according to any one of claims 1 to ~~7~~ 6, wherein the patient has multiple sclerosis.

~~9.~~8. The method according to any one of claims 1 to ~~8~~ 7, wherein the patient determined to be at high risk of developing PML is determined to be at higher risk of developing PML if the patient has received natalizumab for longer than 24 months and has not previously received a non-anti-VLA-4 immunosuppressant therapy, wherein the non-anti-VLA-4 immunosuppressant therapy is selected from mitoxantrone, methotrexate, azathioprine, cyclophosphamide, mycophenolate, anti-CD20 therapy, anti-CD11a therapy, and mycophenolate mofetil.