# Food and Drug Administration
# Center for Drug Evaluation and Research

## Summary Minutes of the Gastrointestinal Drugs Advisory Committee
## March 8, 2018

Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, Maryland

Topic: The committee discussed supplemental new drug application (sNDA) 203214, supplement 18, XELJANZ (tofacitinib) 5 mg and 10 mg tablets, submitted by Pfizer Inc., proposed for the treatment of adult patients with moderately to severely active ulcerative colitis who have demonstrated an inadequate response, loss of response or intolerance to corticosteroids, azathioprine, 6-mercaptopurine or tumor necrosis factor (TNF) inhibitor therapy.

These summary minutes for the March 8, 2018 meeting of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration were approved on March 30, 2018.

I certify that I attended the March 8, 2018, meeting of the Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

**/s/**
Jay R. Fajiculay, PharmD
*Designated Federal Officer, GIDAC*

**/s/**
Jean-Pierre Raufman, MD
*Chairperson, GIDAC*

**Summary Minutes of the Gastrointestinal Drugs Advisory Committee Meeting**
**March 8, 2018**

The following is the final report of the Gastrointestinal Drugs Advisory Committee (GIDAC) meeting held on March 8, 2018. A verbatim transcript will be available in approximately six weeks, sent to the Division of Gastroenterology and Inborn Errors Products and posted on the FDA website at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/ucm593142.htm.
All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

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The Gastrointestinal Drugs Advisory Committee (GIDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on March 8, 2018 at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA and Pfizer Inc. The meeting was called to order by Jean-Pierre Raufman, MD, (Chairperson). The conflict of interest statement was read into the record by Jay R. Fajiculay, PharmD (Designated Federal Officer). There were approximately 200 people in attendance. There were four Open Public Hearing (OPH) speaker presentations.

**Issue:** The committee discussed supplemental new drug application (sNDA) 203214, supplement 18, XELJANZ (tofacitinib) 5 mg and 10 mg tablets, submitted by Pfizer Inc., proposed for the treatment of adult patients with moderately to severely active ulcerative colitis who have demonstrated an inadequate response, loss of response or intolerance to corticosteroids, azathioprine, 6-mercaptopurine or tumor necrosis factor (TNF) inhibitor therapy.

**Attendance:**

**GIDAC Members Present (Voting):** David N. Assis, MD (via phone); Lin Chang, MD; Sandeep Khurana, MBBS; Benjamin Lebwohl, MD, MS; Darrell S. Pardi, MD, MSc; Jean-Pierre Raufman, MD (Chairperson); Lisa L. Strate, MD, MPH

**GIDAC Members Not Present (Voting):** Linda A. Feagins, MD; Rachel L. Rosen, MD, MPH

**GIDAC Member Present (Non-Voting)**: Douglas Levine, MD (Industry Representative)

**Temporary Members (Voting):** Ivan J. Fuss, MD; Mitchell H. Grayson, MD; Joy M. Hugick (Acting Consumer Representative); Beth L. Jonas, MD; H. Clifford Lane, MD; Jennifer R. Lightdale, MD, MPH; Tracy Matson (Patient Representative); Michael Proschan, PhD

**FDA Participants** (**Non-Voting):** Donna Griebel, MD; Tara Altepeter, MD; Lesley Hanes, MD, MSc; Sara Jimenez, PhD

**Designated Federal Officer (Non-Voting):** Jay R. Fajiculay, PharmD

**Open Public Hearing Speakers:** Guy F. (Jeff) Campbell; Megan Polanin (National Center for Health Research); Emily Morgan; Laura Wingate (Crohn's & Colitis Foundation)

