The TOUCH™ Program and Risk Management Plan for the Administration of Natalizumab:

Updated Safety Results From the Use of Natalizumab in Patients With Relapsing Multiple Sclerosis and Crohn’s Disease

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Disclosures

♦ Dr. Bruce Sands is a consultant for Elan Pharmaceuticals and Biogen Idec, Inc.

♦ Drs. Gordon Francis and Gary S. Hogge are employees of Elan Pharmaceuticals, Inc.

♦ Drs. Glyn Belcher, Mariska Kooijmans, Richard Kim, Frances Lynn, and Carmen Bozic are employees of Biogen Idec, Inc.

♦ TYSABRI is a registered trademark and TOUCH is a trademark of Elan Pharmaceuticals, Inc.
Background and Objectives

Natalizumab, a humanized anti-a4 integrin monoclonal antibody, is indicated for:

- Inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn’s disease (CD)
  - with evidence of inflammation, and
  - who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNFα
- Relapsing forms of multiple sclerosis (MS)
Background and Objectives

- Report the outcomes from ongoing risk management plans to further evaluate the safety of natalizumab
  - TYSABRI® Outreach: Unified Commitment to Health (TOUCH™) Prescribing Program
  - Investigating Natalizumab Through Further Observational Research and Monitoring (INFORM) for CD
  - TYSABRI Global Observation Program in Safety (TYGRIS) for MS
  - Pregnancy registry

- Report data on utilization of natalizumab through the end of September 2008
TOUCH™ Prescribing Program, INFORM, TYGRIS, Pregnancy Registry

♦ TOUCH™ Prescribing Program is mandatory as part of the FDA Risk Minimization Action Plans (RiskMAP)
  – Ensure appropriate use of natalizumab and assess the incidence of serious opportunistic infections, including progressive multifocal leukoencephalopathy (PML), and malignancies

♦ CD INFORM and TYGRIS
  – 5 year observational studies of 2000 CD and 5000 MS patients
  – Determine incidence and pattern of serious and/or clinically significant infections, including PML, malignancies, & serious adverse events (SAEs), previous medical histories, efficacy

♦ Prospective patient registry to evaluate the outcomes of pregnancy in women with CD or MS
Update on Estimated Natalizumab Exposure

* Data are as of the end of September 2008

§ Includes ~700 clinical trial patients
TOUCH™: Natalizumab Exposure

♦ Approximately 3400 prescribing physicians in the United States across both indications

♦ 23,989 enrolled patients have received natalizumab treatment (> 99% for MS)
  – Enrolled patients have received a median of 9 natalizumab infusions (minimum = 1, maximum = 31)
  – 313 patients have received natalizumab for CD
    • 230 patients are currently being treated
    • 99 CD patients have received at least 4 infusions
    • 83 patients have discontinued therapy (27%)
TOUCH™: Medication History Over the Previous 12 months in CD Patients

Source: Prior 12-month therapy stated on TOUCH forms received launch-to-date
TYGRIS: Update

♦ As of 23 August 2008, 3905 patients have been enrolled
  – 72% were female and the mean age was 39 years
  – 93% had prior immunomodulatory or immunosuppressant therapy
♦ No unexpected safety issues
♦ Overall SAE incidence was 2.8%
  – Most common SAEs reported were hypersensitivity reactions (0.4%) and urinary tract infection (0.2%)
  – Incidence of SAEs, including hypersensitivity reactions and infections, was similar to that observed in clinical trials
Pregnancy Registry: Results

♦ 64 women have enrolled prospectively

♦ Pregnancy outcomes*
  – 29 pregnancies currently ongoing
  – 25 patients delivered 27 healthy babies, including
    • 5 premature births (2 with twins)
  – 7 spontaneous abortions
  – 2 elective terminations

♦ Pregnancy registry continues to actively recruit both CD and MS patients receiving natalizumab

* One patient declined to continue participation after enrollment with outcome unknown

Data reported are through 23 August 2008
PML Update

- There have been 3 confirmed cases of PML in MS patients receiving natalizumab in the commercial setting
  - 2 cases in EU (31 July 2008) and 1 case in US (29 October 2008)
  - All 3 patients underwent plasma exchange and are alive

- All cases confirmed based on detection of JC virus (JCV) DNA in CSF in the setting of clinical signs and symptoms and MRI findings consistent with diagnosis of PML
Algorithm for Diagnosis of PML

Clinical assessment of new neurological symptoms

If PML suspected due to clinical presentation and MRI not readily available, consider CSF to exclude PML prior to MRI

SUSPEND DOSING

MRI assessment

Cannot exclude PML

CSF assessment

PML unlikely

JCV not detected and low clinical suspicion

Dosing may be resumed*

JCV not detected and high clinical suspicion

Repeat assessment

JCV detected

Treat as PML

*Natalizumab dosing should be restarted only if the diagnosis of PML is excluded and if deemed appropriate for the ongoing treatment of CD. Algorithm is modified based on Kappos L, et al. Lancet Neurol 2007;6:431-441.
Conclusions

