Joint Meeting of GIDAC and DSaRM

Entyvio (vedolizumab)

December 9, 2013

Opening Remarks

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CDER/FDA

Meeting Objective

- To obtain advice regarding the efficacy and safety of Entyvio (vedolizumab) for the proposed ulcerative colitis (UC) and Crohn's disease (CD) indications based on data from the Phase 3 clinical trials:
  - UC: one induction trial and one maintenance trial
  - CD: two induction trials and one maintenance trial

Proposed UC Indication

- "…for reducing signs and symptoms, inducing and maintaining clinical response and remission, and mucosal healing, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist."

Proposed CD Indication

- "…for reducing signs and symptoms, inducing and maintaining clinical response and remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist."

Level of Evidence Requirements

- For each population separately (UC or CD):

Induction
Two A & WC Trials •usual requirement
or
One A & WC Trial* •if meets Level of Evidence Requirements of a single trial# including: • statistically very persuasive • multiple endpoints met • etc.

Maintenance
One A & WC Trial •if supported by induction

*A & WC Trial: Adequate and Well-Controlled Trial
#Evidence of Effectiveness Guidance, 1998

Strength of Evidence for Each Indication

Disease	Induction	Maintenance
UC	Single trial: ✓ Primary ✓ 1st Secondary ✓ 2nd Secondary	Single trial: ✓ Primary ✓ 1st Secondary ✓ 2nd Secondary ✓ 3rd Secondary ✓ 4th Secondary
CD	1st trial: ✓ Primary -- ~~Secondary~~ 2nd trial (TNFα-antag failure pop) -- ~~Primary~~	Single trial: ✓ Primary ✓ 1st Secondary ✓ 2nd Secondary -- ~~3rd Secondary~~

Disease and Unmet Medical Need

Disease	Description	Unmet Medical Need
UC	• Chronic relapsing disease • Diffuse mucosal inflammation of the colon • Surgery potentially curative	• Failed TNFα-antagonists • Not candidates for surgery
CD	• Chronic relapsing disease • Transmural inflammation • May affect any segment of the GI tract • Strictures/fistulae are common	• Failed TNFα-antagonists • Failed natalizumab (indicated for TNFα-antagonist failures)

Natalizumab – Risk of PML; Vedolizumab - Potential Risk of PML

	Natalizumab – Risk of PML	Vedolizumab - Potential Risk of PML	
	Post-Marketing Data	Clinical Trials	*Approval?*
Cases	285*	0	
Risk factors	• Long duration Tx (> 24 mo's) • Prior immunosuppressant (IS) • Anti-JCV Ab (+)	• Not known • *Concomitant IS use:* • limited to Induction in US protocols • Concern of ↑ risk PML/Infections but no evidence from trial data	*If approved, should concomitant IS be limited to induction?*
Risk Estimate	*Any comparisons (vedolizumab vs. natalizumab) of risk will be descriptive – should be interpreted with caution.* • Point Estimate Rate:# • 3.76 cases per 1,000 pts exposed for ≥ 24 months *Additional Limitations:* • *Different populations:* • *Natalizumab: 99% MS 1% CD;* • *Vedolizumab: UC & CD*	• 95% upper bound of true rate based on Rule of 3 (95% confident that true rate is less than 3 over n):† • 95% confident that true rate is less than 3.31 cases per 1,000 pts exposed for ≥ 24 *months* • 95% confident that true rate is less than 2.99 cases per 1,000 pts that received ≥ 24 *infusions*	*Is this an acceptable pre-marketing assessment of the risk of PML?*

*Sept 2012; #Bloomgren et al., 2012; †June 28, 2013 data cutoff

Natalizumab – Risk of PML; Vedolizumab - Potential Risk of PML [cont.]

	Natalizumab – Risk of PML	Vedolizumab - Potential Risk of PML		
	CD Indication	Clinical Trials		*Approval?*
		US	Ex-US	
Entry into Trial / Indicated Population	• Had to have failed TNFα-antagonist	• Had to have failed IS or TNFα-antagonist	• Also allowed enrollment of patients that failed steroids only	*If approved, should the indicated population include patients that failed steroids only?*

Risk Mitigation	• Medication Guide +
	• Elements to Assure Safe Use:
	  • Prescriber certification
	  • Pharmacy/Infusion Site certification
	  • Safe Use Conditions
	  − Pre-infusion checklist
	  − Questionnaires for reauthorization (periodic) and after discontinuation
		• Risk Assessment and Minimization for PML (RAMP) Program:
		  • Neurological exams (Baseline and Periodically)
		  • Algorithm for evaluation of suspected PML
		  • Testing
		  • Referral to PML experts
		  • Post-study follow-up (up to 2 years)
		  • Education of subjects/site personnel
				If approved, are risk mitigation strategies beyond labeling needed?

ensure early detection of PML and timely discontinuation if PML occurs

Overview of Presentations

- FDA Presentations:
  1) Tysabri PML Experience
  2) JC Virus and Pathogenesis of PML
- Applicant Presentations
- FDA Presentations:
  3) CD Efficacy
  4) Clinical Trial Safety and Approach to Risk Assessment
  5) Risk Management Considerations

