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GIDAC Briefing Document

BLA:	125057/232
Applicant:	Abbott Laboratories
Product:	Humira (adalimumab)
Gastroenterology Drugs Advisory Committee Meeting	August 28, 2012

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

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1. EXECUTIVE SUMMARY

1.1 Statement of Purpose

The purpose of this Advisory Committee Meeting is to obtain advice regarding the efficacy and safety of Humira (adalimumab) for the proposed indication based on data from two randomized, double-blind, placebo-controlled trials and one single-arm, open-label trial. The Applicant, Abbott Laboratories, proposes the following indication:

> "HUMIRA is indicated for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy."

The proposed dose for ulcerative colitis (UC) administered by subcutaneous (SC) injection is:

- 160 mg initially (Day 1) (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by
- 80 mg two weeks later (Day 15), followed by
- 40 mg every other week beginning two weeks later (Day 29) (maintenance dose)

1.2 Background

This prior-approval efficacy supplement to the BLA (sBLA) for Humira (adalimumab) was initially submitted on January 25, 2011. A Complete Response (CR) Letter was sent by the Division of Gastroenterology and Inborn Errors Products on November 21, 2011.

The current resubmission, received March 30, 2012, is a complete response to the CR letter, and represents the second review cycle for this sBLA.

1.3 Clinical Summary

The table below summarizes the two controlled clinical trials (Studies 826 and 827) and one open label clinical trial (Study 223) submitted in support of the sBLA.

Table 1: UC Studies

Study	Design	Population	Treatment Duration	Treatment Arms
826 (Induction of Remission Trial)	R, DB, PC	▪ Moderately to severely active UC*	8 weeks	➢ Humira 160/80/40[#] (n=130[‡]) ➢ Humira 80/40[†] (n=130[‡]) ➢ Placebo (n=130[‡])
827 (Induction and Sustained Remission Trial)	R, DB, PC	▪ Moderately to severely active UC* ▪ Prior TNFα-antagonist users (40%)	52 weeks	➢ Humira 160/80/40[#] (n=258) ➢ Placebo (n=260)
223 (Extension Study)	OL	▪ Continuation from Studies 826 and 827	240 weeks planned (ongoing)	➢ Humira 40 EOW or EW (n=592[§])

R: Randomized; DB: Double-blind; PC: Placebo-controlled
*Total Mayo Score ≥ 6 and Endoscopy sub-score ≥ 2 despite concurrent or prior treatment with steroids and/or immunosuppressants.
[#] 160/80/40: 160 mg at Week 0, 80 mg at Week 2, and 40 mg at Week 4 and every other week (EOW) thereafter;
[†] 80/40: 80 mg at Week 0, 40 mg at Week 2, and EOW thereafter;
[‡] n indicates ITT-A3 pre-specified analysis population (after Amendment 3: addition of a third lower dose treatment arm).
[§] Data cutoff date of December 16, 2011. 592 enrolled (349 receiving 40 mg EOW and 243 receiving 40 mg EW); 384 ongoing (255 receiving 40 mg EOW and 129 receiving 40 mg EW); escalation from EOW to EW allowed during study for inadequate response.

Both studies enrolled patients with a Total Mayo Score of ≥ 6 and Endoscopy sub-score of ≥ 2 despite concurrent or prior treatment with steroids and/or immunosuppressants.

Prior TNFα-Antagonist Use: The proposed indicated population is limited to patients that had an inadequate response to conventional therapy (where conventional therapies include mesalamine, immunosuppressants and steroids). Although both studies enrolled patients that met these criteria, the two studies differed on criteria for prior TNFα-antagonist use. In one study, all patients were naïve to prior TNFα-antagonists while in the other study approximately 40% of patients enrolled had lost response to or were intolerant to a prior TNFα-antagonist. See Table 2 below.

Table 2: Prior TNFα-Antagonist Use by Study

Study	Prior TNFα-Antagonist Use Criteria
826 (Induction of Remission Trial)	Excluded patients that previously used a TNFα-Antagonist
827 (Induction and Sustained Remission Trial)	Allowed entry of patients that previously used a TNFα-Antagonist provided they discontinued due to a **loss of response* or intolerance**[#] to the agent.

*Loss of Response: responded previously to a TNFα-antagonist but lost response after at least 2 subsequent doses
[#] Intolerance defined as acute or delayed reaction. (See Appendix 2)

Primary Endpoints: The primary endpoints are summarized below. In both studies, clinical remission was defined as a total Mayo score of ≤2 with no individual sub-score >1.

Table 3: Primary Endpoint by Study

Study	Primary Endpoint
826 (Induction of Remission Trial)	**Clinical Remission at Week 8**
827 (Induction and Sustained Remission Trial)	Ranked Co-Primary Endpoint: (1) **Clinical Remission at Week 8** (2) **Clinical Remission at Week 52**

Study 827 was the only study submitted to support the proposed indication for maintenance of remission. It should be noted that a study design intending to support maintenance of remission should re-randomize subjects that achieve remission at Week 8. Re-randomization at the end of the induction phase to drug or placebo allows the separate effect of maintenance therapy to be evaluated. The design of Study 827 is better suited to support sustained remission (a measure of durability in contrast to maintenance); i.e., if the ranked co-primary endpoint and the first-ranked secondary endpoint of sustained remission (**Clinical Remission at Weeks 8 and 52**) are met.

1.3.1 Efficacy

Key results of the two controlled trials are in the table below.

Table 4: Clinical Remission (Studies 826 and 827)

Study Week	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	95% CI	p-value[‡]
Study 826					
Week 8*	9.2% (12/130)	18.5% (24/130)	**9.3%**	**(0.8%, 17.9%)**	**0.031**
Study 827					
Week 8[#]	9.3% (23/246)	16.5% (41/248)	**7.2%**	**(1.3%, 13.2%)**	**0.019**
Week 52[#]	8.5% (21/246)	17.3% (43/248)	**8.8%**	**(2.9%, 14.8%)**	**0.004**
Weeks 8 and 52[†]	4.1% (10/246)	8.5% (21/248)	**4.4%**	**(0.1%, 9.0%)**	**0.047**

*Clinical Remission at Week 8 is the Primary Endpoint of Study 826.
[#]Clinical Remission at Week 8 is the first ranked Co-Primary Endpoint of Study 827; Clinical Remission at Week 52 is the second ranked Co-Primary Endpoint of Study 827.
[†]Clinical Remission at Weeks 8 and 52 is the first-ranked secondary endpoint of Study 827.
[‡] Based on the chi-squared test for Study 826 and the Cochran-Mantel-Haenszel (CMH) test for Study 827

Although the two trials demonstrated statistically significant improvement with Humira relative to placebo, the concerns below were identified in the CR Letter:

- For Study 826, the conclusions are not considered robust from a statistical perspective because the results are sensitive to alternative analyses. (Specific analyses by the FDA Statistical Reviewer were cited: use of exact testing methods, change in remitter status of one patient in the placebo or Humira group, and adjusting the primary analysis by baseline Mayo score.)
- For both Studies 826 and 827, the appropriate dose may not have been selected.
- For both Studies 826 and 827, the modest improvements in the rates of clinical remission at Week 8 and sustained clinical remission at Weeks 8 and 52 reported (treatment differences relative to placebo) were noted.

The CR Letter also stated that these concerns would be discussed in a future meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC).

Sensitivity analyses conducted by the FDA Statistical Reviewer that led to the concern (in the first bullet above) are summarized in the table below.

Table 5: Alternative Analyses (Study 826 Primary Endpoint)

Alternative Analyses	Placebo	Humira 160/80/40	Humira-Placebo	p-value
Original Analysis* (for reference)	9.2%	18.5%	9.3%	0.031
#1: Fisher's Exact Test (instead of Chi-squared)	9.2%	18.5%	9.3%	**0.047**
#2a: One Humira Patient Changed from Remitter to Non-Remitter#	9.2%	17.7%	8.5%	**0.068**
#2b: One Placebo Patient Changed from Non-Remitter to Remitter#	10.0%	18.5%	8.5%	**0.075**

*The original analysis used the chi-squared test and did not adjust for baseline Mayo scores
#This analysis used Fisher's exact test

Note that for #1, the p value becomes borderline, and that for #2a and #2b, the p value becomes non-significant. In addition to the above, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment difference was not statistically significant (p=**0.085**).

The FDA Clinical Reviewer questioned whether the treatment differences of less than 10% observed in both studies are clinically meaningful and whether the results could be related to the dose selected for the clinical trials (see also Section 1.3.2 Clinical Pharmacology).

The Applicant discussed their approach in responding to the review issues in a meeting with the FDA after the CR Action. The Applicant proposed submitting additional analyses that:

- explore the totality of the data,
- demonstrate the clinical meaningfulness of the clinical results, and
- support a favorable benefit/risk profile.

The Agency advised the Applicant that the resubmission would be accepted for review, but the multiple post hoc analyses proposed would be considered exploratory.

The specific exploratory analyses submitted by the Applicant in the resubmission included the following:

- primary and secondary analyses of Study 826 using the ITT-E population (i.e., all patients enrolled that received study drug or placebo);
- integrated primary and secondary analyses across Studies 826 and 827;
- additional exploratory analyses from Study 827 (e.g., clinical response based on partial Mayo score at Weeks 2, 4, and 8 and clinical response based on full Mayo score at Week 8);
- re-analysis of full and partial Mayo scores at Baseline and Week 52 using average of last 3 days (rather than standard "worst-ranked" methodology)-Study 827;
- all-cause and UC-related hospitalizations (pooled across Studies 826 and 827); and
- exploratory analyses of clinical remission and clinical response status at Week 52 in the subgroup of patients from Study 827 in clinical response at Week 8.
- serious adverse event (SAE)-adjusted days in remission
- number of patients who discontinued due to adverse events (AEs) relative to number of patients in remission at Weeks 8 and 52
- Net Efficacy Adjusted Risk (NEAR) analysis
- Number Needed to Harm (NNH) analyses

The exploratory analyses were difficult to interpret because neither the endpoints nor the comparisons were prospectively defined in the protocols.

1.3.2 Clinical Pharmacology

The available exposure-response data in patients with UC indicate that the dosing regimen for induction phase has not been fully explored. Exposure-response analysis was conducted (using data from Study 827[1]) to evaluate the adequacy of the proposed induction and maintenance doses.

Induction: The exposure-response analysis suggested that a higher induction dose could achieve a greater treatment effect for the induction of clinical remission at Week 8 because of the following observations:

(a) There was an increased remission rate with increased exposures that did not plateau at higher exposures. A statistically-significant (p=0.0002) relationship was established between adalimumab Week 8 trough concentration and clinical remission at Week 8 using logistic regression.
(b) Patients with lower exposures in the induction phase exhibited inadequate response (and switched to open label treatment) earlier than patients with higher exposures.

[1] Study 827 was the only study in which PK data were collected.

Maintenance: A robust exposure-response relationship for the maintenance phase could not be established due to significant drop out and missing PK data.

In light of the modest treatment effect for induction of clinical remission, the exposure-response findings contributed to the concern that the induction dose studied in the two clinical trials may not be optimal.

1.3.2 Safety

No new safety concerns were identified in the submitted studies. Known events associated with the use of Humira are adequately represented in current labeling.

The current labeling for Humira[2] as well as other TNFα-antagonists has a boxed warning for serious infections and malignancies. The following serious adverse reactions are highlighted in the boxed warming for serious infections: tuberculosis, bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. The following serious adverse reactions are highlighted in the boxed warming for malignancies: hepatosplenic T-cell lymphoma (HSTCL) and other lymphomas and malignancies.

1.4 Benefit-Risk Considerations

Ulcerative colitis is a serious chronic condition, which if not adequately treated can have significant impacts on patients' quality of life and may require hospitalization and surgical intervention. Given the variability in efficacy and tolerance of current treatments for UC (e.g., corticosteroids, azathioprine, 6-mercaptopurine, infliximab), the availability of another biologic option would be welcome, particularly in patients with more severe forms of the disease.

The two placebo-controlled trials submitted in support of this Application were adequate, but several limitations introduced uncertainty into the strength and robustness of the efficacy findings. There is additional uncertainty about the degree to which the studied trial populations reflect the intended patient population, particularly regarding use of prior TNF-blockers given that the two studies differed on criteria for prior TNF-blockers use. Moreover, the Applicant provided post-hoc analyses that are of questionable value. Thus, these trials provide moderate evidence of a marginal effect (< 10% over placebo) on efficacy for induction of remission, and even weaker evidence of a lesser effect (<5% over placebo) on sustained remission.

Additionally, we question if there is sufficient evidence to suggest that Humira would offer any clinical advantage in any particular sub-population, including patients who do

[2] Humira Label May 24, 2012 from Drugs@FDA at the following link:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125057s0278lbl.pdf (accessed July 29, 2012)

not respond to Remicade. Because Humira is administered subcutaneously rather than intravenously, Humira may provide an additional convenience benefit; as such, it is possible that Humira, if approved, may be considered as a possible alternative to Remicade in clinical practice to either induce or maintain remission. The sequential use of one product for induction and the other for maintenance was not studied in the clinical trials; there is considerable uncertainty about whether this will result in clinical benefit to the population.

The safety risks of Humira are serious but well-known. The overall safety profile of Humira is acceptable for a TNF-blocker, and no new or unexpected safety concerns were identified that would require additional risk management beyond what is already required. However, Humira has not been shown to provide a safety advantage over the currently marketed therapeutic option.

Therefore, the central review issue is whether the Applicant has adequately demonstrated and provided evidence of benefit sufficient to conclude that the benefit outweighs the risks of Humira for this indication. Specifically, does a) Humira provide a clinically meaningful benefit in patients with moderately to severely active UC; and b) is this purported benefit sufficient to outweigh the drug's serious known risks, considering the availability of another effective treatment (Remicade). In this context, we question the clinical meaningfulness of the observed clinical remission difference (drug vs. placebo) of less than 10%. We acknowledge the potential additional benefit of the subcutaneous Humira formulation; however, moving patients from an effective treatment to potentially less effective treatment, while still exposing them to the comparable serious safety risks, is a concern.

Please consider that additional evidence could help support the evaluation of the benefit-risk assessment for a Humira UC indication. The exposure-response data indicate that an exploration of a higher dose is warranted for induction. Availability of an immunogenicity assay with improved drug tolerance may provide evidence that Humira can provide some advantage in patients susceptible to the development of anti-drug antibodies. Finally, a study that can demonstrate specific benefit to any particular subgroup of patients could increase our confidence that Humira should have a place among the approved treatments for ulcerative colitis.

2. ADVISORY COMMITTEE TOPICS FOR DISCUSSION

The FDA requests that the Advisory Committee consider the following topics during review of this (and the Applicant's) briefing document. These topics are intended to frame the major review issues that will be the foundation for more specific questions posed to the Committee at the meeting.

1. Dose Selection:

Based on the exposure response data and observed treatment effect presented, consider if the dose studied for Humira for UC has been adequately identified. Consider the need for further dose exploration. Also, consider whether this should be done pre- or post-approval.

2. Primary Efficacy Analysis (Studies 826 and 827):

(a) **"Clinically Meaningful Benefit"**:
In defining the term, "Clinically meaningful benefit" to patients with moderately to severe active UC, be prepared to discuss the factors that you consider when determining whether a drug provides a clinically meaningful benefit to patients in this population.

(b) **Induction of Clinical Remission at Week 8:**
Consider if the observed treatment differences in the proportion of patients that achieved induction of clinical remission of 9.3% (95% CI: 0.8%, 17.9%) (Study 826[3]) and 7.2% (95% CI: 1.3%, 13.2%) (Study 827[4]) represent a clinically meaningful benefit?

(c) **Sustained Clinical Remission at Weeks 8 and 52:**
Consider if the observed treatment difference in the proportion of patients that achieved sustained clinical remission of 4.4% (95% CI: 0.1%, 9.0%) (Study 827) represents a clinically meaningful benefit (please explain your vote)

3. Population for Labeling:

The proposed indicated population is: "adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy." The entry criteria for Studies 826 and 827 were based on current disease activity despite concurrent or prior treatment with steroids and/or immunosuppressants. Both studies enrolled TNFα-antagonist naïve treated patients, but Study 827 also allowed entry of patients who previously used a TNFα-antagonist. (Approximately 40% of the patients in Study 827 had previously used a TNFα-antagonist).

[3] The pre-specified analysis population for Study 826 includes exclusively the ITT-A3 population (i.e., patients enrolled after Amendment 3 which added a third lower dose treatment arm).
[4] The pre-specified analysis population for Study 827 includes exclusively the ITT population.

(a) **Regarding the Proposed Indication for Inadequate Response to Conventional Therapy:**
Consider how conventional therapy should be defined for labeling, and whether prior exposure to TNFα-antagonists should be included in the labeled indication. Consider if the results of Studies 826 and 827 constitute substantial evidence of efficacy of Humira in each potential subpopulation of the **proposed indicated population** for induction of clinical remission **and** sustained clinical remission. Consider whether you would recommend labeling specifying that the product is **only indicated for TNFα-antagonist naïve patients**.

4. Additional Pre-Approval Studies:

Consider if additional efficacy studies should be obtained prior to approving Humira for moderately to severely active UC?

Consider the following:

(a) **Dose Selection**

(b) **Study Population** (e.g., inadequate response, lost response, or intolerance to another TNF-α antagonist).

(c) **Generalizability of Population Studied to Clinical Practice**:
Consider if the studies' patient populations, with respect to range of baseline disease severity and use of prior therapies, adequately reflect your expectations of how the drug, if approved for the proposed indication, would be used in clinical practice. Consider the impact that the route of administration, subcutaneous (SC) injection, would be expected to have on the clinical decision to use this product in UC patients (for example, greater or lesser use in a particular subpopulation defined by disease severity and/or use of prior therapies).

6. Benefit-Risk Considerations:

Consider if the expected benefits outweigh the known and potential risks of Humira for the treatment of patients with moderately to severely active UC based on currently available data. Specifically consider particular subpopulation(s) defined by level of disease severity or inadequate response/intolerance to prior therapies.

7. Post-Approval Studies:

If you believe this product should be approved, consider if any additional studies should be recommended post-approval.

3. BACKGROUND

3.1 Humira (adalimumab)

Adalimumab is a chimeric IgG monoclonal antibody that binds to TNFα and blocks its interaction with cell surface receptors, which in turn inhibits TNFα-induced pro-inflammatory effects.

Humira was originally approved for rheumatoid arthritis in 2002. Since then, it has also been found to be effective in treating several other diseases, and it is currently also approved for juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis.

Humira has no specific contraindications. The approved labeling has a boxed warning for serious infections and malignancies, which is part of TNFα-antagonist class labeling. The following serious adverse reactions are highlighted in the boxed warming for serious infections: tuberculosis, bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. The following serious adverse reactions are highlighted in the boxed warming for malignancies: hepatosplenic T-cell lymphoma (HSTCL) and other lymphomas and malignancies. There are also warnings and precautions for hypersensitivity reactions, Hepatitis B virus reactivation, demyelinating disease, cytopenias, use with anakinra, heart failure, autoimmunity, use with live vaccines, and use with abatacept.

The recommended dosing for each of the approved indications is summarized below:

- Rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: 40 mg every other week. It should be noted that the labeling states that patients with rheumatoid arthritis who are not receiving concomitant methotrexate may benefit from increasing the dosing frequency to 40 mg every week.
- Juvenile idiopathic arthritis (patients 4 to 17 years of age): 20 mg every other week (for patients that weigh 15 to 30 kg), and 40 mg every week (for patients that weigh 30 kg or more).
- Plaque psoriasis: initial dose of 80 mg followed one week later by a dose of 40 mg every other week.
- Crohn's disease: same dose as that proposed for UC (i.e., 160 mg, followed two weeks later by a dose of 80 mg, in turn followed two weeks later by a dose of 40 mg every other week).

