Errata to FDA Briefing Document
GI Drugs Advisory Committee Meeting

March 8, 2018

sNDA203214, supplement 18
Tofacitinib

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 inhibitor therapy.

DISCLAIMER:

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the application for tofacitinib proposed for the treatment of moderate to severe ulcerative colitis to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

This document contains errata to the original FDA Briefing Document issued for the Advisory Committee meeting held March 8, 2018.

The erroneous text is identified by a strikethrough, with correction following in bold, unless otherwise specified.

1. Page 9 (Executive Summary)

Tofacitinib is a small molecule inhibitor of Janus associated kinases (JAK).
Tofacitinib was approved (November 2012) at a dose of 5 mg BID for the treatment of adults with moderate to severely active rheumatoid arthritis (RA) who have had inadequate response or intolerance to methotrexate, and for adults with active psoriatic arthritis (~~February 2017~~ **December 2017**) who have had inadequate response or intolerance to methotrexate or other disease modifying antirheumatic drugs.

2. Page 29 (section 4.3 Exposure-Response Analysis for Efficacy)

In the phase 2 trial, fewer patients were either prior TNF inhibitor non-responders (~~40.7~~ ***18.5*** %) or prior users of immunosuppressants (~~18.5~~ ***40.7*** %).

3. Page 38 (Section 5.1)

For the induction non-responder population (IndNR subgroup), an efficacy assessment was repeated 8 weeks later (16 weeks of total trial participation) including centrally read endoscopy at week 16 **(Week 8 of open label LTE)** and ***locally read*** at week 52.

4. *Page 39 (Section 5.1)*

In particular, Mayo score at baseline of the open label extension was higher in those who received 10 mg BID long term treatment (mean ~~8.8~~ **8.2**) compared with those who received 5 mg BID long term treatment (mean ~~7.8~~ **1.2**). (A3921139 Interim CSR Table 17)

5. Page 52, addition to discussion which follows (pertaining to the referenced historical placebo response rates).

The limitations of any cross-study comparison, including those referenced here to estimate of placebo response rates in UC clinical trials, are noted. In particular, there are no well controlled clinical trial data which exactly match this scenario for IndNR subgroup. There are differences between the referenced studies and this group, including the substantial proportion of patients enrolled in the tofacitinib program with a history of prior TNF-blocker failure, the timepoint for assessment of induction of remission at 16 weeks, and the definition of remission including the requirement for resolution of rectal bleeding (subscore of 0).

The Agency acknowledges the limitations, but provided these data as a frame of reference to acknowledge that reported placebo group response rates in Ulcerative Colitis trials can be substantial. We note that across many UC development programs, some concomitant treatments are permitted (such as 5-ASA medications and/or corticosteroids) making a true estimation of placebo only response also challenging. Regardless, it is difficult to

interpret the IndNR subgroup month 2 (week 16 of active treatment) data without a prospectively planned comparator group.

6. Page 55 (Table 15)

Table 1: Exploratory Binary Efficacy Endpoints, Based on FMS with Local Endoscopic Read, for IndNR Subgroup in Study 1139

	whRemission (FMS)				Clinical Response			
	Baseline	Month 2	Month 12	Month 24	Baseline	Month 2	Month 12	Month 24
Induction 10 mgx16 weeks *	1/295 (0.3%)	42/293 (14.3%)	72/289 (24.9%)	40/164 (24.4%)	22/295 (7.5%)	155/293 (52.9%)	121/289 (41.9%)	55/164 (33.5%)
~~Considering all 10 mgin the Induction phase ‡~~		~~42/295 (14.2%)~~	~~72/295 (24.4%)~~	~~40/295 (13.6%)~~		~~155/295 (52.5%)~~	~~121/295 (41.0%)~~	~~55/295 (18.6%)~~

*Includes only patients who received tofacitinib 10 mg BID in Study 1094/1095 and failed to demonstrate clinical response at week 8 (i.e., patients who received ongoing 10 mg BID therapy through 24 months). Denominators are numbers of subjects ~~in the specified category with non-missing values.~~ **who based on their enrollment dates could have reached the specified timepoint at the 08 July 2016 data cutoff date.**