Question 1: CD Efficacy

1. Evidence for vedolizumab efficacy for CD induction is provided by one trial but not supported by a second trial that primarily enrolled a refractory population. Evidence for vedolizumab efficacy for CD maintenance is provided in one trial.

a. **VOTE: Do the available data support the efficacy of vedolizumab for the proposed CD induction indication?** (please explain your vote)

b. **VOTE: Do the available data support the efficacy of vedolizumab for the proposed CD maintenance indication?** (please explain your vote)

c. **DISCUSSION: Please discuss if further studies are needed and what those studies should address.**

Question 2: Safety

2. **VOTE:** Considering the currently available nonclinical and clinical data, **has the applicant adequately characterized the potential risk of PML with vedolizumab to support approval?** (please explain your vote)

Question 3: Safety

3. **VOTE:** If vedolizumab is approved, **should concomitant immunosuppressants be limited to a specific duration (e.g., during induction only)?** (please explain your vote)

Question 4: Benefit-Risk Assessment for UC

4. **VOTE (choose a, b, or c):** Based on currently available efficacy and safety data, **do the benefits outweigh the potential risks of vedolizumab (in particular, PML) to support approval for**:
   a) the proposed UC population that have **failed steroids or immunosuppressants or TNFα-antagonists**?
   b) patients that have **failed immunosuppressants or TNFα-antagonists** (i.e., the indicated population would not include patients that failed steroids only)?
   c) neither a nor b.

Question 5: Benefit-Risk Assessment for CD

5. **VOTE (choose a, b, or c):** Based on currently available efficacy and safety data, **do the benefits outweigh the potential risks of vedolizumab (in particular, PML) to support approval for**:
   a) the proposed CD population that have **failed steroids or immunosuppressants or TNFα-antagonists**?
   b) patients that have **failed immunosuppressants or TNFα-antagonists** (i.e., the indicated population would not include patients that failed steroids only)?
   c) neither a nor b.

Question 6: Safety and Risk Mitigation Strategy Considerations

6. **DISCUSSION: If vedolizumab is approved for the proposed UC or CD indications:**
   a. **Discuss what post-market risk mitigation strategies beyond labeling, if any, would be needed** to ensure that the product's benefits outweigh its risks.
   b. **Discuss what additional safety studies or trials should be conducted, if any.**

Natalizumab (Tysabri®) Experience with Progressive Multifocal Leukoencephalopathy (PML)

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Gastrointestinal Drugs and Drug Safety and Risk Management Advisory Committees (GIDAC and DSaRM) Meeting

December 9, 2013

Outline

- Natalizumab (NTZ, Tysabri®) Background
- Natalizumab Regulatory History
- Natalizumab Risk Evaluation and Mitigation Strategy (REMS)
- Risk of PML with Natalizumab
- Risk of PML in Natalizumab-treated Crohn's Disease Patients

NATALIZUMAB BACKGROUND

Natalizumab Background

- Monoclonal antibody directed against α4β1 and α4β7 integrins.
  - Blocks interaction of α4β1 with vascular cell adhesion molecule-1 (VCAM-1) in the blood-brain barrier.
  - Blocks interaction of α4β7 with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in the Gastrointestinal (GI) tract.
- NTZ reduces inflammation in the Central Nervous System (CNS) and GI tract, thereby alleviating clinical symptoms and reducing the frequency of clinical exacerbations.

Natalizumab Immune Effects

- NTZ substantially decreases the CD4+/CD8+ ratio in the cerebrospinal fluid (CSF) of NTZ-treated patients.
- Markedly depresses CD4+ T-cell count in the CSF relative to the peripheral blood.
- Results in impaired immune surveillance in the brain, and contributes to risk of PML.

Stuve O, Marra CM, Keith JR, et al. Ann Neurol 2006;59:743-47.
Stuve O, Marra C, Bar-Or A, et al. Arch Neurol 2006; 63(10):1383-1387.

