CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210296Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: November 16, 2018
From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 210-296 (BLS-11; monomethyl fumarate; Bafiertam)

NDA 210-296, a 505(b)(2) application, was submitted by Banner Life Sciences LLC on January 18, 2018, to request marketing approval for monomethyl fumarate (MMF) for the treatment of relapsing forms of multiple sclerosis (RMS) in adults. NDA 210-296 relies, in part, on findings of safety and effectiveness of a previously approved drug. The listed drug is Tecfidera (dimethyl fumarate [DMF], approved (NDA 204-063) for the same indication (RMS) on March 27, 2013. Clinical development was conducted under IND 126454.

Under the IND, the sponsor was told that nonclinical studies of MMF, the active metabolite of DMF, would not be needed unless the clinical or CMC data raised safety concerns that required nonclinical assessment (Written Responses, June 19, 2015). However, upon further internal discussion, it was determined that the sponsor would need to "provide a discussion of published literature on potential differences in pharmacological activity between DMF and MMF and implications (if any) for the contribution of DMF and/or MMF to clinical efficacy in patients with MS" (email communication, October 13, 2015).

In the NDA, the sponsor has provided a review of published literature on DMF and MMF, specifically related to a comparison of pharmacological activity. In addition, the sponsor submitted nonclinical in vitro and in vivo studies to qualify impurity (degradant) levels in the drug product; the 13-week toxicity study in rat was submitted on June 8, 2018. The published literature was reviewed by Dr. Lee (Pharmacology/Toxicology NDA Review and Evaluation, NDA 210-296, November 13, 2018); the nonclinical impurity studies were reviewed by Dr. Banks-Muckenfuss (Pharmacology/Toxicology NDA Review and Evaluation, NDA 210296, November 8, 2018).

Review of Published Literature

The sponsor provided the results of a thorough search of the literature and a discussion of the most relevant publications to address the Division's concerns regarding potential differences in pharmacological activity between DMF and MMF that could impact clinical efficacy in RMS. Based on the review of that information, Dr. Lee has concluded that the sponsor's response was adequate and agrees with the sponsor's conclusions that:

- "…there exists no large and compelling body of literature either confirming or refuting the hypothesis that chronic administration of MMF causes substantially different…effects than those observed…with DMF," and
- "…there is no clear clinical implication that any observed nonclinical differences between MMF and DMF will yield significant clinical differences in the effectiveness of MMF…" as compared to DMF for the treatment of RMS."

When DMF is administered orally, there are no detectable levels of DMF in circulation in either animals or humans. According to labeling for the listed drug (Tecfidera),

> In humans, dimethyl fumarate is extensively metabolized by esterases, which are ubiquitous in the gastrointestinal tract, blood, and tissues, before it reaches the systemic circulation. Further metabolism of MMF occurs through the tricarboxylic acid (TCA) cycle, with no involvement of the cytochrome P450 (CYP) system. MMF, fumaric and citric acid, and glucose are the major metabolites in plasma.

In addition, the sponsor has demonstrated bioequivalence between the listed drug and Bafiertam, based on circulating levels of MMF. Therefore, the only apparent basis for a difference in pharmacological activity, relative to efficacy in RMS, would be local effects exerted by DMF, but not MMF. The major limitations of the published literature to address this issue are that (1) the in vivo studies have not distinguished between the actions of DMF and MMF because of the rapid conversion of DMF to MMF and (2) in vitro studies demonstrating biological effects of DMF or MMF in various tissues or cells (e.g., CNS) do not, of course, take into consideration the lack of exposure of those tissues or cells to DMF in vivo. One possible strategy for evaluating the contribution of any local effects of DMF or MMF in vivo would be to conduct a well-designed and rigorous study in a relevant animal (e.g., experimental autoimmune encephalomyelitis) model in which DMF and MMF are administered at doses producing similar circulating levels of MMF; however, it is unclear if such a study would be sufficiently sensitive to detect what may be small differences in effect between DMF and MMF.

Qualification of impurities

As discussed in Dr. Banks-Muckenfuss's review, a number of (b) (4) degradants (b) (4)) were identified in the drug product: (b) (4) The initial release and shelf-life specification set for each of these degradants was NMT (b) (4) %; the qualification threshold is 0.2% (or 3 mg, whichever is lower) for a drug product for which the daily dose is >100 mg to 2 gm. To qualify these degradants, the sponsor conducted an in vitro (b) (4) study, a 13-week oral toxicity study, and an in silico evaluation of two of the degradants.

In the in vitro study (PD17-068), BLS-11 (MMF formulated in excipients) was incubated with (b) (4) for up to 24 hrs. At the end of the 24-hr period, there was a change in the level of only two of the degradants, (b) (4). Interestingly, the (b) (4) were not detected even at the Time 0 point and the levels of BLS-11 (MMF) did not increase over time. The data are summarized in the following sponsor's table.

Peak	Control (% Deg)	T=0 (% Deg)	T=2 hr (% Deg)	T=4 hrs (% Deg)	T=8 hrs (% Deg)	T=24 hrs (% Deg)
(b) (4)						

Considering the presence of (b) (4) in the GI tract, the intestinal enterocyte, and in plasma, the lack of (b) (4) of the degradants is somewhat surprising. However, as the sponsor noted in the report, (b) (4) While it is possible that different results might have been obtained if human (b) (4) had been used, the results of the study, the only in vitro data available, clearly indicate a lack of (b) (4) The sponsor concluded that (b) (4)

In the 13-week oral toxicity study (8379098), BLS-11 (MMF oral solution), stored at 5 or 40 C (then stored for the duration of the study at -20 C until thawed for dosing), was administered to Sprague-Dawley rats (10/sex/group) by oral gavage. The drug batch stored at 5 C contained no degradants (i.e., each either not detected or <LOQ (b) (4) %]); the degraded batch (stored at 40 C) contained the five degradants at the following levels and daily dose (b) (4) ND = not detected).

DEGRADANT	BLS-11	BLS-11 DEGRADED		
	%	%*	mg/kg	mg/m^2
(b) (4)	ND	(b) (4)		
	<LOQ			
	<LOQ			
	ND			
	ND			

*data from Analytical Report on Dose Preparations, Table 2; 3-month values were used for all but the (b) (4)

A standard battery of safety parameters was assessed; no drug-related findings were identified with either drug batch.

At the sponsor's original proposed specification of NMT (b) (4)%, the daily dose in humans would be (b) (4) mg/m^2, which exceeds the daily doses of the (b) (4) degradants administered in the 13-week study, except for that of the (b) (4) At the revised proposed specification of NMT (b) (4)%, the daily dose in humans would be (b) (4) mg/m^2. The degradant amounts tested adequately cover the revised specification. It is unfortunate that the sponsor did not test a higher dose of MMF (with and without degradants). Considering the lack of any drug-related effects, it is likely that higher doses (for MMF and degradants) would have been tolerated.

A computational toxicology (QSAR) assessment was performed to evaluate the mutagenic potential of two of the (b) (4) degradants (b) (4). All three compounds were negative using rule and statistical based methods.

