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Badrul Chowdhury, MD, PhD
Division of Pulmonary, Allergy and
Rheumatology Products (DPARP)
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

NDA 205437
OTEZLA® (apremilast)
Sequence No. 0064

RE: RESPONSE TO PREA NON-COMPLIANCE LETTER AND DEFERRAL EXTENSION REQUESTED

Dear Dr. Chowdhury,

Reference is made to the FDA letter, dated 06 Feb 2017, notifying Celgene of its non-compliance with a postmarketing requirement (PMR) under the Pediatric Research Equity Act (PREA). Celgene's response to the Notification of Non-Compliance with PREA letter and additional Request for Deferral Extension is provided within this submission.

As noted in the FDA letter, Celgene is submitting a cross-reference letter to the IND to which the PMR protocol has been submitted.

Should you have any questions regarding this submission or need additional information, please do not hesitate to contact me.

Sincerely,

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CELGENE RESPONSE TO PREA NON-COMPLIANCE LETTER DATED 06 FEB 2017 AND DEFERRAL EXTENSION REQUESTED

Product Name:	**OTEZLA (apremilast)**
Application Number:	**NDA 205437; NDA 206088 (administratively closed)**
	IND 070270
Sponsor:	**Celgene Corporation**

Reference is made to the FDA letter, dated 06 Feb 2017, notifying Celgene of its non-compliance with postmarketing requirement (PMR) 2791-1 under the Pediatric Research Equity Act (PREA). Celgene's response to the Non-Compliance with PREA Letter and additional Request for Deferral Extension is provided below.

1. CELGENE RESPONSE TO NON-COMPLIANCE LETTER

Reference is made to New Drug Application (NDA) 205437 approved by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on 21 Mar 2014 for the treatment of adults with active psoriatic arthritis (PsA) and NDA 206088 approved by the Division of Dermatology and Dental Products (DDDP) on 23 Sep 2014 for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. On 07 Oct 2014, a General Advice Letter was received from DDDP informing Celgene Corporation (Celgene) that NDA 206088 was administratively closed and that all future submissions should be addressed to the Original NDA 205437 for this drug product. Based on the approval letter for NDA 206088, required pediatric assessments under PREA for subjects aged 6 to 17 years were deferred, specifically PMRs 2791-1 and 2791-2.

Reference is also made to NDA 205437 Annual Report submitted on 18 May 2016 (Sequence Number 0061). Per 21 CFR 314.18, the status of PMRs 2791-1 and 2791-2 were reported in Section 12 Status of Postmarketing Study Commitments of the NDA Annual Report, including the likely causes for site activation and enrollment challenges, the efforts made as part of the strategy to address these issues, as well as the revised timeline of PMR milestones, namely study completion and report submission dates. The specifics of the status update provided in the Annual Report are described below in further detail.

Subsequent to the submission of the NDA Annual Report, the FDA's Database for CDER Postmarket Requirements and Commitments updated the "Explanation of Status" section for Otezla PMR 2791-1, which led Celgene to believe that FDA was updated on the status of the PMRs and that Celgene remained compliant with PREA. Celgene was unaware of the need to submit a Deferral Extension Request under separate cover.

Celgene has been diligent in its efforts to complete Study CC-10004-PPSO-001 to fulfill PMR 2791-1 as quickly as possible. Celgene recognizes the importance of PREA and is fully

committed to fulfill both pediatric postmarketing requirements for Otezla. As instructed in the Non-Compliance with PREA Letter dated 06 Feb 2017, Celgene is formally requesting deferral extensions for its required pediatric assessments as described in the following section.

2. CELGENE REQUEST FOR DEFERRAL EXTENSION

Per 21 CFR 314.18, the status of PMRs 2791-1 and 2791-2 were reported in Section 12 Status of Postmarketing Study Commitments of the NDA Annual Report submitted on 18 May 2016 (Sequence Number 0061), cited below in *italics*:

A. Appropriate reason for deferral

PMR 2791-1: A dose finding, pharmacokinetics and safety trial in subjects with moderate to severe plaque psoriasis between the ages of 6 to 17 years.

Study CC-10004-PPSO-001 is delayed, a revised schedule with study milestones is provided in Table 1. *After Protocol Amendment #1 was submitted in September 2015, the first patient was enrolled in October 2015. As of the cutoff date of 20 Mar 2016, 3 subjects have been enrolled. Celgene believes this may be due to the following site activation and enrollment challenges:*

- *Logistics of the PK assessments, particularly the Day 14, 12 and 24 hour post dose PK assessments. Obtaining these assessments is a challenge due to subjects' time away from school and activities, parents' time away from work, and staffing by site personnel.*
- *Inclusion and exclusion criteria are too restrictive.*
  - *There have been potential subjects with less than 6 months duration of psoriasis or less severe psoriasis than the protocol allows.*
  - *There have been potential subjects with previous biologic experience. The greater availability of biologic therapies globally and the practice of prescribing them for a number of diseases including plaque psoriasis in children have become more common. Excluding patients who have had treatment with biologics has become highly impracticable in terms of recruiting patients for Study CC-10004-PPSO-001.*
- *Procedures. Several identified sites are not willing to participate because of the intensive PK sampling and certain study requirements, such as the completion of the Columbia-Suicide Severity Rating Scale (C-SSRS).*