~~‡Denominator is all patients with baseline data~~

FMS=full Mayo score

Analyzed with NRI for missing data

Source: Reviewer's table, created from applicant's Study 1139 CSR Table 27 (p. 111)

Additional clarification:

Study 1139 is still ongoing. The 1st row is not an observed data analysis; it is the non-responder imputation (NRI) analysis (IndNR, FAS). The number of patients in the denominators included at each time point in the first row represents the number of patients who had reached or would have reached the time points based on date of enrollment and date of data snapshot. For example, there were 164 patients as of the data snapshot who had reached Month 24 or would have reached Month 24 but discontinued before Month 24 based on date of enrollment. Discontinued patients were treated as non-responders for the endpoint. Ongoing patients between two time points were only included in the summary at the earlier time point at which they had reached but were not included in the later time point at which they had not reached.

7. Page 65, (section 6.3.1, Deaths)

"~~Note,the applicant included deaths occurring up to 28 days after last dose of tofacitinib treatment in consideration of deaths for relatedness purposes in the UC studies~~ **Analyses of incidence rate of death were performed by the applicant and FDA incorporating all deaths reported in the UC program."**

8. Page 66, Section 6.3.2 Serious Adverse Events

"The SAE experience of the prior TNF blocker failure subgroup ~~this group~~ is included here as it represents the clinical course of patients, who may follow the applicant's proposed dosing regimen for ***patients with prior TNF blocker failure*** ~~those who fail to achieve response by week8~~ (i.e., continue 10 mg BID longer term)."

9. Page 73, Section 6.3.4 Adverse Events of Special Interest and Associated Safety Analyses

"**Specifically, evaluation and qualification of potential malignancies consisted of a central laboratory pathologist review of biopsies (Histopathology Review) and review of clinical information including central pathologist assessment by** a Malignancy Adjudication Committee (MAC)". ~~Consisted of a central laboratory pathologist review of biopsies assisted in the evaluation and qualification potential malignancies.". The MAC and the central laboratory pathology review are two separate review processes.~~

10. Page 72, Section 6.3.3 Common Adverse Events

The following table should replace Table 23 as it appears in the background document. The change affects only the last column, IndNR 12 month subgroup within the prior TNF blocker failure group.

Table 2: Maintenance Study (Cohort 2) AEs Occurring in at ≥ 2 % of Patients, and at Least 1% Greater than Observed in UC Patients on Placebo, prior TNF blocker failure subgroup

Preferred Term	Placebo (n=79)	Tofacitinib 10 mg BID (n=76)	Tofacitinib 5 mg BID (n=72)	IndNR 12 months* (N=181)
Nasopharyngitis	9 (11.4%)	17 (22.4%)	5 (6.9%)	**39 (9.1%)**
Arthralgia	11 (13.9%)	13 (17.1%)	5 (6.9%)	**15 (3.5%)**
Gastroenteritis	3 (3.8%)	7 (9.2%)	4 (5.6%)	**9 (2.1%)**
Blood creatine phosphokinase increased	4 (5.1%)	7 (9.2%)	2 (2.8%)	**13 (3.0%)**
Elevated Cholesterol Levels**	10 (6.0%)	23 (13.8%)	13 (7.6%)	**11 (6.1%)**
Pyrexia	3 (3.8%)	5 (6.6%)	3 (4.2%)	**6 (1.4%)**

11. Page 77, (Section 6.3.4.2. Herpes Zoster Infections)

"In the randomized, controlled maintenance trial, the applicant reported that there were 10 patients in the tofacitinib 10 mg BID group, 3 patients in the tofacitinib 5 mg BID, and 1 patient in the placebo group who had HZ. ~~This reviewer evaluated the number of HZ infections and found a numerically higher number of patients than reported by the applicant in the tofacitinib 5mg BID (5 cases) and placebo groups (3 cases).~~ In the maintenance trial, there appears to be a possible dose-dependent increase in the rate of HZ infections for those treated with tofacitinib 10 mg BID, compared with tofacitinib 5 mg BID. ~~There was one case of serious HZ infection in each treatment arm of the maintenance study, for a total of 3 in the maintenance trial.~~ **There were no HZ SAEs in the maintenance study."**