3.2 Ulcerative Colitis

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown etiology. Peak age of onset is in the early twenties, but age of onset can vary widely. UC is more common in whites vs. non-whites and in women vs. men. The disease is manifest as mucosal inflammation and mucosal ulceration that occurs in the colon in a continuous segment beginning with the rectum. Extent of involvement varies, but it can include the entire

colon. Involved areas classically show inflammatory changes that are limited to the mucosa, and, depending on severity, there may be extensive, broad-based ulceration.

Clinically, UC presents as a chronic relapsing disease with variable-length bouts of bloody mucoid diarrhea and lower abdominal pain, but there may be long quiescent periods between attacks. There may also be systemic manifestations of the disease, with involvement of joints, eyes, skin, or the hepatobiliary system. Potential serious complications include severe bleeding, toxic megacolon, and perforation. There is a very significant risk of colon cancer with longstanding disease, such that pancolitis of 10 years duration or longer has a 20- to 30-fold increased risk of cancer compared to the general population. Surveillance colonoscopies for patients at higher risk are routinely offered.

3.3 Current Treatment Options for Ulcerative Colitis

Decisions about treatment of UC weigh such factors as disease activity, disease extent and duration, previous treatment attempts and the patient's preference. The goal is to stop the patient's active acute disease (induction of remission) and then maintain the patient in remission.

Aminosalicylate preparations, given orally, rectally or in combination, are the first line of treatment for induction of remission (aminosalicylates are approved to treat mildly or moderately active UC including, for certain products, maintenance of remission). Patients with mild-to-moderate UC that is refractory to aminosalicylates are often advanced to oral corticosteroids (approved to "tide the patient over a critical period") and immunosuppressive agents (e.g., azathioprine or 6-mercaptopurine; widely used but unapproved). Use of any of the preceding has come to be considered part of "conventional therapy."

Currently, Remicade (infliximab) is the only TNFα-antagonist approved for induction and maintenance of remission in patients with moderately to severely active UC who have inadequate response to conventional therapy. Remicade has been shown to be effective in this population and has an acceptable safety profile; however, many patients do not respond initially, lose response over time, and/or develop intolerance.

Colectomy is still required for many when medical therapy fails or when epithelial dysplasia is found on surveillance. Total proctocolectomy with ileal pouch–anal anastomosis (IPAA) is currently the procedure of choice because it preserves anal sphincter function. While the mortality of the procedure is low, long-term morbidity is not. Pouchitis, often intermittent and recurrent, is a prevalent problem with symptoms that include increased stool frequency, urgency, incontinence, seepage, and abdominal and perianal discomfort.

4. CLINICAL / STATISTICAL - EFFICACY

4.1 Overview of Phase 3 Clinical Trials

Studies 826 and 827 were randomized, double-blind, placebo-controlled trials submitted in support of the proposed induction and maintenance indications.

Entry Criteria:

Key entry criteria for each of the studies (826 and 827) were:

- a total Mayo score of 6-12 and an endoscopy subscore of 2-3
- concurrent treatment with oral corticosteroids and/or immunosuppressants or judgment of the investigator that the patient had inadequate response/intolerance to oral corticosteroids and/or immunosuppressants during the past 5 years.

(The full listing of entry criteria for the two studies is provided in APPENDIX 1: Inclusion and Exclusion Criteria.)

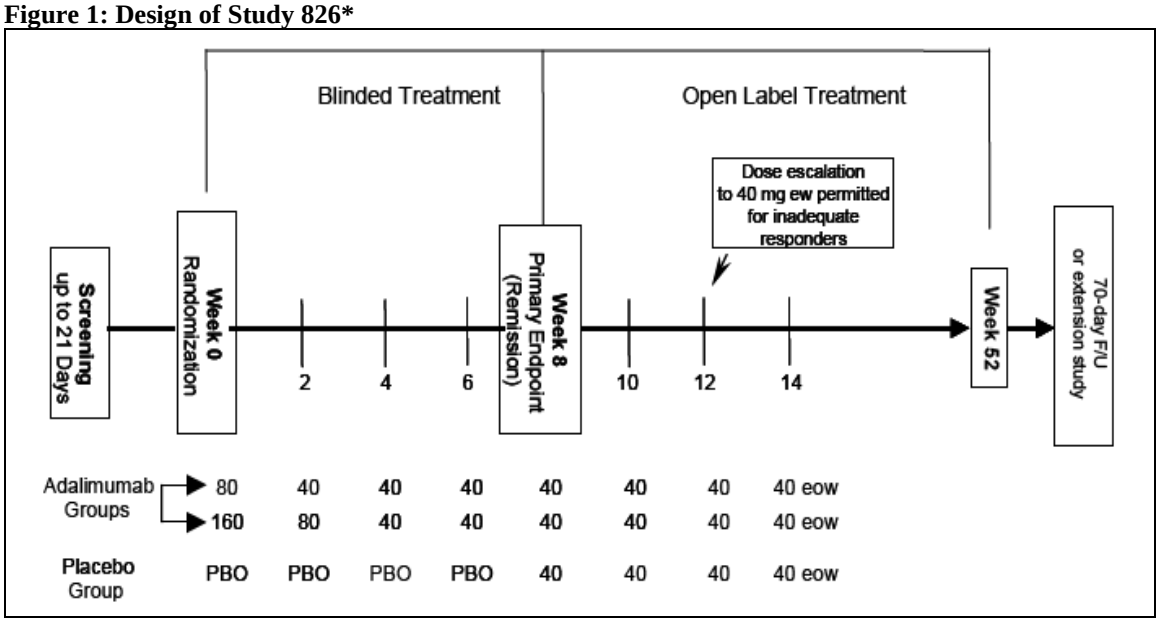
A key difference between the two studies was the following:

- Study 826 excluded patients that previously used an anti-TNF agent whereas
- Study 827 allowed entry of patients that previously used an anti-TNF agent provided they discontinued its use due to a loss of response or intolerance to the agent. (Definitions of Loss of Response and Intolerance to an Anti-TNF Agent for Study 827 are provided in APPENDIX 2: Definitions of Loss of Response and Intolerance to an Anti-TNF Agent (in Study 827).)

Study Design:

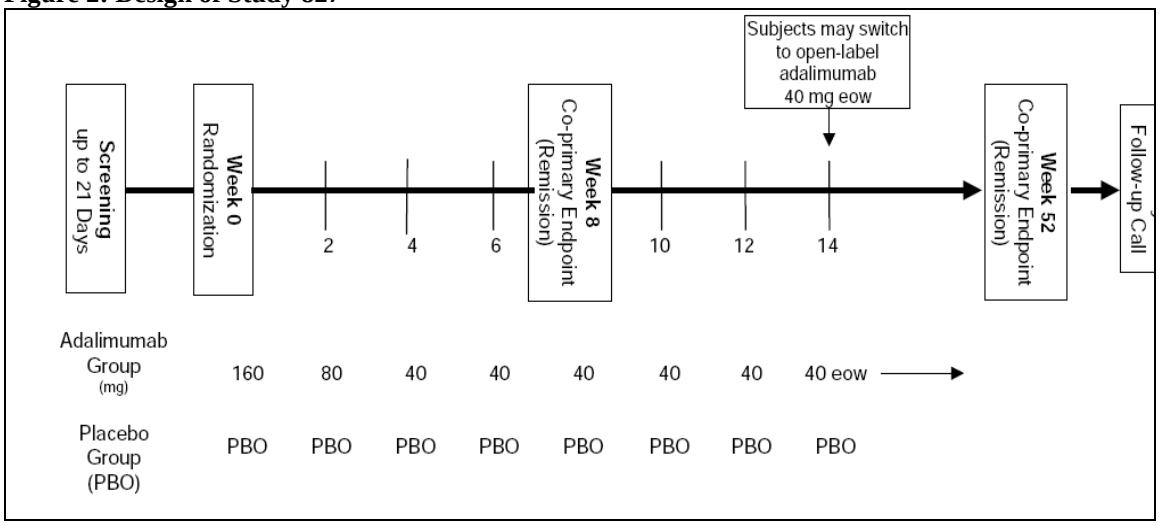
The designs of Studies 826 and 827 are summarized in the figures below.

Figure 1: Design of Study 826*



*after Amendment 3; ITT-E and ITT-A3 definitions are provided in Appendix 3.
from Applicant's submission, Study 826 Protocol Amendment 3, p 608/1444

Figure 2: Design of Study 827



Reference: Applicant's submission, Study 827 Final Protocol p. 1530/1630

Endpoints:

The endpoints are summarized below. In both studies, clinical remission was defined as a total Mayo score of ≤ 2 with no individual subscore >1.

- Study 826: The primary efficacy endpoint of Study 826 was the proportion of subjects in clinical remission at Week 8; in addition, Study 826 included a number of ranked secondary endpoints assessed at Week 8.
- Study 827: Study 827 had a ranked co-primary efficacy endpoint (the proportion of subjects in clinical remission at Week 8, followed by the proportion of subjects in clinical remission at Week 52). In addition, Study 827 included a number of ranked

secondary endpoints assessed at Weeks 8 and/or 52 (the first-ranked secondary endpoint was the proportion of subjects in clinical remission at both Weeks 8 and 52). (The full listing of secondary endpoints for the two studies is provided in Appendix 4.)

Table of Studies Submitted:

The table below summarizes the clinical trials submitted in support of the current application. Note that in addition to Studies 826 and 827, there was a long-term single-arm, open-label trial (Study 223) that is currently ongoing.

Table 6: Overview of Studies 826 and 827

Study	Primary Endpoint	Treatment Arms	Number of patients enrolled ITT-E (ITT-A3)
826	Clinical Remission at Week 8	160/80/40* 80/40[#] Placebo	223 (130) 130 (130) 223 (130)
827	Co-Primary Endpoint: ▪ Clinical Remission at Week 8 ▪ Clinical Remission at Week 52	160/80/40* Placebo	258 260
223*	Long-term safety and tolerability	40 mg[‡]	592[§]

*Humira 160/80/40 SC EOW: 160 mg at Wk 0, 80 mg at Wk 2, and 40 mg at Wk 4 and every other wk
[#]Humira 80/40 SC EOW: 80 mg at Wk 0, 40 mg at Wk 2 and every other wk
[†]Humira 40 mg SC EOW: 40 mg every other wk
[‡]Humira 40 mg SC EOW/EW: every other wk or every wk
[§] Data cutoff date of December 16, 2011. 592 enrolled (349 receiving 40 mg EOW and 243 receiving 40 mg EW); 384 ongoing (255 receiving 40 mg EOW and 129 receiving 40 mg EW); escalation from EOW to EW allowed during study for inadequate response.
For Study 826, the number of patients enrolled is shown as ITT-E (ITT-A3); the definitions of ITT-E and ITT-A3 are provided in Appendix 3.

4.2 Demographics and Baseline Disease Characteristics

Baseline demographic characteristics for the ITT-A3 population of Study 826 and the ITT population of Study 827 are presented in the table below. The ITT-A3 population is defined as all patients with confirmed UC at Baseline who were randomized according to the revised study design described in Amendment 3 (and Amendment 4) and received at least 1 injection of the following induction regimens: Humira 160/80/40 mg, Humira 80/40 mg, or placebo. The ITT-A3 population was the basis for the confirmatory primary efficacy analysis and the ranked secondary efficacy analysis at Week 8.

Table 7: Demographics, Studies 826 and 827

Demographic Subgroup	Study 826 (ITT-A3 Population)			Study 827 (ITT Population)	
	Placebo	Humira 80/40 mg	Humira 160/80/40 mg	Placebo	Humira 160/80/40 mg
N	130	130	130	246	248
Sex (n,%)					
Male	82 (63.1)	78 (60.0)	83 (63.8)	152 (61.8)	142 (57.3)
Female	48 (36.9)	52 (40.0)	47 (36.2)	94 (38.2)	106 (42.7)
Age range (years) (n,%)					
< 40 years	72 (55.4)	63 (48.5)	74 (56.9)	118 (48.0)	136 (54.8)
40 to ≤ 64 years	54 (41.5)	59 (45.4)	51 (39.2)	116 (47.2)	105 (42.3)
≥ 65 years	4 (3.1)	8 (6.2)	5 (3.8)	12 (4.9)	7 (2.8)
Mean ± SD	38.9 ± 12.68	41.6 ± 13.99	38.2 ± 13.46	41.3 ± 13.22	38.6 ± 12.47
Race (n,%)					
Caucasian	117 (90.0)	119 (91.5)	119 (91.5)	234 (95.1)	236 (95.2)
Black	5 (3.8)	6 (4.6)	2 (1.5)	4 (1.6)	7 (2.8)
Hispanic	5 (3.8)	6 (4.6)	4 (3.1)	7 (2.8)	6 (2.4)
Asian	5 (3.8)	5 (3.8)	7 (5.4)	4 (1.6)	1 (0.4)
Other	3 (2.3)	0	2 (1.5)	4 (1.6)	4 (1.6)
Weight					
(mean ± SD), kg	78.7 ±17.42	76.8 ± 15.01	75.5 ± 14.20	77.1 ± 17.31	75.3 ± 17.71
Nicotine use (n,%)					
User	7 (5.4)	8 (6.2)	12 (9.2)	19 (7.8)	20 (8.1)
Ex-user	35 (26.9)	46 (35.4)	37 (28.5)	88 (35.9)	94 (37.9)
Never used	88 (67.7)	76 (58.5)	81 (62.3)	138 (56.3)	134 (54.0)
Alcohol use (n, %)					
Drinker	57 (43.8)	62 (47.7)	62 (47.7)	125 (51.0)	132 (53.2)
Ex-drinker	7 (5.4)	5 (3.8)	9 (6.9)	11 (4.5)	8 (3.2)
Non-drinker	66 (50,8)	63 (48.5)	59 (45.4)	109 (44.5)	108 (43.5)

Study 826 CSR, Table 11 p 191 and Study 827 CSR Table 8 p 226
Table above is taken from the Clinical Review by Aisha Peterson Johnson

In both studies, demographic subgroups were well-balanced between treatment groups.

Baseline Mayo Score and Subscores for the ITT-A3 population of Study 826 and the ITT population of Study 827 are presented in the tables below.

Table 8: Baseline Mayo Score and Subscores, Studies 826 and 827

Baseline Characteristic	Study 826 (ITT-A3 Population)			Study 827 (ITT Population)	
	Placebo	Humira 80/40 mg	Humira 160/80/40 mg	Placebo	Humira 160/80/40 mg
N	130	130	130	246	248
Total Mayo Score (mean ± SD)	8.7 (1.6)	9.0 (1.6)	8.8 (1.6)	8.9 (1.8)	8.9 (1.5)
Subscores					
Endoscopy	2.5 (0.5)	2.5 (0.5)	2.4 (0.5)	2.5 (0.5)	2.5 (0.5)
Rectal Bleeding	1.6 (0.8)	1.7 (0.8)	1.7 (0.9)	1.7 (0.9)	1.7 (0.9)
Stool Frequency	2.4 (0.7)	2.5 (0.7)	2.5 (0.8)	2.6 (0.7)	2.5 (0.7)
Physician's Global Assessment	2.2 (0.5)	2.3 (0.6)	2.2 (0.6)	2.2 (0.6)	2.2 (0.6)

Table above is modified from Study 826 CSR, Table 14.1_5.4.1 p 555, and Study 827 CSR Table 10 p 230

In both studies, baseline total Mayo score and Subscores appeared to be well-balanced between treatment groups.

However, the FDA Statistical Reviewer concluded that there was a statistically significant difference among the distributions of subjects across treatment arms for Total Mayo Score at baseline in the ITT-A3 Set (chi-square p-value 0.0044); i.e., there was a statistically significant difference in the frequencies of Total Mayo score values across the three treatment arms (see number and percentage of patients by each Total Mayo Score value in the table below).

Table 9: Total Mayo Score at Baseline

Total Mayo Score	6	7	8	9	10	11	12
Treatment Arm (n, %)							
Humira 160/80/40	15 (12%)	13 (10%)	24 (18%)	33 (25%)	25 (19%)	15 (12%)	5 (4%)
Humira 80/40	9 (7%)	10 (8%)	36 (27%)	26 (20%)	22 (17%)	17 (13%)	10 (8%)
Placebo	9 (7%)	28 (22%)	19 (15%)	27 (21%)	34 (26%)	8 (6%)	5 (4%)

Modified from Statistics Review by Milton Fan, Page 22.

Previous use of corticosteroids, immunosuppressants, and TNFα-antagonists are summarized in the table below.

Table 10: Previous Use* of Corticosteroids, Immunosuppressants, and TNFα-antagonists

Previous Medication*	Study 826 (ITT-A3 Population)			Study 827 (ITT Population)	
	Placebo	Humira 80/40 mg	Humira 160/80/40 mg	Placebo	Humira 160/80/40 mg
N	130	130	130	246	248
Corticosteroid	110 (85%)	115 (88%)	116 (89%)	217 (88%)	219 (88%)
Azathioprine	49 (38%)	54 (42%)	49 (38%)	122 (50%)	113 (46%)
6-Mercaptopurine	8 (6%)	13 (10%)	10 (8%)	36 (15%)	34 (14%)
TNFα-Antagonist	--	--	--	101 (41%)[#]	98 (40%)[#]

*Use within the past 5 years
[#]All of these patients received prior infliximab except 3 patients in the Humira group (2 received prior golimumab and 1 received prior certolizumab)
(Table above modified from Page 211 of Study 826 CSR and Page 240 of Study 827 CSR.)

In each of the studies, subgroups defined by previous medication use were well-balanced between treatment groups.

4.3 Disposition

Study 826

In Study 826, there were a total of 576 patients randomized. These patients were randomized to Humira 160/80/40 mg (n=223), Humira 80/40 mg (n=130), and placebo (n=223). A total of 575 patients were included in the ITT-E set and a total of 390 patients were included in the ITT-A3 set (the pre-specified primary analysis set). (The definitions of ITT-E and ITT-A3 are provided in Appendix 3.) See the table below.

Table 11: Patient Disposition, Study 826, ITT-A3 population

	Placebo	Humira 80/40	Humira 160/80/40
Randomized	130	130	130
Completed Study	91 (70.0)	86 (66.2)	95 (73.1)
Discontinued Early[a]	39 (30.0)	44 (33.8)	35 (26.9)
Lack of efficacy	26 (20.0)	22 (16.9)	17 (13.1)
AE/SAE	22 (16.9)	19 (14.6)	14 (10.8)
Withdrew consent	3 (2.3)	9 (6.9)	5 (3.8)
Protocol violation	1 (0.8)	1 (0.8)	3 (2.3)
Lost to follow-up	0	3 (2.3)	1 (0.8)
Other[b]	0	4 (3.1)	1 (0.8)
Discontinued prior to Week 8	9 (6.9)	12 (9.2)	9 (6.9)
AE/SAE	6 (4.6)	7 (5.4)	4 (3.1)
Withdrew consent	0	4 (3.1)	1 (0.8)
Lost to follow-up	0	2 (1.5)	0
Lack of efficacy	5 (3.8)	5 (3.8)	2 (1.5)
Protocol violation	0	0	2 (1.5)
Other[c]	0	0	1 (0.8)

Study 826, CSR pp. 181-182/3375

a. Primary reason, patients could have discontinued for more than one reason
b. Reasons recorded as "other" included: diagnosis of CD, loss of response, primary non-responder, UC symptoms not improving, investigator discretion, non-compliance, positive TB skin test, patient wanted to start a family, and total colectomy within the 70-day follow-up period
c. Patient diagnosed with CD

Table above is modified from the Clinical Review by Aisha Peterson Johnson

While 118 patients (30.3%) discontinued Study 826 prior to completion, only 30 patients (7.7%) discontinued prior to the completion of Week 8. Of those patients who discontinued prior to Week 8, the primary reasons for discontinuation were adverse events (4.4%) and lack of efficacy (3.1%). The number of premature discontinuations for lack of efficacy was similar across the placebo and Humira dosage groups prior to Week 8 and during the entire study.