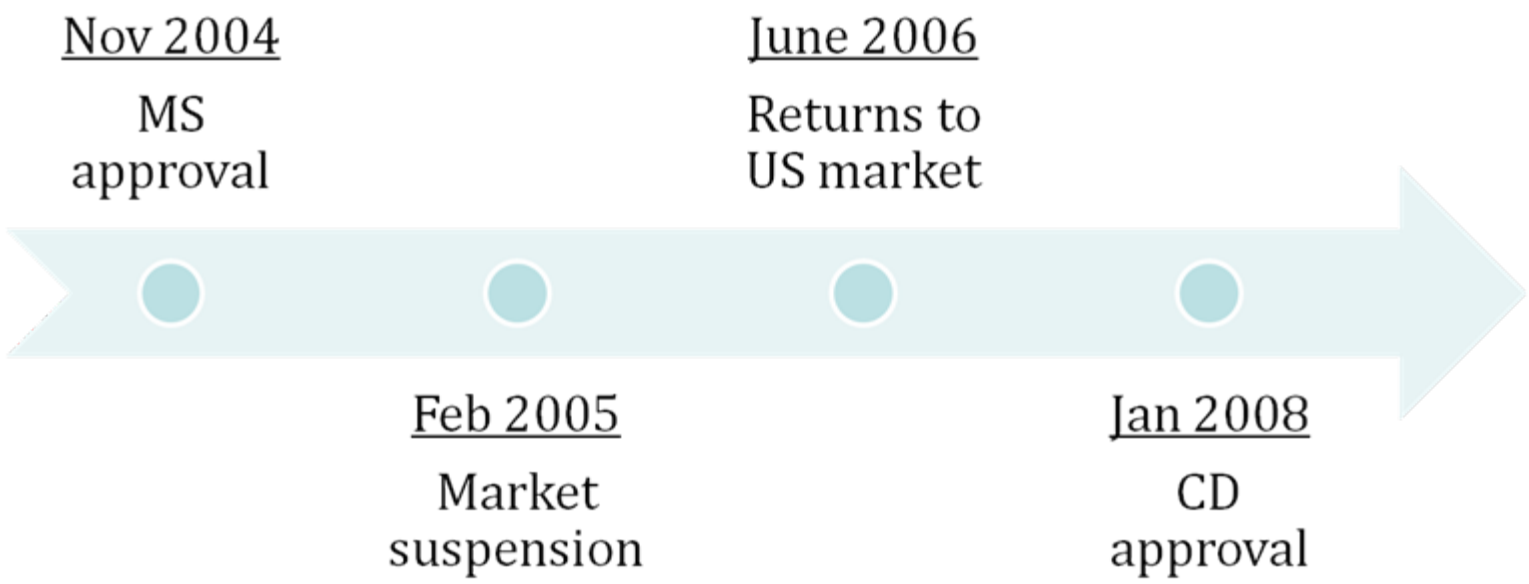
NATALIZUMAB REGULATORY HISTORY

NTZ Regulatory History

- November 23, 2004: Approved in the US for multiple sclerosis (MS).
- February 2005: US Market suspension.
  - Two clinical trials cases of PML in MS patients.
  - One clinical trial case in a Crohn's disease (CD) patient.
- March 2006: FDA Peripheral and Central Nervous Systems Drugs Advisory Committee.
  - Estimated PML Incidence of 1:1000.
  - Voted to re-introduce NTZ to the market.
  - Recommended risk minimization program.

NTZ Regulatory History (cont.)

- June 2006: NTZ returned to US market.
  - Restricted distribution under a Risk Minimization Action Plan (RiskMAP).
  - Postmarketing Safety Study.
- January 14, 2008: NTZ approved for CD.



NTZ Current Indications

- Multiple Sclerosis
  - Monotherapy for relapsing forms of multiple sclerosis.
  - NTZ is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy.
- Crohn's Disease
  - Patients who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α.
  - NTZ should not be used in combination with immunosuppressants or inhibitors of TNF-α.
- 300 mg intravenous every 4 weeks for both MS and CD.

NATALIZUMAB RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Risk Evaluation and Mitigation Strategies (REMS)

- Listed as deemed REMS in accordance with FDA Amendments Act (FDAAA).
- REMS approved October 7, 2011.
  - Medication Guide.
  - Elements to Assure Safe Use (ETASU).
- NTZ only available under a restricted distribution program.
  - Tysabri Outreach: Unified Commitment to Health (TOUCH®) Prescribing Program.
  - Separate program for MS and CD patients.

TOUCH® Program

- Certification and enrollment of prescribers and patients.
  - Recertification every 6 months.
- Restricted distribution and dispensing by specially certified pharmacies and infusion sites.
- Pre-infusion checklist.
  - Ensures patient is authorized and understands Medication Guide.
  - Documents new or worsening neurologic changes.
  - Ensures patient is not immunosuppressed.

TOUCH® Program (cont.)

- Tracks all patients over time.
- Prescribers agree to report, and manufacturer actively solicits, cases of PML and other opportunistic infections.
- Allows safety surveillance of specific adverse events, and especially PML.

PML IN NATALIZUMAB PATIENTS

Progressive Multifocal Leukoencephalopathy (PML)

- Rare demyelinating disease of the brain caused by reactivation of the JC virus.
- Diagnosis requires clinical, neuroimaging, and virologic evidence.
- Usually leads to death or severe disability.
- No effective treatment for PML.