In one additional study (PD17-069), the sponsor tested the stability of an approved drug product, which also contains (b) (4) Therefore, the data do not provide support for the proposed specification for the (b) (4) degradant in Bafiertam.

Conclusions and Recommendation

The sponsor has adequately addressed concerns regarding the potential contribution of DMF itself to the therapeutic effects observed with orally administered DMF and, with the revised degradant specifications, has adequately qualified the degradants that exceed the qualification threshold. Therefore, from a nonclinical standpoint, there is no objection to approval of the NDA.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LOIS M FREED
11/16/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

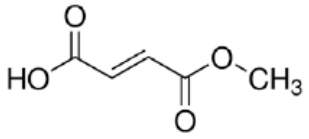
PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	210-296
Supporting documents:	1
Applicant's letter date:	January 18, 2018
CDER stamp date:	January 18, 2018
Product:	Bafiertam (monomethyl fumarate) Delayed-Release Capsule
Indication:	Relapsing forms of multiple sclerosis
Applicant:	Banner Life Sciences
Review Division:	Neurology Products
Reviewer:	Paul Lee, MD
Division Director:	Billy Dunn, MD
Project Manager:	Sandra Folkendt

1 Drug Information

1.1 Drug

Drug Name: monomethyl fumarate
Molecular Formula/Molecular Weight: $C_5H_6O_4$; 130.10 g/mol
Structure (from the sponsor's submission)



Pharmacologic Class: No established pharmacological class

1.2 Relevant IND, NDA

- IND 126454 (monomethyl fumarate; Banner Life Science)
- NDA 204-063 (Tecfidera, dimethyl fumarate) – Listed Drug

2 Nonclinical Review

2.1 Executive Summary

Banner Life Sciences has developed BLS-11 (monomethyl fumarate, MMF, Bafiertam®) for the treatment of relapsing forms of multiple sclerosis (MS). The Applicant has submitted nonclinical findings related to BLS-11 in NDA 210296 as part of a 505(b)(2) application. NDA 210296 references the Agency's prior findings of effectiveness and safety for Tecfidera® (dimethyl fumarate, DMF), the intended listed drug (LD) for the same indication, the treatment of relapsing forms of MS. The Division has questions regarding whether there are data to support the hypothesis that there may be clinical effects of DMF that are not attributable to its metabolite MMF as part of the consideration of a 505(b)(2) application for MMF. The Division had found prior responses from the Applicant to be lacking. In this NDA, the Applicant submitted a literature review and summary of the effects of DMF and MMF. The summary and literature review are nominally sufficient to address the Division's concerns.

2.2 Brief Discussion of Nonclinical Findings

2.2.1 Regulatory History

In pre-IND meeting written responses dated June 19, 2015, the Division agreed that the Applicant's intent to use the 505(b)(2) approval pathway for BLS-11, with Tecfidera® as the LD, appeared acceptable. The Division predicated agreement to this approval pathway upon there being no clinical effects solely attributable to DMF with respect to clinical data as follows:

> *"Additional nonclinical studies will not be needed unless the clinical data indicate differences between Monomethyl Fumarate Delayed Release Capsules and Tecfidera, the reference listed drug (RLD) or unless other safety issues ... arise that would necessitate nonclinical assessment."*

In a follow-up electronic mail response to the Applicant dated October 13, 2015, the Division elaborated on the nonclinical component of the NDA submission and requested a focused literature review as follows:

> *"Based upon further internal discussion, we believe you should also provide a discussion of published literature on potential differences in pharmacological activity between DMF and MMF and implications (if any) for the contribution of DMF and/or MMF to clinical efficacy in patients with MS. Copies of relevant literature should be submitted."*

The request for a review comparing the relative contributions of DMF and MMF reflected the Division's concern that there is extant literature that different fumarate esters possess unique pharmacological activity and that DMF may have immune effects different from those of MMF that may be clinically relevant.

In response to this request, the Applicant provided an initial literature review comprised of six references along with a brief discussion. The provided literature was the result of a search on the topic of "the role of fumaric acid esters in the treatment of MS" and the discussion cited quotations from the approval labeling and review package for the LD, Tecfidera®.
In meeting minutes generated following the pre-NDA meeting held on September 5, 2017, the Division elaborated on a specific need to address the DMF-to-MMF comparison as follows:

> "Although we acknowledge that DMF is not quantifiable in plasma following oral administration of DMF, we suggest that you conduct a more thorough literature review to address whether or not DMF may itself contribute to efficacy. The adequacy of the literature search will be a matter of review."

In the NDA submission, the Applicant includes a fifteen-page discussion and summary of the effects of DMF and MMF with seven lists of references ranging from three to eighty relevant references culled from thousands of references identified in several search results. The Applicant provides a requested discussion of the possibility of DMF acting locally within the intestinal tract as a potential contributor to clinical effectiveness. The submission contains a four hundred-page appendix describing how the Applicant conducted literature searches, the actual citation lists, and the abstracts on topics such as MMF and DMF use in animal models, MMF and DMF relative pharmacodynamics, MMF and DMF in relation to the *Nrf2* gene with or without the word "pathway."

The Applicant's nonclinical submission in this NDA includes several broad arguments as to why an extensive discussion of DMF's immune effects is not necessary as nonclinical support for a 505(b)(2) pathway application. First, the Applicant reiterates the Division's prior agreement that no "new nonclinical studies were required" for this application, as cited above. The Applicant refers to the approval documents for Tecfidera® and the statements that DMF could not be quantified in plasma and as such, MMF is assumed to be the primary active moiety conferring clinical effects even when it is administered as DMF. Lastly, the Applicant states that while fumarate esters such as DMF and MMF reduce inflammation via modulation of the behavior of several immune cell types and activate the nuclear factor (erythroid-derived 2)-like 2 (*Nrf2*) pathway to protect against free radical damage, the precise mechanisms of action of Tecfidera® (DMF) and of MMF remain unknown. As such, the Applicant offers that a comparative discussion of the cellular effects of DMF and MMF is theoretical until future investigations can answer the more basic question of how fumarate esters definitively lead to the observed clinical effects of Tecfidera® or MMF.

The Applicant limits the discussion of the literature obtained in the searches to seven articles from the literature and two FDA documents, the Clinical Pharmacology and Biopharmaceutics Review dated February 12, 2013, and the Office of Generic Drugs Bioequivalence Guidance on DMF dated July 2014. The discussion below will focus on the Applicant's discussion of the seven original articles. Other reviews of the NDA will address bioequivalence claims and as such, the Applicant's citation of the two FDA

documents is to support the argument of bioequivalence of MMF to DMF will not be included in this review. To provide a full accounting of the submitted literature, the following discussion will use a structure parallel to the Applicant's submission.

2.2.2 Submission Discussion

Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis

According to the Applicant, a published abstract by Chun et al. (2015)[1] is the only relevant publication to meet the search criteria for fumarate therapy in the context of the experimental autoimmune encephalomyelitis model. This citation is an abstract from a poster. The Applicant did not submit the poster for review.