♦ >48,000 patients worldwide have received natalizumab

♦ PML continues to appear to be a rare adverse event associated with natalizumab treatment
  – Highlight the importance of the clinical vigilance in monitoring for early signs and symptoms of PML for early detection

♦ Potential strategies to mitigate the risk of PML include
  – Identifying patients at risk of developing PML
  – Monitoring patients to detect PML prior to the development of clinical signs and symptoms
  – Treatments to limit disability and prevent death from PML (e.g., plasma exchange and antiviral therapies [mefloquine])

♦ Preliminary data from these studies
  – Support the favorable benefit-risk profile of natalizumab and suggest a similar safety profile to that seen in previous clinical studies
Backup Slides
PML in Post Marketing: Case 1

- Male 37 years, diagnosed 2006 in EU with aggressive MS
- Naïve to disease-modifying therapies
- Natalizumab monotherapy for ~17 months with very good response
- Slowly progressive focal twitching and weakness of the left arm over a period of 2.5 months
- MRI: Subtle T2 hyperintensity in the pre-central gyrus that slowly progressed during this time
- First CSF negative, second CSF positive for JC virus
- Natalizumab discontinued and patient received 5 plasma exchanges (PE) in 10 days, patient developed IRIS
- Current status: clinically stable and walking with assistance
PML in Post Marketing: Case 2

- Male 52 years, diagnosed 1992 in EU with Relapsing Remitting MS
- 5-year history of azathioprine along with intervals of IFN
- Natalizumab monotherapy for approximately 14 months
- Left hemiparesis initially treated with steroids for presumed MS relapse
- Symptoms, which included early mild cognitive changes, progressed over approximately 2 months, leading to hospitalization
- MRI: 2 large lesions atypical of MS predominantly in white matter, minimal Gd enhancement
- CSF positive for JC virus
- Natalizumab discontinued and the patient started plasma exchange and immunoadsorption, patient developed IRIS
- Current status: clinically stable, hospitalized
PML in Post Marketing: Case 3

♦ Female 59 years, diagnosed with MS in 2001
♦ Multi-year history of treatment with β-interferons, glatiramer acetate, and methotrexate
♦ Natalizumab monotherapy for approximately 14 months
♦ Initial symptoms included subjective memory problems, fatigue, hot flashes (consistent with previous MS flares), speech deterioration, and worsening gait
♦ Progressed to expressive aphasia, slurred speech, worsened memory problems, some numbness in the legs, subjective gait problems
♦ MRI showed multiple non-enhancing lesions, consistent with a diagnosis of PML and the CSF tested positive for JC virus
♦ Patient underwent plasma exchange and treatment with mefloquine, an experimental treatment option for PML
♦ Current status: clinically stable, under care of treating physician
Overview of recent PML cases

♦ Male 37 years, diagnosed 2006 in EU with aggressive MS
  - Naïve to disease-modifying therapies began natalizumab monotherapy for ~17 months
  - Symptoms: slowly progressive focal twitching/weakness of left arm over ~ 2.5 months. MRI: subtle T2 hyperintensity in the pre-central gyrus that slowly progressed, CSF: 1st CSF - for JCV, 2nd +
  - Natalizumab d/c, patient received 5 plasma exchanges (PE) in 10 days, developed IRIS, clinically stable and walking with assistance

♦ Male 52 years, diagnosed 1992 in EU with relapsing remitting MS
  - 5-year Hx of azathioprine and β−IFNs, natalizumab monotherapy for ~14 months
  - Symptoms: Left hemiparesis initially treated with steroids for presumed MS relapse early mild cognitive changes, progressed over ~ 2 months, leading to hospitalization. MRI: 2 large lesions atypical of MS predominantly in white matter, minimal Gd enhancement, CSF: + for JCV
  - Natalizumab d/c, started PE, immunoadsorption, developed IRIS, clinically stable, hospitalized

♦ Female 59 years, diagnosed with MS in 2001
  - Multi-year Hx β−IFNs, glatiramer acetate, & methotrexate, natalizumab monotherapy for ~14 months
  - Symptoms: initial symptoms included subjective memory problems, fatigue, hot flashes (consistent with previous MS flares), speech deterioration, and worsening gait, progressed to expressive aphasia, slurred speech, worsened memory problems, some numbness in the legs, subjective gait problems, MRI: multiple non-enhancing lesions consistent with PML, CSF: + for JCV
  - Natalizumab d/c, PE and Tx with melfloquine, clinically stable, under care of treating physician
Triad for Monitoring and Diagnosis of PML

1. Clinical Vigilance
   - MRI Assessment
   - CSF Assessment
Algorithm for Diagnosis of PML

♦ Clinical vigilance most important method of monitoring for PML
  – Withhold natalizumab until PML can be excluded
  – A thorough neurological assessment should be performed at first presentation of new/worsening clinical signs/symptoms

♦ If neurological assessment cannot rule out PML, a cranial MRI scan with contrast should be performed
  – MRI scan should be compared with previous MRI scan(s), if available
  – MRI alone can not exclude PML; repeat if clinical suspicion remains

♦ If clinical symptoms or MRI lesions remain suspicious for PML, CSF testing for JCV by PCR should be conducted
  – In early PML, CSF can be negative for JCV DNA despite clinical and radiographic findings
  – If JCV not detected, repeat test if clinical suspicion remains
Can this algorithm be shown as a diagram instead?