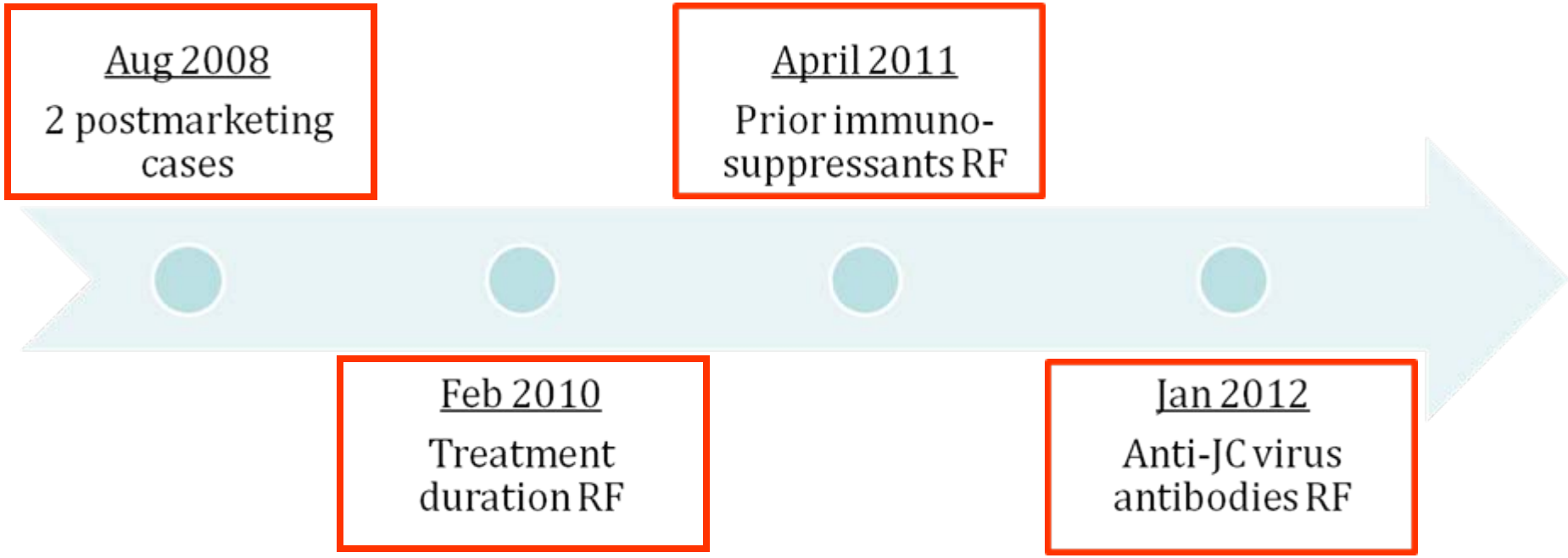
Berger JR, Aksamit AJ, Clifford DB, et al. Neurology 2013;80;1430

Initial PML cases

- Two cases of PML were observed in clinical trials among 1869 MS patients treated with NTZ for a median of 2 years.
  - Both patients receiving NTZ (> 2 years) + interferon beta-1a.
- One PML case identified among 1043 CD patients treated in an NTZ clinical trial.
  - NTZ monotherapy (8 doses).
  - Prior history of immunosuppressant use and leucopenia.
- Estimated PML incidence of 1/1000.
  - 95% CI: 0.2 - 2.8/1000.

PML Surveillance

- Since market re-introduction in June 2006.
- PML risk factors (RF) identified over time.



PML Risk Factors in NTZ Patients

- Longer treatment duration (>2 years)
- Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil)
- Presence of anti-JC virus (JCV) antibodies

PML risk stratified by Risk Factor

Tysabri Exposure†	*Anti-JCV Antibody Positive**	
	No Prior Immunosuppressant Use	*Prior Immunosuppressant Use*
1-24 months	*<1/1,000*	*2/1,000*
25-48 months	*5/1,000*	*11/1,000*

Notes: Based on postmarketing PML data as of September 5, 2012 and Tysabri world-wide use data as of August 31, 2012. US utilization data obtained from TOUCH, non-US data based on NTZ sales data.
†Data beyond 4 years of treatment are limited.
**Risk in anti-JCV antibody positive patients was estimated based on the assumptions that 18% of Tysabri-treated MS patients have a history of prior immunosuppressant treatment and that 55% of Tysabri-treated MS patients are anti-JCV antibody positive. The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with a false negative rate of 3%.*

- **285 cases and cumulative PML risk 2.6/1000 patients**

Tysabri (natalizumab) [package insert]. Cambridge, MA: Biogen Idec; 2013. (http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=c5fdde91-1989-4dd2-9129-4f3323ea2962.

PML IN NATALIZUMAB CROHN'S DISEASE PATIENTS

Postmarketing PML Cases in CD (n=2)

Case #1		Case #2
31 y/o, male	*Demographics*	52 y/o female
35 ~3 years	*NTZ Infusions*	47 ~4 years
Methotrexate, two TNF-α blockers	*Prior Treatment*	Azathioprine, methotrexate, infliximab, adalimumab
Not reported	*Anti-JCV Antibodies*	Positive
Budesonide, hydrocortisone suppository	*Concomitant Medications*	None reported
Resolved with sequelae	*Outcome*	Resolved without sequelae

NTZ Crohn's Disease Timeline

Jan 2008

CD Approval

Aug 2011

1st PML case

Oct 2012

2nd PML case

Risk of PML In NTZ-treated Crohn's Disease Patients

	Confirmed PML Cases	Exposure (patients)	Incidence per 1000 patients (95% CI)
Incidence (CD)	2	1127*	1.77† (0.2, 6.5)
Incidence (MS+CD)	285	~100,000‡	2.63† (2.2, 2.9)

* NTZ Exposure data provided by Biogen Idec from January 14, 2008 (approval date for CD indication) through October 31, 2012.