12. Page 81 (Section 6.3.4.3 Opportunistic Infections and Tuberculosis)

"In addition to the opportunistic HZ cases, four (4) non-HZ infections were adjudicated as opportunistic, ~~all~~ **three** of which occurred in the PD tofacitinib 10 mg group, and one occurred in the PD tofacitinib 5 mg group."

13. Page 82, Section 6.3.4.4 Malignancies, excluding NMSC

"...all malignancy events that occurred in **tofacitinib-treated** patients **occurred** ~~receiving tofacitinib~~ during the LTE study. ~~, except for one case of invasive ductal breast carcinoma that occurred during the maintenance study~~ One event of breast cancer occurred in a placebo-treated subject in the maintenance study."

14. Page 96, Section 6.5, Comparison of Safety Across Indications

Revised Table 38 included below, note that there was a total of 5 patients with "MACE" (as defined by the applicant), including the event of cerebrovascular accident.

Table 3: Cumulative Incidence Rates (per 100 Patient-Years) for Death and Select Safety Events in Patients Treated with Tofacitinib (All Doses Combined) in the UC Cohort 3 Tofacitinib, Rheumatoid Arthritis (All Exposure), and Psoriasis (All Exposure) Programs

Safety Event	Ulcerative Colitis Tofacitinib UC Program (Cohort 3) * N= 1157 PY=1986		Rheumatoid Arthritis (All Exposure) N=7061 PY=22,875		Plaque Psoriasis (All Exposure) N=3663 PY=8955	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Death (all cause)	5 (0.4%)	0.24 (0.08, 0.57)	59 (0.8%)	0.25 (0.19,0.32)	17 (0.5%)	0.18 (0.11, 0.29)
Serious infection	38 (3.3%)	1.87 (1.32, 2.56)	576 (8.2%)	2.48 (2.28,2.69)	119 (3.2%)	1.29 (1.07, 1.54)
Opportunistic infection	22 (2.0%)	1.09 (0.69, 1.66)	90 (1.3%)	0.39 (0.31,0.47)	29 (0.8%)	0.31 (0.21, 0.45)
Non-Herpes Zoster opportunistic infection	4 (0.4%)	0.20 (0.05, 0.50)	34 (0.5%)	0.15 (0.10,0.20)	4 (0.1%)	0.04 (0.01, 0.11)
Herpes Zoster infection	74 (6.4%)	3.80 (2.99, 4.77)	782 (11.1%)	3.63 (3.38,3.90)	209 (5.7%)	2.35 (2.04, 2.69)
Serious Herpes Zoster infection	5 (0.4%)	0.24 (0.08, 0.57)	57 (0.8%)	0.24 (0.18,0.32)	11 (0.3%)	0.12 (0.06, 0.21)
Malignancy (excluding NMSC)*	13 (1.2%)	0.84 (0.45, 1.44)	177 (2.5%)	0.76 (0.65,0.88)	60 (1.6%)	0.65 (0.49, 0.83)
Colorectal cancer	2 (0.2%)	0.10 (0.01, 0.35)	11 (0.2%)	0.05 (0.02,0.08)	3 (0.1%)	0.03 (0.01, 0.09)
Lymphoma	1 (0.1%)	0.05 (0.00, 0.27)	12 (0.2%)**	0.05 (0.03,0.09)	2 (0.1%)	0.02 (0.00, 0.08)
NMSC	15 (1.3%)	0.74 (0.42, 1.23)	129 (1.8%)	0.56 (0.46,0.66)	63 (1.7%)	0.69 (0.53, 0.88)
MACE	~~4 (0.4%)~~ **5 (0.4)**	~~0.20 (0.05, 0.50)~~ **0.25 (0.08, 0.57)**	85 (1.3%)	0.38 (0.30,0.47)	23 (0.6%)	0.25 (0.16, 0.37)
GI perforation (all cases)	4 (0.4%)	0.20 (0.05, 0.50)	28 (0.4%)	0.12 (0.08,0.17)	7 (0.2%)	0.08 (0.03, 0.16)

