



# Gastrointestinal Drugs Advisory Committee Meeting

**BLA 125057/232:  
Adalimumab  
August 28, 2012**

**Andrew E. Mulberg, MD, FAAP  
Division of Gastroenterology and Inborn Errors Products  
CDER/FDA**

# Humira® (adalimumab)

- **Adalimumab is a recombinant human IgG 1 monoclonal antibody specific for human tumor necrosis factor (TNF $\alpha$ ) and blocks its interaction with cell surface receptors, which in turn inhibits TNF $\alpha$ -induced pro-inflammatory effects.**

# Proposed Indication

Original Submission	Resubmission
<p>HUMIRA is indicated for reducing signs and symptoms, and <b>inducing and maintaining induction</b> of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.</p>	<p>HUMIRA is indicated for reducing signs and symptoms, and <b>achieving</b> clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.</p>

# Regulatory History

- **Approved for treatment of Rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis**
- **Dose regimens vary for RA, AS and PP indications:**
  - 20 mg every other week to 40 mg every other week to every week
- **Crohn's disease:**
  - 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

# Regulatory History: UC

- **June 15, 2006**
  - **Pre-IND / Pre-Phase 3 Meeting**
- **November 23, 2010**
  - **Pre-sBLA Meeting**
- **January 25, 2011**
  - **sBLA Original Submission**
- **November 21, 2011**
  - **CR Action**
- **March 30, 2012**
  - **sBLA Re-Submission**

## Regulatory History: UC (cont.)

- **Advice Letter for Study 827 Statistical Analysis Plan (May 24, 2010):**
  - **As designed (without re-randomization at Week 8) the study could only support:**
    - an indication of “sustained clinical remission” at Weeks 8 and 52
    - not “maintenance of clinical remission”

# Background

- **Remicade (infliximab): anti-tumor necrosis factor (TNF) alpha monoclonal antibody**
- **FDA approval for IBD indication:**
  - **1998: Adult CD**
  - **2005: Adult UC**
  - **2006: Pediatric CD**
  - **2011: Pediatric UC**

# Registration endpoints IBD trials

- Induction of remission to defined period, e.g., 8 weeks
- Maintenance of remission requires re-randomization of active versus placebo
  - Assessment at week 52
  - Requires re-randomization of subjects after subjects achieve, e.g., week 8 remission status

# IBD Trial Design Features

- **Sustained Remission (Durability)**
  - No re-randomization allows assessment of natural history of clinical remission
    - Assesses proportion of patients who respond or remit over time
  - Duration of induction at specified time point, e.g., 8 or 52 weeks
  - Concern of immunogenicity related to prolonged exposure
  - Drug exposure continues without assessing need to stop
- **Maintenance of Remission**
  - Requires re-randomization after induction of remission at defined time point
  - Cannot address potential of variability in time to induction of remission
    - Is design too strict to accommodate drugs with different mechanism of action and ability to induce remission?
  - Concern of immunogenicity related to intermittent exposure
  - Stopping drug exposure in one arm allows assessment of need for continued treatment

## Review Issues in CR letter, 11/21/2011

- **Statistically significant improvement with Humira relative to placebo, but concerns included:**
- **Uncertainty regarding the efficacy findings**
  - **Modest improvements (<10% over placebo) in clinical remission at Week 8 and sustained clinical remission (<5% over placebo) at Weeks 8 and 52**
  - **Identification of the optimal dose**
  - **Robustness of results**

# Today's Objective

- **The committee will be asked to consider the efficacy results in the context of their clinical meaningfulness**

# What is Clinically Meaningful?

## – Factors to consider:

- **Magnitude and durability of treatment effect**
- **Seriousness of condition**
- **Expected benefit derived from standard of care**
- **Other benefits i.e. convenience in dosing regimen to improve patient compliance**



# **Overview of Humira® Phase 3 Clinical Studies in Ulcerative Colitis**

**BLA 125057/232 adalimumab  
August 28, 2012**

**Gastrointestinal Drugs Advisory Committee Meeting**

**Klaus Gottlieb, MD, MS, MBA  
FACP, FACG**

**Clinical Reviewer  
Division of Gastroenterology and Inborn Errors Products  
CDER/FDA**

# Outline of Presentation

- Proposed indication
- Overview of UC Studies
- Results Induction and Maintenance with Key Issues identified
- Selected exploratory analyses from the resubmission
- Safety Data

# Proposed Indication

Original Submission	Resubmission
<p>HUMIRA is indicated for reducing signs and symptoms, and <b>inducing and maintaining induction</b> of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.</p>	<p>HUMIRA is indicated for reducing signs and symptoms, and <b>achieving</b> clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.</p>

# Recommended Study Design for Maintenance of Remission

<b>Clinical Outcome</b>	<b>Study Design</b>
	<b>Randomization</b>
Induction of Remission	Percentage of patients who achieve clinical remission at induction time point, e.g., 8 weeks
	<b>Randomization of remitters</b>
Maintenance of Remission	Percentage of patients who achieve clinical remission at maintenance time point, e.g., 52 weeks

