Final Minutes
Joint Gastrointestinal Drugs Advisory Committee (GIDAC) &
Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting
July 31, 2007

Food and Drug Administration
Center for Drug Evaluation and Research

Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland

Summary Minutes of the joint meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on July 31, 2007.

On July 31, 2007 the committee discussed the efficacy and safety of TYSABRI (natalizumab) biological license application (BLA) 125104/33, Biogen Idec, Inc., for patients with moderately to severely active Crohn's disease.

These Summary Minutes for the July 31, 2007 joint meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee were approved on August 21, 2007.

I certify that I attended the July 31, 2007 joint meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____//S//_____
Victoria Ferretti-Aceto, Pharm.D.
Executive Secretary

_____//S//_____
David Sachar, M.D.
Chair

Final Minutes
Joint Gastrointestinal Drugs Advisory Committee (GIDAC) &
Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting
July 31, 2007

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at: http://www.fda.gov/ohrms/dockets/ac/cder07.htm#gdac or http://www.fda.gov/ohrms/dockets/ac/cder07.htm#DrugSafetyRiskMgmt

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Gastrointestinal Drugs Advisory Committee & the Drug Safety and Risk Management Meeting Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 31, 2007 at the Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and the sponsor (Biogen Idec, Inc.). The meeting was called to order by Dr. David B, Sachar, M.D. (Committee Chair); the conflict of interest statement was read into the record by Victoria Ferretti-Aceto (Designated Federal Official). There were approximately 150 persons in attendance. There were 8 speakers for the Open Public Hearing speakers.

Issue: The committee discussed the efficacy and safety of TYSABRI (natalizumab) biological license application (BLA) 125104/33, Biogen Idec, Inc., for patients with moderately to severely active Crohn's disease.

Attendance:
Gastrointestinal Drugs Advisory Committee Members Present (Voting):
David B. Sachar, M.D.; Lin Chang, M.D.; Pankaj Jay Pasricha, M.D.

Drug Safety and Risk Management Advisory Committee Members Present (Voting):
Richard Platt, M.D., M.Sc.; Terry C. Davis, Ph.D.; Sean Hennessy, Pharm.D., Ph.D.; Judith M. Kramer, M.D., M.S.; Timothy S. Lesar, Pharm.D.

Special Government Employee Consultants (Voting):
James R. Couch, Jr., Ph.D.; Ruth S. Day, Ph.D.; Marilyn S. Eichner; Jacqueline S. Gardner, Ph.D., M.P.H.; Carol Lee Koski, M.D.; Alexander H. Krist, M.D.; Arthur Levin, M.P.H.; Robert A. Levine, M.D.; James Neaton, Ph.D.; Lewis S. Nelson, M.D.; Margo Smith, M.D.

Non-voting Participants:
Jose M. Vega, M.D. (Industry Representative)

Gastrointestinal Drugs Advisory Committee Members Not Present:
Alan Lewis Buchman, M.D.; Michael S. Epstein, M.D.; Kenneth Louis Koch, M.D.; Gary Roth Lichtenstein, M.D.; Suzanne Rosenthal

Drug Safety and Risk Management Advisory Committee Members Not Present:
Sander Greenland, Dr. P.H.; Susan Heckbert, M.D., Ph.D.; Annette Stemhagen, Dr. P.H. (Industry Representative)

Final Minutes
Joint Gastrointestinal Drugs Advisory Committee (GIDAC) &
Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting
July 31, 2007

FDA Participants (Non-Voting):
Mark Avigan, M.D., C.M.; Julie Beitz, M.D.; Gerald Dal Pan, M.D., M.H.S.; Joyce Korvick, M.D.; Sandra Kweder, M.D.

Designated Federal Official:
Victoria Ferretti-Aceto, Pharm.D., R.Ph.

Open Public Hearing Speakers:
Douglas Wolf, M.D.-Atlanta Gastrointestinal Associates
Jane Present-Foundation for Research in IBD
Bruce Sands, M.D., M.S.-Massachusetts General Hospital Crohn's & Colitis Center
Stephen Hanauer, M.D.
Lisa Casanova
Melissa Arnett
Michael Gaspari, M.D.