Source: Reviewer's table, adapted from the Applicant's submission dated 26 October 2017, Database lock 29 September 2017. UC Cohort 3 data cutoff date 29 September, 2017; RA data cutoff date 02 March 2017; PsO final database date 18 August 2016. *For Malignancies (excluding NMSC), the incidence rate is based on the PD Tofacitinib 10 mg BID analysis group (PY 1521.28), since these events in the 13 patients did not occur in the PD Tofacitinib 5 mg BID group. The combined IR for the PD tofacitinib 5 and 10 mg BID dosages was 0.64 (0.34, 10.9). Except for death and malignancies and NMSC in the UC Cohort 3, events occurring within 28 days (based on adjudication) following the last dose were included. **Note, per the Applicant: The number of patients with lymphoma decreased from 13 to 12 in the updated RA database. After the 10 May 2016 data cutoff, the start date of 1 lymphoma event was revised such that the start date was outside the 28-day risk period following the last dose. This event was not counted for IR calculation in the updated database, resulting in a decrease of the number of patients with lymphoma by one (1).

15. Page 118, Table 47

Typographical errors in reported percentages as noted in the table below.

Table 47: Cohort 3 Incidence of Liver Enzyme Parameters (Multiples of ULN)

		PD Tofacitinib 10 mg BID (n=971)	PD Tofacitinib 5 mg BID (n=186)	Tofacitinib All (n=1157)
Parameter	**Criteria**	**n (%)**	**n (%)**	**n (%)**
ALT	≥ 1 x ULN	282 (29.0%)	47 (25.3%)	329 (28.4%)
	≥ 2 x ULN	57 (5.9%)	12 (6.5%)	69 (6.0%)
	≥ 3 x ULN	22 (2.3%)	4 (2.2%)	26 (2.2%)
	≥ 5 x ULN	4 (0.4%)	0 (0.0%)	4 (0.3%)
	≥ 10 x ULN	1 (0.1%)	0 (0.0%)	1 (0.1%)
AST	≥ 1 x ULN	200 (20.8%)	48 (25.8%)	248 (21.4%)
	≥ 2 x ULN	37 ~~(38.1)~~ **(3.8%)**	10 (5.4%)	47 (25.5%) **(4.0%)**
	≥ 3 x ULN	16 ~~(16.4%)~~ **(1.6%)**	2 (1.1%)	18 ~~(27.1)~~ **(1.5%)**
	≥ 5 x ULN	10 ~~(10.3)~~ (1.0%)	0 (0.0%)	10 (0.8%)
	≥ 10 x ULN	2 (0.2%)	0 (0.0%)	2 (0.2%)
Total bilirubin	≥ 1 x ULN	98 (10.1%)	28 (15.1%)	126 (10.9%)
	≥ 2 x ULN	15 (1.5%)	6 (3.2%)	21 ~~(18.2)~~ **(1.8%)**
	≥ 3 x ULN	2 (0.2%)	1 (0.5%)	3 (0.3%)
	≥ 5 x ULN	2 (0.2%)	0 (0.0%)	2 (0.2%)

Source: Reviewer's table. JReview v.11.0. Note: A patient can contribute to multiple rows per lab result. Only post-baseline data are summarized in the table.

16. General Clarification:

At multiple points throughout the FDA background document, the term "clinical remission" was used when discussing the primary endpoint.

In this UC development program, the applicant, at request of FDA, used a more stringent definition of "remission" to define the primary endpoint, which required a rectal bleeding subscore of zero (not zero or 1 as has been used historically in other development programs).

When FDA refers to the primary endpoint within the background document, the discussion should refer to "remission" rather than "clinical remission" as described above.