† Confidence interval computed by using an exact method based on the binomial distribution.

‡ World-wide exposure through August 31, 2012 (US data from TOUCH, non-US data from estimated sales)

Limitations of Risk Analysis for PML in NTZ-treated CD Patients

- Cannot stratify by risk factors due to:
  - Limited number of PML cases
  - Limited NTZ exposure
- Unclear if risk factors for overall PML data applicable to CD patients because:
  - Difference in underlying disease (CD vs. MS)
  - Difference in prior immunosuppressant exposure
- If risk factors are applicable to CD patients, their distributions may differ.

NTZ PML Experience Summary

- November 2004: Natalizumab approved for MS.
  - PML cases (n=3) identified from clinical trials led to marketing suspension.
- June 2006: Natalizumab re-introduced to US market for MS.
  - Restricted distribution under TOUCH® program.
  - Initial PML cases identified ~2 years later.
- January 2008: Natalizumab approved for CD.
  - Initial PML case identified ~3.5 years later.
  - Current labeling and REMS ensure informed patients and prescribers, and continual PML surveillance.

Crohn's Disease Efficacy Statistical Considerations

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Gastrointestinal Drugs and Drug Safety and Risk Management Advisory Committees (GIDAC and DSaRM) Meeting

December 9, 2013

Outline

- Study C13007 Design
- Study C13007 Efficacy Endpoints
- Study C13007 Analysis Populations
- Study C13007 Efficacy Results
- Study C13011

Study C13007 Design (Induction)

- Randomized (2:3), double-blind
- Induction
  - 6-week
  - Treatment at Weeks 0 and 2
  - Cohort 1:
    - Double-blind (efficacy analysis)
    - Treatment groups: VDZ 300 mg; PBO
  - Cohort 2:
    - Open-label
    - Treatment: VDZ 300 mg

Study C13007 Design (Maintenance)

- Randomized (1:1:1), double-blind
- Maintenance
  - Additional 46-week (Week 6 – Week 52)
  - Treatment every four weeks from Week 6 to Week 50
  - Treatment groups: Q4W; Q8W; PBO
  - Clinical responders (CDAI-70) from the Cohort 1 VDZ group and Cohort 2

Study C13007
Efficacy Endpoints (Induction)

- Measured at Week 6
- Clinical remission – Primary
- Enhanced clinical response (CDAI-100)
  - Secondary in original protocol
  - Elevated by Applicant to a second primary in an amendment
  - Hochberg multiplicity adjustment method pre-specified
- Mean serum CRP levels (mg/L) – Secondary

Study C13007
Efficacy Endpoints (Maintenance)

- Measured at Week 52
- Primary
  - Clinical remission
- Secondary
  - Enhanced clinical response (CDAI-100)
  - Corticosteroid-free remission
  - Durable clinical remission

Study C13007
Analysis Populations

- Subjects with previous TNFα antagonist exposure ≤ 50%
- Intent-to-Treat (ITT) Population
  - Induction: All randomized subjects received study drug
  - Maintenance: All randomized subjects received study drug *AND* met clinical response (CDAI-70) at Week 6
- Per-Protocol (PP) Population
  - Excluding subjects with screening and baseline CDAI < 210 or > 490
  - Enrollment inclusion criterion: CDAI ≥ 220 and ≤ 450

Study C13007 Disposition (Induction)

	Cohort 1		Cohort 2
	PBO	VDZ	VDZ
ITT/Safety	148	220	747
Completed	137 (93%)	199 (90%)	674 (90%)
Discontinued	11 (7%)	21 (10%)	73 (10%)

Study C13007
Disposition (Maintenance)

	PBO	VDZ Q8W	VDZ Q4W
ITT	153	154	154
Completed	64 (42%)	73 (47%)	82 (53%)
Discontinued	89 (58%)	81 (53%)	72 (47%)

Study C13007
Results (Primary Induction Endpoints)

	Clinical Remission		Enhanced Clinical Response (CDAI-100)	
	PBO N = 148	VDZ N = 220	PBO N = 148	VDZ N = 220
n (%) achieving endpoint at Week 6	10 (6.8%)	32 (14.5%)	38 (25.7%)	69 (31.4%)
95% CI	(2.7%, 10.8%)	(9.9%, 19.2%)	(18.6%, 32.7%)	(25.2%, 37.5%)
Difference from PBO		7.8%		5.7%
95% CI		(1.2%, 14.3%)		(-3.6%, 15.0%)
CMH P-value		0.0206		0.2322

Study C13007
Results (Secondary Induction Endpoint)

