Clinical Pharmacology Review

sBLA Number	103,795/5552
Link to EDR	*\\cdsesub1\evsprod\bla103795\103795.enx* *(SDN 3335, eCTD 0474)*
Submission Date	01/05/2016
Submission Type	Efficacy supplement
Brand Name	Enbrel®
Generic Name	Etanercept
Proposed Indication	Treatment of pediatric patients ages 4 to 17 years with chronic severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Applicant	AMGEN Inc.
Clinical Pharmacology Reviewer	Jie Wang, Ph.D.
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OND Division	CDER/ODEIII/DDDP

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1. SUMMARY

Enbrel® (etanercept) is a recombinant tumor necrosis factor (TNF) receptor Fc fusion protein. Enbrel is currently approved for multiple indications including rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA) in patients aged 2 years or older, psoriatic arthritis (PsA), ankylosing spondylitis (AS), and plaque psoriasis (PsO).

In the current efficacy supplement (sBLA 103,795/5552), the Applicant proposed to add a new indication for Enbrel for the treatment of pediatric patients aged 4 to 17 years with chronic **severe** PsO who are candidates for systemic therapy or phototherapy. To support the proposed pediatric PsO indication, the Applicant conducted two clinical studies: Study 20030211 and its open-label extension Study 20050111.

In 2007, the Applicant submitted the results of Study 20030211 in an efficacy supplement (sBLA 103,795/5350) for the treatment of **moderate-to-severe** pediatric PsO. The Clinical Pharmacology review for supplement 5350 determined that the submitted clinical pharmacology information associated with Study 20030211 was acceptable to support the approval. However, supplement 5350 received a complete response (b) (4) In the current efficacy supplement, the Applicant resubmitted the study report for Study 20030211 and additionally submitted the long-term clinical data from Study 20050111.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed two BLA supplements, i.e., supplement 5350 submitted in 2007 and supplement 5552 submitted in 2015. Overall, the clinical pharmacology information associated with Study 20030211 and Study 20050111 is acceptable to support the approval.

Reviewer's Comments*: The Applicant has changed the proposed pediatric PsO indication from "moderate-to-severe" PsO as proposed in Supplement 5350 to "severe" PsO in the current Supplement 5552. The risk-benefit profile of Enbrel in the target pediatric PsO patient population was discussed in the DODAC meeting held on June 18, 2008. The Clinical review team further discussed the risk-benefit profile of Enbrel for pediatric PsO patients with the FDA internal committee members in the CDER regulatory briefing on July 22, 2016. The Clinical Pharmacology review team defers the determination of whether the risk-benefit profile is acceptable for the "severe" or "moderate-to-severe" pediatric PsO indication to the Clinical review team.*

2. CLINICAL PHARMACOLOGY FINDINGS

This review contributes to the overall clinical pharmacology review for the pediatric psoriasis indication by building upon the Clinical Pharmacology Review of supplement 5350. It focuses on the clinical pharmacology information submitted in supplement 5552 and not previously reviewed under supplement 5350. Specifically, this review assessed the immunogenicity data associated with Studies 20030211 and 20050111 and the review findings are summarized below:

- Approximately 10% (20/208) of subjects developed antibodies to etanercept by Week 48 in Study 20030211 and approximately 16% (33/208) of subjects developed antibodies to etanercept through 6 years of treatment in combined Studies 20030211 and 20050111. None of the anti-drug antibodies (ADA) was reported as neutralizing ADA.

- The formation of ADA did not appear to be associated with decreased serum etanercept concentrations or reduced PASI 75 response rate at Week 12 in Study 20030211. However, a definitive determination of the immunogenicity impacts on PK or efficacy could not be made because of the small number of ADA+ subjects.

2.1 Clinical studies

This section provides a brief summary of study design for Studies 20030211 and 20050111. Study 20030211 had both PK and immunogenicity data up to Week 48. Study 20050111 had immunogenicity data through Week 264 but did not have a PK component.

- **Study 20030211**

  The primary objective of Study 20030211 was to determine the efficacy of etanercept in pediatric subjects with PsO. Study 20030211 consisted of three treatment period: a 12-week double-blind and placebo-controlled treatment period, a 24-week open-label treatment period, and a 12-week randomized double-blind withdrawal-retreatment period (Figure 2.1.a).