# *Actual* Study Design in 827

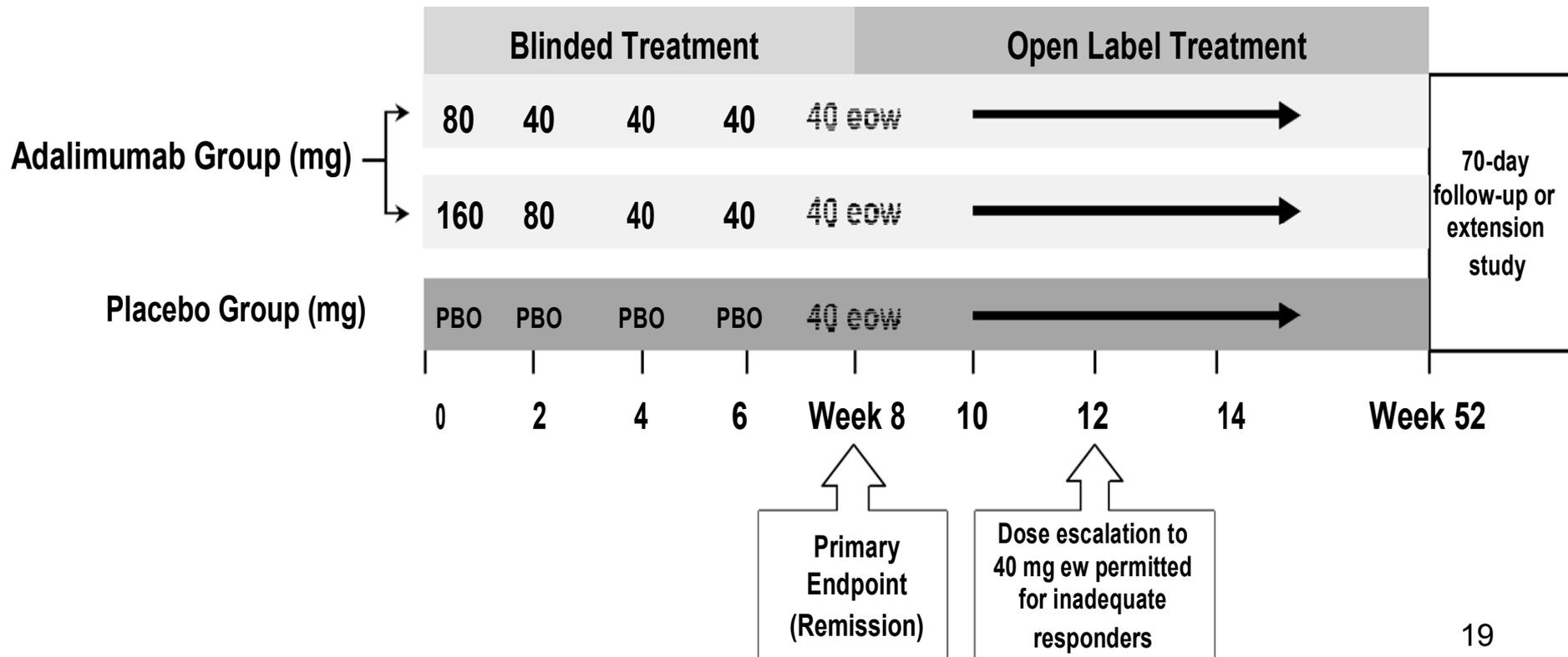
- 1<sup>st</sup> ranked secondary endpoint = response at Week 8 **and** at Week 52
- **No** rerandomization
- This approach reflects durability of response or sustained remission and is not an independent assessment of “maintenance” of remission

# Overview of UC Studies

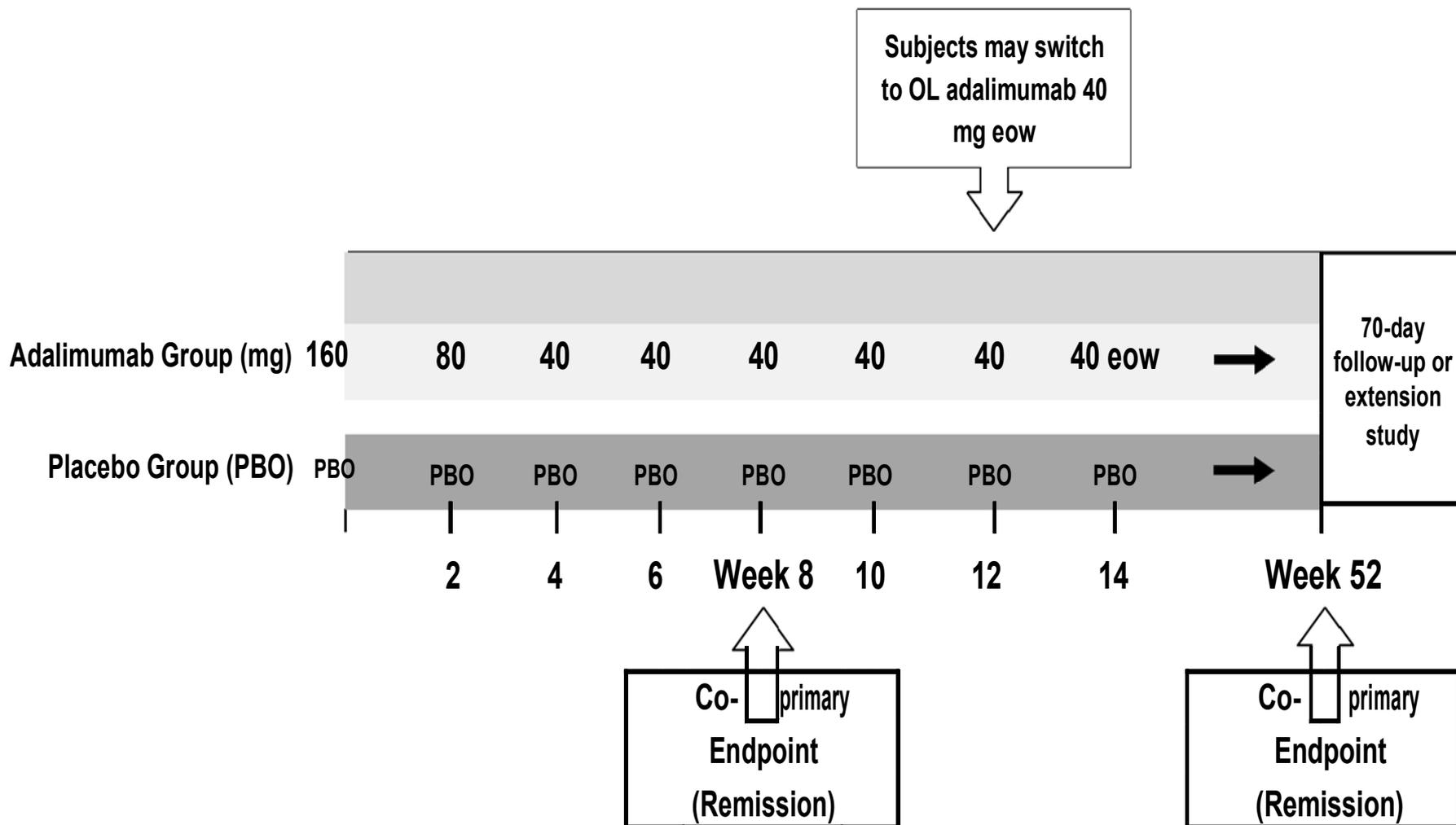
Study	Design	Population	Treatment Duration	Treatment Arms
826 (Induction of Remission Trial)	R, DB, PC	<ul style="list-style-type: none"> <li>Moderately to severely active UC</li> </ul>	8 weeks	<ul style="list-style-type: none"> <li>➤ Humira 160/80/40 (n=130)</li> <li>➤ Humira 80/40 (n=130)</li> <li>➤ Placebo (n=130)</li> </ul>
827 (Induction and Sustained Remission Trial)	R, DB, PC	<ul style="list-style-type: none"> <li>Moderately to severely active UC</li> <li>Prior TNF<math>\alpha</math>-antagonist users (40%)</li> </ul>	52 weeks	<ul style="list-style-type: none"> <li>➤ Humira 160/80/40 (n=258)</li> <li>➤ Placebo (n=260)</li> </ul>
223 (Extension Study)	OL	<ul style="list-style-type: none"> <li>Continuation from Studies 826 and 827</li> </ul>	240 weeks planned (ongoing)	<ul style="list-style-type: none"> <li>➤ Humira 40 EOW or EW (n=592)</li> </ul>