> *Reviewer Comment: The publication by Chun et al. (2015) is an abstract and as such is not a peer reviewed publication. It provides no insight into the question of whether DMF has clinical effects that differ from those of MMF.*

Intestinal Effects and Brain-Gut "Homing"

The Applicant claims a search attempt to elucidate whether DMF or MMF cause different "homing" effects failed to yield any relevant publications.

> *Reviewer Comment: This reviewer agrees that there do not appear to be articles in the current literature specifically addressing differential impacts of DMF and MMF on lymphocytes' ability to traffic between the intestinal mucosa and the CNS. Therefore, there exists no basis for any conclusions about the effects of DMF or MMF on intestinal lymphocytes' ability to translocate to the CNS.*

(b) (4)

> *Reviewer Comment:* (b) (4)
>
> *The Division recognizes that the current therapies approved in MS, including the LD, Tecfidera®, have as a common general mechanism of action some means of altering the immune system such that it is less capable of mounting autoimmune injury directed at CNS targets. Extrapolating any more specific mechanisms of action from most of these therapies to DMF is not appropriate.* (b) (4)
>
> (b) (4)

DMF and MMF in the Intestine and MS

The Applicant provides three published articles[7-9] related to the topic of DMF and MMF in the intestine. A publication by Linker et al (2015)[7] examines the potential effects of DMF within the intestine of EAE mice. A comparison of mice who received DMF after EAE induction to those who received control treatment demonstrates there were more Th1 and Foxp3 positive lymphocytes within the intestinal lamina after 14 days of DMF treatment. The authors concluded that DMF activates the *Nrf2* pathway, which in turn leads to an increase in the number of circulating regulatory lymphocytes. The Applicant states that the article did not mention the role of MMF, and that, because of rapid metabolism by tissue-resident esterases, it is likely that only the proximal portion of the duodenum is exposed to DMF.

Reviewer Comment: This publication is an abstract and is not a peer reviewed journal article. There are neither data nor discussion of whether the cells identified in this article shifted to a regulatory phenotype because of DMF, MMF, or both. I did not consider this abstract in this review. The submission also includes an abstract from Gogas et al. (2010)[8] comparing a non-DMF prodrug form of MMF to DMF in mice with EAE. This abstract presentation was not a peer reviewed publication and discusses a substance that was not MMF or DMF. It will not be reviewed.

The Applicant cites a publication by Brennan et al. (2013)[9] that compared the effects of single doses of DMF and MMF in healthy mice. The authors reported that the overall transcriptional outcomes of acute exposures to DMF and MMF are largely similar across tissues and appear to reflect the expected outcomes associated with activation of *Nrf2* pathway. However, the authors note the existence of treatment by tissue specific differences leading the conclusion that "[t]he incomplete overlap of transcriptional signatures induced by DMF and MMF indicates that not all DMF pharmacodynamic effects are conveyed through MMF, as may have been predicted due to the rapid in vivo

metabolism of DMF to MMF." The Applicant acknowledges the authors' conclusions but adds the important caveats that this study was not performed in EAE mice, and the findings are transcriptional changes following a single dose of DMF and MMF, whereas chronic administration of fumarates is necessary for clinical efficacy in treating autoimmune diseases.[10]

> *Reviewer Comment: This publication is an abstract from a poster presented in 2013 by an author who at the time of presentation was identified as an employee of Biogen, the manufacturer of Tecfidera®. A search using a public search engine located the author's archived Ph.D. thesis,[11] which includes the differential tissue activation data. The thesis findings agree with the abstract statement that the overall activation profile of acute exposures to DMF and MMF are qualitatively similar and consistent with Nrf2 pathway activation in mice of the five classical* Nrf2 *target genes* NQO1*,* AKR1B8*,* GCLC*,* SRXN1 *and* TRXND1*. The author notably states in her thesis methods, "to parallel in vivo studies all* in vitro *cultures were treated with MMF." Brennan and colleagues subsequently authored several papers based on the thesis findings related to DMF and MMF,[12-14] the most significant of which, Brennan et al. (2015)[12] is a comparison of several MMF salts to DMF in their respective abilities to deplete glutathione following prolonged exposure in vitro. The authors note that DMF caused glutathione depletion in human-derived spinal cord astrocyte cultures whereas MMF did not. Brennan and colleagues[12] concluded, "fumaric acid esters may have significantly different biochemical properties that divergently impact cellular pathways, including activation of the NRF2 pathway and modulation of cellular [glutathione]. Based on these findings, it would be expected that these in vitro differences would manifest in different pharmacodynamic and pharmacokinetic properties in vivo. The clinical consequences of these differences remain to be explored." Taken together, these findings provide contradictory evidence for DMF and MMF effects being similar. It is noteworthy that the initial studies used an acute dose of DMF and MMF in rodents, but the findings related to glutathione depletion are derived* from in vitro *studies of human cell cultures. It is difficult to extrapolate from these different studies to clinical implications, if any, that may exist between chronic administration of DMF and MMF in patients with MS. Many of the above findings are not published as peer reviewed scientific papers and therefore have no merit in this review.*

<u>Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and Nrf2- pathway Activation</u>

The Applicant offers the Brennan et al. (2013)[9] work discussed above and a publication by Gillard et al. (2015)[15] as being the only relevant results of a literature search on the topic of differences in *Nrf2* pathway activation between DMF and MMF.

The inclusion of the Gillard et al., (2015)[15] publication is new to this submission and tested the ability of DMF and several MMF salt formulations to alter NF-κB pathway responses. The Applicant observes that NF-κB pathways are implicated in autoimmune diseases that cause chronic inflammation. The authors of this publication show data that

DMF caused dose-dependent reductions in NF-κB-dependent gene transcription and cytokine production that were not seen as robustly in association with MMF. The publication provides data showing how these NF-κB effects are independent of *Nrf2* activation. The Applicant states that the authors of the publication acknowledged that NF-κB is one pathway and fumarates have different effects on different pathways relevant to chronic inflammation and autoimmune diseases.

> *Reviewer Comment: The authors of the Gillard et al. (2015)[15] publication disclosed they were all employees of Biogen, the manufacturer of Tecfidera® (DMF). NF-κB reduction as a mechanism underlying the efficacy of treatments for MS remains theoretical.[16] NF-κB activation within the immune cells of the central nervous systems of patients with MS appears to be the most critical site for potential therapeutic impact.[17] Therefore, it is unlikely that an anti-inflammatory effect mediated by reduced NF-κB activation confined to the lymphocytes resident in the proximal small bowel could play a significant role in the observed efficacy of DMF, with the caveat that, as noted above, there exists a gap in the literature regarding any capability of intestinal resident lymphocytes to relocate to the CNS to play a role in MS.*

Applicant Discussion and Conclusions

In conclusion, the Applicant states, "[t]he conventional wisdom is that MMF is for all intents and purposes the active moiety of DMF..." and further suggests that the Division's acceptance of another monomethyl fumarate product, ALKS 8700, in the 505(b)(2) approval pathway, is supportive of this reasoning. The Applicant states that only two reports were found of differential effects of DMF and MMF *in vitro* and that the differences may not be relevant to MS therapy. The Applicant concludes that the rapid metabolism of DMF to MMF means very little DMF exposure occurs, and, even if DMF did cause differences, those relatively small effects would pale in comparison to the systemic effects of MMF.