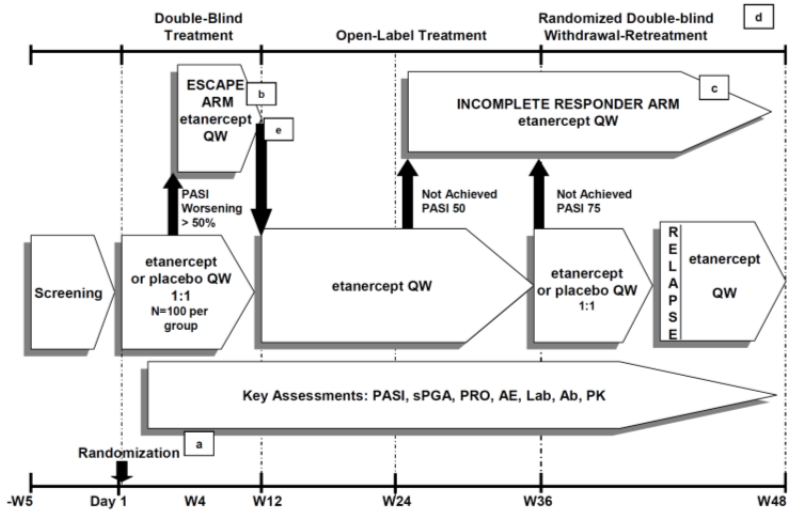

Figure 2.1.a. Design for Study 20030211. (*Data source: Figure 7-1, CSR 20030211.*)

- During the 12-week double-blind and placebo-controlled treatment period (Day 1−Week 12), subjects received SC administration of either placebo or etanercept 0.8 mg/kg (up to an intended dose of 50 mg) weekly (etanercept QW).
- During the 24-week open-label treatment period (Weeks 13−36), all subjects received etanercept QW. At Week 24, PASI 50 responders remained on etanercept QW; and subjects who did not achieve a PASI 50 response either discontinued the study or entered the incomplete responder arm. Subjects who entered the incomplete responder arm continued to receive etanercept QW through week 48 and had the option to receive topical standard of care treatment. At Week 36, subjects were evaluated to determine whether they achieved a PASI 75 response.
- During the 12-week withdrawal-retreatment period (Weeks 37−48), subjects (not including subjects already in the incomplete-responder arm) who achieved a PASI 75 response were randomized to placebo or etanercept QW. When their disease relapsed (i.e., loss of PASI 75), subjects resumed open-label etanercept QW through Week 48. Subjects who did not achieve a PASI 75 response at Week 36 either discontinued the study or entered the incomplete-responder arm. Subjects who entered the incomplete-responder arm continued to receive etanercept QW through Week 48 and had the option to receive topical standard of care treatment.

Pharmacokinetics

Blood samples for measurement of serum etanercept concentrations were collected at Baseline and at Weeks 12, 24 and 48.

Immunogenicity

Blood samples for immunogenicity assessment were collected at Baseline and at Weeks 12 and 48.

- **Study 20050111**

  The primary objective of Study 20050111 was to evaluate the long-term safety of etanercept in pediatric subjects with PsO. Study 20050111 was an open-label extension study for eligible subjects from Study 20030211. These subjects received etanercept QW (0.8 mg/kg, up to an intended dose of 50 mg) for 264 weeks or until the quarterly visit after their 18th birthday, whichever came last.