# Study Design 826

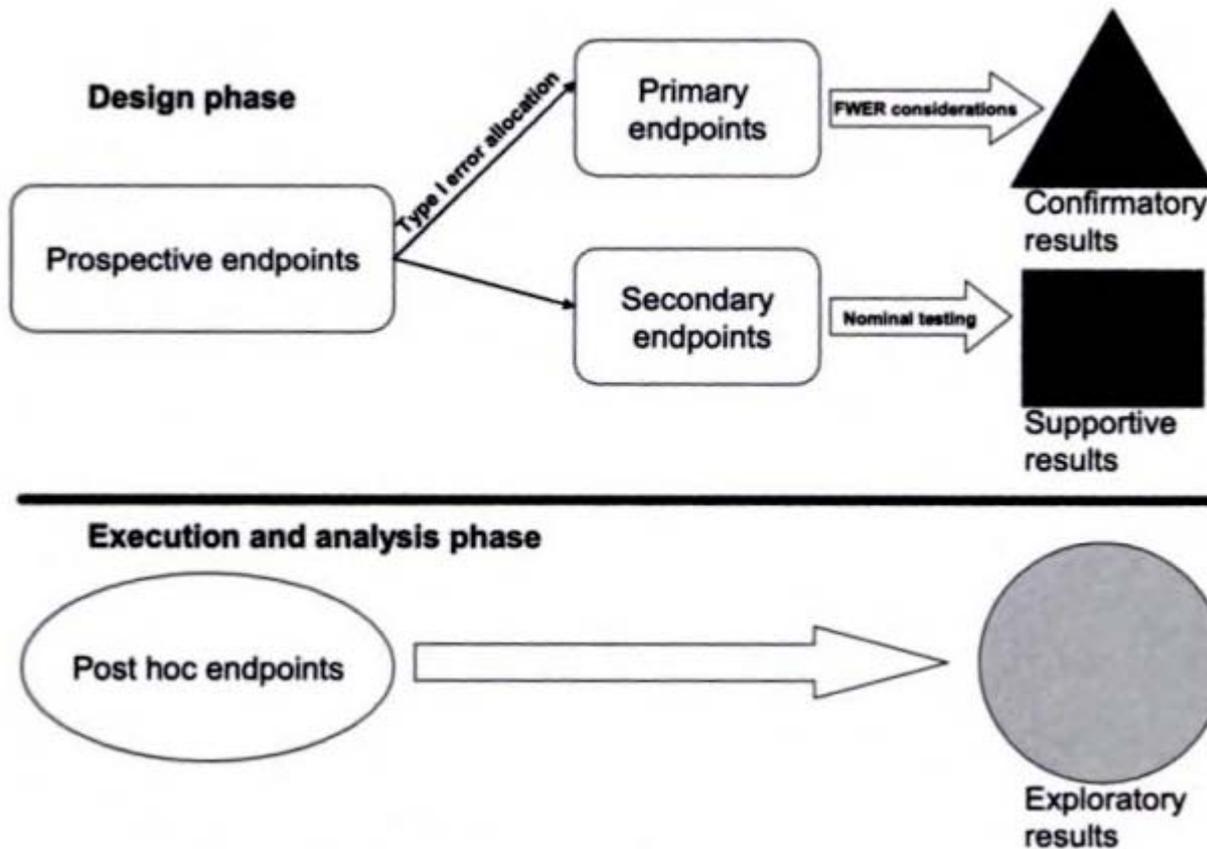
After the addition of the 80/40 dosing group



# Study Design 827



# Endpoints in Clinical Trials



# Endpoints

- Primary Endpoint - describes how the most important aspect of the disease is affected by the intervention
- Co-Primary Endpoint - two or more primary endpoints are considered equally important
- Secondary Endpoints
  - Ranked (1., 2., 3...): To allow for hierarchical hypothesis testing
  - Not ranked

# Primary Endpoints

## 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: <ul style="list-style-type: none"> <li>▪ Clinical Remission at Week 8</li> <li>▪ Clinical Remission at Week 52</li> </ul>	160/80/40 Placebo	258 260

# Key Entry Criteria

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

# ITT definitions (Study 826)

Population	Definition
ITT-E	<p><b>All patients</b> with confirmed UC at Baseline who were <b>randomized at any time</b> 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</p>
<p><b>ITT-A3</b> (prespecified)</p>	<p><b>All patients</b> with confirmed UC at Baseline who were <b>randomized according to the revised study design</b> 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</p>

## Key population differences between 826 vs. 827 (Induction)

- 826 ***excluded*** patients that previously used an anti-TNF $\alpha$  agent
- 827 ***allowed*** entry of patients that previously used an anti-TNF $\alpha$  agent, provided use discontinued due to a loss of response or intolerance

# Baseline Characteristics

- Generally well balanced between subgroups

## 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
<b>N</b>	130	130	130	246	248
<b>Total Mayo Score</b> (mean ± SD)	8.7 (1.6)	9.0 (1.6)	8.8 (1.6)	8.9 (1.8)	8.9 (1.5)
<b>Subscores</b>					
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

# Mayo Score: Analysis by binned scores (Study 826)

## Total Mayo Score at Baseline 826

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%)
Placebo	9 (7%)	28 (22%)	19 (15%)	27 (21%)	34 (26%)	8 (6%)	5 (4%)

Modified from Statistics Review by Milton Fan, Page 22.