Bruce E. Sands, 11/14/2008
Immune Reconstitution Syndrome (IRS) or Immune Reconstitution Inflammatory Syndrome (IRIS)

♦ Condition seen in some AIDS or immunosuppression cases
  – Characterized by initial immune system recovery, followed by an overwhelming inflammatory response to the previously acquired opportunistic infection, that paradoxically may make the symptoms of the initial infection worse

♦ If the CD4 count rapidly increases (due to effective treatment of HIV or removal of other causes of immunosuppression), a sudden increase in the inflammatory response may produce a worsening of damage to the infected tissue

♦ Though IRIS can be potentially dangerous, it may also be indicative of potential long-term recovery from the opportunistic infection


Plasma Exchange: Background

♦ Immune reconstitution improves outcomes in immunosuppressed patients who develop PML\textsuperscript{1,2}

♦ Plasma exchange is an established method for removal of large molecules from the peripheral circulation\textsuperscript{3}

♦ Plasma exchange may lead to immune reconstitution and may improve prognosis in the event of PML by accelerating removal of natalizumab from the peripheral circulation

Model Simulation of 5 Plasma Exchange Sessions

- **Final natalizumab infusion**
- **PLEX sessions**

- **Plasma Natalizumab Concentration (μg/mL)**
- **α4-integrin Receptor Binding (%)**

- 90% CI, α4-integrin receptor binding
- 90% CI, natalizumab concentrations
- Mean α4-integrin receptor binding
- Mean natalizumab concentrations
- <1 μg/mL

Bhupendra O. Khatri et al. Presentation #S22.005. 60th Annual Meeting of the American Academy of Neurology (16 April 2008).
Plasma Exchange: Conclusions

- Plasma exchange was effective at accelerating the normal decline of serum natalizumab concentration over time in all patients.

- Decreases in serum natalizumab concentrations to undetectable or very low levels (<1 μg/mL) resulted in subsequent decreases in \( \alpha 4 \)-integrin receptor saturation.

- In a pilot study in MS patients receiving natalizumab:
  - Plasma exchange was generally well tolerated.
  - There were no study discontinuations due to adverse events.
  - All patients resumed scheduled infusions of natalizumab as part of their MS therapy.

- Plasma exchange may be a suitable technique for rapidly removing natalizumab from the peripheral circulation in rare, but clinically appropriate, situations.

Bhupendra O. Khatri et al. Presentation #S22.005. 60th Annual Meeting of the American Academy of Neurology (16 April 2008).
CD INFORM: INVESTIGATING NATALIZUMAB THROUGH FURTHER OBSERVATIONAL RESEARCH AND MONITORING

♦ FDA Post-Approval Commitment: 5 year observational study of 2000 CD patients treated with natalizumab
  – Initiated in June 2008

♦ Objectives
  – 1° - Determine the incidence and pattern of serious and/or clinically significant infections, malignancies, and other serious adverse events (SAEs) in patients with CD treated with natalizumab
  – 2° - Evaluate disease severity over time in CD patients treated with natalizumab based on changes in the Harvey-Bradshaw Index (HBI)

♦ Other data collected include
  – JC Viral DNA, or other laboratory testing for opportunistic infections
  – ImmunKNOW assay on a subset of patients to assess the state of their immune function
TYGRIS
TYSABRI Global Observation Program in Safety

- Global observational study to evaluate the long-term safety of natalizumab in a clinical practice setting in MS
  - Largest long-term safety study of any MS therapy ever conducted
- Expected enrollment: ~5000 patients with MS worldwide
- Patients evaluated at baseline and every 6 months for 5 yrs
- Information collected
  - Medical / MS history
  - Prior use of immunomodulatory, antineoplastic, or immunosuppressive agents
  - All serious adverse events (SAEs), including PML and other serious opportunistic infections (OIs), and malignancies
Pregnancy Registry: Background and Methods

♦ A patient registry to evaluate the outcomes of pregnancy in women with CD or MS exposed to natalizumab
  – Pregnant women who were exposed to natalizumab at any time during the 3 months before conception or during pregnancy
  – Pregnancies where the outcome is unknown (prospective reports)
  – Pregnancy reports where the outcome is known (retrospective reports) will be collected and analyzed separately

♦ The following information will be collected within 4 weeks of the estimated date of delivery
  – Pregnancy outcome
  – Infant characteristics (gestational age, gender, weight, length, Apgar scores, and birth order for multiple births)
  – Description or attribution of any birth defect