***The Agenda proceeded as follows:***

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| Call to Order and<br>Introduction of Committee | **Jean-Pierre Raufman, MD**<br>Chairperson, Gastrointestinal Drugs Advisory Committee (GIDAC) |
| Conflict of Interest Statement | **Jay Fajiculay, PharmD**<br>Designated Federal Officer<br>Division of Advisory Committee and Consultant Management (DACCM), CDER, FDA |
| FDA Introductory Remarks | **Tara Altepeter, MD**<br>Clinical Team Leader<br>Division of Gastroenterology and Inborn Errors Products (DGIEP)<br>Office of Drug Evaluation (ODE) III<br>Office of New Drugs (OND), CDER, FDA |
| **APPLICANT PRESENTATIONS** | **Pfizer, Inc.** |
| Introduction | **Lou Ferrara**<br>Director, Regulatory Affairs<br>Pfizer, Inc. |
| Ulcerative Colitis: A Clinician's Prospective / Unmet Medical Need | **William Sandborn, MD**<br>Chief, Division of Gastroenterology<br>Director, Inflammatory Bowel Disease Center<br>University of California, San Diego |
| Tofacitinib Ulcerative Colitis Development Program and Efficacy | **Eric Maller, MD**<br>Executive Director, UC Development Program<br>Inflammation and Immunology, Pfizer Inc |
| Safety of Tofacitinib in Ulcerative Colitis Development Program | **Chinyu Su, MD**<br>Senior Director, Global Clinical Lead UC<br>Inflammation and Immunology, Pfizer Inc |
| Risk Management | **Thomas Jones, MD**<br>Senior Director, Safety Risk Management<br>Pfizer Inc |
| Benefit-Risk and Conclusion | **Michael Corbo, PhD**<br>Senior VP, Chief Development Officer<br>Inflammation and Immunology, Pfizer Inc |
| Clarifying Questions | |
| **BREAK** | |

**FDA PRESENTATIONS**

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| Clinical Pharmacology Findings of Tofacitinib for Treatment of Moderately to Severely Active Ulcerative Colitis (UC) | **Dilara Jappar, PhD**<br>Clinical Pharmacology Review<br>Division of Clinical Pharmacology III<br>Office of Clinical Pharmacology<br>Office of Translational Sciences (OTS), CDER, FDA |
| Analyses of Efficacy Data for Proposed Dosing Regimens | **Sara Jimenez, PhD**<br>Mathematical Statistician<br>Division of Biostatistics III,<br>Office of Biostatistics (OB). OTS, CDER, FDA |
| Focused Tofacitinib UC Program Safety Evaluation | **Lesley Hanes, MD, MSc** |
| Remarks About Results from Truven Marketscan® | **Joel Weissfeld, MD, MPH**<br>Medical Officer<br>Division of Epidemiology I<br>Office of Surveillance and Epidemiology, CDER, FDA |
| Tofacitinib Development Program: Pediatric Ulcerative Colitis | **Melanie Bhatnagar, MD**<br>Medical Officer<br>Division of Pediatric and Maternal Health<br>ODE IV, OND, CDER, FDA |

Clarifying Questions

**LUNCH**

Clarifying Statements from Industry

**OPEN PUBLIC HEARING**

Questions to the Committee and Committee Discussion

**BREAK**

Questions to the Committee and Committee Discussion (cont.)

**ADJOURNMENT**

***Question to the Committee:***

1. **DISCUSSION:** The Applicant has proposed an induction dosing regimen of 10 mg BID for a total of 16 weeks in patients who have not achieved "adequate therapeutic benefit" by week 8 based on exploratory analyses of trial data in patients who continued induction treatment when they had not achieved clinical response defined as a decrease from baseline in Mayo score of ≥3 points and ≥30%,

with an accompanying decrease in the subscore of rectal bleeding of ≥ 1 point or subscore for rectal bleeding of 0 or 1.

a. Please discuss the adequacy of the efficacy data to support the use of the 10 mg BID dosing for extended induction therapy for a total of 16 weeks in patients who have not achieved "adequate therapeutic benefit" by week 8.

b. Please discuss the adequacy of the safety data to support the use of the 10 mg BID dosing for induction for a total of 16 weeks in patients who have not achieved "adequate therapeutic benefit" by week 8.