# Results: Induction of Clinical Remission

## 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)	<b>9.3%</b>	<b>(0.8%, 17.9%)</b>	<b>0.031</b>
827	9.3% (23/246)	16.5% (41/248)	<b>7.2%</b>	<b>(1.3%, 13.2%)</b>	<b>0.019</b>

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

# Issue (Induction) Clinical Meaningfulness

- Are differences of
  - 9.3% (C.I. 0.8% - 17.9%) (826)
  - and 7.2 % (C.I. 1.3% - 13.2%) (827)
 in the induction rates over placebo clinically meaningful?

# Historical effect size of infliximab juxtaposed to effect size in 826 (Induction)

	ACT 1 (infliximab)		826 (adalimumab)	
<b>Effect size (remission)</b>	<b>23.9 %</b>		<b>9.3 %</b>	
	CI 13.0% -34.6%		CI 0.8% - 17.9%	
Remission Rate on Placebo	14.9 %		9.2 %	
Remission Rate on TNF- $\alpha$ -blocker	38.8%		18.5%	
<b>Demographics / Disease Activity</b>				
Age (years)	42.4 $\pm$ 14.3		38.2 $\pm$ 13.46	
Disease Duration	5.9 years		6.1 years	
Prior Anti-TNF use	No		No	
Mean Mayo Score upon entry	Active	Placebo	Active	Placebo
	8.5 $\pm$ 1.7	8.4 $\pm$ 1.8	8.8 $\pm$ 1.61	8.7 $\pm$ 1.56
Extensive UC (pancolitis)	47.1%		46.2%	
Not on steroids or immunomodulators at baseline	15 %		23.8 %	
<b>Study Design Highlights</b>				
Number of patients	121/group		130/group	
Activity Index	Mayo		Mayo	
Definition of remission/response	Same		Same	
Non-Responder Imputation	Yes		Yes	

# Issue (Induction)

## Robustness of Results (826)

- The significance of the analysis results is sensitive to the use of exact testing methods
  - 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
- If the primary analysis is adjusted for the different baseline Mayo scores, the treatment differences were not significant ( $p=0.085$ , CMH Test).

# Secondary Endpoint: Steroid-free remission (827)

## Ranked Secondary Endpoints, Study 827

Ranked Secondary Endpoint		Placebo N=246	Humira (160/80/40 mg) N=248	p-value
8	Discontinued corticosteroid use before Week 52 and achieved remission, Week 52	5.7% (8)	13.3% (20)	0.035

Study 827, CSR p 354/3632

# Issue: Secondary Endpoint Clinical Response at Week 8 (826 & 827)

**Clinical Response at Week 8 (Study 826 ITT-A3 & Study 827)**

Clinical Response at Week 8	Placebo	Humira 160/80/40	p value
Study 826 (1 <sup>st</sup> ranked 2 <sup>o</sup> endpoint)	58/130 (44.6%)	71/130 (54.6%)	0.107
Study 827 (2 <sup>nd</sup> ranked 2 <sup>o</sup> endpoint)	85/246 (34.6%)	125/248 (50.4%)	0.001

Clinical response per Mayo score

- Decrease in Mayo score of  $\geq 3$  points from Baseline AND
- Decrease in Mayo score of  $\geq 30\%$  from Baseline AND
- Decrease in the RBS  $\geq 1$  or an absolute RBS of 0 or 1

# Issue (Induction): Treatment Effects in Subgroups - Immunosuppressants (827)

Patients on azathioprine or 6-MP at baseline did not appear to benefit from treatment with Humira

**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.

# Results: Remission Rates in 827

## 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)	<b>7.2%</b>	<b>(1.3%, 13.2%)</b>	<b>0.019</b>
Week 52	8.5% (21/246)	17.3% (43/248)	<b>8.8%</b>	<b>(2.9%, 14.8%)</b>	<b>0.004</b>
Weeks 8 and 52	4.1% (10/246)	8.5% (21/248)	<b>4.4%</b>	<b>(0.1%, 9.0%)</b>	<b>0.047</b>

# Issue: Clinical Meaningfulness (827)

- Is a treatment difference of approximately 4% for the *sustained clinical remission* first-ranked secondary endpoint clinically meaningful?

# Issue: Robustness of Secondary endpoint in 827

- The secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed **only marginal significance (0.047)** in favor of adalimumab
  - The significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, **p=0.062**)
- Only 23 % of patients on placebo and 33 % of patients on Humira continued to week 52

# Patient disposition in 827

	Placebo	Humira
Total	246	248
Rescue prior to week 52	135 (55 %)	116 (47 %)
Discontinued during DB	55 (22 %)	50 (20 %)
<b>Completed</b> to week 52 on DB	<b>56</b> <b>(23%)</b>	<b>82</b> <b>(33%)</b>

DB: double blind

# Issue: Treatment Effects in Subgroups – Prior TNF- $\alpha$ -antagonist

Patients that had lost response to or were intolerant to another anti-TNF agent did not appear to achieve remission with Humira at 8 weeks in study 827

**Remission Results, by prior anti-TNF use, Study 827**

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

# Exploratory Analyses in the Resubmission

- Net Efficacy Adjusted Risk (NEAR) Analysis
- Hospitalizations

# Net Efficacy Adjusted Risk (NEAR): Exploratory Analysis

- Attempt to combine clinical efficacy and safety into a single measure
  - Endpoint: Safety event-free treatment success
  - Compare the odds of experiencing the redefined endpoint in the Humira group to the odds in the placebo group
  - NEAR OR > 1: Benefit-risk ratio favors Humira group (per Applicant's interpretation)

## NEAR: Issues/Limitations

- Assumes that treatment success has equal weight to a safety event
- Sponsor's analyses limited to safety events occurring during the same timeframe used to assess the efficacy endpoint.
  - Short-term efficacy not balanced with long-term safety
- Method focuses on safety-event free treatment success. Other scenarios not presented.
- Sponsor's analyses lumps events into a single endpoint (e.g., All SAEs), leading to a loss of specificity of outcome

# Hospitalization Analysis (pooled data)

- Sponsor submitted pooled data from Hospitalization Analysis set
- Patients receiving Humira have lower risks c/w placebo of being hospitalized (all-cause) with a nominal p-value below 0.05