Study 827

There were a total of 518 patients randomized into Study 827 at 103 global sites. Of those patients randomized, 24 patients from 3 sites were excluded from the ITT analysis set due to site non-compliance. See the table below.

Table 12: Patient Disposition, Study 827, ITT population

	Placebo	Humira 160/80/40
ITT Analysis Set	246	248
Completed Study	131 (53.3)	164 (66.1)
Discontinued Early[a]	115 (46.7)	94 (37.9)
Lack of efficacy	70 (28.5)	63 (25.4)
AE/SAE	25 (10.2)	12 (4.8)
Withdrew consent	4 (1.6)	8 (3.2)
Protocol violation	5 (2.0)	1 (0.4)
Lost to follow-up	0	1 (0.4)
Other[b]	11 (4.5)	9 (3.6)
Discontinued prior to Week 8	36 (14.6)	23 (9.3)
AE/SAE	10 (4.1)	5 (2.0)
Withdrew consent	2 (0.8)	1 (0.4)
Lost to follow-up	0	0
Lack of efficacy	15 (6.1)	13 (5.2)
Protocol violation	3 (1.2)	1 (0.4)
Other[c]	6 (2.4)	3 (1.2)

Study 827 CSR p. 220, Table 5

a. Primary reason, patients could have discontinued for more than one reason

b. Reasons recorded as "other" included: diagnosis of CD, loss of response, primary non-responder, UC symptoms not improving, investigator discretion, non-compliance, positive TB skin test, patient wanted to start a family, and total colectomy within the 70-day follow-up period

c. patient diagnosed with CD

Table above is modified from the Clinical Review by Aisha Peterson Johnson

While 209 patients (42.3%) discontinued Study 827 prior to completion, only 59 patients (11.9%) discontinued prior to the completion of Week 8. Of those patients who discontinued prior to Week 8, the primary reasons for discontinuation were adverse events (3.0%) and lack of efficacy (5.7%). The number of premature discontinuations for lack of efficacy was similar across the placebo and Humira groups prior to Week 8 and during the entire study.

4.4 Protocol Violations

Study 826

Major protocol violations are shown in the table below.

Table 13: Major Protocol Violations, ITT-E and ITT-A3 Populations

	Placebo	Humira 80/40 mg	Humira 160/80/40 mg
ITT-E patients	222	130	223
Failed inclusion /exclusion criteria	24 (10.8%)	9 (6.9%)	11 (4.9%)
Developed withdrawal criteria/was not withdrawn	0	0	1 (0.3%)
Wrong treatment or incorrect dose	12 (5.4%)	10 (7.7%)	14 (6.3%)
Prohibited Concomitant medication	19 (8.6%)	13 (10.0%)	14 (6.3%)
ITT-A3 patients	130	130	130
Failed inclusion /exclusion criteria	8 (6.2%)	9 (6.9%)	8 (6.2%)
Developed withdrawal criteria/was not withdrawn	0	0	1 (0.8%)
Wrong treatment or incorrect dose	10 (7.7%)	10 (7.7%)	11 (8.5%)
Prohibited Concomitant medication	11 (8.5%)	13 (10.0%)	8 (6.2%)

Study 826 CSR Tables 14.1_2.3 and 2.4 pp 517-518/3375
Table above modified from the Clinical Review by Aisha Peterson Johnson.

The proportion of patients with protocol violations was similar across the three treatment arms. The most common protocol violation was prohibited concomitant medication for both the ITT-E and ITT-A3 populations.

Study 827

Major protocol violations are shown in the table below.

Table 14: Major Protocol Violations, ITT Population

Deviation Category	Placebo N = 246	Adalimumab N = 248	Total N = 494
Inclusion/Exclusion Criteria Violation	32 (13.0)	40 (16.1)	72 (14.6)
Developed Withdrawal Criteria/Was Not Withdrawn	0	0	0
Received Wrong Treatment or Incorrect Dose	26 (10.6)	31 (12.5)	57 (11.5)
Received Excluded Concomitant Treatment	55 (22.4)	45 (18.1)	100 (20.2)

Table above is taken from Page 223 of the Study 827 Clinical Study Report

The proportion of patients with protocol violations was similar for the two treatment arms. The most common protocol violation was received excluded concomitant treatment.

4.5 Induction of Clinical Remission Results

The key results and the key issues identified in the previous review cycle are presented below.

4.5.1 Key Results (Induction)

The induction of clinical remission results for Studies 826 and 827 (Humira 160/80/40 arm versus placebo) are provided in the table below. Statistically significant but modest efficacy results are demonstrated for both studies for the primary endpoint of clinical remission at Week 8.

Table 15: Induction of Clinical Remission (Week 8)

Study	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	95% CI	p*-value
826	9.2% (12/130)	18.5% (24/130)	**9.3%**	**(0.8%, 17.9%)**	**0.031**
827	9.3% (23/246)	16.5% (41/248)	**7.2%**	**(1.3%, 13.2%)**	**0.019**

Clinical remission was defined as a total Mayo score of ≤2 with no individual subscore >1.
Study 826: Primary endpoint was clinical remission at Week 8.
Study 827: Ranked co-primary efficacy endpoint was the proportion of subjects in clinical remission at Week 8, followed by the proportion of subjects in clinical remission at Week 52.
*Chi-squared for Study 826, CMH for Study 827

A number needed to treat (NNT) analysis[5] was performed by the FDA Statistical Reviewer. The results for the induction of clinical remission endpoints were as follows: (a) Study 826: NNT=10.8 (95% CI: 5.7, 111); and (b) Study 827: NNT=13.9 (95% CI: 7.6, 76.9).

In the Humira 80/40 group, the clinical remission rate at Week 8 was 10.0% (13/130); there was no statistically significant difference in clinical remission observed between the Humira 80/40 treatment arm and the placebo arm (p=0.833).

Although both trials demonstrated statistically significant improvement for adalimumab treatment relative to placebo, the FDA Statistical Reviewer noted that statistical significance is lost in Study 826 if the responder status of 1 patient in the adalimumab 160/80/40 group is changed from responder to non-responder, or if the responder status of 1 placebo-treated patient is changed from non-responder to responder. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study 826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the

[5] Number needed to treat (NNT) = NNT = 1 / [(IMPact/TOTact) – (IMPcon/TOTcon)] where: IMPact = number of patients given active treatment achieving the target; TOTact = total number of patients given the active treatment; IMPcon = number of patients given a control treatment achieving the target; and TOTcon = total number of patients given the control treatment [Source: http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/nnt.pdf (accessed August 1, 2012)]

significantly different baseline Mayo scores, the treatment differences were not significant (p=0.085). Moreover the significance of the analysis results is sensitive to the use of exact testing methods.

Ranked secondary endpoint results for Studies 826 and 827 are shown in Appendix 5.

4.5.2 Key Issues Identified (Induction)

Issue #1: Clinical Meaningfulness of the Observed Treatment Difference (Studies 826 and 827)

The FDA Clinical Reviewer questioned the clinical meaningfulness of the observed treatment difference of less than 10%. Although there are limitations of cross-study comparisons, the FDA Clinical Reviewer noted that the treatment differences observed were numerically lower than those observed for the only currently approved TNFα-antagonist product for UC (see Section 4.8 of this Briefing Document).

Issue #2: Robustness of Data (Study 826)

The FDA Clinical and Statistical Reviewers questioned the robustness of the data in Study 826 for the reasons summarized below. Although the analyses presented below are post hoc, these were driven by concerns raised from the data.

Issue #2a: Adjustment for Baseline Mayo Score (Study 826)

Because the FDA Statistical Reviewer noted that the Mayo scores were significantly different at Baseline (chi-squared test; p=0.0044) (see Section 4.2 of this Briefing Document), the reviewer conducted a post hoc analysis that controlled for baseline Mayo scores (see table below). The FDA Statistical Reviewer was concerned that after adjustment for Baseline Mayo Score, the treatment difference was no longer statistically significant (see the table below).

Table 16: Post-hoc Analysis of the Proportion of Subjects with Remission at Week 8 Controlling for Mayo score at Baseline (Study 826)

Mayo Score at baseline	Placebo Rate	Adalimumab 80/40 Rate	p-value[a]	Adalimumab 160/80/40 Rate	p-value[a]
6	2/9 (22.2%)	5/9 (55.6%)		5/15 (33.3%)	
7	1/28 (3.6%)	1/10 (10.0%)		2/13 (15.4%)	
8	4/19 (21.1%)	4/36 (11.1%)		5/24 (20.8%)	
9	3/27 (11.1%)	1/26 (3.9%)		5/33 (15.2%)	
10	2/34 (5.9%)	1/22 (4.6%)		3/25 (12.0%)	
11	0/8 (0.0%)	0/17 (0.0%)		3/15 (20.0%)	
12	0/5 (0.0%)	1/10 (10.0%)		1/5 (20.0%)	
Combined			0.9748		**0.0852**

[a]p-values obtained from Cochran-Mantel-Haenszel test.
Table above is taken from the Statistical Review.

Issue #2b: Changing the Remission Status of a Single Subject (Study 826)

The FDA Statistical Reviewer identified one patient in the Humira 160/80/40 arm that may have been misclassified as a remitter; the Reviewer noted that it is still unclear and debatable whether or not that particular patient was correctly classified. In order to analyze the possible effect of such a misclassification, the FDA Statistical Reviewer conducted post hoc sensitivity analyses to determine the effect of changing the remission status of a single subject. The FDA Statistical Reviewer concluded that the significance of the overall Study 826 analysis results are sensitive to the classification status based on a single subject. The value of Fisher's Exact Test becomes greater than 0.05 if the remission status of one patient (0.8% change) in either treatment group changes. Specifically, if the status of one Humira patient changes from remitter to non-remitter [Case 1] or one patient in the placebo group changes from non-remitter to remitter [Case 2], the value of Fisher's Exact Test changes to 0.068 and 0.075, respectively. See table below.

Table 17: Remission Rate, 0.8% Change Sensitivity Analysis (Study 826; ITT-A3)

	Placebo	Humira 160/80/40 mg	Difference	p*-value
Original Data	9.2%	18.5%	9.3%	0.047
Case 1	9.2%	17.7%	8.5%	**0.068**
Case 2	10.0%	18.5%	8.5%	**0.075**

Non-responder imputation (NRI) - all patients with missing remission values were considered to be non-remitters
*p-value calculated using Fisher's Exact Test

Issue #2c: Use of Exact Testing Methods (Study 826)

To further examine the robustness of the data (given the above concerns), the FDA Statistical Reviewer examined the sensitivity of the pre-specified chi-squared analysis to exact testing methods. It should be noted that these results are exploratory post hoc analyses. Using the chi-squared test, the calculated p-value is 0.031 (see below). However, using the Fisher's Exact Test (an analysis method that is more conservative than the Chi-squared approximation), the p-value is 0.047. This value borders on statistical significance. The FDA Statistical Reviewer concluded that the analysis results are sensitive to the use of the Fisher's exact test method (used in place of the pre-specified test of significance, the Chi-squared test method). Coupled with the above concerns (b and c), the borderline statistical significance contributes to the concern that the conclusions are not robust from a statistical perspective. See the table below.

Table 18: Chi-squared and Fisher's Exact Test, Study 826 Induction (ITT-A3)

Analysis	Test of Significance	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	p-value
Original Analysis	Chi-squared	9.2% (12/130)	18.5% (24/130)	9.3%	0.031
Exact Testing Methods	Fisher's Exact Test	Same	Same	Same	**0.047**

From Statistical Review

Issue #3: Consistency of Treatment Effects (Study 826)

The FDA Clinical and Statistical Reviewers questioned the consistency of treatment effects in Study 826 because the first ranked secondary endpoint (clinical response per Mayo score at Week 8) did not show evidence of a treatment benefit (see the table below).

Table 19: First-Ranked Secondary Endpoint (Study 826; ITT-A3)

	Placebo	Humira 160/80/40	p value
Clinical Response at Week 8	58/130 (44.6%)	71/130 (54.6%)	0.107

Table above modified from the Clinical Review.

(See all twelve ranked secondary endpoint results for Study 826 in Appendix 5.)

Issue #4: Consistency of Treatment Effects (Study 827)

The FDA Clinical and Statistical Reviewers also questioned the consistency of treatment effects in Study 827 because an important subgroup analysis based on use of azathioprine or 6-mercaptopurine at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo (see table below).

Table 20: Subgroup Analysis based on use of Azathioprine or 6-MP (Study 827; Week 8)

Azathioprine or 6-MP at Baseline	Placebo	Humira 160/80/40	Difference (Humira-Placebo)
Yes	12/80 (15.0%)	12/93 (12.9%)	-2.1%
No	11/166 (6.6%)	29/155 (18.7%)	12.1%

The table above is modified from the Clinical Review.

(See other selected subgroup analyses in Appendix 6.)

4.6 Maintenance of Clinical Remission / Sustained Clinical Remission Results

The key results and the key issues identified in the previous review cycle are presented below.

4.6.1 Key Results (Maintenance / Sustained Remission)

Study 827 had a ranked co-primary efficacy endpoint: the proportion of subjects in clinical remission at Week 8, followed by the proportion of subjects in clinical remission at Week 52. Sustained clinical remission was defined as being in remission at both Weeks 8 and 52. This was the first-ranked secondary endpoint of Study 827. See table below.

Table 21: Clinical Remission (Study 827)

Week	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	95% CI	p-value[‡]
Week 8[#]	9.3% (23/246)	16.5% (41/248)	**7.2%**	**(1.3%, 13.2%)**	**0.019**
Week 52[#]	8.5% (21/246)	17.3% (43/248)	**8.8%**	**(2.9%, 14.8%)**	**0.004**
Weeks 8 and 52[†]	4.1% (10/246)	8.5% (21/248)	**4.4%**	**(0.1%, 9.0%)**	**0.047**

[#]Clinical Remission at Week 8 is the first ranked Co-Primary Endpoint of Study 827; Clinical Remission at Week 52 is the second ranked Co-Primary Endpoint.
[†]Clinical Remission at Weeks 8 and 52 is the first-ranked secondary endpoint
[‡] Cochran-Mantel-Haenszel (CMH) test

A number needed to treat (NNT) analysis was performed by the FDA Statistical Reviewer. The results for the sustained clinical remission endpoint were NNT=23 (95% CI: 12, 667).

See other ranked secondary endpoints in APPENDIX 5: Ranked Secondary Endpoint Results.

It should be noted that Study 827 was the only study submitted to support the proposed indication for maintenance of remission. However, a study design intending to support maintenance of remission should re-randomize subjects that achieve remission at Week 8. Re-randomization at the end of the induction phase to drug or placebo allows the separate effect of maintenance therapy to be evaluated. The design of Study 827 is better suited to support sustained remission (a measure of durability in contrast to maintenance); i.e., if the ranked co-primary endpoint and the first-ranked secondary endpoint of sustained remission (Clinical Remission at Weeks 8 and 52) are met. (This point was communicated to the Applicant in a pre-submission advice letter about the Statistical Analysis Plan of Study 827.)

4.6.2 Key Issues Identified (Maintenance / Sustained Remission)

Issue #1: Clinical Meaningfulness of the Observed Treatment Difference

The FDA Clinical Reviewer questioned the clinical meaningfulness of a treatment difference of approximately 4% for the sustained clinical remission first-ranked secondary endpoint. Although there are limitations of cross-study comparisons, the FDA Clinical Reviewer noted that the treatment difference observed was numerically lower than that observed for the only currently approved TNFα-antagonist product for UC (see Section 4.8 of this Briefing Document).

Issue #2: Robustness of Data

The FDA Statistical Reviewer noted that although the clinical remission rates at Weeks 8 and 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed marginal significance in favor of adalimumab (see Table 21).

The FDA Statistical Reviewer further noted that the significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062) and may not be reliable due to extensive missing data. For both the sustained clinical remission endpoint and the Week 52 co-primary endpoint, there were large numbers of early drop-outs and/or subjects with missing data at Week 52: 78% placebo vs. 69% adalimumab. The high rate of data missing not-at-random undermine reliance on the estimated treatment effect.

4.7 Additional Exploratory Subgroup Analyses

4.7.1 Prior Anti-TNF Use (Study 827)

Study 827 allowed entry of patients with prior use of infliximab or other anti-TNF agents. The ranked co-primary endpoint evaluation used a two-sided CMH test and adjusted for prior exposure to infliximab or other anti-TNF agents. An exploratory subgroup analysis of remission results by prior anti-TNF use are summarized in the table below.

Table 22: Remission Results, by prior anti-TNF use, Study 827

Anti-TNF stratification	Week 8				Week 52			
	Placebo	Humira 160/80/40	Δ	p-value*	Placebo	Humira 160/80/40	Δ	p-value*
No prior anti-TNF	11.0% (16/145)	21.3% (32/150)	10.3%	0.017	12.4% (18/145)	22.0% (33/150)	9.6%	0.029
Prior anti-TNF	6.9% (7/101)	9.2% (9/98)	2.3%	0.559	3.0% (3/101)	10.2% (10/98)	7.2%	0.039

* p-values are for information only and do not represent formal statistical testing. Information from Table 22, CSR Study 827, p254/3632

At Week 8, a numerically higher treatment difference was observed in the subgroup of patients with no prior anti-TNF use compared to the subgroup of patients with prior anti-TNF use. At Week 52, a similar treatment difference was observed in the subgroup of patients with no prior anti-TNF use compared to the subgroup of patients with prior anti-TNF use.

The FDA Clinical Reviewer was concerned that these results (particularly Week 8) suggest that patients that had lost response to or were intolerant to another anti-TNF agent may not benefit from Humira; it should be noted that this is the only study that enrolled patients that previously used an anti-TNF agent. This result draws into question the issues regarding the efficacy of anti-TNF agents in the case of prior anti-TNF failures. There are implications regarding the optimal progression of therapy with individual agents. Additional studies will be needed to answer this question.

Other selected subgroup analyses (Studies 826 and 827) are shown in APPENDIX 6: Selected Subgroup Analyses.

4.7.2 Baseline Mayo Score (Studies 826 and 827)

Study 826

Subgroup analyses by baseline Mayo Score are shown in the table below.

Table 23: Clinical Remission at Week 8 in Subgroups based on Baseline Mayo Score (Study 826; ITT A-3)

Baseline Mayo Score Category	Clinical Remission* at Week 8			Δ (160/80/40 – Placebo)
	Placebo	80/40	160/80/40	
<10	12.0% (10/83)	13.6% (11/81)	20.0% (17/85)	8.0%
≥10	4.3% (2/47)	4.1% (2/49)	15.6% (7/45)	11.3%

* Clinical remission was defined as a total Mayo score of ≤2 with no individual subscore >1.

The percentage of patients in Study 826 that met the primary endpoint of clinical remission at Week 8 in the Baseline Mayo Score of < 10 and ≥ 10 categories appeared to be similar.

Study 827

Subgroup analyses by baseline Mayo Score are shown in the tables below.