The agenda was as follows:

Call to Order and Introductions	**David Sachar, M.D. (Chair)** Gastrointestinal Drugs Advisory Committee (GIDAC)
Conflict of Interest Statement	**Victoria Ferretti-Aceto, Pharm.D.** Designated Federal Official, GIDAC/DSaRM
Introduction/Background	**Joyce A. Korvick, M.D., M.P.H.** Director, Division Gastroenterology Products, CDER/FDA

Sponsor Presentation – Biogen Idec, Inc.:

Introduction	**David Feigal, M.D., MPH** Senior Vice President, Regulatory Affairs, Biometrics and Global Pharmacovigilance & Risk Management, Elan Pharmaceuticals, Inc.
Crohn's Disease	**William Sandborn, M.D.** Professor of Medicine Gastroenterology Mayo Clinic
Efficacy Data	**Stephen Jones, MBBS** Director, Clinical Development Elan Pharmaceuticals, Inc.
Safety Data	**Gordon Francis, M.D.** Senior Vice President, Clinical Development Elan Pharmaceuticals, Inc.
Risk-Management Plan	**William Maier, MPH, PhD** Senior Director, Epidemiology Elan Pharmaceuticals, Inc.

Clinical Perspective	**William Sandborn, M.D.** Professor of Medicine Gastroenterology Mayo Clinic
	Questions from the Committee
	Break

FDA Presentation :

Progressive Multifocal Leukoencephalopathy	**Margo Smith, M.D.** Associate Program Director, Department of Medicine Washington Hospital Center
Clinical Review	**Anil Rajpal, M.D.** Medical Reviewer Division of Gastroenterology Products, CDER/FDA
Postmarketing Safety and RiskMAP	**Claudia Karwoski, Pharm.D**. Risk Management Team Leader OSE, CDER/FDA
	Questions from the Committee
	Lunch
	Open Public Hearing
	Committee Discussion
	Questions to the Committee
	Adjournment

Questions to the Committee:

1. The proposed indication states that "Tysabri is indicated for inducing and maintaining sustained response and remission, and eliminating corticosteroid use in patients with moderately to severely active Crohn's disease with inflammation, as evidenced by elevated CRP level or another objective marker".

   Do the available data support the efficacy of Tysabri in patients with moderately to severely active Crohn's disease (CD) with inflammation, as evidenced by elevated CRP level or another objective marker:

   a. For the induction of sustained response and remission?
   b. For the maintenance of sustained response and remission?
   c. In eliminating corticosteroid use?
   d. Is elevated CRP level a logical or clinically meaningful restriction?

- ***Most of the Committee agreed that there was at least a modest response in the populations studied, with evidence showing stronger support for maintenance than for induction of response and remission.***
- ***There were concerns expressed by the Committee regarding the lack of available data on the safety of long term exposure to this product.***
- ***Elevated CRP in these trials may have selected patients who were less likely to have a placebo response. Most Committee members indicated that CRP level alone is not reliable as an indicator of disease course, so that other objective laboratory and clinical markers should also be acceptable as evidence of active inflammation.***

(See transcript for detailed discussions)

2. The proposed indication also states that Tysabri is "generally recommended for patients who have had an inadequate response to, or are unable to tolerate conventional Crohn's disease therapies."

   a. Do the available data support the efficacy of Tysabri in this patient population?

   b. Is there a subset of the CD population in which the increased risk of PML in patients taking Tysabri might be acceptable? Please discuss the following candidate CD patient populations:

      1) Inadequate response to other available commonly used individual and combined treatments (5-ASAs, steroids, azathioprine, 6-MP, methotrexate, infliximab, adalimumab). Specify which individual or combined treatments.
      2) Specific level of disease severity. Specify criteria.
      3) Other disease characteristics or potential benefits that make the risks acceptable. Specify what these would be.

c. For the subgroups designated above please discuss:

1) Whether these subgroups have been adequately identified and described in the clinical studies
2) Whether the currently available exploratory analysis of those subgroups provides adequate support for your recommendation.

- ***Many on the Committee agreed that it would be best to restrict use of this product to patients who have had an inadequate response to all available therapies (specifically including immunomosuppressants, steroids and TNF-alpha inhibitors, or who are intolerant to these therapies, or for whom these therapies are contraindicated). Almost all felt, however, that disease requiring prolonged high-dose steroids or prolonged cyclosporine for control should not be considered adequately responsive.***
- ***Concerns were expressed by the Committee that this product should not be used in certain patients, including those at risk for opportunistic infections. In addition, there was concern that concomitant use of immunomodulators or prolonged steroid administration should be avoided.***
- ***Most of the Committee expressed concern that the sponsor's proposed indication statement was insufficiently specific in defining inadequate response and conventional therapies.***

(See transcript for detailed discussion)

3. Are there sufficient data to support maintenance therapy of CD with monotherapy versus combined treatment with corticosteroids and/or immunosuppressants?

