

**Summary Minutes of the
Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
Holiday Inn Washington/College Park, College Park, Maryland**

November 17, 2011

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

**These summary minutes for the Gastrointestinal Drugs Advisory Committee meeting of
the Food and Drug Administration were approved on January 16, 2012.**

**I certify that I attended the November 17, 2011 meeting of Gastrointestinal Drugs
Advisory Committee of the Food and Drug Administration and that these minutes
accurately reflect what transpired.**

_____/s/_____
Minh Doan, Pharm.D.
Acting Designated Federal Officer, GIDAC

_____/s/_____
Jean-Pierre Raufman, M.D.
Committee Chair, GIDAC

The Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 17, 2011, at the Holiday Inn Washington, DC/College Park, The Ballroom, 10000 Baltimore Avenue, College Park, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA. The meeting was called to order by Jean-Pierre Raufman, M.D. (Committee Chairperson); the conflict of interest statement was read into the record by Minh Doan, Pharm.D. (Acting Designated Federal Officer). There were approximately 110 persons in attendance. There were no registered speakers for the Open Public Hearing session.

Issue: The committee discussed recommendations to the Agency on the design and size of premarketing cardiovascular safety development programs necessary to support approval of products in the class of serotonin (5-hydroxytryptamine) receptor 4 (5HT4) agonists for the proposed indications of chronic idiopathic (of unknown cause) constipation (CIC), constipation predominant irritable bowel syndrome (IBS-C), gastroparesis, and gastroesophageal reflux disease that does not respond to a proton pump inhibitor.

Attendance:

Gastrointestinal Drugs Advisory Committee Members Present (Voting):

Garnet Anderson, Ph.D., William Hasler, M.D., Atul Kumar, M.D., Jean-Pierre Raufman, M.D. (Chairperson), Steven Solga, M.D., Gagan Sood, M.D.

Acting Industry Representative to the Gastrointestinal Drugs Advisory Committee (Non-Voting):

Jonathan Fox, M.D., Ph.D. (Acting Industry Representative)

Special Government Employee Consultants (Temporary Voting Members):

Henry R. Black, M.D., John Bloom, V.M.D., Ph.D., Christopher Granger, M.D., F.A.C.C., Martin L. Greene, M.D., Sanjay Kaul, M.D., Tracy Matson (Patient Representative), Jeffrey Richig, D.V.M., Rachel Rosen, M.D., Bo Shen, M.D., F.A.C.G.

Regular Government Employee Consultants (Temporary Voting Members):

Diane Bild, M.D., M.P.H., Jonathan Kaltman, M.D., Michael Lauer, M.D., Yves Rosenberg, M.D., M.P.H., Brennan Spiegel, M.D., John R. Teerlink, M.D., F.A.C.C., Udho Thadani, M.D., M.R.C.P.

Gastrointestinal Drugs Advisory Committee Members Not Present:

Ronald Fogel, M.D., Jill Sklar (Consumer Representative)

FDA Participants (Non-Voting):

Joyce Korvick, M.D., M.P.H., Robert Fiorentino, M.D., M.P.H., Aisha Johnson Peterson, M.D., M.P.H., Sue-Chih Lee, Ph.D., Mat Soukup, Ph.D.

Acting Designated Federal Officer:

Minh Doan, Pharm.D.

Open Public Hearing Speakers:

None

The agenda was as follows:

Call to Order and Introduction of
Committee

Jean-Pierre Raufman, M.D.
Committee Chairperson,

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|---|--|
| | Gastrointestinal Drugs Advisory Committee (GIDAC) |
| Conflict of Interest Statement | Minh Doan, Pharm.D. Acting Designated Federal Officer |
| <u>FDA Presentations</u> | |
| Introductions/Opening Remarks | Joyce Korvick, M.D., M.P.H. Deputy Director for Safety, Division of Gastroenterology and Inborn Errors Products (DGIEP), Office of Drug Evaluation III (ODE III), Office of New Drugs (OND), CDER, FDA |
| Background and Historical Overview | Aisha Peterson Johnson, M.D., M.P.H. Medical Officer, DGIEP, ODE III OND, CDER, FDA |
| <u>Sponsor's Presentations</u> | <u>Johnson & Johnson Pharmaceutical Research & Development (J&JPRD), LLC</u> |
| General Overview | Sheldon Sloan, M.D., M.Bioethics Internal Medicine Portfolio Leader Established Products, J&JPRD |
| Non-clinical Cardiovascular Safety | Rob Towart, B.Sc., Ph.D., MRQA Director Licensing and Brand Support Center of Excellence for Cardiovascular Safety, J&JPRD |
| Clinical Pharmacology | Erik Mannaert, Ph.D. Senior Director, Clinical Pharmacology Therapeutic Area Head, Established Products J&JPRD |
| Clinical and Post Marketing Safety | Sheldon Sloan, M.D., M.Bioethics Internal Medicine Portfolio Leader, Established Products, J&JPRD |
| Questions from the Committee | |
| <u>FDA Presentations (cont.)</u> | |
| Tegaserod: Nonclinical | Ke Zhang, Ph.D. Pharmacologist, DGIEP, ODE III OND, CDER, FDA |

Tegaserod: Clinical Pharmacology

Insook Kim, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology III
(DCP III), Office of Clinical
Pharmacology (OCP), Office of
Translational Sciences (OTS), CDER
FDA

Tegaserod: Clinical

**Aisha Peterson Johnson, M.D.,
M.P.H.**
Medical Officer, DGIEP, ODE III
OND, CDER, FDA

Questions from the Committee

BREAK

Sponsor's Presentations

Theravance, Inc.

Preclinical Properties of Velusetrag (TD-5108)
and TD-8954, Selective 5-HT₄ Receptor
Agonists

David Beattie, Ph.D.
Senior Director, Pharmacology
Theravance, Inc.

Questions from the Committee

FDA Presentations (cont.)

ATI-7505 (Naronapride): Nonclinical

Sushanta Chakder, Ph.D.
Pharmacologist, DGIEP, ODE III
OND, CDER, FDA

ATI-7505 (Naronapride): Clinical
Pharmacology

Insook Kim, Ph.D.
Clinical Pharmacology Reviewer
DCP III, OCP, OTS, CDER, FDA

ATI-7505 (Naronapride): Clinical

**Aisha Peterson Johnson, M.D.,
M.P.H.**
Medical Officer, DGIEP, ODE III
OND, CDER, FDA

Questions from the Committee

FDA Presentations (cont.)

Summary

Robert Fiorentino, M.D., M.P.H.
Medical Team Leader, DGIEP
ODE III, OND, CDER, FDA

Statistical Considerations

Eugenio Andraca-Carrera, Ph.D.
Mathematical Statistician, Division of
Biostatistics VII, Office of Biostatistics
OTS, CDER, FDA

Questions from the Committee

LUNCH

Open Public Hearing

Committee Discussion and Questions to the Committee

BREAK

Committee Discussion and Questions to the Committee (cont.)

ADJOURNMENT

Questions to the committee:

1. **VOTE:** For new products in the class, can nonclinical, clinical pharmacology, and clinical data, such as those presented for the newer 5-HT₄ agonists, dispel (i.e., alleviate the need for a “dedicated” safety study) the cardiovascular safety concerns (e.g., prolonged QT interval, ischemic events) raised by the clinical safety experience of the previously approved 5-HT₄ agonists?
 - a. If yes, specify on which data you are relying.

Yes: 14 No: 8 Abstain: 0

Members who voted “Yes” felt the unmet need for medications in these patient populations and the lack of a strong signal for cardiovascular toxicity outweighed the potential risks. Members commented that assumptions for these new agents appeared to be made based on older agents in the class, but were not convinced that cardiovascular toxicity is a class effect. However, members expressed lingering concerns for the potential of drug-induced cardiovascular toxicity, but felt that those concerns could be addressed in studies to evaluate efficacy and a “dedicated” safety study was not necessary.