> *Reviewer Comment: The Applicant's broad assertion that DMF and MMF both promote* Nrf2 *pathway activation is supported by the extant nonclinical literature. However, this reviewer rejects the argument that the rapid conversion of DMF to MMF means that DMF cannot have any* in vivo *effects. DMF is present sufficiently, both in terms of quantity and in terms of time within the proximal small intestine[18] -- a site replete with lymphoid tissue -- to exert effects such as its ability to impart a regulatory phenotype onto lymphocytes.[7] While MMF appears to be able to replicate most of DMF's capability to exert this Th1 shift, there are no studies of DMF and MMF on gut-brain homing to assure us that a difference might exist in how DMF and MMF exposures affect subsequent lymphocyte behavior. A contributory effect of DMF in promoting a regulatory phenotype within a subpopulation of lymphocytes may be smaller in magnitude than systemic effects of MMF on circulating and lymph resident white blood cells but may still be clinically apparent as a change in a relevant marker of efficacy. It is conjecture that any effects attributable to DMF on intestinal lymphocytes may*

be real but be so much smaller in magnitude than the systemic effects of MMF that the loss of the local DMF effects on intestinal lymphocytes will not lead to an evident diminution in clinical efficacy for MMF-based therapy.

In the Appendix materials, the Applicant discusses the table below and the literature cited in creating it to assert that, despite few known specific differences in effects at the cellular level between DMF and MMF, both DMF and MMF have effects best summarized as the ability "to enhance the antioxidant pathways and to inhibit reactive oxygen species" as a means of reducing inflammation and possibly promoting cell survival.

The Applicant ultimately concludes that potential differential effects of DMF and MMF likely are moot because "DMF is completely absorbed in the small intestine, and only small amounts are recovered in the feces (<1%) and urine. This and the differences in their respective half-lives: DMF has a short half-life of ~12 minutes inside the body whereas MMF has a half-life of 36 hours ... would imply that the efficacy of DMF/MMF in MS (especially when given as the approved *b.i.d.* dosing) is quasi [*sic*] entirely attributable to MMF."

The Applicant reprints the following table from Al-Jaderi and Maghazach (2016)[19] which demonstrates one of the most complete published summaries of the differences between the immune effects of DMF and MMF.

Table 1: Applicant Table, Immunoregulatory Effects of DMF and/or MMF on Immune Cells (Source: Applicant Submission, 4.3.5, Appendix, page 6 of 6)

Table 1 – Immunoregulatory effects of DMF and/or MMF on various immune cells[1]

Cell type	Molecule	Cytokine/other molecules involved	Effect(s)	Reference[2]
T cells	DMF/MMF	↓IFN-γ, ↓TNF-α, ↓IL-17, ↑IL-4, ↑IL-5, ↑IL-10, ↓CXCR3, ↓CCR6	↓Bcl-2, ↑Apoptosis, ↓Th1, ↓Th17, ↑Th2, ↓CD4, ↓CD8, ↑Treg	(17, 18, 27, 32, 42, 44, 61)
B cells	DMF	↑Nrf2→↑GSH→↓ROS, ↓NF-kB	↓Bcl-2, ↑Apoptosis, ↓CD19 B cells	(17, 18)
Monocytes	DMF	↑Nrf2, ↓NF-kB	No effect on cell numbers, ↑Antioxidant response	(18, 77)
DCs	DMF/MMF	↓GSH→↑HO-1, ↓NF-kB, ↓IL-6, ↓IL-12, ↑IL-10, ↓TNF-α↓, E-cadherin	↑Apoptosis, ↓plasmacytoid DCs, ↓DC maturation, ↓type I DCs, ↑type II DCs	(17, 22, 25–27, 31, 32)
NK cells	DMF/MMF	↑NKp46, ↑CD107, ↑Granzyme B	↓CD56dim NK cells, No effect on CD56bright numbers, ↑CD56bright NK cells lysis of tumor cells, ↑Lysis of DCS	(17, 18, 21, 22)
Macrophages	DMF	↑Nrf2, ↓mRNA of IFN-γ, ↓mRNA of TNF-α, ↓mRNA of IL-6, ↓mRNA of IL-17, ↑mRNA of IL-4, ↑mRNA of IL-10	↓M1 macrophages, ↑M2 macrophages	(68)
Neutrophils	DMF/MMF	↓HCA2	↓Number of infiltrating neutrophils	(20)
Keratinocytes	DMF	↓IL-12, ↓IL-23, ↓TNF, ↓IFN-γ, ↑IL-10, ↓IL-6, ↓TGF-α	↓Proliferation of keratinocytes	(37)
Endothelial cells	DMF	↓TNF-α, ↓ICAM-1, ↓VCAM-1, ↓E-selection, ↑Nrf2	↓BBB permeability→↓Immune cell migration	(41, 54, 55, 65)
Microglia	DMF/MMF	↓IL-1, ↓IL-6, ↓TNF-α, ↓NO, ↑Nrf2→↑GSH→↓ROS, ↓NF-kB, ↑NQO-1, ↑HO-1, ↑HCAR2	↑Antioxidant response, switching activated microglia from pro-inflammatory to neuroprotective	(49, 50, 52)
Astrocytes	DMF/MMF	↑Nrf2→↑GSH→↓ROS, ↓NF-kB, ↓IL-1, ↓IL-6, ↓TNF-α, ↓NO	↑Antioxidant response	(50, 52, 58)
Neurons	DMF	↑Nrf2→↑GSH→↓ROS	↓Apoptosis, ↑Neurons survival under oxidative stress	(47, 58)
Tumor cells	DMF	Arrest the cell cycle at G2-M, ↓pro-apoptotic	↓Proliferation of melanoma cells, ↓Proliferation of tumor cells, ↑Apoptosis	(73)

Notes:
[1] Produced verbatim from Al-Jaderi and Maghazach, 2016. [2] As shown in Al-Jaderi and Maghazach, 2016
Abbreviations: IFN = interferon; TNF = tumor necrosis factor; IL= Interleukin; CXCR3 = Chemokine receptor; CCR6 = Chemokine receptor type 6; GSH = Glutathione ;HO = Heme oxygenase **1**; NF-kB = nuclear factor kappa-light-chain-enhancer of activated B cells;NKp46 = Natural Killer; CD07 = ; HCA2 = hydroxycarboxylic acid receptor 2;NO = Nitric Oxide;Nrf2 = nuclear factor erythroid 2-related factor 2; ROS = Reactive Oxygen Species;NQO-1 = quinone oxidoreductase 1;HCAR2 = Hydroxycarboxylic Acid Receptor 2; BBB = blood brain barrier; Bcl-2 = B-cell lymphoma 2

Reviewer Comment: The Al-Jaderi and Maghazach (2016) reference had been included in the previous submission from the Applicant, but the Applicant had not discussed this reference. This publication is arguably the most comprehensive effort in the extant literature to compare the known effects of DMF and MMF. The Applicant's summary discussion of Al-Jaderi and Maghazach (2016)[19] is cursory but satisfies a minimum expectation of comparing the cellular and biochemical effects of DMF and MMF in the literature. The Applicant's assessment fails to appreciate a key hypothetical conclusion of the publication, that DMF prevents "presenting encephalitogen to autoreactive T cells" and that MMF may be superior to DMF in this respect.[19] Therefore, the authors of the publication suggest that MMF may be more effective than DMF at preventing lymphocytes from becoming autoreactive, a process thought to underlie the initiation and relapsing processes of MS.[20] Whether this possible reduction in autoreactivity could create a clinical difference between MMF and DMF is unclear.