CRP Level (mg/L)	PBO N = 148	VDZ N = 220
N	147	220
Baseline mean (SD)	23.6 (27.85)	24.1 (27.23)
Week 6 mean (SD)	19.9 (30.05)	21.1 (26.92)
Change from baseline mean (SD)	-3.6 (30.04)	-2.9 (16.28)
Change from baseline median	-0.5	-0.9
10th and 90th percentile	(-27.6, 12.1)	(-20.6, 10.3)
Wilcoxon P-value		0.9288

Study C13007
Results (Primary "Maintenance" Endpoint)

Clinical Remission	PBO N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154
n (%) achieving clinical remission at Week 52	33 (21.6%)	60 (39.0%)	56 (36.4%)
95% CI	(15.1%, 28.1%)	(31.3%, 46.7%)	(28.8%, 44.0%)
Difference from PBO		17.4%	14.7%
95% CI		(7.3%, 27.5%)	(4.6%, 24.7%)
CMH P-value		0.0007	0.0042

Study C13007
Results (Secondary "Maintenance" Endpoints)

n (%) achieving endpoint at Week 52	PBO N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154
Enhanced Clinical Response (CDAI-100)	46 (30.1%)	67 (43.5%)	70 (45.5%)
Difference from PBO		13.4%	15.3%
95% CI		(2.8%, 24.0%)	(4.6%, 26.0%)
CMH P-value		0.0132	0.0053
Corticosteroid-free Clinical Remission	**N = 82** 13 (15.9%)	**N = 82** 26 (31.7%)	**N = 80** 23 (28.0%)
Difference from PBO		15.9%	12.9%
95% CI		(3.0%, 28.7%)	(0.3%, 25.5%)
CMH P-value		0.0154	0.0450
Durable Clinical Remission	22 (14.4%)	33 (21.4%)	25 (16.2%)
Difference from PBO		7.2%	2.0%
95% CI		(-1.5%, 16.0%)	(-6.3%, 10.2%)
CMH P-value		0.1036	0.6413

Study C13011 (Design)

- Induction only
- Randomized (1:1), double-blind
- Treatment at Weeks 0, 2, and 6
- Treatment groups: VDZ 300 mg; PBO
- Enrolled ~75% subjects with previous TNFα antagonist failure
- Enrollment inclusion criterion: CDAI ≥ 220 and ≤ 400

Study C13011 (Population)

- TNFα-failure subpopulation: TNFα antagonist failure subpopulation
- Overall population: TNFα antagonist failure and TNFα antagonist naïve subjects

Study C13011 (Endpoints)

- Measured at Weeks 6 and 10
- Primary
  - Clinical remission at Week 6 in TNFα-failure subpopulation
- Secondary
  - Clinical remission at Week 6 in overall population
  - Clinical remission at Week 10 in TNFα-failure subpopulation and overall population
  - Sustained clinical remission in TNFα-failure subpopulation and overall population
  - Enhanced clinical response (CDAI-100) at Week 6 in TNFα-failure subpopulation

Study C13011 (Disposition)

	TNFα-Failure Subpopulation		Overall Population	
	PBO	VDZ	PBO	VDZ
ITT	157	158	207	209
Completed	145 (92%)	151 (96%)	192 (93%)	196 (94%)
Discontinued	12 (8%)	7 (4%)	15 (7%)	13 (6%)

Study C13011 (Week 6 Results)

Clinical Remission at Week 6	TNFα-Failure Subpopulation		Overall Population	
	PBO N = 157	VDZ N = 158	PBO N = 148	VDZ N = 220
n (%)	19 (12.1%)	24 (15.2%)	25 (12.1%)	40 (19.1%)
95% CI	(7.0%, 17.2%)	(9.6%, 20.8%)	(7.6%, 16.5%)	(13.8%, 24.5%)
Difference from PBO		3.0%		6.9%
95% CI		(-4.5%, 10.5%)		(0.1%, 13.8%)
CMH P-value		0.4332		NA

Study C13011 (Week 10 Results)

Clinical Remission at Week 10	TNFα-Failure Subpopulation		Overall Population	
	PBO N = 157	VDZ N = 158	PBO N = 207	VDZ N = 209
n (%)	19 (12.1%)	42 (26.6%)	27 (13.0%)	60 (28.7%)
95% CI	(7.0%, 17.2%)	(19.7%, 33.5%)	(8.5%, 17.6%)	(22.6%, 34.8%)
Difference from PBO		14.4%		15.5%
95% CI		(5.7%, 23.1%)		(7.8%, 23.3%)
CMH P-value		NA		NA

CD Efficacy Summary

	Induction Phase			Maintenance Phase	
Study C13007	Primary	✓	✗	Primary	✓
	Secondary	✗		Secondary	✓
					✓
					✗
Study C13011	Primary	✗			
	Secondary	?			