Celgene has initiated a mitigation strategy to enhance recruitment. Key components of the strategy include identifying new sites for participation as well as considering amending the protocol with the following:

- *Removal of the 24 hour PK assessment, as the 12 hour assessment still allows for intensive PK sampling.*

- *Allow inclusion of subjects who have been previously exposed to a systemic biologic therapy for psoriasis or other indication, provided that the last dose has been given at least 5 terminal half-lives prior to enrollment.*

B. New timelines for PMR 2791-1 and 2791-2

Table 1: Status/Timeline for PMR 2791-1 – Delayed

Milestone	*Original Schedule*	*Revised Schedule*	*Status*
Final Protocol Submission:	*3/2015*	*3/2015*	*Completed*
Study Completion:	*7/2016*	*12/2017*	*Delayed*
Final PK Report Submission:	*1/2017*	*6/2018*	*Delayed*

PMR 2791-2: A safety and efficacy trial in pediatric subjects with moderate to severe plaque psoriasis between the ages of 6 to 17 years.

As of the cutoff date of 20 Mar 2016, this safety and efficacy trial is delayed due to the delay of the pharmacokinetic and safety trial, CC-10004-PPSO-001. A revised schedule with study milestones is provided in Table 2.

Table 2: Status/Timeline for PMR 2791-2 – Delayed

Milestone	*Original Schedule*	*Revised Schedule*	*Status*
Final Protocol Submission:	*3/2017*	*8/2018*	*Delayed*
Study Completion:	*3/2019*	*10/2020*	*Delayed*
Final Report Submission:	*9/2019*	*4/2021*	*Delayed*

C. Updates on certification, pediatric study plans, and evidence of due diligence

There are no significant updates to the information required on 21 USC 355c(a)(3)(A)(ii), namely Celgene's original certification for deferral of pediatric assessment and the pediatric study plan, as amended in the NDA Annual Report submission from 18 May 2016.

Regarding evidence of our due diligence, since the preparation of the 18 May 2016 NDA Annual Report submission, Celgene has been diligent in its efforts to complete Study CC-10004-PPSO-001 to fulfill PMR 2791-1 as quickly as possible. Study Protocol CC-10004-PPSO-001 (to fulfill PMR 2791-1) has been amended (Amendment #2 dated 29 Apr 2016; IND 070270 Sequence Number 0550 submitted 13 May 2016) and additional sites were activated as described

above in the planned mitigation strategy. Celgene has and continues to regularly engage sites with enrollment updates and study newsletters to encourage screening efforts.

As of 07 Mar 2017, enrollment has improved since Protocol Amendment #2, with Group 1 (aged 12-17 years) fully enrolled and 10 evaluable subjects enrolled in Group 2 (aged 6-11 years). However, Group 2 currently has no evaluable 6 or 7 year old subjects after four months of recruitment. Celgene plans to focus enrollment efforts on 6 and 7 year old subjects in order to assess their pharmacokinetic profile and determine the appropriate dose(s) for this age group in the efficacy and safety study (PMR 2791-2). Because of the challenges in recruiting these youngest subjects in Group 2, the study is still delayed from the original schedule outlined in the NDA 206088 approval letter. Therefore, Celgene is requesting a deferral extension for PMR 2791-1 with the revised schedule provided in Table 1, based on the previously shared unforeseen site activation and enrollment challenges. Additionally, the safety and efficacy trial is also delayed due to the delay of the of the pharmacokinetic and safety trial, CC-10004-PPSO-001. Therefore, Celgene is also requesting a deferral extension for PMR 2791-2 with the revised schedule provided in Table 2.

Celgene recognizes the importance of PREA and is fully committed to fulfill both pediatric postmarketing requirements for Otezla as quickly as possible. Celgene has been diligent in its efforts to complete Study CC-10004-PPSO-001. With the revised timelines proposed above, Celgene is confident in being able to complete the required pediatric assessments.

D. Timing of Deferral Extension Request

Please note our deferral extension request was made in the 18 May 2016 NDA Annual Report submission (NDA 205437; Sequence Number 0061), received by the Agency on the same day. This deferral extension request was made 7 months prior to the date that the deferral would have expired (January 2017). This was not less than the 90 days required by 21 USC 355c(a)(3(B)(ii); however, we were unaware that this request should have been made separately to the Division and not part of our annual report on the status of our pediatric studies.

Please see our request for deferral extension on pages 2-3 of Section 12 Status of Postmarketing Study Commitments of the NDA Annual Report.