2.3 Recommendations

The major obstacles in reviewing the extant literature to address the Division's concern, that there could there be different clinically relevant effects caused by DMF that cannot be achieved with MMF alone, are several.

The Applicant's repetitive and limited Appendix materials provide the important recognition that very few publications exist on the topics of DMF and MMF regarding mechanistic explanations of how they treat multiple sclerosis. When one examines the extant literature closely, investigators who perform studies using "DMF" do not typically parse out the relative contributions of DMF and MMF to observed findings. The investigators in all but a few publications assume (if they make mention at all) that, because tissue esterases rapidly convert DMF to MMF, that MMF is the primary driver of any study's results and therefore conflate DMF and MMF results as the same.

Building on the assumption that DMF and MMF cause generally the same effects, there is a general postulate (assumed but not rigorously evaluated) that fumarate esters are effective anti-inflammatory therapies for autoimmune diseases despite any subtle differences in mechanisms of action. Because of this hypothesized homogeneity of fumarate efficacy, there are few publications examining the actual differences in mechanisms of action between the different fumarate esters. Publications that do examine differences between DMF and MMF speculate on the clinical implications, but follow-up clinical studies that build on these nonclinical findings are non-existent.

Nevertheless, even with the significant limitations noted above, there is a literature discussing effects of DMF, MMF, or fumarate esters that examines each of these entities' *in vivo* and *in vitro* mechanisms separately. The Applicant's NDA submission discussion includes several noteworthy articles, most prominently the publication of Gillard et al. (2015),[15] and the literature search results of the current submission under consideration contain significant publications such as Ahuja et al. (2016).[21] Therefore,

the Applicant's submission satisfies a minimal standard for an adequate survey of the literature on this focused topic.

However, as noted above, there exists a paucity of peer-reviewed materials to address the question of whether DMF and MMF possess different clinical effects, and therefore the question of clinical efficacy differences between DMF and MMF in MS cannot be answered using the extant medical and scientific literature.

The Applicant's literature review was broad and without depth (an unavoidable consequence of there being little depth to this topic) but did address the Division's request for additional submitted materials on this topic. Many of the materials provided were published abstracts from poster presentations. The Applicant did not submit and was unable to acquire the full poster presentations with the abstracts. The abstracts are not peer-reviewed publications, and I therefore consider them in evaluating the applicant's position.

This reviewer acknowledges two conclusions from the Applicant's literature review and summary. First, there exists no large and compelling body of literature either confirming or refuting the hypothesis that chronic administration of MMF causes substantially different transcriptional, antioxidant, or cellular effects than those observed in association with DMF. Second, there is no clear clinical implication that any observed nonclinical differences between MMF and DMF will yield significant clinical differences in the effectiveness of MMF as compared to Tecfidera® in the treatment of relapsing MS.

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/s/

PAUL R LEE
11/14/2018

LOIS M FREED
11/14/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	210296
Supporting document/s:	1, 8, 9, 24
Applicant's letter date:	1/18/18, 5/18/18, 6/8/18, 10/23/18
CDER stamp date:	1/18/18, 5/18/18, 6/8/18, 10/23/18
Product:	BAFIERTAM™ (monomethyl fumarate) Delayed-Release Capsule, 95 mg
Indication:	Relapsing forms of multiple sclerosis
Applicant:	Banner Life Sciences, LLC
Review Division:	DNP
Reviewer:	Melissa Banks-Muckenfuss, PhD
Supervisor:	Lois Freed, PhD
Division Director:	Billy Dunn, MD
Project Manager:	Sandy Folkendt, RPM

Disclaimer:
Except as specifically identified, all data and information discussed below and necessary for approval of NDA 210296 are owned by Banner Life Sciences or are data for which Banner Life Sciences has obtained a written right of reference.
Any information or data necessary for approval of NDA 210296 that Banner Life Sciences does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are for descriptive purposes only and are not relied upon for approval of NDA 210296.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Bafiertam™ (monomethyl fumarate delayed release capsules) has been developed by Banner Life Sciences LLC for the treatment of relapsing forms of multiple sclerosis. This is a 505(b)(2) NDA application, citing Tecfidera® (dimethyl fumarate [DMF] capsules) as the listed drug. Monomethyl fumarate (MMF) is the active metabolite of dimethyl fumarate.

1.2 Brief Discussion of Nonclinical Findings

The sponsor relied on the Agency's prior findings of safety and effectiveness for Tecfidera (the listed drug; DMF). To support the scientific bridge between MMF and DMF, the sponsor submitted the requested literature review to address the potential for DMF to have pharmacological effects not shared by MMF (i.e., the potential that DMF may itself contribute to efficacy in multiple sclerosis). This issue was addressed separately in a review by Dr. Lee.

Impurities were identified in the drug product that required qualification to support the sponsor's proposed specifications. Therefore, the sponsor conducted a 13-week bridging toxicity study in rats to qualify the drug product (b) (4) impurities. The study tested one dose level of a relatively clean drug product and one dose level of a drug product held for stability under accelerated conditions, compared to control. However, at the dose level selected, the achieved dose of the identified (b) (4) impurities in the 13-week toxicity study did not provide adequate margins to the proposed product specifications for the (b) (4) (b) (4)%). The sponsor was asked to (b) (4) the drug product and stability specifications for the (b) (4) impurities to a level which is considered acceptable (i.e. (b) (4)%), and the sponsor has agreed.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, NDA 210296 is recommended for approval.

1.3.2 Additional Nonclinical Recommendations

A juvenile animal toxicology will be required to support pediatric development; this study may be conducted post-approval.

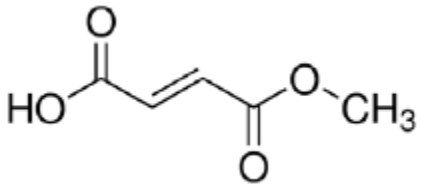
1.3.3 Labeling

The nonclinical information for the labeling for Bafiertam will be consistent with the current labeling for the listed drug, Tecfidera.