Table 24: Clinical Remission at Week 8 in Subgroups based on Baseline Mayo Score (Study 827; ITT)

Baseline Mayo Score Category	Clinical Remission* at Week 8		Δ (160/80/40 – Placebo)
	Placebo	160/80/40	
<10	12.9% (18/140)	20.3% (32/158)	7.4%
≥10	4.8% (5/105)	10.2% (9/88)	5.4%

* Clinical remission was defined as a total Mayo score of ≤2 with no individual subscore >1.

Table 25: Clinical Remission at Week 52 in Subgroups based on Baseline Mayo Score (Study 827; ITT)

Baseline Mayo Score Category	Clinical Remission* at Week 52		Δ (160/80/40 – Placebo)
	Placebo	160/80/40	
<10	11.4% (16/140)	18.4% (29/158)	7.0%
≥10	4.8% (5/105)	15.9% (14/88)	11.1%

* Clinical remission was defined as a total Mayo score of ≤2 with no individual subscore >1.

The percentage of patients in Study 827 that met the primary endpoints of clinical remission at Weeks 8 and 52 in the Baseline Mayo Score of < 10 and ≥ 10 categories appeared to be similar.

4.8 Additional Discussion: Cross-Study Comparisons with Remicade

For adult patients with moderately to severely active UC, there is currently a product on the market—Remicade (infliximab). Remicade is also a TNFα-antagonist.

Although there are limitations of cross-study comparisons, the questions raised about the clinical meaningfulness of the statistically significant differences observed between Humira and placebo in this application prompted the reviewers to refer back to the Remicade trials for context.

The Remicade registration trials for the UC indication were ACT 1 and ACT 2. ACT 1 enrolled 121 patients in the 5 mg/kg arm, 122 patients in the 10 mg/kg arm, and 121 patients in the placebo arm. ACT 2 enrolled 121 patients in the 5 mg/kg arm, 120 patients in the 10 mg/kg arm, and 123 patients in the placebo arm.

Induction of Clinical Remission: Remicade registration trials revealed an induction of clinical remission (Week 8) treatment difference (Remicade-placebo) of 24% (ACT 1) and 28% (ACT 2) with the 5 mg/kg dose (approved dose for UC). This is numerically higher than the treatment difference for induction observed with Humira in Studies 826 and 827, 9.3% and 7.2%, respectively (see Table 4). It should be noted that although the studies of Remicade and Humira used the same primary endpoint for induction of clinical remission (i.e., total Mayo score of ≤2 with no individual subscore >1 at Week 8), there were other differences in the study populations that make it difficult to perform a cross-study comparison; for example, approximately 40% of the Study 827 population consisted of patients that had received prior treatment with TNFα-antagonists whereas in the studies of Remicade, patients were TNFα-antagonist naive.

Maintenance of Clinical Remission/Sustained Clinical Remission: The treatment difference for the sustained clinical remission endpoint seen in the Remicade maintenance study (ACT 1) was 13%. This treatment difference is numerically higher than the treatment difference for the sustained clinical remission endpoint observed with Humira in Study 827, 4.4% (see Table 4). However, it should be noted that the definition of sustained clinical remission differed between the Remicade study (ACT 1) and the Humira study (827). The Remicade study (ACT 1) defined sustained clinical remission as clinical remission at Weeks 8, 30, and 54; in contrast, the Humira study (827) defined sustained clinical remission as clinical remission at Weeks 8 and 52. [The definition of clinical remission was the same for both the Remicade study (ACT 1) and the Humira study (827); i.e., total Mayo score of ≤2 with no individual subscore >1]. Another key difference in the study populations that make it difficult to perform a cross-study comparison (also noted for induction) is that approximately 40% of the Study 827 population consisted of patients that had received prior treatment with TNFα-antagonists whereas in the corresponding Remicade study, patients were TNFα-antagonist naive.

A number needed to treat (NNT) analysis was performed for the induction of clinical remission and maintenance of clinical remission/sustained clinical remission endpoints for Remicade by the FDA Statistical Reviewer. The results for the induction of clinical

remission endpoints were as follows: (a) ACT 1: NNT=4.2 (95% CI: 2.9, 7.6); and (b) ACT 2: NNT=3.5 (95% CI: 2.7, 5.3). The results for the sustained clinical remission endpoint were NNT=7.7 (95% CI: 4.6, 20.6).

It is important to note that there are numerous limitations of cross-study comparisons. There may be known or unknown differences in the design or conduct of trials. Even if many of the characteristics of the study populations (such as distribution of Mayo score, proportion that are TNFα-antagonist naïve, proportion with baseline steroid or immunosuppressant use) are similar across the two studies, there are unmeasurable differences in the study populations that would render cross-study comparisons unreliable, so results need to be interpreted with caution.

5. EXPLORATORY ANALYSES PERFORMED BY APPLICANT

The applicant conducted several exploratory analyses of data from Studies 826 and 827.

The Applicant proposed that these exploratory analyses:

- examine the totality of the efficacy data,
- demonstrate the clinical relevance and robustness of the efficacy data, and
- support a favorable benefit/risk profile for the dosing regimen studied.

Because of the concerns stated in the CR Letter (i.e., Study 826 results are sensitive to alternative analyses and the conclusions are not considered robust from a statistical perspective, the appropriate dose may not have been selected for the two studies, and the improvements in the rates of clinical remission at Week 8 and sustained clinical remission at Weeks 8 and 52 reported relative to placebo were modest), the FDA Reviewers examined these data to determine if there is evidence of a clinically meaningful benefit.

The FDA Reviewers concluded the following regarding the exploratory analyses:

- The exploratory analyses were difficult to interpret because neither the endpoints nor the comparisons were prospectively defined in an analysis plan.
- The exploratory analyses did not adequately address the concerns from the original review.

Overview of Exploratory Analyses:

The specific exploratory analyses submitted by the Applicant in the resubmission included the following:

- primary and secondary analyses of Study 826 using the ITT-E population (i.e., all patients enrolled that received study drug or placebo);
- integrated primary and secondary analyses across Studies 826 and 827;
- additional exploratory analyses from Study 827 (e.g., clinical response based on partial Mayo score at Weeks 2, 4, and 8 and clinical response based on full Mayo score at Week 8);
- re-analysis of full and partial Mayo scores at Baseline and Week 52 using average of last 3 days (rather than standard "worst-ranked" methodology)-Study 827;
- all-cause and UC-related hospitalizations (pooled across Studies 826 and 827); and
- exploratory analyses of clinical remission and clinical response status at Week 52 in the subgroup of patients from Study 827 in clinical response at Week 8.
- serious adverse event (SAE)-adjusted days in remission
- number of patients who discontinued due to adverse events (AEs) relative to number of patients in remission at Weeks 8 and 52
- Net Efficacy Adjusted Risk (NEAR) analysis
- Number Needed to Harm (NNH) analyses

The exploratory analysis of dose escalation from EOW to EW in the open label Study 223 (submitted as part of the Study 223 Interim Clinical Study Report) is also included in this section.

Due to the exploratory nature of these analyses, the p-values presented are presented for reference only and not intended to represent any formal statistical testing or basis for statistical inference.

Exploratory Analysis #1 (Applicant): Adjustment for Baseline Mayo Score

Exploratory Analysis #1 is summarized in the table below. This was submitted by the Applicant in the current review cycle in response to the FDA Statistical Reviewer's analysis in the first review cycle (also described in the table below).

Table 26: Exploratory Analysis #1 (Applicant): Adjustment for Baseline Mayo Score (Study 826 Primary Endpoint)

Analysis	Description	p-value
Original (for reference)	▪ Did not adjust for Baseline Mayo Score ▪ Used the chi-squared test	0.031
FDA Statistical Reviewer (1st cycle)	▪ Adjusted for Baseline Mayo Score (categorizing by score)* ▪ Used the CMH test	0.0852
#1a (Applicant)	▪ Adjusted for Baseline Mayo Score (categorizing by quartiles)# ▪ Used the CMH test	0.034
#1b (Applicant)	▪ Adjusted for Baseline Mayo Score (categorizing by tertiles)# ▪ Used the CMH test	0.034
#1c (Applicant)	▪ Adjusted for Baseline Mayo Score (categorizing by median)# ▪ Used the CMH test	0.028

CMH: Cochran-Mantel-Haenszel
*See Section 4.5 of this Briefing Document (Robustness of Data–Study 826: Adjustment for Baseline Mayo Scores) and Section 4.2 of this Briefing Document
#See Appendix 7 of this Briefing Document.

It should be noted that the FDA Statistical Reviewer's analysis of adjustment for baseline Mayo scores was cited in the CR Letter as an example of the results being sensitive to alternative analyses (see Section 1.3.1 of this Briefing Document). The additional analyses by the Applicant are alternative ways to adjust for baseline Mayo score but are less sensitive than the Reviewer's method. Moreover these results are hypothesis generating as the methods of categorization (by quartiles, tertiles, and median) were not pre-specified.

Exploratory Analysis #2 (Applicant): Week 8 Remission Rates Across Analysis Populations

Exploratory Analysis #2 is summarized in the table below. The pre-specified analysis populations for Study 826 and Study 827 were the ITT-A3 and ITT populations, respectively. In addition to these analysis populations, the Applicant provided Week 8

Clinical Remission rates for additional analysis populations (ITT-E, previously defined; ITT-non-A3 and IAS-E, defined in the table below).

Table 27: Exploratory Analysis #2 (Applicant): Week 8 Remission Rates Across Analysis Populations (Study 826)

Study	Analysis Population	Placebo N	Humira 160/80/40 N	Rate (95% CI)	p-value
826	ITT-A3	130	130	**9.2** (0.9, 17.6)	0.031
826	ITT-non-A3*	92	93	**7.5** (-0.3, 15.3)	0.062
826	ITT-E	222	223	**8.5** (2.6, 14.4)	0.005
827	ITT	246	248	**7.1** (1.2, 12.9)	0.019
826, 827	IAS-E[#]	468	470	**8.1** (3.8, 12.1)	<0.001

The ITT-A3 and ITT-E populations of Study 826 were defined previously.
*The ITT-non-A3 population is defined as the population prior to Amendment 3 that received Humira or placebo.
[#]The IAS-E population (Induction and Maintenance Analysis Set) includes the ITT-E population of 826 and the ITT population of 827
(Table above is summarized from Figure on Page 47 of the March 30, 2012 sBLA Resubmission.)

The FDA Clinical Reviewer and FDA Statistical Reviewer concluded that the results from the additional analysis populations (i.e., ITT-non-A3, ITT-E, and IAS-E) are post hoc and do not alleviate concerns of the pre-specified analyses.

Exploratory Analysis #3 (Applicant): Primary and Secondary Analyses of Study 826 Using the ITT-E and IAS-E Population

Exploratory Analysis #3 is summarized in the tables below. The Applicant provided the primary and secondary analyses of Study 826 using the ITT-E population (as opposed to the ITT-A3 population) and the IAS-E population.

Table 28: Exploratory Analysis #3a (Applicant): Primary and Secondary Analyses of Study 826 Using the ITT-E Population (Study 826)

	Placebo N = 222	ADA 160/80/40 N = 223		Treatmen Differenc
Endpoint	**n (%)**	**n (%)**	***P* value[a]**	**(%)**
Primary				
Clinical remission per FM	16 (7.2)	35 (15.7)	0.005	8.5
Ranked Secondary				
Clinical response per FM	95 (42.8)	116 (52.0)	0.051	9.2
Mucosal healing (endoscopy subscore ≤ 1)	79 (35.6)	99 (44.4)	0.056	8.8
Rectal bleeding subscore (RBS) ≤ 1	147 (66.2)	162 (72.6)	0.140	6.4
Physician's global assessment (PGA) ≤ 1	98 (44.1)	119 (53.4)	0.050	9.2
Stool frequency subscore (SFS) ≤ 1	81 (36.5)	95 (42.6)	0.185	6.1

FM: Full Mayo Score

a. P value based on CMH test with in/not in the ITT-A3 Analysis Set as the stratification factor.
Note: According to the NRI analysis, all missing clinical remission values were considered to be non-remission.
(Table above modified from Page 48 of the sBLA Resubmission dated March 30, 2012)

Table 29: Exploratory Analysis #3b (Applicant): Primary and Secondary Analyses of Study 826 Using the IAS-E Population (Study 826)

	Placebo		ADA 160/80/40			Treatmer Differenc
Endpoint	**N**	**n (%)**	**N**	**(%)**	***P* value[a]**	**(%)**
Primary						
Clinical remission per FM	468	37 (7.9)	470	75 (16.0)	< 0.001	8.1
Ranked Secondary						
Clinical response per FM	468	176 (37.6)	470	240 (51.1)	< 0.001	13.5
Mucosal healing (endoscopy subscore ≤ 1)	468	152 (32.5)	470	200 (42.6)	0.002	10.1
RBS ≤ 1	468	286 (61.1)	470	335 (71.3)	0.001	10.2
PGA ≤ 1	468	188 (40.2)	470	232 (49.4)	0.005	9.2
SFS ≤ 1	468	149 (31.8)	470	188 (40.0)	0.010	8.2

FM: Full Mayo Score
a. P value based on CMH test with 3 levels of stratification: 1) subjects in Study M06-826, 2) subjects in Study M06-827 with prior anti-TNF exposure; and 3) subjects in Study M06-827 without prior anti-TNF exposure.
Note: According to the NRI analysis, all missing clinical remission values were considered to be non-remission. (Table above modified from Page 49 of the sBLA Resubmission dated March 30, 2012)

The FDA Clinical Reviewer and FDA Statistical Reviewer concluded that the results from the primary and secondary analyses in the ITT-E and IAS-E populations are post hoc and do not alleviate concerns regarding the results of the pre-specified analyses.

Exploratory Analysis #4 (Applicant): Clinical Remission and Response at Week 52 in Week 8 Clinical Remitters (Study 827)

Exploratory Analysis #4 is summarized in the table below. The Applicant performed an analysis of the rates of Clinical Remission and Clinical Response at Week 52 in the subgroup of patients that achieved Clinical Remission at Week 8.

Table 30: Exploratory Analysis #4 (Applicant): Clinical Remission and Response at Week 52 in Week 8 Clinical Remitters (Study 827)

Analysis	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	p-value*
Original Analysis (for reference): Sustained Clinical Remission (Remission at Wks 8 and 52)	4.1% (10/246)	8.5% (21/248)	4.4%	0.047
#4a: Clinical *Remission* at Week 52 (in Week 8 Clinical Remitters)	43.5% (10/23)	51.2% (21/41)	**7.7%**	**0.618**
#4b: Clinical *Response* at Week 52 (in Week 8 Clinical Remitters)	52.2% (12/23)	63.4% (26/41)	**11.2%**	**0.400**

(Table above summarized from Pages 161-162 of the March 30, 2012 sBLA Resubmission.)

The FDA Clinical Reviewer concluded that the results of the analysis of Clinical Response and Clinical Remission at Week 52 in the subgroup of patients that achieved Clinical Remission at Week 8 are not informative and serve only as an exploratory comparison.

Exploratory Analysis #5 (Applicant): Clinical Response Based on Partial Mayo Score at Weeks 2, 4, and 8

To explore the timing of the onset of Humira, the Applicant explored the clinical response based on partial Mayo (PM) score at Weeks 2, 4, and 8. The analysis revealed that the treatment difference (Humira-placebo) was greatest at Week 2 and smallest at Week 4. However, the clinical response rates increased from Week 2 through Week 8 for both placebo and Humira patients. See Table 31, below.

Table 31: Exploratory Analysis #5 (Applicant): Clinical Response per PM Score at Weeks 2, 4, and 8, and per FM at Week 8, Study 827

	Number (%) of Subjects			
Study Visit	Placebo N = 246	ADA N = 248	Treatment Difference[a] (%)	*P* value[b]
Week 2 PM	49 (19.9)	97 (39.1)	19.2	< 0.001
Week 4 PM	78 (31.7)	113 (45.6)	13.9	0.002
Week 8 PM	86 (35.0)	123 (49.6)	14.6	0.001
Week 8 FM	85 (39.2)	125 (55.6)	16.4	< 0.001

a. Percent difference between active treatment and placebo.

b. *P* value to compare adalimumab with placebo was based on CMH test.

Notes: According to the NRI method, all missing clinical response values were considered to be nonresponses.

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The FDA Clinical Reviewer concluded that the analysis of PM scores for Weeks 2 through 8 may suggest that patients respond early to treatment with Humira; however, this analysis does not reveal if patients who respond at Week 2 continue to be in response at Weeks 4 and 8 or if they subsequently lose that response prior to Week 8. Further, the

FDA Clinical Reviewer concluded that no statistical inferences can be made due to the exploratory nature of these analyses.

Exploratory Analysis #6 (Applicant): Re-analysis from Study 827 Using Average of Last 3 days (Rather than Standard "Worst-Ranked" Methodology)

In the pre-specified Statistical Analysis Plan (SAP), full Mayo (FM) scores were calculated using worst-rank methodology (i.e. the worst subscore from the past 3 days of the patient subject diary for Stool Frequency Score (SFS) and Rectal Bleeding Score (RBS) was used to calculate the Mayo score for each visit). To evaluate the possible impact of worst score versus average score methodology in Study 827, the Applicant undertook an exploratory analysis of selected patients from sites with readily-available diary data and re-calculated FM scores using the average SFS and RBS subscores from the three days prior to each visit.

To conduct this analysis, the Applicant included patients who had completed Study 827 and were currently participating in the long-term Study 223. The Applicant included three to four patients from each of the thirteen sites who reported still having readily-available diary data of both placebo and Humira patients. In the end, data from only 16 patients was used for this analysis. The results of this exploratory analysis revealed that using the average method to calculate SFS and RBS (instead of the worst-rank method) may have resulted in Week 52 FM and PM scores that were 0.59 points lower. See Table 32, below.

Table 32: Exploratory Analysis #6: Full Mayo (FM) and Partial Mayo (PM) Scores Using Worst-case vs. Average Scores, Study 827

	Baseline	Week 52	Δ[a]	Overall Δ[b]
FM Scores				
ADA, N = 9				
Worst score from the past 3 days	9.11	2.89	6.22	
Average score from the past 3 days	9.00	2.33	6.67	
Difference between Δ of worst score and average score[b]				–0.45
Placebo, N = 7				
Worst score from the past 3 days	9.57	4.29	5.28	
Average score from the past 3 days	9.00	3.86	5.14	
Difference between Δ of worst score and average score[b]				0.14
Absolute Difference between Adalimumab and Placebo				**0.59**
PM Scores				
ADA, N = 9				
Worst score from the past 3 days	6.44	2.00	4.44	
Average score from the past 3 days	6.33	1.44	4.89	
Difference between Δ of worst score and average score[b]				–0.45
Placebo, N = 7				
Worst score from the past 3 days	6.86	2.86	4.00	
Average score from the past 3 days	6.29	2.43	3.86	
Difference between Δ of worst score and average score[b]				0.14
Absolute Difference between Adalimumab and Placebo				**0.59**

a. Δ – Difference between scores at Baseline and Week 52.
b. Overall Δ – difference between Δ of the worst score and average score.

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The analysis was completed with data from only 16 of the 494 patients who participated in Study 827. The FDA Clinical Reviewer concluded that with such a small sample size, no meaningful information can be obtained. In addition, the FDA Clinical Reviewer concluded that these data cannot be relied upon for statistical inference given their *post-hoc* nature.