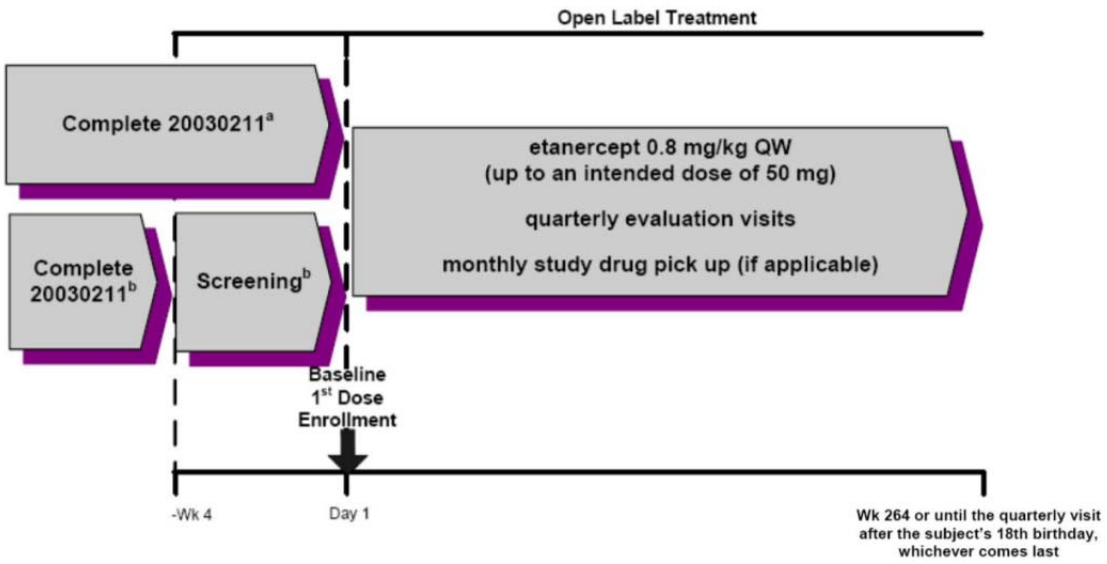

Figure 2.1.b. Design for Study 20050111. (*Data source: Figure 7-1, CSR 20050111.*)

Pharmacokinetics

Study 20050111 did not collect PK samples.

Immunogenicity

Blood samples for immunogenicity assessment were collected at Baseline, at Weeks 48, 96, 144, 168 and 264.

***Reviewer's comments**: The Office of Clinical Pharmacology reviewed Study 20030211 originally submitted in Supplement 5350 and has determined that the Clinical Pharmacology information in Study 20030211 was acceptable. The current Clinical Pharmacology review focuses on the immunogenicity data associated with Studies 20030211 and 20050111. The Clinical Pharmacology review for Supplement 5350 did not include assessment of the immunogenicity impact on PK or efficacy because the Applicant did not provide such information at that time; we have included the immunogenicity impact assessment in the current review.*

2.2 Immunogenicity results

2.2.1 What is the incidence of the formation of anti-drug antibodies (ADA) to etanercept?

Approximately 10% (20/208) of subjects developed antibodies to etanercept by Week 48 in Study 20030211 and approximately 16% (33/208) of subjects developed antibodies to etanercept through 6 years of treatment in combined Studies 20030211 and 20050111 (*Source of Data: section 4, Summary of Clinical Pharmacology Studies*). None of the ADA was reported as neutralizing ADA (NAb). A total of 210 subjects received at least 1 dose of etanercept and 208 subjects had serum samples available for immunogenicity testing in Studies 20030211 and 20050111.

***Reviewer's comments**: The OBP review team has determined that the immunogenicity assays were not appropriately validated for testing of the pediatric PsO patient population (Internal Wrap-up Meeting, August 30, 2016). The OBP review team also pointed out that it may not be feasible to re-test the immunogenicity samples using improved assays because the pediatric PsO clinical trials were conducted more than 10 years ago. Enbrel has been approved for multiple indications including JIA in patients aged 2 years or older; and, to our knowledge, development of antibodies to etanercept has not been reported as a clinical concern. The clinical studies in pediatric PsO patients in the current supplement also did not show that ADA development was associated with a clinical impact on PK or efficacy (see Section 2.2.2 of this review). We also note that the immunogenicity incidence in pediatric PsO patients is numerically higher than that reported in the adult PSO patients, which is somewhat reassuring that the lack of appropriate assay validation does not appear to have impeded the ability of the assay to detect ADA. Given these factors, we would recommend to use the currently available clinical data to inform the immunogenicity section of the label for the pediatric PsO indication, although we acknowledge the limitations of the immunogenicity assays and agree that the reported incidence of ADA and NAb may not be accurate.*

We agree with the OBP review team that the assay should be properly validated as a post-marketing activity. In the future, when the Applicant pursues new indications for either the approved or new patient populations, the Applicant should conduct appropriate immunogenicity assessment using validated assays and evaluate clinical impact of ADA.