2 Drug Information

2.1 Drug

Generic Name	monomethyl fumarate
Code Name	BLS-11
Chemical Name	methyl fumarate (IUPAC)
Molecular Formula/Molecular Weight	$C_5H_6O_4$; 130.10 g/mol
Structure or Biochemical Description	(from the sponsor's submission)



Pharmacologic Class	No EPC

2.2 Relevant INDs, NDAs, BLAs and DMFs

This application

IND 126454	BLS-11	monomethyl fumarate	Bafiertam™

Other applications

RLD	NDA 204063	dimethyl fumarate	Tecfidera

2.3 Drug Formulation

The sponsor provided the following information for the drug product (below).

Table 1. Composition of capsule fill and shell

Capsule Fill Formulation			
Component	**Function**	**Amount per capsule (mg)**	**Quality Standard**
Monomethyl Fumarate	Active Ingredient	95.0	Specifications See 3.2.S.4.1
(b) (4)	(b) (4)		National Formulary (NF)
(b) (4) (Povidone K30)			United States Pharmacopeia (USP)
(b) (4) (Polyoxyl 40 Hydrogenated Castor Oil)			USP
Lactic Acid			USP
Theoretical Total Fill Weight			
Capsule Shell Formulation			
Component	**Function**	**Amount per capsule (mg)**	**Quality Standard**
Gelatin, (b) (4)	(b) (4)		NF
(b) (4) (b) (4) Sorbitol and Sorbitans Solution)			NF, European Pharmacopeia (EP)
(b) (4)			USP
Titanium Dioxide			USP

2.4 Comments on Novel Excipients

None indicated.

2.5 Comments on Impurities/Degradants of Concern

No drug substance impurities were identified as requiring qualification. (b) (4)

Analysis of the drug product formulation demonstrated five (b) (4) impurities (see the sponsor's stability specifications, below).

(b) (4)

The proposed specification for [redacted] did not require further qualification. To address the identified [redacted] impurities, the sponsor submitted a 13-week toxicity study of the drug product containing the impurities; however, levels of the impurities tested in that study were not adequate to support the proposed specifications for the drug product [redacted] impurities. The sponsor was asked to [redacted] the specifications for the [redacted] impurities to [redacted]%, and the sponsor has agreed. See the **Integrated Summary and Safety Evaluation** for discussion.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical use for Bafiertam the same as that for Tecfidera, that is BID oral dosing for the treatment of patients with relapsing forms of multiple sclerosis. Bafiertam is be taken at 190 mg BID (i.e., MRHD of 380 mg/day). The sponsor stated that the proposed single administration dose of Bafiertam (MMF; i.e., 190 mg administered as two 95 mg capsules) has been shown to be bioequivalent to Tecfidera (DMF, 240 mg delayed-release capsules).

2.7 Regulatory Background

The following issue was identified and communicated to the sponsor in the 74-day letter (dated 3/27/18):

> 2) You conducted an in vitro study (PD17-068) to assess [redacted] using [redacted] However, the data from that study demonstrated conversion of the [redacted] but not the [redacted] If you have additional information regarding the potential for in vivo conversion of [redacted], it should be submitted to the NDA.

The sponsor responded in the cover letter to the 120-day safety update amendment (dated 5/18/18), stating that the 13-week rat toxicity study was being submitted "in the absence of a suitable in vivo or in vitro assay to assess the conversion."

3 Studies Submitted

3.1 Studies Reviewed

Study PD17-068: [redacted] BLS-11 [redacted] Study Report)
Study Report [redacted]-17-013: In Silico Mutagenicity Evaluation of Monomethyl Fumarate and Impurities

Study 8379098 (BLS-11): 13-Week, Repeat-Dose, Impurity Qualification Study in Rats with BLS-11

10 Special Toxicology Studies

10.1 Impurities

Study PD17-068: (b) (4) BLS-11 (b) (4) Study Report)
Non-GLP, dated 10/13/17

During development of BLS-11, the sponsor stated that (b) (4) To support this position, the sponsor conducted an in vitro assay using BLS-11 with impurities (Lot #14700841MA, which was held for 6 months at 40ºC/75%RH) in the presence of (b) (4) (purchased from (b) (4)). Samples were analyzed immediately (i.e., T=0), and at 2, 4, 8, and 24 hours incubation at 37ºC. In the study, as conducted, the levels of the (b) (4) only (i.e., not the (b) (4) were reduced. The study was not definitive, and issues with its conduct were noted (e.g., the level of BLS-11 was reportedly not increased, as might be expected, as a result of the (b) (4). Of particular interest is the last sentence of the report, which reads, (b) (4)

Study title: 13-Week, Repeat-Dose, Impurity Qualification Study in Rats with BLS-11

Study no.:	8379098 (Sponsor: BLS-11)
Study report location:	EDR, SDN9
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/20/17
GLP compliance:	Yes (FDA), except Drug characterization
QA statement:	Yes

Drug information: (from the sponsor, below)

3.2.1 Test Article 1

Test Article	Storage	Lot No[a]	Retest Date[b]	Content[c]	Total Impurities
BLS-11	In a freezer, set to maintain -10 to -30°C	PD17-066-0950005	26 Feb 2018	8.1 mg/mL (initial) 8.5 mg/mL(retest)	(b) (4)% (initial) (b) (4)% (retest)

a Prepared from capsules stored at 5°C.
b Data from the Analytical Development Report in the Appendix; retest conducted at the end of the 13-week study.
c Provided preformulated in water at a theoretical concentration of 10 mg/mL.

(The sponsor stated that (b) (4) was the only degradation product observed (i.e., (b) (4)% initially, and (b) (4)% at end of study).)

3.2.2 Test Article 2

Test Article	Storage	Lot No[a]	Retest Date[b]	Content[c]	Total Impurities
BLS-11, containing impurities	In a freezer, set to maintain -10 to -30°C	PD17-066-0954075	26 Feb 2018	8.0 mg/mL (initial) 8.3 mg/mL(retest)	(b) (4)% (initial) (b) (4)% (retest)

a Prepared from capsules stored at 40°C and 75% humidity.
b Data from the Analytical Development Report in the Appendix; retest conducted at the end of the 13-week study.
c Provided preformulated in water at a theoretical concentration of 10 mg/mL.

Test Article 2 (BLS-11 containing impurities) was prepared from BLS-11 capsules stored at 40°C/75% relative humidity. BLS-11 containing impurities was considerably degraded due to the exposure of BLS-11 capsules to stressful conditions (40°C/75% relative humidity). The total level of impurities (frozen stability data; degradation products) was (b) (4)% initially and (b) (4)% at the end of this study. (b) (4) (b) (4) (b) (4) were the major impurities present in BLS-11 containing impurities. At the end of this study, (b) (4) (b) (4) (b) (4) remained the same as initial.

Methods (See summary table from the sponsor, below)

Frequency of dosing:	QD
Route of administration:	PO, gavage
Dose volume:	2.5 mL/kg
Species/Strain:	Sprague Dawley Crl:CD(SD) rats CRL (Raleigh, NC)
Age:	8 to 9 weeks old
Weight:	M: 244 to 326 g; F: 177 to 243 g
Deviation from study protocol:	Dose formulation concentrations were adjusted to actual concentrations (see below).