Exploratory Analysis #7 (Applicant): All-Cause and UC-related Hospitalizations (Pooled Across Studies 826 and 827)

In a further exploratory analysis, the Applicant presented pooled data from Studies 826 and 827 to evaluate hospitalization rates with active drug and placebo. As previously pointed out, these two studies had significant design differences that make pooling of data for efficacy analysis highly problematic. The chief concerns are that patients in Study 826 were naïve to TNF-alpha-antagonists whereas 40 % of subjects in Study 827 were anti-TNF-experienced. Moreover, a protocol change (Amendment 3) in Study 826 led to the addition of the lower dose treatment arm. The hospitalizations of these patients were not used for the Applicant's hospitalization analysis because they "did not perform

significantly better than subjects randomized to placebo for the primary endpoint."[6] Whether this is a valid reason is arguable: (1) This is a post-hoc justification; (2) a lower dose may not translate into an improvement in the Mayo score (primary endpoint), however, it may stabilize the patient enough to prevent a hospitalization.

While the Applicant presents data from several different sensitivity analyses which support their general conclusion (patients on active drug have fewer hospitalizations), other types of sensitivity analyses are not given: For example, results broken out by individual studies (826 and 827 not pooled) would be of interest and also an analysis that keeps patients on the low dose arm in Study 826 (pre-amendment) in the analysis.

The tables below are given for the purpose of reference.

Table 33: Exploratory Analysis 7a: All-Cause, UC and UC- or Drug-Related Hospitalizations (Hospitalization Analysis Set)

Outcome	n/PYs at Risk[a] (%) ADA 160/80/40[b] N = 471	n/PYs at Risk[a] (%) Placebo N = 468	Relative Risk of ADA/Placebo (95% CI)	*P* value[c]
All-cause hospitalization	67/379 (18)	56/214 (26)	0.7 (0.5, 1.0)	0.030
UC-related hospitalization	45/389 (12)	47/216 (22)	0.5 (0.4, 0.8)	0.002
UC- or drug-related hospitalization	53/385 (14)	51/215 (24)	0.6 (0.4, 0.8)	0.005

a. Reflected as denominator in the columns.
b. Combined including 40 mg every other week (eow) and every week (ew).
c. P values based on Z score.
Note: The Hospitalization Analysis Set includes subjects in the IAS-E Analysis Set minus adalimumab 80/40 mg subjects in Study M06-826.
(Table above taken from Page 67 of the March 30, 2012 sBLA Resubmission.)

Table 34: Exploratory Analysis #7b: Poisson Regression Analysis of All-Cause, UC and UC- or Drug-Related Hospitalizations (Hospitalization Analysis Set)

Outcome	E/PYs at Risk[a] (%) ADA 160/80/40[b] N = 471	E/PYs at Risk[a] (%) Placebo N = 468	*P* value[c]
All-cause hospitalization	83/401 (21)	69/224 (31)	0.0151
UC-related hospitalization	54/401 (13)	57/224 (25)	0.0008
UC- or drug-related hospitalization	63/401 (16)	61/224 (27)	0.0023

a. Reflected as denominator in the columns.
b. Combined including 40 mg eow and ew.
c. P values based on Poisson regression with time offset.
Note: Numbers in parentheses represent the number of hospitalizations on an annualized basis. The Hospitalization Analysis Set includes subjects in the IAS-E Analysis Set minus adalimumab 80/40 mg subjects in Study M06-826.
(Table above taken from Page 68 of the March 30, 2012 sBLA Resubmission.)

[6]Adalimumab Risk of Hospitalization and Colectomy R&D/12/280 submitted with the March 30, 2012 sBLA Resubmission.

The FDA Clinical Reviewer concluded that the analyses are post hoc and do not alleviate concerns regarding the results of the pre-specified analyses.

An Information Request was sent to the Applicant to address the additional concerns about pooling of data across studies and the selective exclusion/inclusion of portions of the ITT population. The Applicant recently responded to this request and provided analyses of hospitalization data for each study and treatment arm separately; this data is currently being reviewed.

Exploratory Analysis #8 (Applicant): Partial Mayo Score Before and After Dose Escalation in Study 223

Exploratory Analysis #8 is summarized in the tables below.[7] This analysis is directly related to the CR Letter concern that the appropriate adalimumab dose for the pivotal efficacy trials may not have been selected (see Section 1.3.1 of this Briefing Document). It is possible that the modest clinical remission rates observed in Studies 826 and 827 may be a reflection of an inadequate dose. It should also be noted that the Applicant is proposing the addition of a statement in the label that consideration may be given to increasing the dosing frequency of Humira from 40 mg EOW to 40 mg EW for patients who respond and then lose their response.

Study 223 allowed patients to escalate their dose from EOW to EW at Week 12 (if they entered from a blinded cohort) or at Week 2 (if they entered from an open label cohort) if they are inadequate responders or experience a disease flare (both defined based on specific partial Mayo Score and change in partial Mayo Score).

Of the total of 498 patients, 116 entered on 40 mg EW dosing from a previous study, 339 entered on 40 mg EOW dosing and did not dose escalate in Study 223, and 43 patients dose escalated from 40 mg EOW to 40 mg EW in Study 223.

Of the 43 patients that dose escalated, the number (percentage) of patients who dose escalated by week is shown in the table below:

Table 35: Number (Percentage) of Patients who Dose Escalated by Week (Study 223)

Week*	0	2	4	8	12	24	36	48	60	72	84	96
Number (%) of Patients Who Dose Escalated	0	2 (0.4%)	7 (1.4%)	8 (1.6%)	0	11 (2.2%)	5 (1.0%)	4 (0.8%)	4 (0.8%)	2 (0.4%)	0	0

*Partial Mayo Score Assessments were scheduled to occur on all these weeks.
(Table above summarized from Page 270 of the Study 223 Interim CSR dated March 13, 2012.)

Partial Mayo scores among subjects who switched from EOW dosing to EW dosing are shown in the table below.

[7] The analysis of dose escalation in Study 223 was submitted by the Applicant as part of the Study 223 Interim Clinical Study Report.

Table 36: Partial Mayo Score Before and After Dose Escalation, As Observed (ITT-1 Analysis Set)

	Adalimumab 40 mg eow/ew, N = 498		
Measurement Time Points	n	Mean ± SD[a]	Median[a]
Last partial Mayo score on adalimumab eow	43	6.0 ± 1.93	6.0
Last partial Mayo score on adalimumab ew	39	3.3 ± 2.23	3.0
Change	39	–2.6 ± 2.45	–3.0

eow = every other week; ew = every week; ITT = intent-to-treat
a. Mean and median scores calculated based on last available Mayo score while on eow dosing and on ew dosing. Four subjects did not have a post-Baseline partial Mayo score available while on ew dosing due to the data cut-off of 31 December 2009.
Note: Summary includes only subjects who switched from eow to ew during this study.
(Table above taken from Page 119 of the Study 223 Interim Clinical Study Report dated March 13, 2012.)

The FDA Clinical Reviewer noted that Partial Mayo scores among subjects who switched from EOW dosing to EW dosing decreased by 50% (from last EOW = 6.0 to last EW value = 3.0). However, the FDA Clinical Reviewer concluded that these data have limited informational value regarding added efficacy of a higher dose because there was no randomization to EOW or EW, the analysis was not pre-specified, and the underlying study was open-label.

Exploratory Analysis #9 (Applicant): Serious Adverse Event (SAE)-Adjusted Days in Remission

The Applicant performed an exploratory analysis adjusting the days of clinical remission for days of serious adverse events (SAEs) leading to treatment discontinuation in Study 827. In this analysis, the mean days of SAEs leading to treatment discontinuation was subtracted from days of clinical remission. Despite the mean duration of SAEs being similar between the Humira 180/60 and placebo groups (4.11 and 4.64 days, respectively), the difference in SAE-adjusted days in clinical remission was statistically significantly different between groups. This difference is driven by the large difference in days of clinical remission (85.32 vs. 52.87 days in the Humira and placebo groups, respectively; p-value < 0.001). Therefore, it is unclear what additional information the SAE-adjusted analysis of days of clinical remission provides beyond what can be inferred from the analysis that only considered days of clinical remission. Furthermore, the clinical meaningfulness of this analysis is unclear given the pooling of all SAE time without accounting for type of event and the timing of the event in relation to clinical remission, if remission occurred.

Exploratory Analysis #10 (Applicant): Number of Patients who Discontinued Due to Adverse Events Relative to Number of Patients in Remission at Weeks 8 and 52

The Applicant conducted an exploratory analysis of Study 827 comparing the proportion of patients who achieved clinical remission at both Weeks 8 and 52 between treatment groups relative to those that had any AE that led to treatment discontinuation. For the

individual endpoints, the ADA group had more subjects in clinical remission at both Weeks 8 and 52 (21 vs. 10, ADA and placebo respectively; Fisher p-value = 0.062) and fewer patients who discontinued due to an AE (22 vs. 30, ADA and placebo respectively; Fisher p-value=0.244). From these frequencies, the Applicant estimates that for every placebo subject who achieved clinical remission at both week 8 and week 52, 3.0 placebo subjects discontinued due to AEs; for ADA, the ratio is 1.0. The clinical meaningfulness of the ratios is unclear. This approach lumps together all AEs that led to treatment discontinuation and therefore lacks in specificity of AE. This approach of lumping events can obscure imbalances between treatment groups for individual AEs.

The Applicant included a summary risk benefit measure, which is the ratio of the by-treatment risk to benefit ratios (Table 37). Specifically, the ratio of risk of discontinuing treatment due to AE to clinical remission in the placebo and ADA group is 30/10 (3.0) and 22/21 (1.0), respectively. The Applicant interprets this ratio as "placebo subjects are three times more likely to experience an AE leading to discontinuation than ADA subjects for the same level of clinical efficacy (measured by achieving clinical remission at Week 8 and Week 52)". The interpretation of this ratio of ratios is problematic for the following reasons: 1) the proportion of clinical efficacy differs between treatment groups, 2) this analysis does not fix the level of clinical efficacy in the estimation, and 3) this analysis assumes a one-to-one exchangeability for the efficacy and safety outcomes.

These same issues apply to the Applicant's risk benefit ratio obtained for subjects who discontinued treatment prematurely relative to the number of subjects in clinical remission at week 8 and clinical response at week 52 (results not presented).

Table 37: Number of Subjects who Discontinued Due to AEs Relative to the Number of subjects in Clinical Remission at Week 8 and Week 52 During the DB Period: Adalimumab Versus Placebo (Study M06-827 ITT Analysis Set; NRI)

	Placebo N = 246	ADA N = 248	*P* value
Subjects who discontinued due to AEs	30	22	
Subjects in clinical remission at Weeks 8 and 52	10	21	
Benefit/risk ratio (95% CI)	3.0 [1.5, 6.2]	1.0 [0.6, 1.9]	0.027

(Adapted from Applicant's Table 14 in resubmission)

Exploratory Analysis #11 (Applicant): Net Efficacy Adjusted Risk (NEAR) Analysis

The Applicant conducted an exploratory analysis combining clinical efficacy and safety into a single estimate. Their approach redefined the efficacy endpoint by only considering subjects with the efficacy response who also did not experience a particular safety event (i.e. a specific safety event-free treatment success). The odds of experiencing a safety event-free treatment success in the ADA group were then compared to the odds in the placebo group. The Applicant referred to this analysis as the Net Efficacy Adjusted for

Risk (NEAR), which is discussed in a paper by Boada and colleagues[8,9]. The Applicant interprets a NEAR OR larger than one as a benefit-risk ratio in favor of ADA compared to placebo. Using pooled data from the placebo and ADA 160/80/40 mg group from Studies 826 and 827 (IAS-E analysis set), NEAR ORs were calculated for clinical response per Full Mayo (FM) and Partial Mayo (PM) score at Week 8 for the following two safety events: serious infections, and SAEs (which included serious infections).

Beyond issues raised previously about lumping together various safety endpoints and performing a pooled analysis, the ability of this NEAR analysis to quantify benefit-risk in a clinically meaningful way is highly questionable. The limitations of this approach are threefold. First, this approach implicitly assumes that the clinical benefit of having a clinical response is of equal importance/weight as experiencing a specific safety event. Such an assumption was not justified by the Applicant and is likely inappropriate due to the varying degree of safety events considered. The implication of this one-to-one exchange of efficacy for safety is illustrated by considering two hypothetical examples. In the first example, suppose that one ADA randomized study patient died. Using the NEAR approach, the estimated NEAR OR would differ minimally from the estimated OR from an analysis of only efficacy ignoring the potential safety concerns. In the second example, consider the week 8 remission analysis (per FM) which has 180/468 responses in the placebo group and 241/471 in the ADA group. Suppose there were 61 SAEs all occurring in the ADA group and they all occurred in patients that had a clinical response. In this case, the number of SAE-free treatment successes in the ADA group is 180/471 compared to 180/468 for placebo. In this extreme scenario (which has an alarming safety signal), per this approach and the Applicant's interpretation, the NEAR OR would be below one suggesting ADA has an unfavorable benefit-risk ratio; however, if there were 60 (or fewer) SAEs (still a large signal), the ADA group would have a favorable benefit-risk ratio. These examples suggest incongruence between the proposed quantification of benefit-risk (based on an adapted version of the NEAR) to how clinical benefit is considered along with risk.

A second limitation is that the comparison only contrasts the favorable aspects of benefit-risk, i.e. the numerator value is based on patients with clinical benefit and who did not experience the specific safety event of interest. Other aspects of benefit-risk that can be obtained from the cross-classification of the efficacy response and safety event, such as

[8] Boada JN, Boada C, García-Saíz M, et al. Net Efficacy Adjusted for Risk (NEAR): a simple procedure for measuring risk:benefit balance. PLoS One. 2008;3(10):e3580).

[9] The NEAR approach described in the publication is considered flawed. By obtaining expected counts from the marginal event counts, one is implicitly assuming that the efficacy and safety endpoints are independent. Such an assumption is incorrect and was not discussed in the source article. Further, as a consequence of their approach, if group A has a greater percentage of patients with a positive efficacy endpoint and fewer AEs compared to group B, with probability 1 the odds of treatment group A will be larger than the odds for group B (i.e., the OR>1).

In addition, the Applicant's NEAR analysis differs from the approach described in the paper by Boada et al (2008). The difference is that the Applicant uses the observed number of subject that had an AE-free treatment success, whereas the source publication uses the expected numbers based on the marginal event counts within treatment groups.

the proportion of patients that *did not* have a clinical response (e.g. no remission) but *did* have an AE that led to treatment discontinuation, are not presented in the Applicant's NEAR analysis.

A third limitation is that the comparison only considers short-term efficacy with short-term risk. The problem with this is that short-term efficacy assessment is not done without also considering long-term risk when one assesses the overall risk benefit of a product. The failure of the analysis to incorporate temporal considerations, in addition to the above points, is sufficient reason to question the results from this analysis.

Exploratory Analysis #12 (Applicant): Number Needed to Harm (NNH) Analysis

The number needed to harm (NNH) corresponds to the number of patients needed to treat with Humira compared to placebo to result in one adverse event (SAE, AE leading to discontinuation, serious infections and malignancies). Estimates were derived by taking the inverse of the risk difference (1/difference of proportions) based on pooled data from the UC studies or from combined data from the UC and CD studies. Several point estimates were provided by the sponsor; however, it is unclear how clinically meaningful these values are without inclusion of confidence intervals, considering estimates when including data on all Humira exposures (not just on exposure to the Humira 160/80 treatment group) and understanding the type of events included (e.g. category of AEs leading to treatment discontinuation lacks in specificity of event).

The table below provides estimates of the NNH based on combined data from the two UC studies (826 and 827) using data collected up to 52 weeks. Two estimates are provided; one based on the inverse of the difference in proportion of events between placebo and the Humira 180/60 group and the second between placebo and all Humira. In addition, 95% CI (based on asymptotic method) are included to provide a measure of variability around the NNH estimates. The proportion of all SAEs in the placebo and Humira 160/80 groups are 10.1% and 8.3% respectively resulting NNH of -55 (1/(0.083-0.101)) with a 95% CI (-18, 53). This suggests a lower risk of SAE (when holding all other outcomes constant) in the Humira group. When including all ADA data, the proportion of SAEs in the placebo and Humira groups is 10.1% and 25.1%, respectively resulting in a NNH of 7 with a 95% CI (5, 9) suggesting a higher risk in the Humira group. Therefore, the interpretation of NNH varies greatly depending on the data included in the pooled estimate. Also, note that the confidence intervals around several estimates presented in the table include infinity suggesting that the possibility of no difference between regimens cannot be ruled out.

Table 38: NNH Values based on Data for 0-52 Weeks (UC Studies 826 and 827 Combined)

Event	Placebo (n=483)	Humira 160/80 (n=480)	All Humira (n=1010)
All SAEs	49 (10.1)	40 (8.3)	254 (25.1)
NNH (95% CI)		*-56 (-18, 53)*	*7 (5, 9)*
AE leading to Treatment D/C	46 (9.5)	36 (7.5)	206 (20.4)
NNH (95% CI)		*-49 (-18, 65)*	*9 (7, 14)*
Serious Infections	8 (1.7)	4 (0.8)	58 (5.7)
NNH (95% CI)		*-122 (-40, 148)*	*24 (17, 47)*
Malignancy (excl. NMSC)	1 (0.2)	1 (0.2)	15 (1.5)
NNH (95% CI)		*77280 (-102, 102)*	*78 (44, 423)*

Event counts based on those reported in Sponsor's Table 26 of AC Briefing Document, NNH estimates based on inverse of the risk difference (Humira-placebo), a negative NNH suggests decreased risk in Humira group relative to placebo, a positive value suggests increased risk in Humira relative to placebo

The sponsor also provided estimates on the number needed to treat (NNT) for clinical remission, response, mucosal healing and IBDQ response. The issues raised above also apply to these analyses of NNT along with limitations in pooling data for efficacy assessments.