# Hospitalization (individual analysis sets)

<b>Analysis Set Outcome</b>	<b>ADA 80/40 P value vs. Placebo</b>	<b>ADA 160/80 P value vs. Placebo</b>
<b>Study M06-826 ITT-E Safety Analysis Set</b>		
All-cause hospitalization	0.117	0.046
UC-related hospitalization	0.038	0.012
<b>Study M06-826 ITT-A3 Safety Analysis Set</b>		
All-cause hospitalization	0.570	0.442
UC-related hospitalization	0.392	0.205
<b>Study M06-827 ITT Safety Set</b>		
All-cause hospitalization	n/a	0.271
UC-related hospitalization	n/a	0.060

If individual studies are analyzed nominal p-values no longer suggest that the risk of hospitalization is lower with adalimumab

# Safety Overview

- Safety profile comparable to current product labeling
- The most commonly reported SAE was ulcerative colitis
- the most common AEs were
  - Ulcerative colitis
  - Nasopharyngitis
  - Headache
  - Arthralgia



# Gastrointestinal Drugs Advisory Committee Meeting

## **Humira<sup>®</sup> (adalimumab)**

**Nitin Mehrotra, Ph.D.**

**Division of Pharmacometrics  
Office of Clinical Pharmacology  
OTS/CDER/FDA**

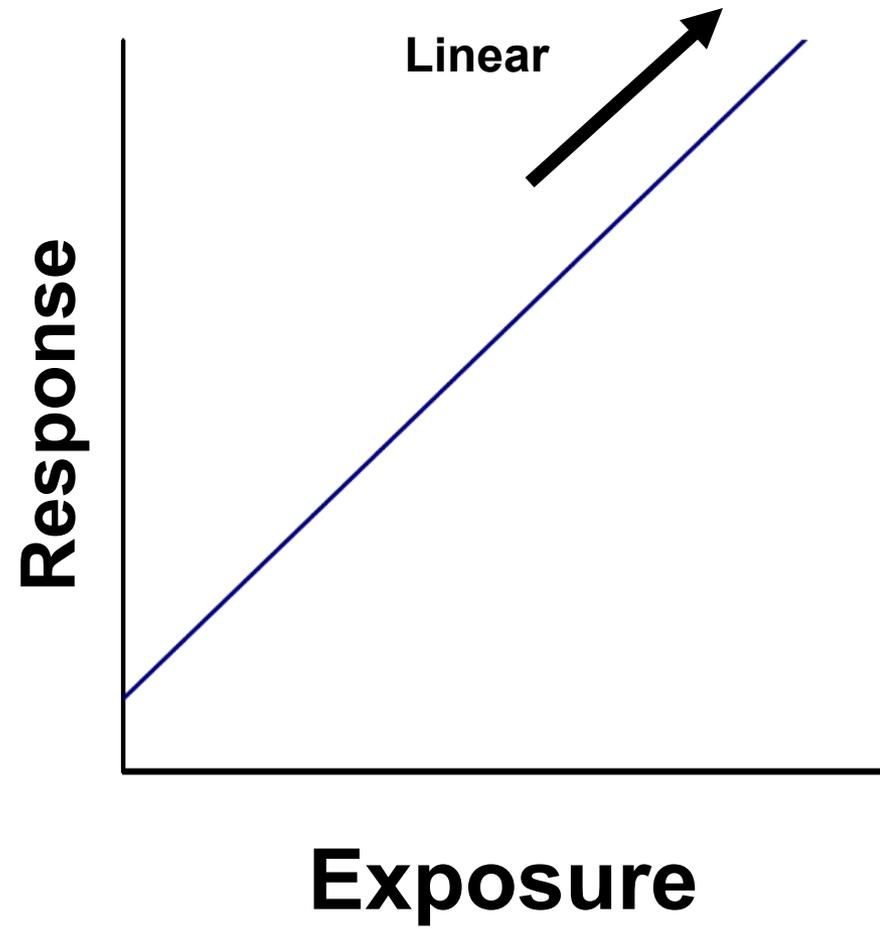
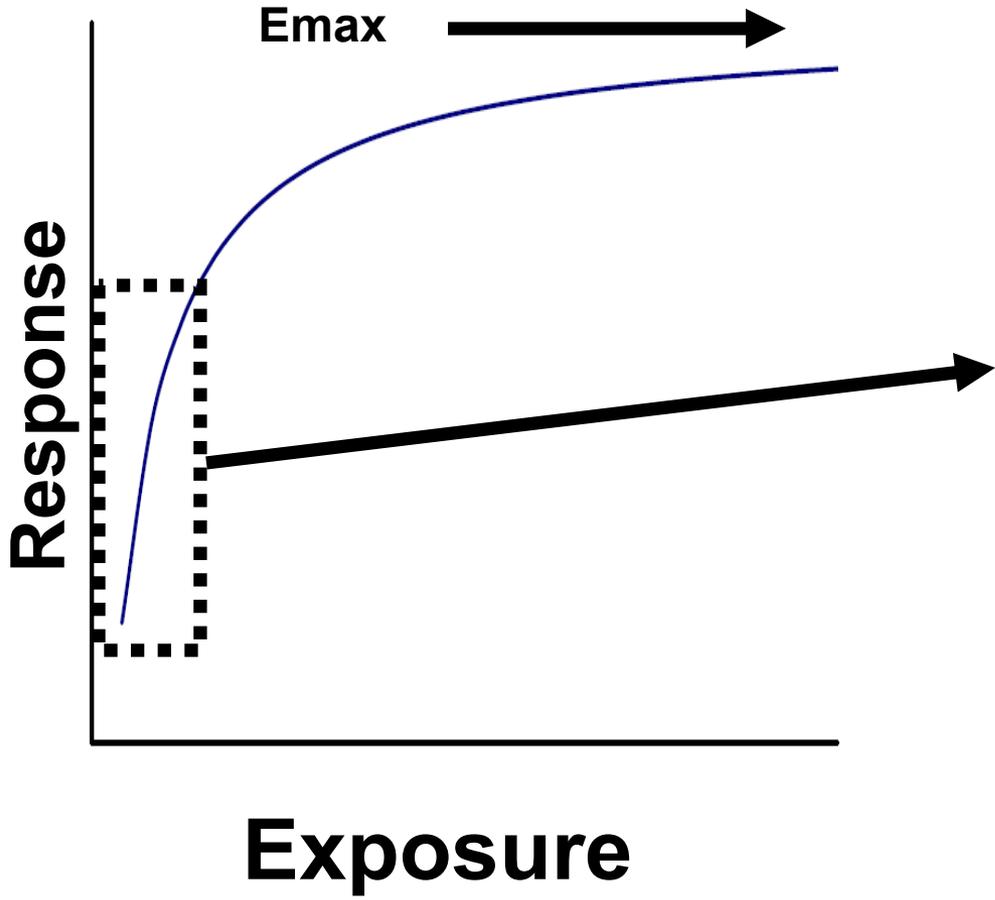
**Aug 28, 2012**

# Relevant Question for the Committee

## **Dose Selection:**

**VOTE (YES/NO):** Based on the exposure response data and observed treatment effect presented, has the optimal Humira dose for treatment of moderately to severely active ulcerative colitis (UC) been adequately established? Please comment on the need for further dose exploration.