Crohn's Disease Efficacy: Clinical Considerations

Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management
December 9, 2013

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CDER/FDA

Points to Consider

- How do the 2 induction primary endpoints in C13007 relate to each another?
- Is winning only one of two related primary endpoints in the C13007 induction study convincing when not supported by a secondary endpoint (CRP)?
- How can we/ should we use the exploratory results in C13011?
  - Do they support a third dose that was not part of the primary analysis?
- What is the significance of the "maintenance" phase results in view of
  - one successful induction study and one that failed on the primary endpoint?
  - The primary endpoint of the maintenance phase study was a "snapshot" of remission at week 52 (i.e., the secondary analysis of "durable remission" failed)

Crohn's Disease: Proposed Indication and Dosage

Adult Crohn's Disease
Reducing signs and symptoms, inducing and maintaining clinical response ***and*** remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist.

DOSAGE AND ADMINISTRATION
300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter.

Crohn's Disease: Focus on Induction Studies

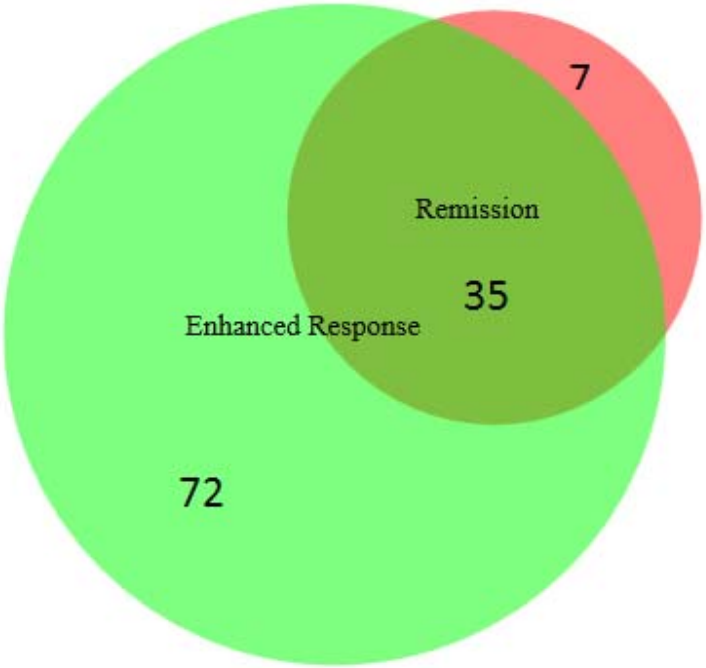
Study	C13007		C13011	
Endpoint	Primary	1st secondary	Primary	1st secondary
Induction	endpoint met□	endpoint not met	endpoint not met	no formal hypothesis testing allowed[j]
Maintenance	endpoint met	endpoint met	n/a	n/a

□ one of two alternative endpoints met
[j] nominally significant

Endpoints in C13007 Induction

	Illustration with Boolean operators	Narrative Description
Used for the induction phase of C13007	Primary Endpoint 1 **OR** Primary Endpoint 2	**Definition:** In order to be considered efficacious *at least one* of the two primary endpoints needs to be met.

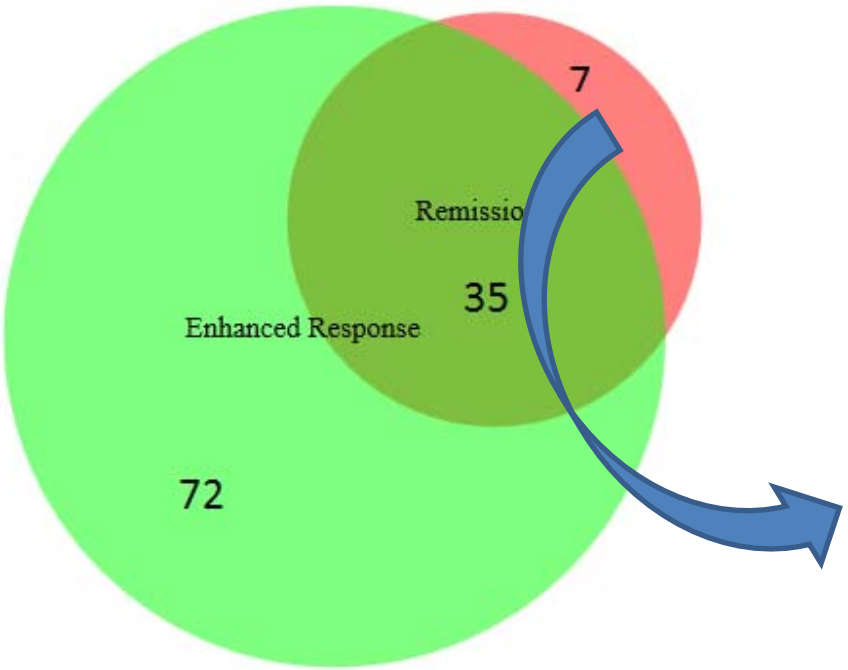
C 13007 – Induction Primary Endpoints



Overlap of **Clinical Remission** with "**Enhanced Clinical Response"** at Week 6, VDZ and PBO:

7 patients in Clinical Remission did not meet criteria for "Enhanced Clinical Response“ (CDAI-100)