Members who voted “No” felt that the potential for cardiovascular toxicity was apparent and additional safety studies were necessary to dispel concerns.

In general, members agreed that high-risk for cardiovascular disease patient populations should be included in studies in order to obtain a true index of cardiovascular risk. In addition, it was noted that the heterogeneous nature of these patient populations warranted further review of the cardiovascular safety of these agents when used in with other medication.

Please see the transcript for detailed discussion.

2. **VOTE:** Among the uses for which 5-HT₄ agonists are being developed, (chronic-idiopathic constipation, constipation predominant irritable bowel syndrome, gastroparesis, other

functional motility disorders), is there an indication for which you would be unwilling to accept an increased cardiovascular risk?

- a. If yes, specify on which data you are relying
- b. For those that you are willing to accept an increased risk, state the level of risk you would find unacceptable (e.g., Hazard Ratio).

Yes: 9 No: 11 Abstain: 2

Members who voted “No” were inclined to accept an increased cardiovascular risk depending on the severity of the condition. Several members noted that the ultimate decision would have to be made by the patient.

Members who voted “Yes” felt that for chronic-idiopathic constipation and possibly other functional motility disorders, they would not be willing to accept an increased cardiovascular risk because of the availability of other treatment options. Members noted, however, that for gastroparesis and possibly constipation predominant irritable bowel syndrome, they would be more willing to accept an increased cardiovascular risk.

Please see the transcript for detailed discussion.

3. **VOTE:** Does the Committee recommend a “dedicated” cardiovascular safety trial (a trial in which the primary objective is to define cardiovascular risk) to demonstrate the safety of 5-HT₄ agonists?

Yes: 4 No: 17 Abstain: 1

Members who voted “Yes” felt that rising concerns of cardiovascular safety with other agents on the market justifies a “dedicated” safety trial in these new agents. Several members noted that such trials are feasible and further assessment of these agents in high-risk populations is necessary.

Members who voted “No” voiced concerns about potential cardiovascular side effects, but still felt that a “dedicated” cardiovascular safety trial was not necessary. Several members mentioned that post-marketing observation was essential to catch any potential signals for cardiovascular toxicity. In addition, the feasibility of such trials was questioned and concerns about costs were raised. Members who voted “No” also recommended that the efficacy trials conducted to support approval should be designed with numbers large enough to detect a cardiovascular safety signal. The magnitude of that number was not specified by committee members

Please see the transcript for detailed discussion.

4. **DISCUSSION:** If you voted yes to Question #3, for each of the following populations, discuss whether you recommend that the trial be conducted prior to or post-approval?
 - a. CIC
 - b. IBS-C
 - c. Gastroparesis
 - d. Other functional motility disorders

In general among the four members that voted “yes” some felt that “dedicated” safety trials should be conducted prior to approval for chronic-idiopathic constipation, constipation predominant irritable bowel syndrome and other functional motility disorders, but possibly post-approval for gastroparesis. Another member felt that for all populations, the trials should be done prior to approval. One member expressed that trials could be done prior to approval which would require a higher margin, then done post-approval with a lower margin.

Please see the transcript for detailed discussion.

5. **DISCUSSION:** Discuss the characteristics which would define the “enriched population” for a “dedicated” cardiovascular study.

Members commented that an “enriched population” should include patients at high risk for cardiovascular disease and should not exclude patients on concomitant medications. Various members commented on specific characteristics to define an “enriched population” which included patients with high coronary calcium scores, elderly patients, diabetics, patients with peripheral vascular disease, and patients with chronic kidney disease.

Please see the transcript for detailed discussion.

6. **DISCUSSION:** What elements to assess cardiovascular safety should be included in a standard phase 3 efficacy trial to assure accurate ascertainment of cardiovascular adverse events?

Members mentioned adjudication committees, electronic medical records as part of an integrated health care system, and case report forms, as elements to assess cardiovascular safety in standard phase 3 efficacy trials. Members noted, however, that endpoints should be clearly defined because of discordance associated with adjudication committees.

Please see the transcript for detailed discussion.

The session adjourned at approximately 5:00 p.m.