# Linear and Emax Relationship



# Sponsor's Exposure-Response Analysis

- Limitations:
  - (1) Assumption of Emax model
  - (2) Assumption of a fixed value for Emax
- Results:
  - Force the predicted probability of remission to plateau at Emax
- Assumptions not supported by observed data
  - The remission rate at week 8 increases with exposures and does not plateau over the observed concentration range

## Dose Selection for Adult UC

- Proposed dosing regimen for UC is same as that for Crohn's disease,
  - Plus option of dose escalation in maintenance phase
- No Phase 2 dose ranging studies
  - At a pre-Phase 3 meeting in 2006 for the UC indication, the FDA expressed concern about proceeding with the same dosing regimen as Crohn's disease

# Exposure-Response Analysis for the Maintenance Phase

- Robust Exposure-Response relationship could not be developed due to substantial number of patients with missing PK data
- Difficult to interpret the results due to patients switching to OL, dose escalation and missing data for Week 52

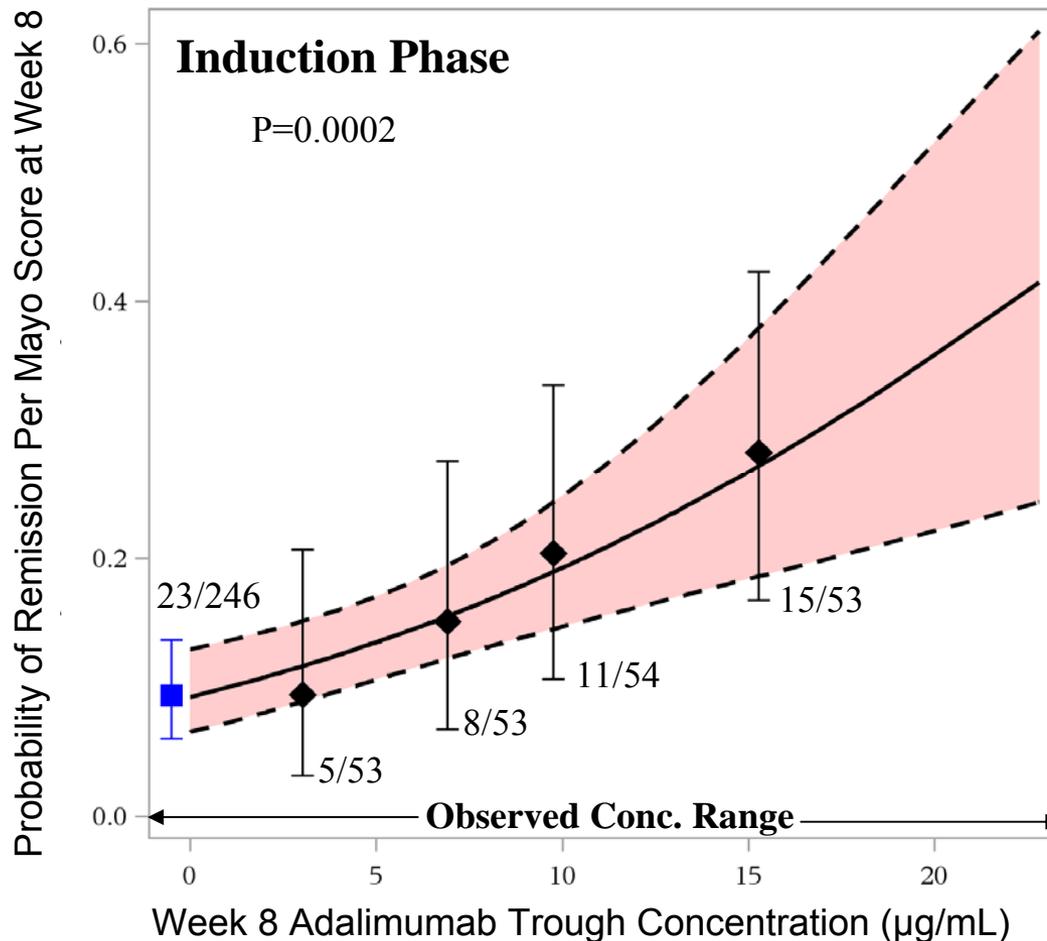


# Exposure-Response Analysis for the Induction Phase

# Agency's Exposure-Response Analysis for Induction Phase (M-827)

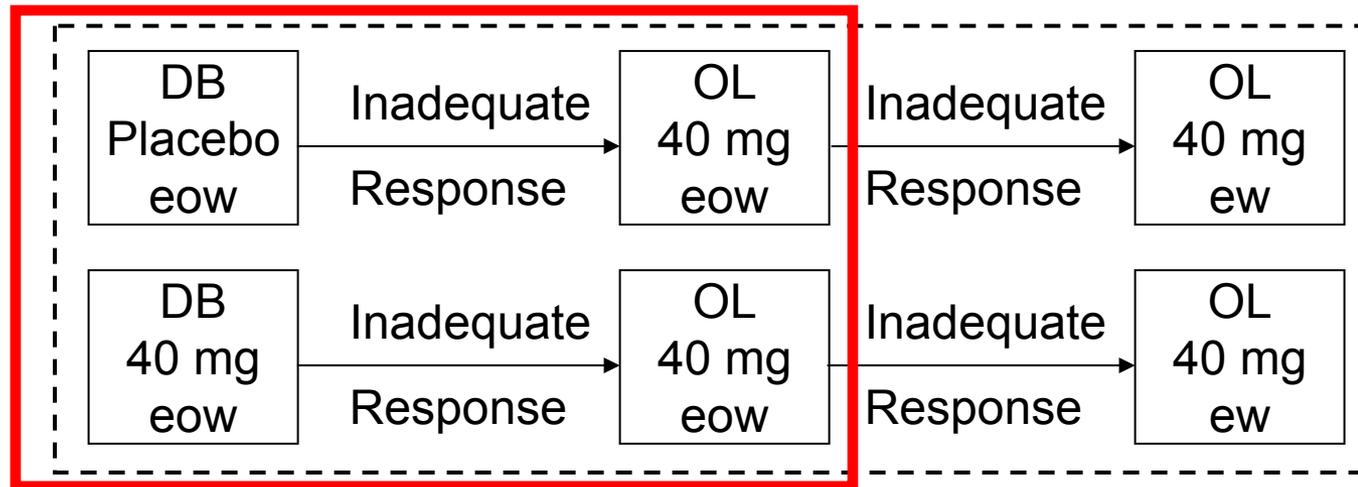
- Exposure : Week 8 concentration
- Response: Week 8 clinical remission
- N= 213 patients
- Two analyses
  - Probability of remission (Logistic Regression)
  - Time to inadequate response (Time to Event Analysis)