Group[a]	No. of Animals		Dose Level[b] (mg/kg/day)	Dose Concentration[c] (mg/mL)
	Males	Females		
1 (Control)	10	10	0	0
2 (BLS-11)	10	10	20	8
3 (BLS-11, with impurities)	10	10	20	8

a Group 1 was administered control article only (deionized water).

b Nominal dose levels of 25 mg/kg/day were based on a theoretical concentration of 10 mg/mL; however, measured concentrations were 80% of nominal, and so the actual dose levels were assumed to be 20 mg/kg/day.

c The BLS-11 and BLS-11, with impurities, were dosed as supplied by the Sponsor at a nominal concentration of 10 mg/mL; however, measured concentrations were 8 mg/mL.

Observations and Results

Mortality

There was no early mortality.

Clinical Signs

There were no drug-related clinical signs.

Body Weights

No clearly drug-related changes in body weight or body weight gain were observed. Males administered BLS-11 with impurities exhibited slightly increased body weight gain (9% compared to control, with a 5% increase in mean body weight on D91), but this difference was small and was not observed in females.

Food Consumption

No clear drug-related effects were observed.

Hematology

Prothrombin time was slightly increased (2-4%, [ss]) in treated males. The clinical pathologist considered the change incidental because it was small and not observed in females.

Clinical Chemistry

BUN was slightly reduced (15%, [ss]) in treated females. The clinical pathologist considered the change incidental because the change was small, it was not seen in males, and there was a "lack of correlative findings" in the histopathological evaluation. However, some evidence of renal changes was observed in the study.

Urinalysis

RBCs were observed in the urine of two BLS-11-treated males.

Gross Pathology

Discolored kidney or liver was reported in individual animals; any relationship to drug was unclear.

Organ Weights

Liver weight (relative to body) was slightly increased (8%, [nss]) in males administered BLS-11 with impurities. Relative kidney weights were slightly increased in both male BLS-11-treated groups compared to control (8% [ss] and 14% [ss] in BLS-11 and BLS-11 with impurities, respectively). The sponsor indicated that the increased kidney weights were not likely drug-related because they did not have clinical or anatomical pathology correlates, were not seen in females, and resulted primarily from a few individuals; however, a drug-related effect "could not be definitively excluded."

Histopathology

Adequate Battery	Yes (see histopathology inventory)
Separate, Signed Report	Yes (signature only page)
	(b) (4)
Peer Review	No

Histological Findings

The pathologist reported no drug-related alterations and indicated that the observed alterations in kidney all represented early incidental changes that commonly occur in rats (e.g., chronic progressive nephropathy; Frazier et al., 2012). Minimal fibrosis in the kidney of the male treated with BLS-11 with impurities correlated with discolored kidney reported macroscopically. In addition to the renal changes discussed by the pathologist, minimal hemorrhage in the heart of one female (pathologist considered the observation in the male to be an agonal change), minimal erosion of the stomach, and minimal mineralization of the ovary was observed in individual animals treated with BLS-11 with impurities. In a BLS-11-treated male, minimal hypoplasia of the testis was observed (testicular changes are noted in the Tecfidera label). See observations in selected tissues, below, from the sponsor's summary table.

Tissue/ Observation	Group/Sex: / Number of Animals:	1/M 10	2/M 10	3/M 10	1/F 10	2/F 10	3/F 10
Kidney	Number Examined:	10	10	10	10	10	10
	Unremarkable:	0	1	0	0	2	2
Fibrosis							
	finding not present -	10	10	9	9	10	10
	minimal 1	0	0	1	1	0	0
	Total Incidence:	0	0	1	1	0	0
Mineralization, tubule							
	finding not present -	8	9	6	5	4	4
	minimal 1	2	1	4	2	3	5
	slight 2	0	0	0	3	3	1
	Total Incidence:	2	1	4	5	6	6
Stomach, Glandular	Number Examined:	10	10	10	10	10	10
	Unremarkable:	10	10	10	10	10	9
Erosion							
	finding not present -	10	10	10	10	10	9
	minimal 1	0	0	0	0	0	1
	Total Incidence:	0	0	0	0	0	1
Heart	Number Examined:	10	10	10	10	10	10
	Unremarkable:	9	10	8	10	10	9
Hemorrhage							
	finding not present -	10	10	9	10	10	9
	minimal 1	0	0	1	0	0	1
	Total Incidence:	0	0	1	0	0	1
Thyroid	Number Examined:	10	10	10	10	10	10
	Unremarkable:	10	8	9	9	9	8
Infiltrate, mononuclear cell							
	finding not present -	10	10	9	10	10	8
	minimal 1	0	0	1	0	0	2
	Total Incidence:	0	0	1	0	0	2
Lung	Number Examined:	10	10	10	10	10	10
	Unremarkable:	8	10	6	10	9	5
Infiltrate, macrophages, alveolus							
	finding not present -	9	10	7	10	9	8
	minimal 1	1	0	2	0	0	2
	slight 2	0	0	1	0	1	0
	Total Incidence:	1	0	3	0	1	2

Mineralization							
	finding not present -	10	10	10	10	10	9
	minimal 1	0	0	0	0	0	1
	Total Incidence:	0	0	0	0	0	1
Mineralization, vessel							
	finding not present -	10	10	9	10	10	9
	minimal 1	0	0	1	0	0	1
	Total Incidence:	0	0	1	0	0	1
Ovary	Number Examined:	0	0	0	10	10	10
	Unremarkable:	0	0	0	10	10	8
Mineralization							
	finding not present -	0	0	0	10	10	8
	minimal 1	0	0	0	0	0	2
	Total Incidence:	0	0	0	0	0	2
Testis	Number Examined:	10	10	10	0	0	0
	Unremarkable:	9	9	10	0	0	0
Hypoplasia							
	finding not present -	10	9	10	0	0	0
	minimal 1	0	1	0	0	0	0
	Total Incidence:	0	1	0	0	0	0

Toxicokinetics

Not performed.

Dosing Solution Analysis

The dosing formulations used during the study were not tested. Test articles were provided preformulated by the sponsor (provided "as individual vials sufficient for daily administration") and stored frozen at -20°C. Although the nominal concentration of both BLS-11 and BLS-11 with impurities was 10 mg/mL, concentration analyses showed the concentration to be approximately 8 mg/mL. Stability (i.e., assessing concentrations of the degradant (b) (4) impurities) was analyzed for the BLS-11 and BLS-11 with impurities samples at initiation of the study, and after 1 and 3 months of frozen storage (data from the sponsor, below).