***Committee Discussion:*** *The committee members stated that although the additional 8 weeks of clinical data were not placebo controlled, the observation that 50% of patients who were initial non-responders eventually demonstrated clinical response in the subsequent 8 weeks of tofacitinib therapy favors an efficacy benefit of the product. Limitations were noted, including 1) lack of a diverse patient population enrolled in clinical trials compared to those diagnosed with UC in the clinical setting; especially since the African American population may experience a more severe course of UC compared to other ethnic groups, 2) lack of statistical rigor of these conclusions of efficacy (the possibility that this apparent efficacy may be due to chance) and 3) lack of data regarding if continuing at 5mg BID for the subsequent 8 weeks also would have been efficacious.*

*Overall, the committee generally agreed that the potential benefits outweigh risks for an additional 8 weeks of induction treatment. Patients with UC have limited treatment options, and extension of treatment with this product might serve as a better alternative than performing a colectomy. Given the mechanism of action, a longer duration of time (more than 8 weeks) may simply be required to fully appreciate a therapeutic effect. Please see the transcript for details of the committee discussion.*

2. **VOTE:** Do you recommend the inclusion of this dosing regimen for this population in the product label?

**a.** If you recommended inclusion of this dosing regimen in the product label, please discuss how inadequate therapeutic benefit that merits extension of induction treatment should be distinguished from inadequate therapeutic benefit that should prompt discontinuation of tofacitinib therapy

***YES: 15*** ***NO: 0*** ***ABSTAIN: 0***

***Committee Discussion:*** *The committee unanimously agreed for the inclusion of the 10 mg BID dosing regimen for the proposed patient population in the product label. The panel stressed the importance of a patient and provider discussion regarding the benefits versus risks of the product. The panel further commented that patients with UC are a patient population desperate for new treatment options, and it would be better to try treating with this drug a little longer, than to abandon a potentially efficacious therapy at 8 weeks, when patients may have no other available therapeutic options. Moving forward, the committee stated additional information is warranted, such as data on the efficacy of long term treatment with 10mg vs 5mg, among patients who had inadequate response at week 8, but did respond to the additional 8 weeks of 10mg BID*

*by week 16 of treatment, analysis of potential biomarkers, and of other safety signals. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** For adult patients with moderately to severely active UC with an inadequate response, loss of response, or intolerance to TNF blocker therapy:

    a. Please discuss the adequacy of the efficacy data to support the use of the 10 mg BID dosing as continuous maintenance treatment.

    b. Please discuss the adequacy of the safety data to support the use of the 10 mg BID dosing as continuous maintenance treatment.

***Committee Discussion:*** *Some committee members commented that the effect size difference was impressive, and appeared to be more than seen with other approved therapies in this sub-population of those who have failed TNF-inhibitor therapy. Some members commented that the strength of data supporting a difference between the 2 doses was weak – that increased efficacy of 10mg BID in this subgroup may be due to chance, and that safety concerns need to be considered. There was also discussion regarding the difference between intolerance and lack of efficacy to prior TNF blocker therapies. Regarding the proposed indication, it was suggested that this should be limited to what was studied and observed in clinical trials; the studied population of "prior TNF failures" included primarily those who failed TNF-blocker therapy (very few patients in the clinical trials had prior "intolerance" to TNF). Members noted that intolerance to TNF may not truly reflect a refractory disease state. Others felt that the higher dose should be available to any patient with severe/refractory disease (in the opinion of the provider) not only those who have failed TNF blocker. It was also identified that the safety data available may be inadequate, since it is limited to only one year, but that the product may be expected to be used for several years; some members questioned whether the dose in this population could be decreased after a year of therapy, without a negative impact on ongoing efficacy. Overall, there was general support of the 10 mg BID dose in this population. Please see the transcript details of the committee discussion.*

4. **VOTE:** Do you recommend inclusion of this dosing regimen for this population in the product label?

