DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125160/S-283

SUPPLEMENT APPROVAL

UCB, Inc.
Attention: Jennifer King
Regulatory Affairs Americas
1950 Lake Park Drive, Building 2100
Smyrna, GA 30080

Dear Ms. King:

Please refer to your Supplemental Biologics License Application (sBLA), dated July 24, 2017, received July 24, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for CIMZIA® (certolizumab pegol).

We also refer to our approval letter dated May 24, 2018 which contained the following errors:

- The submit and received date for the sBLA was noted as July 24, 2018. The sBLA submit and received date was July 24, 2017.
- On pages 2, 4, and 5 the referenced INDs (b) (4), respectively, are incorrect. The correct application is IND 100348.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain May 24, 2018, the date of the original approval letter.

This Prior Approval supplemental biologics application proposes a new indication for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is

identical to the enclosed labeling (text for the prescribing information, text for the patient package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.
Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than 6 years because necessary studies are impossible or highly impracticable. This is because:

- The prevalence of psoriasis in the 0 to less than 6 years age group is low (with the highest prevalence published of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

- Live vaccinations (MMR, varicella) are usually given in this age group, limiting the treatment of this pediatric population with certolizumab.

We are deferring submission of your pediatric study for ages 6 to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

3408-1	Conduct a Pharmacokinetics (PK), Safety, and Efficacy Study in pediatric subjects 6 to less than 18 years of age with moderate to severe psoriasis (with a duration of exposure to certolizumab pegol of at least one year).

The timetable you submitted on May 08, 2018 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2019
Study Completion:	02/2025
Final Report Submission:	12/2025

Submit the protocol to your IND 100348, with a cross-reference letter to this BLA.

Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk: for the presence of binding and neutralizing anti-drug antibodies in the proposed population as well as an unexpected serious risk of maternal, fetal and infant toxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3408-2	Utilize the validated immunogenicity assays developed under PMC 3408-5 and PMC 3408-6 to analyze the immunogenicity profile of certolizumab pegol using banked patient samples from Phase 3 trials CIMPASI-1, CIMPASI-2, and CIMPACT. Evaluate the impact of immunogenicity on pharmacokinetics, efficacy, and safety in subjects with psoriasis based on the immunogenicity data generated with the newly validated assays.

The timetable you submitted on May 08, 2018 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12//2018
Study Completion:	06/2019
Final Report Submission:	09/2019

3408-3 A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to certolizumab pegol during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life. You may expand a current prospective registry to include women who are exposed to certolizumab pegol for the treatment of plaque psoriasis.

The timetable you submitted on May 08, 2018 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12//2019
Study Completion:	07/2029
Final Report Submission:	01/2030

3408-4 Conduct a retrospective cohort study using claims or electronic medical record data or a case control study to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to certolizumab pegol during pregnancy compared to an unexposed control population.

The timetable you submitted on May 08, 2018 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2020
Study Completion:	09/2026
Final Report Submission:	09/2027

Submit the protocol(s) to your IND 100348, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3408-5 Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to certolizumab pegol, including procedures for the accurate detection of binding antibodies to certolizumab pegol in the presence of certolizumab pegol levels expected in the serum or plasma at the time of patient sampling. In addition, an assessment of the contribution of binding antibodies to PEG should also be evaluated.

The timetable you submitted on May 08, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2018

3408-6 Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to certolizumab pegol, including procedures for the accurate detection of neutralizing antibodies to certolizumab pegol in the presence of certolizumab pegol levels that are expected in the serum or plasma at the time of patient sampling.

The timetable you submitted on May 08, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2018

Submit clinical protocols to your IND 100348 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should

include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Barbara Gould, Chief, Project Management Staff, at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
05/24/2018