Table 2: Frozen Stability Data – Degradation Products

	PD17-066-0954075 (40°C/75% RH)		
Degradation Product	Initial (% Deg)	1 Month (% Deg)	3 Month/EOD (% Deg)
(b) (4)			
	PD17-066-0950005 (5°C)		
Degradation Product	Initial (% Deg)	1 Month (% Deg)	3 Month/EOD (% Deg)
(b) (4)			

EOD = End of Dosing; 3 Month Test Date – 26 Feb 2018; ND = None Detected
Reference: RD1319 p.74, 78, RD1309 p.166, RD1317 p. 19-20

Structural alerts requiring assessment were not indicated for the (b) (4) impurities. In addition to the 13-week toxicity study, the sponsor provided an in-silico analysis of the (b) (4) of (b) (4) to support the lack of potential mutagenicity (see below, from the sponsor's submission). In vitro genetic toxicology studies of the (b) (4) impurities were not conducted.

Table 1: Summary of *In silico* Mutagenicity Findings

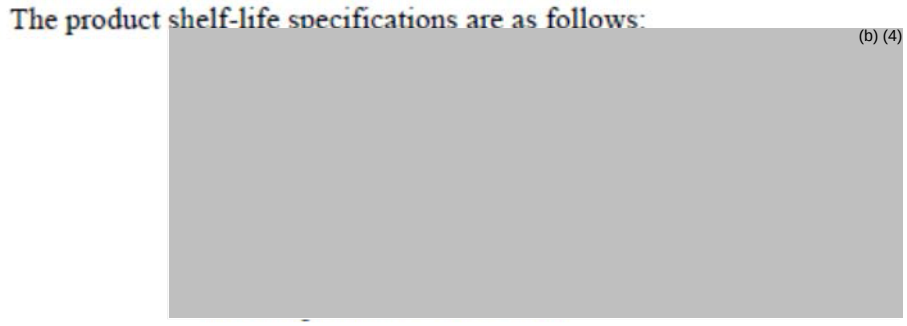
Structure	Rule Based	Statistical Based		Overall Prediction	Control Class[1]
	DEREK	Model Applier (E coli/Sal mut)	Case Ultra GT1_A7B/GT1_AT_Ecoli		
(b) (4)	N	N	N	N	5
	N	N	N	N	5
	N	N	N	N	5

N= negative;
[1] Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions (ICH M7, 2015).

11 Integrated Summary and Safety Evaluation

This 505(b)(2) NDA application for BLS-11 (monomethyl fumarate; MMF) identified Tecfidera® (dimethyl fumarate) as the listed drug for all nonclinical information, with the exception of qualification of drug product impurity specifications specific to this formulation. The scientific bridge to the listed drug was substantiated by a reasonable pharmacodynamic and pharmacokinetic bridge (i.e., the pharmacologic mechanism(s) underlying efficacy in MS is reasonably expected to be similar [see Dr. Lee's review for details] and the systemic exposures at the recommended human dose (RHD) of MMF are considered bioequivalent to those after administration of the RHD of dimethyl fumarate).

Regarding BLS-11 drug product specific impurities, the sponsor proposed the following drug product initial release and shelf-life specifications (below from the sponsor):



The proposed specifications (b) (4)% require qualification per ICH Q3B. (b) (4) was considered qualified because (b) (4) and the level is also supported by limits in approved products (i.e., the IID lists the maximum potency per unit dose of (b) (4) as (b) (4) mg). The sponsor attempted to qualify the limit for (b) (4) by demonstrating its presence in an approved (b) (4) product. The commercial (b) (4) product formed (b) (4) under accelerated/stress conditions; however, this study did not support the specification of (b) (4)% for the (b) (4) in the drug product (at initial release and shelf-life). The sponsor stated that the (b) (4) formed in the drug product (i.e., (b) (4) Therefore, the sponsor conducted a 13-week toxicity study of degraded BLS-11 capsules to support the specifications for drug product (b) (4) impurities.

The 13-week study tested BLS-11 or BLS-11 with impurities (0 or 20 mg/kg QD) by oral gavage in Sprague Dawley rats. BLS-11 with impurities contained (b) (4)

(b) (4)

. No clear impurity-related adverse effects of treatment with BLS-11 with impurities were observed; however, the levels of the impurities present did not provide adequate qualification for the sponsor's proposed specifications of (b) (4)% (see calculated dose comparisons, below). Based on the levels of the impurities tested in the 13-week toxicity study in rats (and in consultation with the CMC review team), a specification of (b) (4)% is acceptable for the (b) (4) impurities. It is reasonably supported (i.e., mg/m^2 margins of approximately 1 to 4x) by the levels of the (b) (4) tested in the 13-week toxicity/qualification study.

Dose Comparison

Impurity	*DP Daily Dose (in mg/kg)*	*Impurity Level Tested*	*Impurity Dose (in mg/kg)*	*Impurity Dose (in mg/m^2)*	*mg/m^2 Margin @ (b) (4)*	*mg/m^2 Margin @*
RAT						
(b) (4)						
HUMAN		*Proposed Specification*				
Sponsor's Proposed Specification for each (b) (4) above	(b) (4)					

Although the accepted specification for the (b) (4) impurities (b) (4)%) (b) (4) the qualification threshold of 0.2%, in vitro genetic toxicology assays were not requested. The (b) (4) impurities are related to (b) (4). MMF has been tested in a full genetic toxicology battery as well as carcinogenicity studies (see the labeling for the listed drug, Tecfidera®); (b) (4) a common excipient, and an endogenous substance.

12 Appendix/Attachments

Appendix 1: Literature References

Frazier et. al. (2012) Proliferative and nonproliferative lesions of the rat and mouse urinary system. Toxicol Pathol; 40:12S-86S.

Appendix 2: Histopathology Inventory

Study	13W Impurity
Species	Rat
Adrenals	X*
Aorta	X
Bone Marrow smear	
Bone (femur)	X
Brain	X*
Cecum	X
Cervix	X*[a]
Colon	X
Duodenum	X
Epididymis	X*
Esophagus	X
Eye	X
Fallopian tube	X*[a]
Gall bladder	n/a
GALT (Peyer's patch)	X
Gross lesions	X
Harderian gland	X
Heart	X*
Ileum	X
Injection site	n/a
Jejunum	X
Kidneys	X*
Lachrymal gland	
Larynx	
Liver	X*
Lungs	X
Lymph nodes, cervical	
Lymph nodes mandibular	X
Lymph nodes, mesenteric	X

Mammary Gland	X (F)
Nasal cavity	
Optic nerves	X
Ovaries	X*[a]
Pancreas	X
Parathyroid	X
Peripheral nerve	X (sciatic)
Pharynx	
Pituitary	X*
Prostate	X*
Rectum	X
Salivary gland	X
Sciatic nerve	X
Seminal vesicles	X (with coagulating gland)
Skeletal muscle	X (biceps femoris)
Skin	X
Spinal cord	X
Spleen	X*
Sternum	X
Stomach	X
Testes	X*
Thymus	X*
Thyroid	X*
Tongue	X
Trachea	X
Urinary bladder	X
Uterus	X*
Vagina	X
Zymbal gland	

X, histopathology performed
*, organ weight obtained
[a], Organs weighed together; ovary/oviduct and uterus/cervix.

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/s/

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