6. CLINICAL PHARMACOLOGY

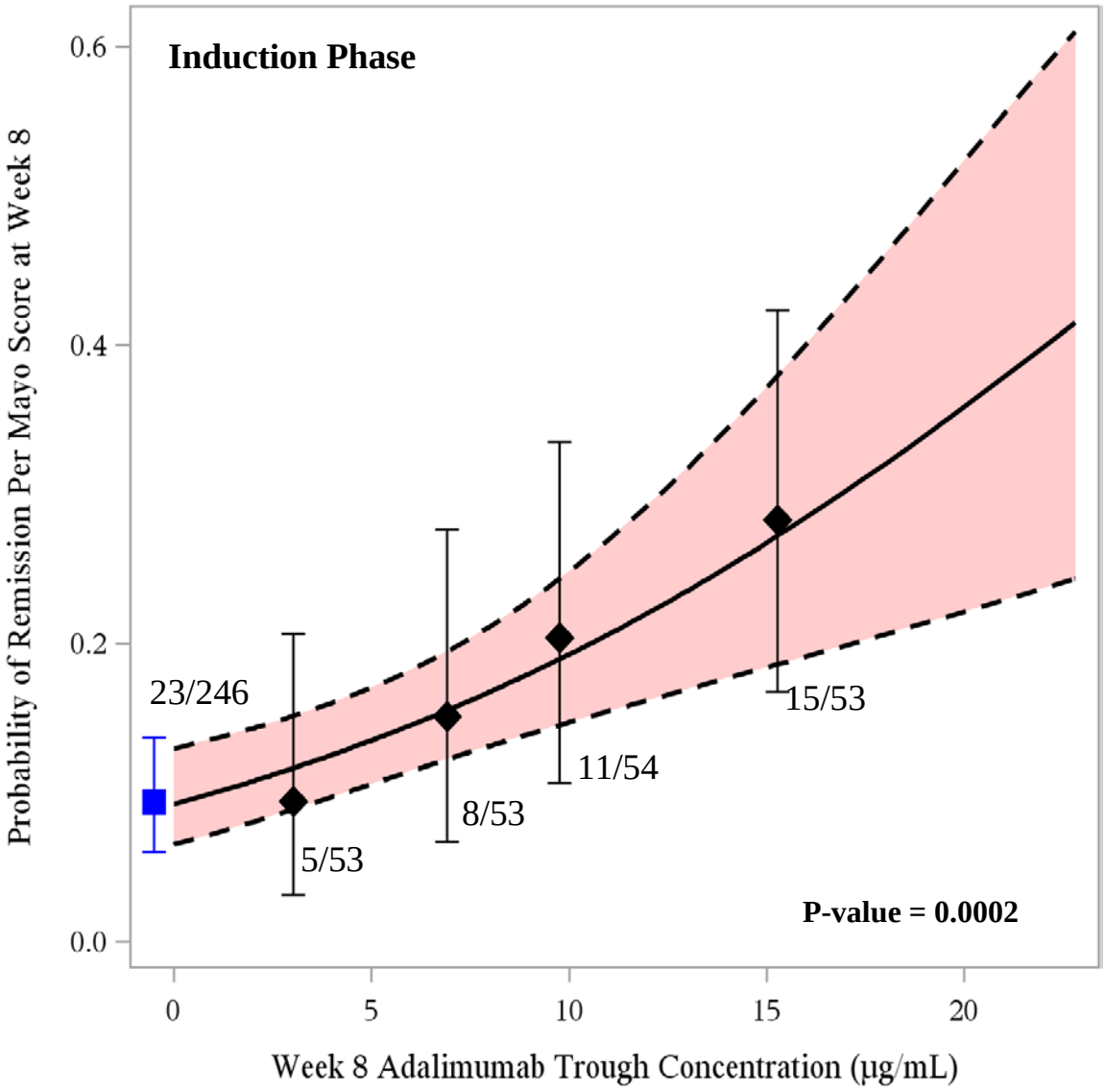
6.1 Exposure-Response Analysis

The available exposure-response data in subjects with UC indicate that the dosing regimen for induction phase has not been fully explored. Therefore, the clinical efficacy of Humira in this population can not be considered adequately evaluated. Exposure-response (clinical remission per Mayo score at Week 8) analysis by the FDA was performed using a logistic regression model with intercept and slope. However, the Applicant utilized an E_{max} logistic regression model. It is important to note the limitations of using E_{max} logistic regression for establishing the relationship between exposures and induction of clinical remission at Week 8. The observed data from Study 827 indicate that the maximum clinical remission rate is not reached within the observed range of exposures. The E_{max} structure, however, forces the model to predict a plateau for response (induction of clinical remission). Therefore, the choice of E_{max} model may not be appropriate.

6.1.1 Induction Dosing Regimen

Exposure-efficacy analysis was conducted to evaluate the adequacy of the proposed induction dose. Data from Study M06-827 was used in the analysis because this was the only study in which PK data was collected. The relationship between probability of achieving clinical remission per Mayo score at week 8 and adalimumab week 8 trough concentrations was modeled using multivariate logistic regression. The results showed that week 8 adalimumab trough concentration ($p=0.0003$), baseline Mayo score ($p<0.0001$), and prior-anti-TNF therapy at baseline ($p=0.025$) all were significantly related to week 8 remission. Patients with higher concentrations have higher probability of induction of clinical remission. Patients with prior anti-TNF therapy have lower probability of induction of clinical remission which is consistent with the observed clinical data. In addition, patients with higher baseline mayo scores have less probability of induction of clinical remission at Week 8. Notably, the increase in remission rate with increase in adalimumab concentration does not appear to plateau over the range of observed trough concentrations (Figure 3), suggesting that a higher dose may increase the probability of remission at Week 8.

Figure 3: Probability of remission at Week 8 increases with increasing Week 8 adalimumab trough concentrations.
Logistic regression model of the probability of remission per Mayo score at week 8 as a function of week 8 adalimumab trough concentrations. The mean and 95% CI interval for observed remission versus the mean observed concentration in the quartiles are represented by the black diamonds and bars, and the placebo group is represented by the blue square and bars.



Subjects who exhibited inadequate response during the maintenance phase of Study M06-827 were able to switch from their double-blind (DB) treatment assignment to open-label (OL) adalimumab 40 mg every other week (eow) starting at Week 12. Inadequate response was defined as:

- Partial Mayo score greater than or equal to their Baseline score on 2 consecutive visits at least 14 days apart (for subjects with a partial Mayo score of 4 to 7 at Baseline).

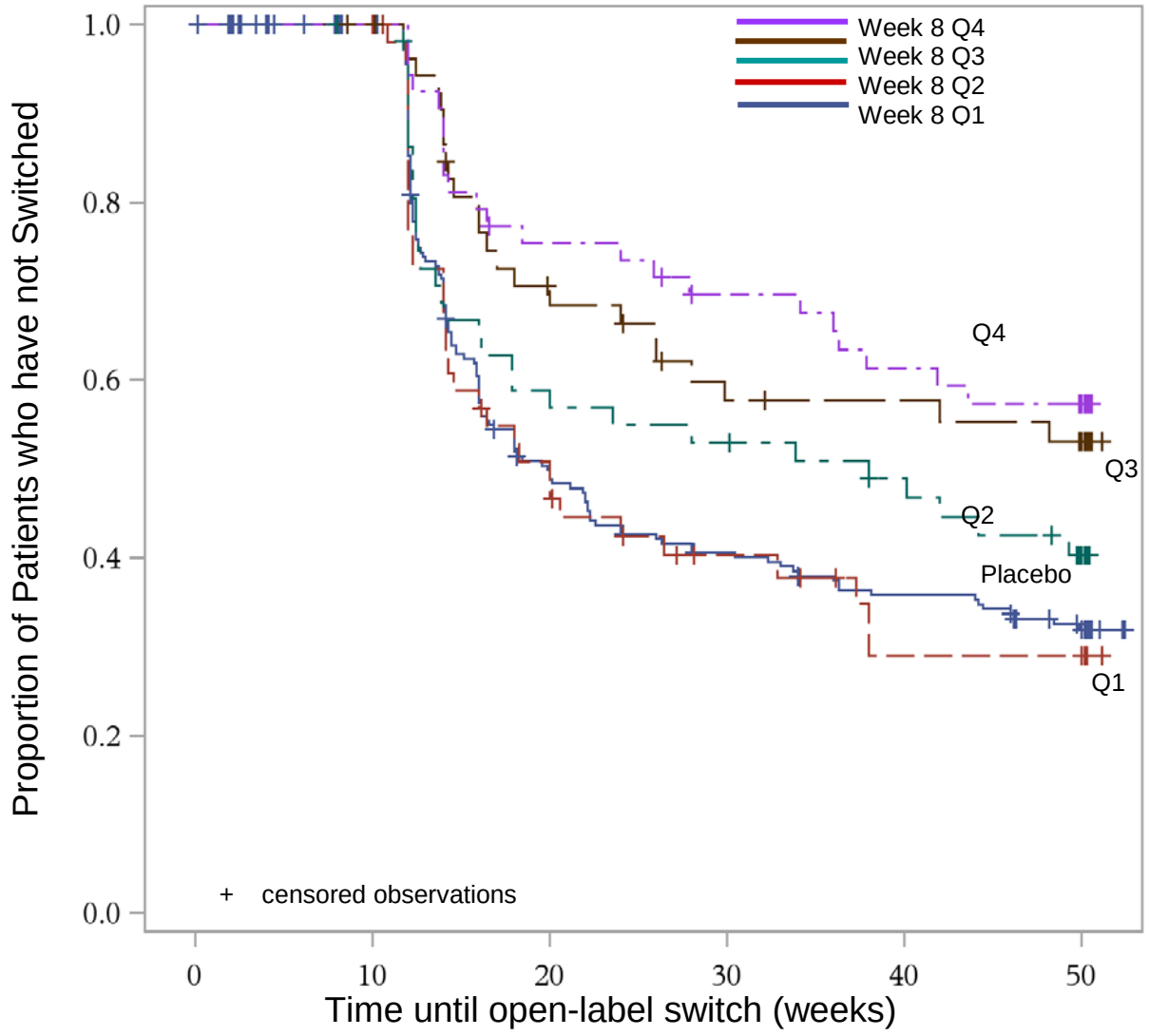
- Partial Mayo score ≥ 7 on 2 consecutive visits at least 14 days apart (for subjects with a partial Mayo score of 8 or 9 at Baseline).

Kaplan Meier analysis was conducted to examine if higher concentrations in the induction phase were associated with an increase in time to open-label switch (i.e., inadequate response). Subjects were grouped into Week 8 adalimumab trough concentration quartiles and a placebo group (Figure 4). The plot suggests that subjects with higher Week 8 concentrations maintain response (i.e. did not exhibit inadequate response) over a longer period of time compared to subjects with lower Week 8 concentrations who switch to open label earlier. In addition, the proportion of subjects who did not switch to open label increases with increasing concentration (32% for placebo, 29% for Q1, 40% for Q2, 53% for Q3, and 57% for Q4).

A univariate proportional hazards model for open label switch was explored using Week 8 adalimumab trough concentration as well as various subject risk factors (such as age, baseline Mayo score, prior exposure to anti-TNF therapy, weight, etc.) as covariates. The Week 8 adalimumab concentration (p=0.0006) and prior exposure to anti-TNF therapy (p=0.0031) were statistically significant covariates indicating that patients with lower concentrations or prior exposure to anti-TNF have higher risk to switch to open label. A multivariate proportional hazards model showed that Week 8 adalimumab concentration is significant (p=0.0008) after accounting for prior exposure to anti-TNF therapy. The hazard ratio for Week 8 adalimumab trough concentration (HR=0.93) indicates that increasing the concentration by 1 μg/mL decreases hazard for open-label switch by 7%. The results suggest that time to open-label switch due to inadequate response increases with increasing concentrations after correcting for potentially confounding risk factors.

Figure 4: Low Week 8 adalimumab concentration quartiles are associated with earlier time to open label switch.

Kaplan-Meier plot of the proportion of subjects who have not switched vs. week 8 adalimumab trough concentration quartile. Patients who did not switch to open label were censored and are indicated by the "+" symbol.



6.1.2 Maintenance Dosing Regimen

A robust exposure-response relationship for the maintenance phase could not be established due to significant drop out and missing PK data.

6.1.3 Summary

In summary, the exposure-response analysis for the induction of clinical remission at Week 8 supports the following conclusions:

- An increase in adalimumab concentration is associated with an increase in clinical remission rate at week 8. This relationship does not reach a plateau over the range of concentrations observed at the proposed induction dose.
- Patients with lower adalimumab concentrations in the induction phase exhibited inadequate response (and switched to open label treatment) earlier than patients with higher adalimumab concentrations.

Thus, considering this relationship of exposures with clinical remission and maintenance of response along with the modest treatment effect for the induction of clinical remission, a higher dose for the induction phase may provide greater benefit to UC patients. It is important to note that the Applicant did not conduct phase 2 dose-finding studies for the UC indication, but rather selected the dose and dosing regimen that is approved for the CD indication for the Phase 3 adult UC clinical trials. Furthermore, it should be noted that the Applicant has not tested a dosing regimen higher than 160/80/40 in their clinical development program.

6.2 Immunogenicity

Development of antibodies is a risk of many biologic therapies including TNFα-antagonist products. For example, the development of Human Anti-Chimeric Antibodies (antibodies against infliximab) may lead to infusion reactions and/or reduced duration of efficacy. Humira is humanized; thus, it is hypothesized that there will be less development of anti-drug antibodies; however, the subcutaneous administration route is expected to produce higher immunogenicity than the intravenous route.

Although the immunogenicity data presented in the prescribing information can be interpreted as infliximab having a higher immunogenicity rate, such numerical comparisons are not advised due to limitations in the methodologies used. In addition, a numerically higher incidence rate than that in the prescribing information has been reported in a recently published long-term cohort study of RA patients taking Humira.[10] For the current application, unfortunately, the assessment of immunogenicity was not adequate because most samples were not appropriately evaluated due to the drug interference in the assays for anti-adalimumab antibody (AAA) measurement, and therefore, whether Humira actually offers immunogenicity advantages remains unknown.

[10]Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg, PA, Lems WF, et al Development of Antidrug Antibodies Against Adalimumab and Association with Disease Activity and Treatment Failure During Long-term Follow-up. JAMA April 13, 2011 vol 305 no 14 p1460-1468).

7. SAFETY

7.1 Exposure

Across all three studies, the mean duration of exposure to Humira was 542.5 days (range 14 to 1,475 days). Of the 1,010 patients in the All Humira Set, 60.0% (606) used Humira for greater than 12 months, 49.6% were exposed for greater than 18 months, and 35.4% were exposed for greater than 24 months. (See the table of exposure in Appendix 8.)

7.2 Deaths

There was one death reported in the three studies submitted in this Application. The patient (72902) died at age 36 on Day 543 of Humira (9 days after his last dose). He was a Caucasian male randomized to Humira 160/80/40 mg in Study 827 and continued on Humira in Study 223. During this study, the patient dose-escalated to Humira 40 ew. The patient had a non-serious event of flu syndrome, head pain, body aches, and fever 3 days prior to his death. He was found in respiratory arrest by his mother and transferred to a hospital where resuscitation efforts were unsuccessful. Autopsy revealed a bilateral adrenal hemorrhage secondary to an infectious process, the etiology of which could not be determined from the autopsy. The death was considered possibly related to study drug.

7.3 Serious Adverse Events:

SAEs are summarized below by Induction Set, Maintenance Set, and All Humira Set:

Induction Set:

During the 8 week induction periods of Studies 826 and 827, a total of 610 patients were exposed to Humira. Serious adverse events (SAEs) were reported in 5 patients (3.8%) taking Humira 80/40 mg and 25 patients (5.2%) taking Humira 160/80/40 mg. In comparison, 40 patients (8.3%) in the placebo group reported an SAE. The most commonly reported SAEs were in the gastrointestinal disorders System Organ Class. In all treatment groups, the most commonly reported MedDRA preferred term was ulcerative colitis. (See table of SAEs by SOC (Induction Set) in Appendix 8.)

Maintenance Set:

Patients in the Maintenance Set were enrolled in Study 827 and received at least one dose of study drug between Weeks 8 and 52. Of these, 11 patients (4.9%) in the placebo group and 15 patients (6.4%) in the Humira group reported at least one SAE. Similar to the induction set, the most commonly reported SAE was ulcerative colitis.

All Humira Set:

Among all patients exposed to Humira in Studies 826, 827, and 223, a total of 223 patients (22.1%) reported at least one SAE. Similar to the induction and maintenance sets, the most commonly reported SAE was ulcerative colitis. (See table of SAEs by SOC (All Humira Set) in Appendix 8.)

7.4 Common Adverse Events:

Common AEs are summarized below by Induction Set, Maintenance Set, and All Humira Set:

Induction Set:

During the randomized, double-blind, eight-week induction period of studies 826 and 827, a total of 282 placebo patients (58.4%) and 335 Humira patients (54.9%) reported an adverse event. The most common adverse events reported by patients in any treatment group were ulcerative colitis, headache, and nasopharyngitis. (See table of Common AEs (Induction Set) in Appendix 8.)

Maintenance Set:

Of patients in the Maintenance Set (i.e., received blinded treatment from Week 8 through Week 52 in Study 827), 152 (68.2%) of placebo patients and 172 (73.5%) of Humira patients reported an AE. The most commonly reported AE was ulcerative colitis. Other common AES are in the current label. (See table of Common AEs (Maintenance Set) in Appendix 8.)

All Humira Set:

Overall, 845 patients (83.7%) reported at least one adverse event while taking Humira. The most common AEs reported were ulcerative colitis (31.8%), nasopharyngitis (16.7%), and arthralgia (10.4%). (See table of Common AE's (All Humira Set) in Appendix 8.)

7.5 Dose-Response

The Clinical Reviewer concluded that there was no clear trend of higher incidence of AEs with increasing Humira dose seen in the UC studies.

7.6 Discussion Regarding other TNFα-Antagonists

There are known serious adverse events associated with the use of Humira and other TNFα-antagonists. These known risks include malignancies, serious infections, serious allergic reactions, hepatitis B virus reactivation, new onset or exacerbation of demyelinating disease, new or worsening heart failure, and lupus-like syndrome. According to current Remicade labeling the incidence of infusion reactions was 20%. In Humira UC studies, the incidence of injection site reactions was 20%. The incidence of infections in Remicade-treated patients was 36%. In Humira UC studies, the incidence of infections in Humira patients was 38% (maintenance set).

APPENDIX 1: Inclusion and Exclusion Criteria

Study 826

Inclusion Criteria:
A subject will be eligible for study participation if he/she meets all of the following:

1. Male or female ≥ 18 years of age.
2. Diagnosis of ulcerative colitis for greater than 90 days prior to Baseline.
3. Diagnosis of active ulcerative colitis confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy during the Screening Period, with exclusion of infection.
4. Active ulcerative colitis with a Mayo Score of 6-12 points and endoscopic subscore of 2-3 despite concurrent treatment with oral corticosteroids and/or immunosuppressants as defined below:
   - Stable (± 5 mg) corticosteroid dose (prednisone of ≥ 20 mg/day or equivalent) for at least 14 days prior to Baseline.
   - At least a 90 day course of azathioprine or 6-MP prior to Baseline, with a dose of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet formulation), or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time. Subject must be on a stable dose for at least 28 days prior to Baseline.

   Concurrent therapy will not be required for subjects who were previously treated with corticosteroids or immunosuppressants (azathioprine or 6-MP) during the past 5 years and in the judgment of the investigator have failed to respond to or could not tolerate their treatment.
5. Must be able to self-administer or has caregiver who can reliably administer subcutaneous injections.
6. Must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
7. Female must be either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or is of childbearing potential and practicing one of the following methods of birth control throughout the study and for 150 days after study completion:
   - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD)
   - Oral or parenteral contraceptives for 90 days prior to study drug administration
   - A vasectomized partner
8. The results of the serum pregnancy test performed at the Screening Visit and urine pregnancy test performed at the Baseline Visit must be negative.
9. Judged to be in generally good health by the investigator.

Exclusion Criteria:
A subject will be excluded from the study if he/she meets any of the following criteria:

1. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, or ileostomy for ulcerative colitis or is planning bowel surgery.
2. Received infliximab or any other anti-TNF agent in the past.