# Probability of Remission Increases with Increasing Adalimumab Concentrations



# Patients with Inadequate Response Switched to Open Label Adalimumab

## Beginning Week 12...



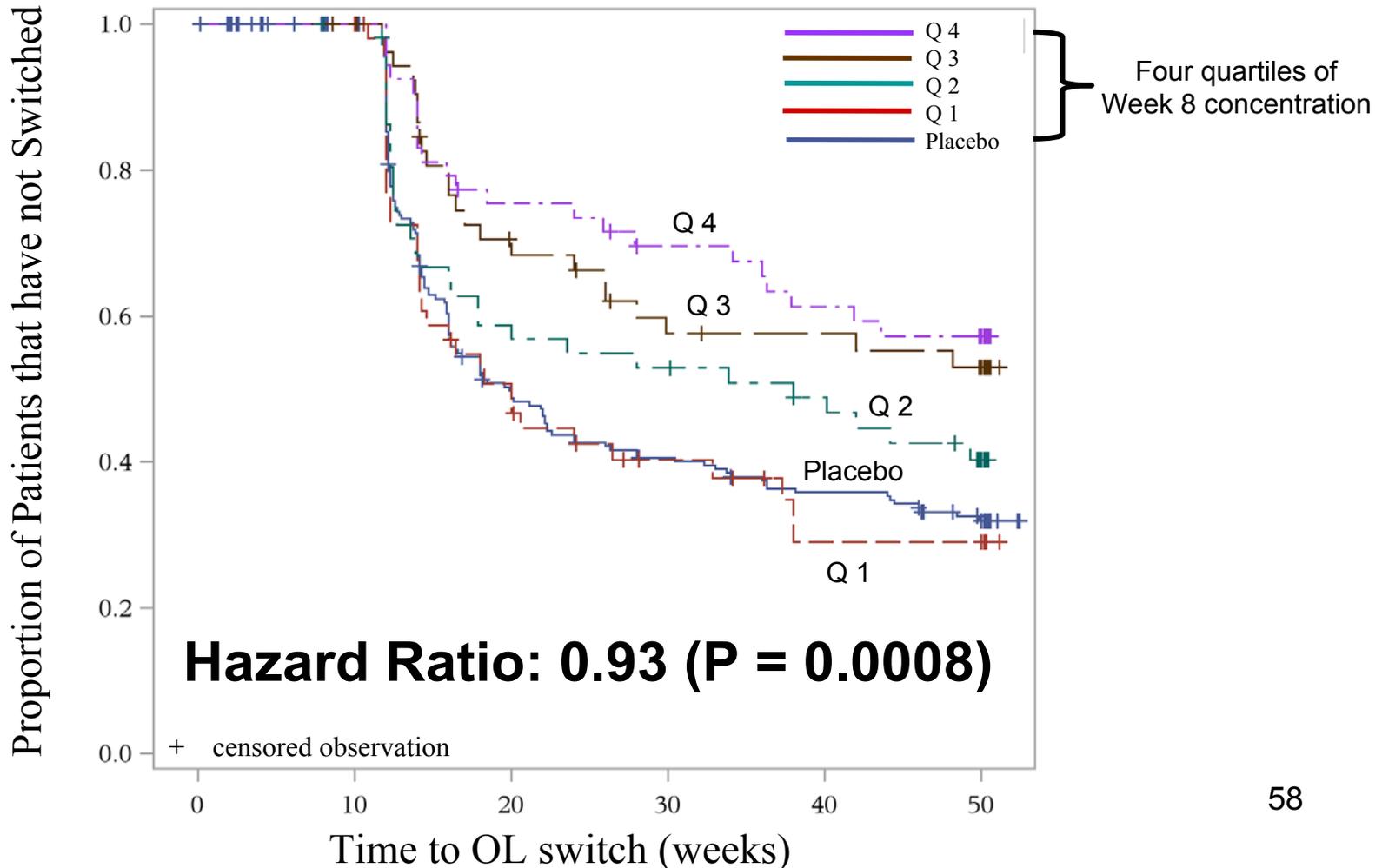
\* *Inadequate response was defined as:*

- *Partial Mayo score  $\geq$  Baseline score on 2 consecutive visits at least 14 days apart (partial Mayo score of 4 to 7 at Baseline)*
- *Partial Mayo score  $\geq$  7 on 2 consecutive visits at least 14 days apart (partial Mayo score of 8 or 9 at Baseline)*

## Approximately 50% of Patients had Inadequate Response in Placebo and Adalimumab Arm

	Total subjects	Switched to Open Label Adalimumab
Placebo	246	135 (55%)
Adalimumab 160/80/40 mg	248	116 (47%)

# Inadequate Response Occurred Earlier in Patients with Lower Concentrations



# Summary

- ❑ A higher dose may provide additional benefit for inducing clinical remission
  - Remission rate does not plateau over observed concentration range
  - Inadequate response occurred earlier in patients with lower adalimumab concentrations
- ❑ Limitation: Dosing regimen higher than 160/80/40 mg has NOT been tested



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Humira® (adalimumab)  
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**Anil Rajpal, MD, MPH  
Division of Gastroenterology and Inborn Errors Products  
CDER/FDA**

# Outline

- Summary of Results
- Key Issues
  - Dose
  - Supportive Evidence
  - Robustness of Results
- Questions