***YES: 15*** ***NO: 0*** ***ABSTAIN: 0***

***Committee Discussion:*** *The committee discussed that the benefits of having tofacitinib 10 mg BID as an option outweigh the safety risks observed in clinical trials. Additionally, it was stated that the 10 mg BID dosing regimen should be based on clinical judgement, and that it would be helpful if the Applicant is able to provide information regarding when the 5 mg BID dosing regimen is appropriate for use in patients with history of TNF blocker failure (for example, could patients decrease the long term dose ("step down" from 10mg BID to 5mg BID, once they reach "deep remission?"). Committee members stated that the adult UC patient population is desperate for treatment options, and with additional follow-up it is possible to mitigate the potential risks associated with tofacitinib treatment. Please see the transcript details of the committee discussion.*

5. **VOTE:** Do you recommend that the Applicant conduct a post-marketing efficacy trial in this population comparing a 10 mg BID continuous dosing regimen versus a regimen of 10 mg induction and 5mg BID as maintenance?

***YES: 7*** ***NO: 8*** ***ABSTAIN: 0***

***Committee Discussion:*** *The committee was split in regards to recommending that the Applicant conduct post-marketing efficacy trials in this patient population at differing dosage regimens. Those who voted, 'YES,' stated that they would like to see step-down data (reducing dose from 10 mg to 5 mg after remission had been achieved and sustained, for example after a year of treatment) for safety and efficacy reasons, and that these data could be collected during post-marketing studies. Additionally, members proposed incorporating the use of the newly approved shingles vaccine into a post-marketing trial to provide useful safety information on the potential to mitigate the risk of shingles in this population. Those who voted, 'NO,' stated that it would be difficult to enroll patients to complete a comparison study, especially if the drug is already approved at a certain strength and regimen. It was also stated that given difficulties with enrolling UC clinical trials, there may be more pressing clinical questions to study than confirming the efficacy of a lower dose strength regimen. Please see the transcript details of the committee discussion.*

6. **DISCUSSION:** Please discuss if additional post-marketing evaluation of safety is warranted, and the mechanism(s) you recommend (e.g., registry, observational study, etc.) for such evaluation.

***Committee Discussion:*** *The committee discussed the strong need for post-marketing evaluation to identify safety signals. Pros and cons were identified for both a registry system and study. Members noted that enrollment would be easier for a registry compared to a study; however, in this case, it was recommended that a study would have greater benefits than a registry as a study provides a more structured system for clinicians to identify safety signals. Please see the transcript details of the committee discussion.*

7. **DISCUSSION:** Please discuss the following:

    a. Any unique characteristics of the pediatric UC population that should be taken into account when planning the tofacitinib pediatric development program. Please consider the ontogeny of the immune system and the described mechanism of action of tofacitinib.

    b. Given the safety concerns (malignancy and serious infections) described with long term use of 10 mg BID and the severity of UC in the pediatric population, please recommend the maximum dose that should be targeted for evaluation for long term treatment in pediatric UC

    c. Please discuss whether you recommend limiting enrollment in the pediatric trials (and subsequent pediatric indications) to patients who have failed other biologic therapies.

***Committee Discussion:*** *The committee discussed that a formal definition of pediatric population should be identified (e.g., down to 2 years versus 4 years of age). In the youngest patients (those less than 4-6 years of age) there are theoretical safety concerns due to the developing immune system. The importance of excluding early onset IBD-like patients with monogenetic disorders was stressed. It was noted that due to the broad activity of stat signaling pathways, greater safety concerns in younger patients (compared to TNF blockers) may exist.*

*Additional information, such as on exon sequencing and prior exposure to Epstein Barr Virus, should be collected and reviewed during a pediatric trial.*

*The committee discussed that an equivalent weight-based dose exposure in pediatric UC patients that is comparable to that observed from 10 mg BID dosing in adult UC patients is an appropriate dosing regimen for the pediatric population. Appropriate dosing is important since one of the quickest reasons for treatment failure is underdosing.*

*Regarding limiting use of the drug, it was discussed that it does take some time to gain a broader safety experience with the drug as it gains general use in the adult population post approval, so it may be appropriate to use tofacitinib in patients who have failed other forms of treatment. Alternatively, another panel member stated that in the right age group, tofacitinib might be a helpful drug that does not necessarily require treatment failure if it can be shown to work well. Panel members were open to consideration of permitting treatment naïve pediatric patients into a tofacitinib pediatric study.*

The meeting was adjourned at approximately 3:45 p.m.