3. Received previous treatment with adalimumab or previous participation in an adalimumab clinical study.
4. Received cyclosporine, tacrolimus, mycophenolate mofetil, or methotrexate within 60 days prior to Baseline.
5. Received intravenous corticosteroids within 14 days prior to Screening and during the Screening Period.
6. Received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to the Screening Visit and during the Screening Period.
7. Current diagnosis of fulminant colitis and/or toxic megacolon.
8. Subjects with disease limited to the rectum (ulcerative proctitis).
9. Current diagnosis of indeterminate colitis.
10. Current diagnosis and/or history of Crohn's disease.
11. Currently receiving total parenteral nutrition (TPN).
12. Discontinued use of azathioprine, or 6-MP within 28 days of Baseline.
13. Discontinued use of corticosteroid within 14 days of Baseline.
14. Subjects using aminosalicylates for less than 90 days prior to Baseline or not on a stable dose for at least 28 days prior to Baseline or discontinued use within 28 days of Baseline.
15. Subjects with positive Clostridium difficile (C. difficile) stool assay.
16. Persistent chronic or active non-UC related infections requiring treatment with intravenous (iv) antibiotics, iv antivirals, or iv antifungals within 30 days prior to Baseline or oral antibiotics, oral antivirals, or oral antifungals within 14 days prior to Baseline.
17. History of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix. If the Screening colonoscopy/flexible sigmoidoscopy shows evidence of dysplasia or a malignancy, subject may not be enrolled in the study.
18. History of Listeria, Histoplasmosis, chronic or active Hepatitis B infection, human immunodeficiency virus (HIV), immunodeficiency syndrome, central nervous system (CNS) demyelinating disease, or untreated tuberculosis (TB).
19. Female subject who is pregnant or breast-feeding or considering becoming pregnant during the study. There should be at least a 150-day period between the last dose of study drug and either conception or initiation of breast-feeding in women of childbearing potential.
20. Poorly controlled medical condition, such as uncontrolled diabetes with documented history of recurrent infections, unstable ischemic heart disease, congestive heart failure, recent cerebrovascular accident and any other condition, which in the opinion of the investigator, would put the subject at risk by participation in the protocol.
21. Received any investigational agent within 30 days or 5 half lives prior to Baseline (whichever is longer).
22. History of clinically significant drug or alcohol abuse during the past year.
23. Subjects with known hypersensitivity to the excipients of adalimumab as stated in the label.
24. Subjects with any prior exposure to Tysabri® (natalizumab).
25. Subjects currently taking both budesonide and prednisone (or equivalent) simultaneously.

Study 827

Inclusion Criteria:
A subject will be eligible for study participation if he/she meets all of the following:

1. Male or female ≥ 18 years of age.
2. Diagnosis of ulcerative colitis for greater than 90 days prior to Baseline.
3. Diagnosis of active ulcerative colitis confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy during the Screening Period, with exclusion of infection.
4. Active ulcerative colitis with a Mayo Score of 6-12 points and endoscopy subscore of 2-3 despite concurrent treatment with oral corticosteroids and/or immunosuppressants as defined below:
   - Stable (± 5 mg) corticosteroid dose (prednisone ≥ 20 mg/day or equivalent) for at least 14 days prior to Baseline, or maintenance corticosteroid dose (prednisone ≥ 10 mg/day and < 20 mg/day or equivalent) for at least 40 days prior to Baseline.
   - At least a 90 day course of azathioprine or 6-MP prior to Baseline, with a dose of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet formulation), or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time. Subject must be on a stable dose for at least 28 days prior to Baseline.

   Concurrent therapy will not be required for subjects who were previously treated with corticosteroids or immunosuppressants (azathioprine or 6-MP) during the past 5 years and in the judgment of the investigator have failed to respond to or could not tolerate their treatment.
5. Subjects may be included if they have previously used an anti-TNF agent (except adalimumab) and discontinued its use due to a loss of response or intolerance to the agent (see Appendix 2 for Loss of Response and Intolerance definitions).
6. Must be able to self-administer or has caregiver who can reliably administer subcutaneous injections.
7. Must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
8. Female subjects must be either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or is of childbearing potential and practicing one of the following methods of birth control throughout the study and for 150 days after study completion:
9. Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD)
10. Oral or parenteral contraceptives for 90 days prior to study drug administration
11. A vasectomized partner
12. The results of the serum pregnancy test performed at the Screening Visit and urine pregnancy test performed at the Baseline Visit must be negative.
13. Judged to be in generally good health by the investigator.

Exclusion Criteria:

A subject will be excluded from the study if he/she meets any of the following criteria:

1. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, or ileostomy for ulcerative colitis or is planning bowel surgery.
2. Received previous treatment with adalimumab or previous participation in an adalimumab clinical study.
3. Received cyclosporine, tacrolimus, mycophenolate mofetil, or methotrexate within 60 days prior to Baseline.
4. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
5. Received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to the Screening Visit or during the Screening Period.
6. Current diagnosis of fulminant colitis and/or toxic megacolon.
7. Subject with disease limited to the rectum (ulcerative proctitis).
8. Current diagnosis of indeterminate colitis.
9. Current diagnosis and/or history of Crohn's disease.
10. Currently receiving total parenteral nutrition (TPN).
11. Subject using aminosalicylates for less than 90 days prior to Baseline or not on a stable dose for at least 28 days prior to Baseline or discontinued use within 28 days of Baseline.
12. Subject with positive Clostridium difficile (C. difficile) stool assay.
13. Subject who has previously used infliximab or any anti-TNF agent within 56 days of Baseline.
14. Subject who has previously used infliximab or any anti-TNF agent and has not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction.
15. Persistent chronic or active non-UC related infections requiring treatment with intravenous (iv) antibiotics, antivirals, or antifungals within 30 days prior to Baseline or oral antibiotics, antivirals, or antifungals within 14 days prior to Baseline.

APPENDIX 2: Definitions of Loss of Response and Intolerance to an Anti-TNF Agent (in Study 827)

The following is taken from Pages 1601-1602 of the Study 827 protocol.

Subjects who have previously been exposed to an anti-TNF agent, including infliximab, must meet one of the two conditions defined below.

Loss of Response:

The investigator judges the subject to have responded to the anti-TNF agent in the past and demonstrated a loss of response by meeting one of the following criteria after the last dose (Note: a subject with prior infliximab exposure must have responded to a dose of ≥ 5 mg/kg and demonstrated loss of response ≥ 14 days after they received at least 2 subsequent and sequential doses of ≥ 5 mg/kg at an interval not exceeding 56 days)

- Experienced an overall lack of improvement
- Experienced a worsening of the following, but not inclusive, UC related signs/symptoms:
  - Stool frequency
  - Abdominal pain
  - Rectal bleeding
  - Fever
  - Weight loss

Intolerance to Anti-TNF agent:

A subject is defined as intolerant when, in the opinion of the investigator, therapy was discontinued as a result of a significant acute or delayed reaction to the medication. A reaction is considered significant if at least one of the clinical characteristics listed below is reported by history and is documented in progress notes or other source documents.

- Acute Reactions
  An adverse reaction, whether immunologically or non-immunologically based, which occurs during or within 24 hours of administration of an anti-TNF agent that is manifested by one or more of the sign/symptoms listed below and is judged to be related to the medication.
  - Fever > 100°F
  - Chills or rigors
  - Itching
  - Rash
  - Flushing
  - Urticaria or angioedema
  - Breathing difficulties (dyspnea, chest pain or tightness, shortness of breath, wheezing, stridor)
  - Clinical hypotension (pallor, diaphoresis, faintness, syncope), or orthostatic decrease in blood pressure

- Delayed Reactions
  An adverse reaction occurring more than 24 hours and < 14 days after anti-TNF agent administration manifested by one or more of the following signs/symptoms and is judged to be related to the medication.
  - Myalgias
  - Arthralgias
  - Fever > 100°F
  - Malaise
  - Rash

APPENDIX 3: ITT-E and ITT-A3 Definitions (Study 826)

The ITT-E and ITT-A3 definitions of Study 826 are shown below followed by discussion about Protocol Amendments 3 and 4.

Population	Definition
ITT-E	All patients with confirmed UC at Baseline who were randomized at any time during the study and received at least 1 injection of the following induction regimens: Humira 160/80/40 mg, Humira 80/40 mg, or placebo
ITT-A3	All patients with confirmed UC at Baseline who were randomized according to the revised study design described in Amendment 3 (and Amendment 4) and received at least 1 injection of the following induction regimens: Humira 160/80/40 mg, Humira 80/40 mg, or placebo

Amendment 3 was finalized 06 August 2007 (approximately 8 months after the study began). The change was introduced for the following primary reasons:

1. To change the blinded study drug period from 12 weeks to 8 weeks and add the 80/40 mg Humira induction dosing arm.
2. To revise the inclusion criteria to clarify that current therapy with either a corticosteroid or an immunosuppressant will satisfy these inclusion criteria and to simplify the interpretation of the corticosteroid dosage requirements.
3. To expand the birth control methods listed in the inclusion criteria.
4. To expand the exclusion criteria to include any prior biological therapy and not just infliximab or other anti-TNF agents.
5. To remove methotrexate as an exclusionary medication.
6. To decrease the exclusionary duration for therapy with cyclosporine, tacrolimus, or mycophenolate mofetil from 60 days to 30 days prior to Baseline.
7. To expand prohibited therapies to exclude biologic therapies including natalizumab and abatacept.
8. To add colectomy rates as a secondary efficacy variable.
9. To revise the sample size determination to reflect the inclusion of an additional adalimumab treatment arm.

Amendment 4 was finalized 12 March 2009 (approximately 2 years, 4 months after the study began). The change was introduced to update the contact information for various study personnel and to update the statistical section of the protocol to reflect changes in the secondary efficacy variables.

APPENDIX 4: Secondary and Other Endpoints

Study 826

Ranked secondary efficacy variables assessed at Week 8 included (in the statistical hierarchical order):

1. Proportion of patients with clinical response per Mayo score at Week 8 (Humira 160/80/40 versus placebo).
2. Proportion of patients with mucosal healing at Week 8 (Humira 160/80/40 versus placebo).
3. Proportion of patients with Rectal Bleeding sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 160/80/40 versus placebo).
4. Proportion of patients with Physician's Global Assessment sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 160/80/40 versus placebo).
5. Proportion of patients with stool frequency sub-score indicative of mild disease (≤ 1) at Week 8 (Humira160/80/40 versus placebo).
6. Proportion of patients with clinical response per Mayo score at Week 8 (Humira 80/40 versus placebo).
7. Proportion of patients with mucosal healing at Week 8 (Humira 80/40 versus placebo).
8. Proportion of patients with rectal bleeding sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 80/40 versus placebo).
9. Proportion of patients with Physician's Global Assessment sub-score indicative of "normal or mild disease" (or numerical score ≤ 1) at Week 8 (Humira 80/40 versus placebo).
10. Proportion of patients with stool frequency sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 80/40 versus placebo).
11. Proportion of IBDQ responders at Week 8 (Humira 160/80/40 versus placebo).
12. Proportion of IBDQ responders at Week 8 (Humira 80/40 versus placebo).

Non-ranked secondary efficacy variables:

- Proportion of patients with response per Partial Mayo Score at Weeks 2, 4, and 6.
- Proportion of patients with Rectal Bleeding sub-score indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Proportion of patients with Physician's Global Assessment sub-score indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Proportion of patients with Stool Frequency sub-score indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Change from Baseline in total Inflammatory Bowel Disease Questionnaire (IBDQ) score at Week 8.
- Change from Baseline in SF-36 at Week 8.
- Change from Baseline in Partial Mayo Score at Weeks 2, 4, 6, and 8.
- Change from Baseline in Mayo Score at Week 8.
- Time to clinical response per Partial Mayo Score (up to Week 8).

Descriptive statistics were to be presented for the OL period of the study through Week 52, including, but not limited to, the following efficacy variables:

- Proportion of patients with remission at both Week 8 and at Week 52.
- Proportion of patients with remission at Week 52.
- Proportion of patients with response per Mayo Score at both Week 8 and Week 52.
- Time in clinical response per Partial Mayo Score.
- Proportion of patients with mucosal healing at both Week 8 and Week 52.
- Proportion of patients with mucosal healing at Week 52.
- Proportion of patients using corticosteroids at Baseline in remission at Week 8 who had discontinued corticosteroids and were in remission at Week 52.
- Proportion of patients using corticosteroids at Baseline who had discontinued corticosteroids and were in remission at Week 52.
- Proportion of patients using corticosteroids at Baseline who had discontinued corticosteroids for at least 90 days and were in remission at Week 52.
- Time in steroid-free clinical response per Partial Mayo Score for patients who were using corticosteroids at Baseline.
- Proportion of patients requiring dose escalation to 40 mg ew.
- Proportion of patients achieving response at Week 52 after dose escalation
- Proportion of patients achieving remission at Week 52 after dose escalation for a) patients who had not achieved response per Partial Mayo Score prior to dose escalation and b) patients who had achieved response per Partial Mayo Score but lost response (had inadequate response) prior to dose escalation.
- Proportion of patients achieving minimal rectal bleeding (Rectal Bleeding subscore ≤ 1) at Week 52.
- Proportion of patients achieving minimal rectal bleeding (Rectal Bleeding subscore ≤ 1) at both Week 8 and Week 52.
- Time in minimal rectal bleeding (Rectal Bleeding subscore ≤ 1).
- Proportion of patients randomized to placebo who achieve clinical response by Partial Mayo Score at Week 16.
- Proportion of patients who are IBDQ responders at Week 52.
- Change from Baseline in IBDQ at Week 52.
- Change from Baseline in SF-36 at Week 52.
- Change from Baseline in Mayo Score at Week 52.
- Change in Partial Mayo Score overtime.
- Colectomy rates during the study

<u>Study 827</u>

Ranked Secondary Variables:

1. Proportion of patients with remission (sustained) at both Weeks 8 and 52.
2. Proportion of patients who achieve response per Mayo Score at Week 8 and Week 52.
3. Proportion of patients who discontinue corticosteroid use and achieve remission at Week 52.

4. Proportion of patients who discontinue corticosteroid use for at least 90 days and achieve remission at Week 52.
5. Proportion of patients with response per Mayo Score (sustained) at both Weeks 8and 52.
6. Proportion of patients who discontinue corticosteroid use and achieve remission (sustained) at both Weeks 32 and 52.
7. Proportion of patients who are IBDQ responders at Week 52.
8. Proportion of patients who are IBDQ responders at Week 8.

Non-ranked Secondary Variables:

- Proportion of patients who achieve clinical remission at Week 32.
- Proportion of patients who achieve remission (sustained) throughout Weeks 8, 32, and 52.
- Proportion of patients who achieve clinical response at Week 32.
- Proportion of patients who achieve response per Mayo Score (sustained) throughout Weeks 8, 32, and 52.
- Proportion of patients who achieve response per Partial Mayo Score over time.
- Time to response per Partial Mayo Score.
- Time in response per Partial Mayo Score.
- Proportion of patients who discontinue corticosteroid use for at least 90 days and achieve remission at Week 32.
- Proportion of patients who discontinue corticosteroid use and achieve remission at Week 32.
- Proportion of patients who have discontinued corticosteroid use at each time point after Week 8.
- Time in steroid-free response per Partial Mayo Score for patients who were using corticosteroids at Baseline.
- Proportion of patients who are IBDQ responders at Week 32.
- Proportion of patients who are IBDQ responders (sustained) at both Weeks 8 and 52.
- Proportion of patients who are IBDQ responders (sustained) throughout Weeks 8, 32 and 52.
- Proportion of patients with IBDQ score $\geq$ 170 over time.
- Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score over time.
- Change from Baseline in Short Form-36 Questionnaire (SF-36) over time.
- Change from Baseline in Mayo Score over time.
- Change from Baseline in endoscopy score over time.

APPENDIX 5: Ranked Secondary Endpoint Results

Study 826

Twelve ranked secondary variables were tested in a hierarchical order. Statistically significant results had to be achieved for a comparison to allow evaluation of a subsequent endpoint. The first ranked endpoint (clinical response per Mayo score at Week 8 in the Humira 160/80/40 mg treatment group versus placebo) had a p-value of 0.107 (statistical non-significance).

Table 39: Ranked Secondary Endpoint Results, Study 826 (ITT-A3; NRI)

	Number (%) of Subjects		
Proportion of Subjects With:[a]	**Placebo N = 130**	**Adalimumab 160/80/40 N = 130**	***P* value[b]**
1. Clinical response at Week 8	58 (44.6)	71 (54.6)	0.107
2. Mucosal healing at Week 8	54 (41.5)	61 (46.9)	0.382
3. RBS ≤ 1 at Week 8	86 (66.2)	101 (77.7)	0.038
4. PGA ≤ 1 at Week 8	61 (46.9)	78 (60.0)	0.035
5. SFS ≤ 1 at Week 8	49 (37.7)	63 (48.5)	0.080
	Placebo N = 130	**Adalimumab 80/40 N = 130**	
6. Clinical response at Week 8	58 (44.6)	67 (51.5)	0.264
7. Mucosal healing at Week 8	54 (41.5)	49 (37.7)	0.526
8. RBS ≤ 1 at Week 8	86 (66.2)	91 (70.0)	0.506
9. PGA ≤ 1 at Week 8	61 (46.9)	70 (53.8)	0.264
10. SFS ≤ 1 at Week 8	49 (37.7)	47 (36.2)	0.797
	Placebo N = 130	**Adalimumab 160/80/40 N = 130**	
11. IBDQ response at Week 8	75 (57.7)	79 (60.8)	0.614
	Placebo N = 130	**Adalimumab 80/40 N = 130**	
12. IBDQ response at Week 8	75 (57.7)	70 (53.8)	0.532

IBDQ = Inflammatory Bowel Disease Questionnaire; PGA = physician's global assessment subscore; RBS = rectal bleeding subscore; SFS = stool frequency subscore

a. Listed in rank order, as indicated by the number preceding each endpoint variable.

b. *P* value for differences between active treatment group and placebo from chi-square test (or Fisher's exact test if ≥ 20% of the cell have an expected count < 5).

Copied and electronically reproduced from Applicant's Table 37, CSR, Study 826 p 223/3375

Study 827

Fifteen ranked secondary variables were tested in a hierarchical order. Statistically significant results had to be achieved for a comparison to allow evaluation of a subsequent endpoint.

