



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)**  
**Joint Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) and the**  
**Drug Safety and Risk Management Advisory Committee (DSaRM)**  
**Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland**  
**FINAL AGENDA**  
**July 31, 2007**

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*The Committees will discuss 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.*

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8:00 a.m.	<b>Call to Order and Introductions</b>	<b>David Sachar, M.D. (Chair)</b> Gastrointestinal Drugs Advisory Committee (GIDAC)
8:10 a.m.	<b>Conflict of Interest Statement</b>	<b>Victoria Ferretti-Aceto, Pharm.D.</b> Designated Federal Official, GIDAC/DSaRM
8:15 a.m.	<b>Introduction/Background</b>	<b>Joyce A. Korvick, M.D., M.P.H.</b> Director, Division Gastroenterology Products, CDER/FDA

**SPONSOR PRESENTATIONS:**

8:20 a.m.	<b>Introduction</b>	<b>David Feigal, M.D., MPH</b> Senior Vice President, Regulatory Affairs, Biometrics and Global Pharmacovigilance & Risk Management Elan Pharmaceuticals, Inc.
8:25 a.m.	<b>Crohn's Disease</b>	<b>William Sandborn, M.D.</b> Professor of Medicine Gastroenterology Mayo Clinic
8:35 a.m.	<b>Efficacy Data</b>	<b>Stephen Jones, MBBS</b> Director, Clinical Development Elan Pharmaceuticals, Inc.
8:55 a.m.	<b>Safety Data</b>	<b>Gordon Francis, M.D.</b> Senior Vice President, Clinical Development Elan Pharmaceuticals, Inc.
9:20 a.m.	<b>Risk-Management Plan</b>	<b>William Maier, MPH, PhD</b> Senior Director, Epidemiology Elan Pharmaceuticals, Inc.
9:40 a.m.	<b>Clinical Perspective</b>	<b>William Sandborn, M.D.</b> Professor of Medicine Gastroenterology Mayo Clinic
9:50 a.m.	<b><i>Questions to the Sponsor</i></b>	
10:10 a.m.	<b>Break</b>	

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**FDA PRESENTATIONS:**

10:25 a.m.	<b>Progressive Multifocal Leukoencephalopathy</b>	<b>Margo Smith, M.D.</b> Associate Program Director, Department of Medicine Washington Hospital Center
10:40 am	<b>Clinical Review</b>	<b>Anil Rajpal, M.D.</b> Medical Reviewer Division of Gastroenterology Products, CDER/FDA
11:15 a.m.	<b>Postmarketing Safety and RiskMAP</b>	<b>Claudia Karwoski, Pharm.D.</b> Risk Management Team Leader OSE, CDER/FDA
11:35 a.m.	<i>Questions to the FDA</i>	
12:00 p.m.	<b>Lunch</b>	
1:00 p.m.	<b>Open Public Hearing</b>	
2:30 p.m.	<i>Questions to the Committee and Recommendations</i>	
3:00 p.m.	<b>Break</b>	
3:15 p.m.	<i>Questions to the Committee and Recommendations</i>	
5:00 p.m.	<b>Adjourn</b>	

**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**GASTROINTESTINAL DRUGS ADVISORY COMMITTEE**  
**Member Roster**

**CHAIR**

**David B. Sachar, M.D.**

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**Food and Drug Administration**  
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**Member Roster**

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**\*Consumer Representative**

**\*\* Industry Representative**



**Joint Meeting of the Gastrointestinal Drugs Advisory Committee and the  
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**July 31, 2007**

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

***Participant Roster***

**GASTROINTESTINAL DRUGS ADVISORY COMMITTEE**

**MEMBERS PRESENT (Voting)**

**David B. Sachar, M.D. (Chair)**

Director Emeritus  
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Annenberg Building, Room 5-207  
New York, NY

**Pankaj Jay Pasricha, M.D.**

Chief, Division of Gastroenterology and  
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4.106 McCullough Building  
301 University Boulevard  
Galveston, TX

**Lin Chang, M.D.**

Co-Director, Center for Neurovisceral Sciences  
and Women's Health  
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**(Non-voting)**

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**MEMBERS PRESENT (Voting)**

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**Joint Meeting of the Gastrointestinal Drugs Advisory Committee and the  
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July 31, 2007**

*Participant Roster (continued)*

**TEMPORARY VOTING MEMBERS**

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**July 31, 2007**

***Tysabri (natalizumab) for Crohn's Disease***

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

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## *Questions to the Advisory Committee*

4. a. 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)?  
b. How might these risks be impacted by current CD treatment strategies for induction and maintenance (e.g. 'step-up', 'top-down', steroid sparing)?
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.
  - b. Safety data (studies) that should be obtained prior to approving Tysabri for Crohn's disease? If so, please describe.
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)?
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
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.

## **PUBLIC CONDUCT DURING FDA ADVISORY COMMITTEE MEETINGS**

The FDA would like to ensure that advisory committee meetings proceed in an orderly fashion, are conducted in a safe and secure environment, that the right of free speech is protected, and that the ability of FDA Advisory Committees and Panels to accomplish their objectives is not disrupted. Therefore, the following procedures will be followed:

- An interested person who wishes to be assured of the right to make an oral presentation during the Open Public Hearing portion of an advisory committee meeting should register with FDA before the meeting. See 21 CFR 14.29(b). Those who have not registered before the meeting will only be invited to speak at the discretion of the Chair, and should submit their request to FDA officials at the registration desk on the day of the meeting.
- Open Public Hearing participants who are designated to speak may be questioned only by the Chair or other members of the Committee.
- Audience members may not present comments or questions to the Committee unless recognized by the Chair.
- Attendees may be subject to security screening, such as presenting identification, passing through metal detectors, and inspection of briefcases, packages, etc.
- Attendees at the meeting are asked to maintain order and not display behavior that is disruptive to the meeting (i.e., shouting from the audience, loud outbursts).
- The committee Chair or Designated Federal Official will note on the record any disruptive behavior and will ask the person to cease the behavior or else leave the meeting room.
- We ask that attendees not approach the advisory committee table area before, during, or after the meeting without permission from a Designated Federal Official/Executive Secretary.