- ***The Committee found no evidence for lesser efficacy of monotherapy and therefore agreed that concomitant immunomodulator or prolonged steroid therapy should be discouraged.***

(See transcript for detailed discussions)

4a. What risks associated with the use of Tysabri in Crohn's disease are important for a risk-benefit assessment (e.g. PML, hypersensitivity, infection, malignancy, other)?

- ***Most of the Committee agreed that all of the above mentioned risk factors should be considered in the risk-benefit assessment. Additional risks identified were: 1) opportunistic infections, especially in immunosuppressed populations, 2) liver injury, and 3) overall mortality.***

4b. How might these risks be impacted by current CD treatment strategies for induction and maintenance (e.g. 'step-up', 'top-down", steroid sparing)?

The Committee did not address this question directly, except by explicitly ruling out the use of Tysabri anywhere but late in the therapeutic sequence.

(See transcript for detailed discussions)

5. Considering the currently available data, and taking into account the preceding discussion of specific populations, proposed use, and anticipated risks, are there additional:

a. Efficacy data (studies) that should be obtained prior to approving Tysabri for Crohn's disease? If so, please describe.

Some of the committee members commented that the efficacy and safety data are not robust and that additional studies should be conducted in the populations for whom the benefits are expected to outweigh the risks. However, most of the committee stated that they did not believe any additional studies should be required for approval.

b. Safety data (studies) that should be obtained prior to approving Tysabri for Crohn's disease? If so, please describe.

The committee expressed concern that existing studies do not have sufficient numbers or follow-up periods to quantitate the risks that are of greatest concern, especially PML, opportunistic or reactivated latent infections, and liver toxicity. The committee agreed therefore that follow-up must take place throughout the post-marketing period for risk/benefit considerations.

(See transcript for detailed discussion)

6. Commonly used therapies for CD include corticosteroids, immunosuppressants, and/or biological agents (e.g. TNF-alpha blockers). If Tysabri were to be approved for Crohn's disease:

a. Should treatment with Tysabri be prohibited based on duration of prior use and/or total doses of these therapies?
   1) What should the washout period be for prior use? Respond for each of the therapies.

b. What should the period of concomitant use of steroids be?
   1) Is six months for steroid tapering acceptable?
   2) What should the maximum period of concomitant steroid use be for CD flares?

c. Do you recommend use of any other concomitant therapy besides steroids for CD flares (e.g. immunosuppressants, or anti-TNF agents)?

- ***Most of the Committee felt that a period of six months was appropriate for steroid withdrawal and that failure to achieve this goal was an indication to discontinue Tysabri.***

- ***Likewise, they felt that a single course of steroids might be reasonable to control a single flare while on Tysabri, but that repeated flares should also provide indication for stopping this drug.***

(See transcript for detailed discussions)

7. If Tysabri were to be approved for Crohn's disease, what specific requirements, if any, would you recommend for CD patients, either upon initiation of Tysabri or for ongoing monitoring? In particular, please discuss:

   a. MRI of the brain
   b. General physical exam
   c. Full neurologic exam (by a neurologist)
   d. Brief physical function questionnaire
   e. Cognitive testing (e.g. brief screening questionnaire, more quantitative assessments, etc)
   f. JC virus assay in serum and/or cerebrospinal fluid

- ***Many on the Committee agreed that for CD patients, baseline general physical exams, including full neurological exams (with cognitive testing) would be most appropriate. Baseline MRIs and JC virus assay of body fluids were not considered helpful, although these studies should be performed in patients with newly emerging neurologic symptoms.***

(See transcript for detailed discussion)

8. Based on currently available efficacy and safety data, should Tysabri be approved for the treatment of Crohn's disease, assuming that an effective risk management plan is in place? Specify for which CD patient population Tysabri should be indicated.

YES: 12 NO: 3 ABSTAIN: 2

- ***The consensus was that the product should only be approved for use in patients who did not have an adequate response to all available therapies for CD, are intolerant to these therapies, or for whom other therapies are contraindicated.***
- ***It was generally agreed by all members of the committee that there is a need for continued, intensive post-marketing surveillance and continued restricted distribution.***

(See transcript for detailed discussion)

Final Minutes
Joint Gastrointestinal Drugs Advisory Committee (GIDAC) &
Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting
July 31, 2007

The Committee adjourned at approximately 5:45 P.M.