Table 40: Ranked Secondary Endpoints, Study 827

Ranked Secondary Endpoint		Placebo N=246	Humira (160/80/40 mg) N=248	p-value
1	Sustained remission, Week 8 and Week 52	4.1% (10)	8.5% (21)	0.047
2	Response, Week 8	34.6% (85)	50.4% (125)	<0.001
3	Response, Week 52	18.3% (45)	30.2% (75)	0.002
4	Sustained Response, Week 8 and Week 52	12.2% (30)	23.8% (59)	<0.001
5	Mucosal healing, Week 8	31.7% (78)	41.1% (102)	0.032
6	Mucosal healing, Week 52	15.4% (38)	25.0% (62)	0.009
7	Sustained Mucosal healing, Week 8 and Week 52	10.6% (26)	18.5% (46)	0.013
8	Discontinued corticosteroid use before Week 52 and achieved remission, Wee5 52	5.7% (8)	13.3% (20)	0.035
9	PGA (physician's global assessment) ≤1, Week 8	37.4% (92)	46.0% (114)	0.058
10	SFS (stool frequency sub-score) ≤1, Week 8	28.5% (70)	37.9% (94)	0.028
11	RBS (rectal bleeding sub-score) ≤1, Week 8	58.1% (143)	70.2% (174)	0.006
12	Discontinued corticosteroid use ≥9 days before Week 52 and achieved remission at Week 52	5.7% (8)	13.3% (20)	0.035
13	Discontinued corticosteroid use and achieved sustained remission at both Weeks 32 and 52	1.4% (2)	10.0% (15)	0.002
14	IBDQ responders at Week 52	16.3% (40)	26.2% (65)	0.007
15	IBDQ responders at Week 8	45.5% (112)	58.1% (144)	0.006

Study 827, CSR p 354/3632

APPENDIX 6: Selected Subgroup Analyses

Study 826: Induction of Clinical Remission (Wk 8)

Table 41: Subgroup Analyses: Induction of Clinical Remission (Wk 8) [Study 826]

Subgroup	Placebo	Humira 160/80/40	Difference (Humira-Placebo)
Gender			
Male	7/82 (8.5%)	13/83 (15.7%)	7.2%
Female	5/48 (10.4%)	11/47 (23.4%)	13.0%
Age			
<40	9/72 (12.5%)	16/74 (21.6%)	9.1%
40-64	3/54 (5.6%)	7/51 (13.7%)	8.1%
≥65	0/4 (0.0%)	1/5 (20.0%)	20.0%
Race			
White	10/117 (8.5%)	22/119 (18.5%)	10.0%
Non-white	2/13 (15.4%)	2/11 (18.2%)	2.8%
Weight			
< 70 kg	5/35 (14.3%)	11/45 (24.4%)	10.1%
≥70 kg	7/95 (7.4%)	13/85 (15.3%)	7.9%
CRP			
<10.0 mg/L	7/95 (7.4%)	21/101 (20.8%)	13.4%
≥10.0 mg/L	4/32 (12.5%)	2/25 (8.0%)	-4.5%
Smoker			
Ex-smoker	2/35 (5.7%)	6/37 (16.2%)	10.5%
Smoker	0/7 (0.0%)	4/12 (33.3%)	33.3%
Non-smoker	10/88 (11.4%)	14/81 (17.3%)	5.9%
Corticosteroid Use at baseline			
Yes	8/89 (9.0%)	12/71 (16.9%)	7.9%
No	4/41 (9.8%)	12/59 (20.3%)	10.5%
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	2/52 (3.8%)	8/51 (15.7%)	11.9%
No	10/78 (12.8%)	16/79 (20.3%)	7.5%

Reproduced from Statistical Review

Study 827: Induction of Clinical Remission (Wk 8)

Table 42: Subgroup Analyses: Induction of Clinical Remission (Wk 8) [Study 827]

Subgroup	Placebo	Humira	Difference (Humira-Placebo)
Gender			
Male	13/152 (8.6%)	23/142 (16.2%)	7.6%
Female	10/94 (10.6%)	18/106 (17.0%)	6.4%
Age			
<40	8/118 (6.8%)	23/136 (16.9%)	10.1%
40-64	13/116 (11.2%)	17/105 (16.2%)	5.0%
≥65	2/12 (16.7%)	1/7 (14.3%)	-2.4%
Race			
White	23/234 (9.8%)	38/236 (16.1%)	6.3%
Non-white	0/12 (0.0%)	3/12 (25.0%)	25.0%
Weight			
< 70 kg	7/91 (7.7%)	16/95 (16.8%)	9.1%
≥70 kg	16/155 (10.3%)	25/153 (16.3%)	6.0%
Prior Anti-TNF Treatment			
No	16/145 (11.0%)	32/150 (21.3%)	10.3%
Yes	7/101 (6.9%)	9/98 (9.2%)	2.3%
CRP			
<10.0 mg/L	20/169 (11.8%)	35/180 (19.4%)	7.6%
≥10.0 mg/L	3/77 (3.9%)	6/67 (9.0%)	5.1%
Smoker			
Ex-smoker	7/88 (8.0%)	15/94 (16.0%)	8.0%
Smoker	2/19 (10.5%)	2/20 (10.0%)	-0.5%
Non-smoker	14/138 (10.1%)	24/134 (17.9%)	7.8%
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	12/80 (15.0%)	12/93 (12.9%)	-2.1%
No	11/166 (6.6%)	29/155 (18.7%)	12.1%
Corticosteroid Use at baseline			
Yes	13/140 (9.3%)	31/150 (20.7%)	11.4%
No	10/106 (9.4%)	10/98 (10.2%)	0.8%

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Study 827: Clinical Remission at Wk 52

Table 43: Clinical Remission at Wk 52 [Study 827]

Subgroup	Placebo	Humira	Difference (Humira-Placebo)
Gender			
Male	18/152 (11.8%)	23/142 (16.2%)	4.4%
Female	3/94 (3.2%)	20/106 (18.9%)	15.7%
Age			
<40	11/118 (9.3%)	27/136 (19.9%)	10.6%
40-64	9/116 (7.8%)	16/105 (15.2%)	7.4%
≥65	1/12 (8.3%)	0/7 (0.0%)	-8.3%
Race			
White	21/234 (9.0%)	38/236 (16.1%)	7.1%
Non-white	0/12 (0.0%)	5/12 (41.7%)	41.7%
Weight			
< 70 kg	5/91 (5.5%)	20/95 (21.1%)	15.6%
≥70 kg	16/155 (10.3%)	23/153 (15.0%)	4.7%
Prior Anti-TNF Treatment			
No	18/145 (12.4%)	33/150 (22.0%)	9.6%
Yes	3/101 (3.0%)	10/98 (10.2%)	7.2%
CRP			
<10.0 mg/L	18/169 (10.7%)	35/180 (19.4%)	8.7%
≥10.0 mg/L	3/77 (3.9%)	8/67 (11.9%)	8.0%
Smoker			
Ex-smoker	9/88 (10.2%)	12/94 (12.8%)	2.6%
Smoker	0/19 (0.0%)	5/20 (25.0%)	25.0%
Non-smoker	12/138 (8.7%)	26/134 (19.4%)	10.7%
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	8/80 (10.0%)	17/93 (18.3%)	8.3%
No	13/166 (7.8%)	26/155 (16.8%)	9.0%
Corticosteroid Use at baseline			
Yes	10/140 (7.1%)	25/150 (16.7%)	9.6%
No	11/106 (10.4%)	18/98 (18.4%)	8.0%

Reproduced from Statistical Review

APPENDIX 7: Applicant's Exploratory Analysis #1 (Adjustment for Baseline Mayo Score)

Table 44: Number and Percent of Subjects with Remission (NRI) per Mayo Score at Week 8 by Mayo Score Categories (Quartile) at Baseline (ITT-A3 Analysis Set)

BASELINE MAYO SCORE [A] REMISSION AT WEEK 8	PLACEBO n (%)	ADA 160/80/40 MG n (%)	P-VALUE @
			0.034*
< 25TH PERCENTILE (8)	(N=37)	(N=28)	
YES	3 (8.1)	7 (25.0)	
NO	34 (91.9)	21 (75.0)	
DIFFERENCE IN PROPORTION[B]		16.9	
95% CONFIDENCE INTERVAL[C]		(-1.4, 35.2)	
>= 25TH PERCENTILE (8) AND < MEDIAN (9)	(N=19)	(N=24)	
YES	4 (21.1)	5 (20.8)	
NO	15 (78.9)	19 (79.2)	
DIFFERENCE IN PROPORTION[B]		-0.2	
95% CONFIDENCE INTERVAL[C]		(-24.7, 24.3)	
>= MEDIAN (9) AND < 75TH PERCENTILE (10)	(N=27)	(N=33)	
YES	3 (11.1)	5 (15.2)	
NO	24 (88.9)	28 (84.8)	
DIFFERENCE IN PROPORTION[B]		4.0	
95% CONFIDENCE INTERVAL[C]		(-13.0, 21.1)	
>= 75TH PERCENTILE (10)	(N=47)	(N=45)	
YES	2 (4.3)	7 (15.6)	
NO	45 (95.7)	38 (84.4)	
DIFFERENCE IN PROPORTION[B]		11.3	
95% CONFIDENCE INTERVAL[C]		(-0.8, 23.4)	

(Table above taken from Page 152 of the sBLA Resubmission dated March 30, 2012.)

Table 45: Number and Percent of Subjects with Remission (NRI) per Mayo Score at Week 8 by Mayo Score Categories (Tertile) at Baseline (ITT-A3 Analysis Set)

BASELINE MAYO SCORE [A] REMISSION AT WEEK 8	PLACEBO n (%)	ADA 160/80/40 MG n (%)	P-VALUE @
			0.034*
< 33TH PERCENTILE (8)	(N=37)	(N=28)	
YES	3 (8.1)	7 (25.0)	
NO	34 (91.9)	21 (75.0)	
DIFFERENCE IN PROPORTION[B]		16.9	
95% CONFIDENCE INTERVAL[C]		(-1.4, 35.2)	
>= 33TH PERCENTILE (8) AND < 67TH PERCENTILE (10)	(N=46)	(N=57)	
YES	7 (15.2)	10 (17.5)	
NO	39 (84.8)	47 (82.5)	
DIFFERENCE IN PROPORTION[B]		2.3	
95% CONFIDENCE INTERVAL[C]		(-12.0, 16.7)	
>= 67TH PERCENTILE (10)	(N=47)	(N=45)	
YES	2 (4.3)	7 (15.6)	
NO	45 (95.7)	38 (84.4)	
DIFFERENCE IN PROPORTION[B]		11.3	
95% CONFIDENCE INTERVAL[C]		(-0.8, 23.4)	

(Table above taken from Page 153 of the sBLA Resubmission dated March 30, 2012.)

Table 46: Number and Percent of Subjects with Remission (NRI) per Mayo Score at Week 8 by Mayo Score Categories (Median) at Baseline (ITT-A3 Analysis Set)

BASELINE MAYO SCORE [A] REMISSION AT WEEK 8	PLACEBO n (%)	ADA 160/80/40 MG n (%)	P-VALUE @
			0.028*
< MEDIAN (9)	(N=56)	(N=52)	
YES	7 (12.5)	12 (23.1)	
NO	49 (87.5)	40 (76.9)	
DIFFERENCE IN PROPORTION[B]		10.6	
95% CONFIDENCE INTERVAL[C]		(-3.8, 24.9)	
>= MEDIAN (9)	(N=74)	(N=78)	
YES	5 (6.8)	12 (15.4)	
NO	69 (93.2)	66 (84.6)	
DIFFERENCE IN PROPORTION[B]		8.6	
95% CONFIDENCE INTERVAL[C]		(-1.2, 18.5)	

(Table above taken from Page 154 of the sBLA Resubmission dated March 30, 2012.)

APPENDIX 8: Pertinent Safety Data

Extent of Exposure:

Table 47: Extent of Exposure, All Humira Set (Months)

Months of Exposure	Humira 40 mg every week N=402	Humira 40 mg every other week N=608	All Humira N=1010
0-1	402 (100%)	608 (100%)	1010 (100%)
>1-2	402 (100%)	560 (92.1%)	962 (95.2%)
>2-12	245 (60.9%)	379 (60.5%)	606 (60.0%)
>12-24	143 (35.6%)	262 (43.1%)	405 (40.1%)
≥24-32	59 (14.7%)	138 (22.7%)	197 (19.5%)
>32-33	52 (12.9%)	121(19.9%0	173 (17.1%)
>33-36	44 (10.0%)	102 (16.8%)	146 (14.5%)
>36-42	27 (6.7%)	62 (10.2%)	89 (8.8%)
>46-48	2 (0.5%)	6 (1.0%)	8 (0.8%)
>48	1 (0.2%)	2 (0.3%)	3 (0.3%)
Mean ± SD (days)	532.2 ± 344.03	549.3 ± 396.45	542.5 ± 376.38
Median (days)	497.0	571.0	517.5
Range (days)	35-1475	14-1470	14-1475
Total number of Humira Injections			
Mean ± SD	62.1 ± 43.14	42.4 ± 28.66	50.2 ± 36.41
Median	50.0	42.5	46.0
Range	3-199	1-112	1-199

Table 5 & 6, 4-month Safety Update p 115-120/6263

SAE's (Induction Set):

Table 48: Serious Adverse Events by System Organ Class, Induction Set

System Organ Class	Placebo N=483	Humira 80/40 N=130	Humira 160/80/40 N=480
Blood and lymphatic system disorders	2 (0.4)	0	2 (0.4)
Cardiac disorders	0	0	1 (0.2)
Gastrointestinal disorders	29 (6.0)	3 (2.3)	16 (3.3)
Infections and infestations	8 (1.6)	2 (1.6)	3 (0.6)
Investigations	1 (0.2)	0	
Neoplasms benign, malignant and unspecified	2 (0.4)	0	0
Nervous System Disorders		0	1 (0.2)
Psychiatric Disorders	1 (0.2)	0	1 (0.2)
Renal and urinary disorders	1 (0.2)	0	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	3 (0.6)	0	1 (0.2)
Skin and subcutaneous tissue disorders	4 (0.8)	0	1 (0.2)
Vascular disorders	2 (0.4)	0	2 (0.4)

Source: ISS Table 25, p 49/139

SAE's (All Humira Set):

Table 49: SAEs Reported by ≥2 Patients, All Humira Set

System Organ Class Preferred Term	Humira 40 mg ew N=402	Humira 40 mg eow N=608	All Humira N=1,010
	n (%)		
Any SAE	90 (22.4)	133 (21.9)	223 (22.1)
Blood and lymphatic system d/o			
Anemia	5 (1.2)	2 (0.3)	7 (0.7)
Cardiac disorders			
Coronary artery disease	1 (0.2)	2 (0.3)	3 (.03)
Gastrointestinal disorders			
Abdominal pain	1 (0.2)	3 (0.5)	4 (0.4)
Colitis	2 (0.5)	1 (0.2)	3 (0.3)
Ulcerative colitis	44 (10.9)	51 (88.4)	95 (9.4)
Crohn's disease	2 (0.5)	0	2 (0.2)
Gastrointestinal dysplasia	0	2 (0.3)	2 (0.2)
Inguinal hernia	2 (0.5)	1 (0.2)	3 (0.3)
Large intestine perforation	0	2 (0.3)	2 (0.2)
Peritonitis	0	2 (0.3)	2 (0.2)
Rectal hemorrhage	0	2 (0.3)	2 (0.2)
Small intestinal obstruction	1 (0.2)	1 (0.2)	2 (0.2)
General disorders and administration site conditions			
Noncardiac chest pain	1 (0.2)	1 (0.2)	2 (0.2)
Hepatobiliary disorders			
Cholelithiasis	1 (0.2)	1 (0.2)	2 (0.2)
Infections and infestations			
Abdominal abscess	0	3 90.5)	3 (0.3)
Anal abscess	0	4 (0.7)	4 (0.4)
Appendicitis	3 (0.7)	5 (0.8)	8 (0.8)
Cytomegalovirus colitis	1 (0.2)	1 (0.2)	2 (0.2)
Herpes zoster	1 (0.2)	2 (0.3)	3 (0.3)
Lobar pneumonia	3 (0.7)	1 (0.2)	4 (0.4)
Perirectal abscess	2 (0.5)	0	2 (0.2)
Respiratory tract infection	1 (0.2)	1 (0.2)	2 (0.2)
Investigations			
Weight decreased	1 (0.2)	1 (0.2)	2 (0.2)
Musculoskeletal and connective tissue d/o			
Arthralgia	2 (0.5)	0	2 (0.2)
Backpain	0	2 (0.3)	2 (0.2)
Intervertebral disc protrusion	0	2 (0.3)	2 (0.2)
Osteoarthritis	0	4 (0.7)	4 (0.4)
Neoplasms benign, malignant, and unspecified			
B-cell lymphoma	1 (0.2)	2 (0.3)	3 (0.3)
Uterine leiomyoma	1 (0.2)	1 (0.2)	2 (0.2)
Renal and urinary disorder			
Nephrolithiasis	0	2 (0.3)	2 (0.2)
Renal failure acute	2 (0.5)	0	2 (0.2)
Respiratory, thoracic, and mediastinal d/o			
Pulmonary embolism	1 (0.2)	1 (.2)	2 (.2)
Surgical and medical procedures			
Abortion induced	0	3 (0.5)	3 (0.3)
Vascular disorders			
Deep vein thrombosis	3 (0.7)	2 (0.3)	5 (0.5)

4-Month Safety Update p.189-191, Table 24

Common AE's (Induction Set):

Table 50: TEAEs Reported by ≥2% of Patients, Induction Set

MedDRA System Organ Class Preferred Terms	Placebo N=483	Humira 80/40 N=130	Humira 160/80/40 N=480	Total Humira N=610
	n(%)			
Blood and lymphatic system disorders				
Anemia	14 (2.9)	2 (1.5)	9 (1.9)	11(1.8)
Gastrointestinal Disorders				
Abdominal Pain	15 (3.1)	3 (2.3)	6 (1.3)	9 (1.5)
Abdominal tenderness	5 (1.0)	3 (2.3)	3 (0.6)	6 (1.0)
Colitis Ulcerative	59 (12.2)	10 (7.7)	35 97.3)	45 (7.4)
Dyspepsia	6 (1.2)	3 (2.3)	8 (1.7)	11 (1.8)
Nausea	16 (3.3)	4 (3.1)	10 (2.1)	14 (2.3)
Toothache	0	3 (2.3)	2 (0.4)	5 (0.8)
General Disorders and Administration Site Conditions				
Fatigue	12 (2.5)	2 (1.5)	18 (3.8)	20 (3.3)
Influenza like illness	10 (2.1)	2 (1.5)	1 (0.2)	3 (0.5)
Injection site pain	11 (2.3)	2 (1.5)	12 (2.5)	14 (2.3)
Pyrexia	14 (2.9)	3 (2.3)	8 (1.7)	11 (1.8)
Infections and Infestations				
Influenza	8 (1.7)	3 (2.3)	3 (0.6)	6 (1.0)
Nasopharyngitis	23 (4.8)	6 (4.6)	26 (5.4)	32 (5.2)
Upper Respiratory Infection	12 (2.5)	6 (4.6)	5 (1.0)	11 (1.8)
Musculoskeletal And Connective Tissue Disorders				
Arthralgia	9 (1.9)	5 (3.8)	10 (2.1)	15 (2.5)
Nervous System Disorders				
Headache	42 (8.7)	9 (6.9)	20 (4.2)	29 (4.8)
Psychiatric Disorders				
Insomnia	10 (2.1)	1 (0.8)	5 (1.0)	6 (1.0)
Skin and subcutaneous Tissue Disorders				
Acne	6 (1.2)	3 (2.3)	9 (1.9)	12 (2.0)
Erythema	2 (0.4)	3 (2.3)	8 (1.7)	11 (1.8)
Rash	5 (1.0)	5 (3.8)	4 (0.8)	9 (1.5)

Adapted from Applicant's Table 42, ISS p 203-204/5677

Common AE's (Maintenance Set):

Table 51: Common AEs, Maintenance Set

MedDRA Preferred Term	Placebo N=223	Humira 160/80/40 N=234
	N (%)	
Any Adverse Event	152 (68.2)	172 (73.5)
Colitis ulcerative	37 (16.6)	39 (16.7)
Nasopharyngitis	11 (4.9)	26 (11.1)
Abdominal pain	12 (5.4)	18 (7.7)
Arthralgia	9 (4.0)	17 (7.3)
Headache	15 (6.7)	11 (4.7)
Nausea	12 (5.4)	9 (3.8)

Source: Table 16, ISS

Common AE's (All Humira Set):

Table 52: Common AEs, All Humira Set

MedDRA System Organ Class Preferred Terms	
	n (%)
Blood and lymphatic system disorders	
Anemia	61 (6.0%)
Gastrointestinal Disorders	
Abdominal Pain	70 (6.9%)
Colitis Ulcerative	321 (31.8%)
Nausea	73 (7.2%)
General Disorders and Administration Site Conditions	
Fatigue	79 (7.8%)
Pyrexia	62 (6.1%)
Infections and Infestations	
Nasopharyngitis	169 (16.7%)
Upper Respiratory TractInfection	83 (8.2%)
Sinusitis	59 (5.8%)
Bronchitis	50 (5.0)
Musculoskeletal And Connective Tissue Disorders	
Arthralgia	105 (10.4%)
Back Pain	56 (5.5%)
Nervous System Disorders	
Headache	98 (9.7%)
Respiratory Tract Disorders	
Cough	63 (6.2%)
Oropharyngeal Pain	58 (5.7%)
Skin and subcutaneous Tissue Disorders	
Rash	62 (6.1%)

Source: Table 20, ISS