2.2.2 What are the impacts of ADA on etanercept PK and efficacy?

The formation of ADA did not appear to be associated with decreased serum etanercept concentrations or reduced PASI 75 response rate at Week 12 in Study 20030211. However, a definitive determination of the immunogenicity impacts on PK or efficacy could not be made because of the small number of ADA+ subjects.

The mean±SD serum etanercept concentrations at Week 12 were 1.3±0.8 mcg/mL (n=7) and 1.6 ± 0.8 mcg/mL (n=89) in ADA+ and ADA- subjects, respectively. In general, the trough serum etanercept concentrations in ADA+ subjects were within the range of those in ADA- subjects at Weeks 12 and 48 (Figure 2.2.2). At Week 12, 57% (4/7) ADA+ subjects achieved PASI 75 response in comparison to 60% (53/89) in ADA- subjects. A similar assessment after treatment for 48 weeks has not been conducted because the study design is not suitable for such an assessment.

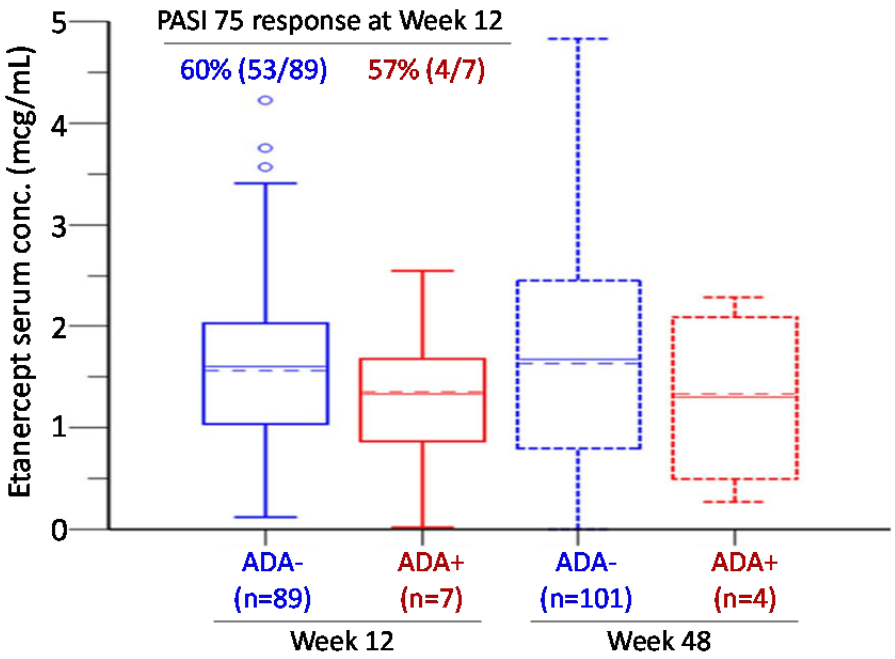

Figure 2.2.2. Etanercept serum concentrations at Weeks 12 and 48 and PASI 75 response rate at Week 12 by ADA status in Study 20030211. Among the ADA+ subjects in Study 20030211, only 7 subjects and 4 subjects had etanercept concentration data at Week 12 and Week 48, respectively. Similarly, 89 and 101 of the ADA- subjects in Study 20030211 had etanercept concentration data at Week 12 and Week 48, respectively. Abbreviations: ADA, anti-drug antibodies. (*Data source: Figure 4, Table 7, Table 8, Summary of Clinical Pharmacology Studies*)

3. APPENDIX: CLINICAL PHARMACOLOGY REVIEW FOR EFFICACY SUPPLEMENT (sBLA 103,795/5350)

The Clinical Pharmacology Review (by Abimbola Adebowale, Ph.D. and Jang-Ik Lee, Pharm.D., Ph.D.) for efficacy supplement sBLA 103,795/5350 is attached below.

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/s/

JIE WANG
09/01/2016

YOW-MING C WANG
09/02/2016