# Summary of Results – 826 & 827

## Study 826 (1<sup>o</sup> Endpoint):

Endpoint	Week	Placebo	Humira	Δ	95% CI	p-value
1 <sup>o</sup>	Wk 8	9.2% (12/130)	18.5% (24/130)	<b>9.3%</b>	<b>(0.8%, 17.9%)</b>	<b>0.031</b>



## Study 827 (1<sup>o</sup> and First-Ranked 2<sup>o</sup> Endpoints):

Endpoint	Week	Placebo	Humira	Δ	95% CI	p-value
Co-1 <sup>o</sup>	Wk 8	9.3% (23/246)	16.5% (41/248)	<b>7.2%</b>	<b>(1.3%, 13.2%)</b>	<b>0.019</b>
	Wk 52	8.5% (21/246)	17.3% (43/248)	<b>8.8%</b>	<b>(2.9%, 14.8%)</b>	<b>0.004</b>
2 <sup>o</sup> (1 <sup>st</sup> -rank)	<i>Both Wks 8 and 52</i>	4.1% (10/246)	8.5% (21/248)	<b>4.4%</b>	<b>(0.1%, 9.0%)</b>	<b>0.047</b>



# Dose

- Observed Treatment Effect (Studies 826 & 827)
  - 160/80/40 SC vs. Placebo
  - Concern that appropriate dose not selected
- Exposure-Response Data (Study 827)
  - Induction:
    - Suggested  $\uparrow$  dose  $\rightarrow$   $\uparrow$  treatment effect
  - Maintenance:
    - No conclusion
- Concern that optimal dose for UC not identified

# Study 826 - Lack of Supportive Evidence

- Lack of supportive evidence (from 2<sup>o</sup> endpoint results):

	Ranked 2 <sup>o</sup> Endpoint	Humira vs. Placebo (p-value)
1	Clinical Response Wk 8	54.6% vs. 44.6% (p= <b>0.107</b> )

# Study 827 – Had Supportive Evidence

- Supportive evidence (from 2<sup>o</sup> endpoint results):

Ranked 2 <sup>o</sup> Endpoint		Humira vs. Placebo (p-value)
1	Clinical Remission Wk 8 & Wk 52	8.5% vs. 4.1% (p= <b>0.047</b> )
2	Clinical Response Wk 8	50.4% vs. 34.6% (p< <b>0.001</b> )
3	Clinical Response Wk 52	30.2% vs. 18.3% (p= <b>0.002</b> )
4	Clinical Response Wk 8 & Wk 52	23.8% vs. 12.2% (p< <b>0.001</b> )
5	Mucosal healing Wk 8	41.1% vs. 31.7% (p= <b>0.032</b> )
6	Mucosal healing Wk 52	25.0% vs. 15.4% (p= <b>0.009</b> )
7	Mucosal healing Wk 8 & Wk 52	18.5% vs. 10.6% (p= <b>0.013</b> )
8	D/ced steroid use before Wk 52 & achieved Clinical Remission Wk 52	13.3% vs. 5.7% (p= <b>0.035</b> )

# Robustness of Results – 826 & 827

## Study 826 (1<sup>0</sup> Endpoint):

Endpoint	Week	Concern about Robustness of Results
1 <sup>0</sup>	Wk 8	<ul style="list-style-type: none"> <li>• Use of exact testing methods                             <ul style="list-style-type: none"> <li>– Results sensitive to remission status of a single subject</li> </ul> </li> <li>• Adjustment for Baseline Mayo scores</li> </ul>

## Study 827 (1<sup>0</sup> and First-Ranked 2<sup>0</sup> Endpoints):

Endpoint	Week	Concern about Robustness of Results
Co-1 <sup>0</sup>	Wk 8	<ul style="list-style-type: none"> <li>• none</li> </ul>
	Wk 52	<ul style="list-style-type: none"> <li>• none</li> </ul>
2 <sup>0</sup> (1 <sup>st</sup> -rank)	<i>Both Wks 8 and 52</i>	<ul style="list-style-type: none"> <li>• Use of exact testing methods</li> </ul>

# Benefit/Risk Considerations

- Identification of the optimal dose
- Clinical meaningfulness of the observed treatment differences
- Risks generally similar to other TNF $\alpha$ -antagonists



# Questions to the Advisory Committee

# 1. Dose Selection

## **Vote:**

Based on the exposure-response data and observed treatment effect presented, has the optimal Humira dose for treatment of moderately to severely active ulcerative colitis (UC) been adequately established?

Please comment on the need for further dose exploration.

## **2. Efficacy Analysis (Studies 826 and 827)**

- (a) Clinically Meaningful Benefit**
- (b) Clinical Remission at Week 8**
- (c) Clinical Remission at Week 52**
- (d) Clinical Remission at Both Weeks 8  
and 52**

## 2(a) Clinically Meaningful Benefit

### Discussion:

Please discuss the factors that you consider in defining the term “**clinically meaningful benefit**” in patients with moderately to severely active UC.

## 2(b) Clinical Remission at Week 8

### Vote:

Do the observed treatment differences (Humira 160/80/40 versus placebo) in the proportion of patients that had clinical remission at Week 8 of **9.3%** (95% CI: 0.8%, 17.9%) (Study 826) and **7.2%** (95% CI: 1.3%, 13.2%) (Study 827) represent a clinically meaningful benefit?

## 2(c) Clinical Remission at Week 52

- (i) **Vote:** Does having clinical remission at Week 52 represent a clinically meaningful endpoint?
  
- (ii) **Vote:** Does the observed treatment difference in the proportion of patients that had clinical remission at Week 52 of **8.8%** (95% CI: 2.9%, 14.8%) (Study 827) represent a clinically meaningful benefit?

## 2(d) Clinical Remission at Both Weeks 8 and 52

### Vote:

Does the observed treatment difference in the proportion of patients that had clinical remission at both Weeks 8 and 52 of **4.4%** (95% CI: 0.1%, 9.0%) (Study 827) represent a clinically meaningful benefit?

# 3. Additional Pre-Approval Studies

## **Vote:**

Are there additional efficacy studies that should be conducted prior to approving Humira for moderately to severely active UC?

# 4. Benefit-Risk Considerations

## **Vote:**

Do 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?

If YES, specify whether your answer is limited to particular subpopulation(s) defined by level of disease severity or inadequate response/intolerance to prior therapies.

# 5. Post-Approval Studies

## Discussion:

If you believe this product should be approved for moderately to severely active UC, are there any additional studies you would recommend post-approval?