Study Title:

Analysis of John Cunningham virus (JCV) antibody index in MS patients treated with teriflunomide (SWITCH-JCV)

This is an addendum to add JCV antibody index test for patients who had participated in the previously approved study: SWITCH (Switching Relapsing Multiple Sclerosis Patients Treated with Natalizumab at Risk for Progressive Multifocal Leukoencephalopathy to Teriflunomide: Is this safe and effective?)

Investigators & Site information:

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Funder:

Sanofi Genzyme

Protocol Addendum:

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Background rationale for the proposed addendum:

1. John Cunningham virus (JCV) is the responsible organism for the development of progressive multifocal encephalopathy (PML). Multiple sclerosis (MS) patients treated with natalizumab (NTZ), who have evidence of exposure to JCV have a significantly elevated risk, as high as 12/1000 patients, of developing PML, necessitating the elective transition of patients off NTZ.
2. JCV is a member of the polyoma virus family, and closely related to BK virus. BK virus has been found to be a significant threat to destroy transplanted kidneys and there is growing evidence that treatment with leflunomide, the pro-drug of teriflunomide (TFM) clears BKV from the kidney.
3. Our previously approved SWITCH protocol assessed the clinical efficacy of TFM in MS patients transitioned off NTZ solely because they have evidence of exposure to JCV, as determined by the presence of serum anti-JCV IgG. Previous work by other investigators has demonstrated a close correlation between positive anti-JCV antibody titers and the presence of active JCV infection.
4. Because there is evidence that JCV is closely related to its fellow polyoma virus BKV, and that BKV is cleared by treatment with the TFM pro-drug leflunomide, we propose to determine if treatment of the JCV antibody positive patients currently enrolled in the approved protocol results in reduction in, or reversion to negative, of the anti-JCV antibody titer as measured by the JCV antibody Index, a commercially available assay which is used internationally as the standard for evidence of JCV exposure in NTZ-treated patients.

Study Hypothesis:

TFM will inhibit JCV proliferation and there will be a reduction, or conversion to negative of the anti-JCV antibody Index in patients enrolled in this study being treated with TFM.

Study Objective:

To study the number of patients experiencing a reduction in the anti-JCV antibody Index value in patients who had received at least one dose of TFM during participation in the SWITCH protocol.

Study Population:

The 55 patients, who were taken off NTZ because of a positive anti-JCV ab titer and received at least one dose of daily 14 mg TFN as part of the SWITCH study, will be contacted to obtain written informed consent for a blood draw to collect a follow-up serum sample for the anti-JCV Index test.

Methods:

We propose, after signed informed consent, to draw a follow-up serum sample within 30 days of consent to determine if there has been a change in the anti-JCV ab Index value. Patients who consent to participate in this sub-study will have the blood draw at a local, contracted Quest Diagnostic Lab. The study coordinator will perform a chart review and use prior collected information from the SWITCH study to collect duration of TFM therapy and use of other DMT(s) if patient is no longer being treated with TMF. Each patient will be contacted via phone 5 ± 2 days after their blood draw to collect and assess adverse events. Analysis will include the number and percentage of patients reverting to negative titers, and the relationship between the total number of TFM doses received and/or duration of TFM therapy, and subsequent anti-JCV ab Index.

Statistical Analysis:

For patients who received at least one dose of TFM in the SWITCH protocol and consented to additional anti-JCV Index testing in the sub-study protocol, we will examine:

1. The number and percentage of patients reverting to negative anti-JCV antibody status
2. The number and percentage of patients having a reduced anti-JCV antibody index but still positive anti-JCV antibody status
3. The relationship between dosing of TFM and a) change in anti-JCV antibody index, and b) change in anti-JCV antibody status using correlation and regression analyses
4. AEs and SAEs will be summarized

Study Population:

Eligibility Criteria:

1. Must have been enrolled in the SWITCH protocol and received at least 1 dose of 14mg TFM during the study period.
2. Must be willing to sign written informed consent for this JCV sub-study and follow the protocol requirements.

Adverse Events:

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution. Pre-existing conditions which worsen during the study period are to be reported as AEs. The patient should be followed and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized.

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 5 ± 2 days following the blood draw or study discontinuation/termination, whichever is earlier.

Serious Adverse Events:

A serious Adverse Event (SAE) means any adverse event fitting the description above but also containing at least one of the following:

- Death
- Life threatening experience which places the patient at immediate risk of death from the event as it occurred.
- Full Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- Other significant medical event, per investigator judgment

AE and SAE Reporting:

Any occurrence of a SAE during the conduct of the study will be reported on a MedWatch Form FDA 3500 to the Providence Regional Research Regulatory Office via email or fax 503-215-6547 within 24 hours of the investigator learning of the event. The site will also report the SAE to the IRB of record per its policy, if the SAE meets the IRB reporting requirements. As the regulatory sponsor, the Providence Regulatory Manager will be responsible for submitting the MedWatch Form FDA 3500 to the funder.