The Seven Outliers Did Not Meet Enrollment Criteria



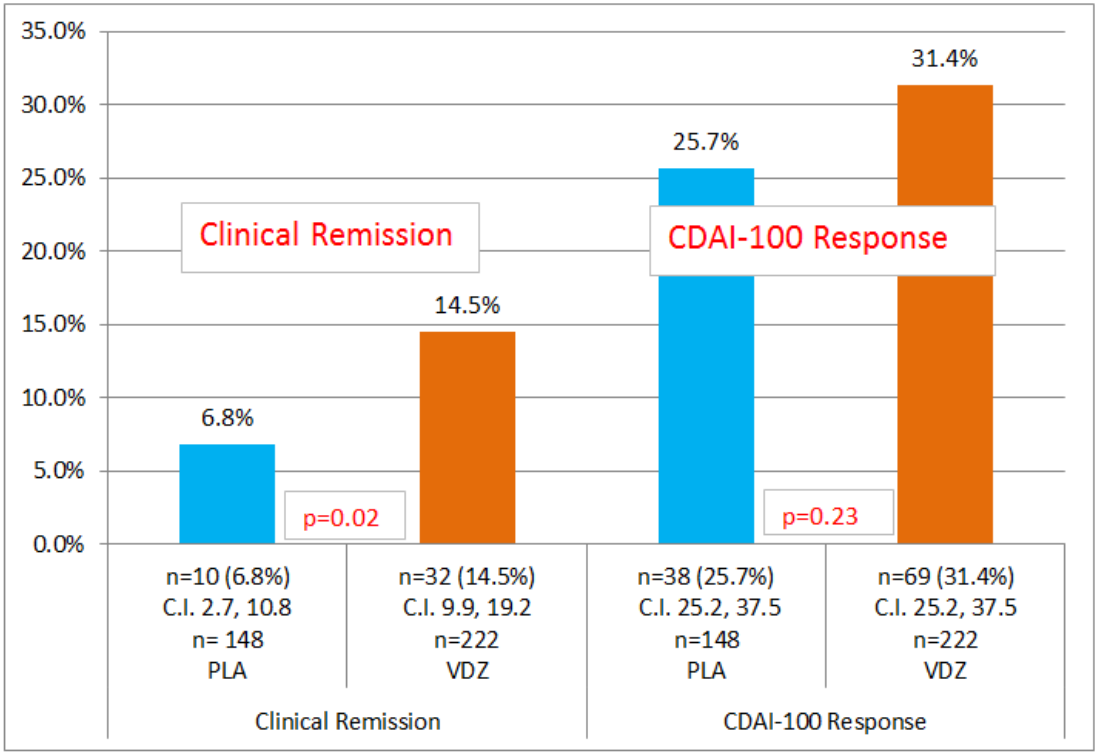
Overlap of **Clinical Remission** with "**Enhanced Clinical Response"** at Week 6, VDZ and PBO:

7 patients in Clinical Remission did not meet criteria for "Enhanced Clinical Response“ (CDAI-100)

All 7 outliers did not meet baseline enrollment criteria: 2 were in the placebo arm (baseline scores 155 and 191). 5 were in the vedolizumab arm (baseline scores 132, 142, 192, 213, and 218).

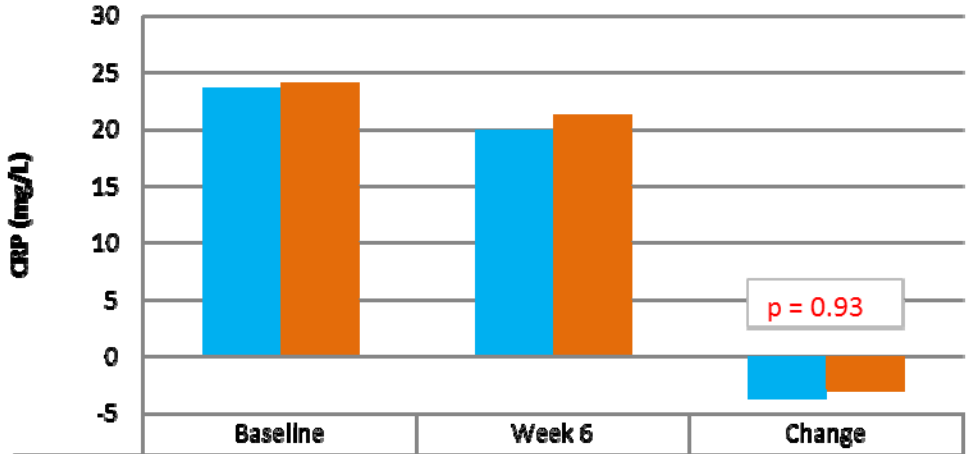
C13007 Induction Endpoints at 6 Weeks

Primary Endpoints in C13007



In the induction phase of C13007 patients received VDZ at week 0 and 2 only.

C13007 Secondary Endpoint: No Trend for VDZ in Lowering CRP Values at Week 6



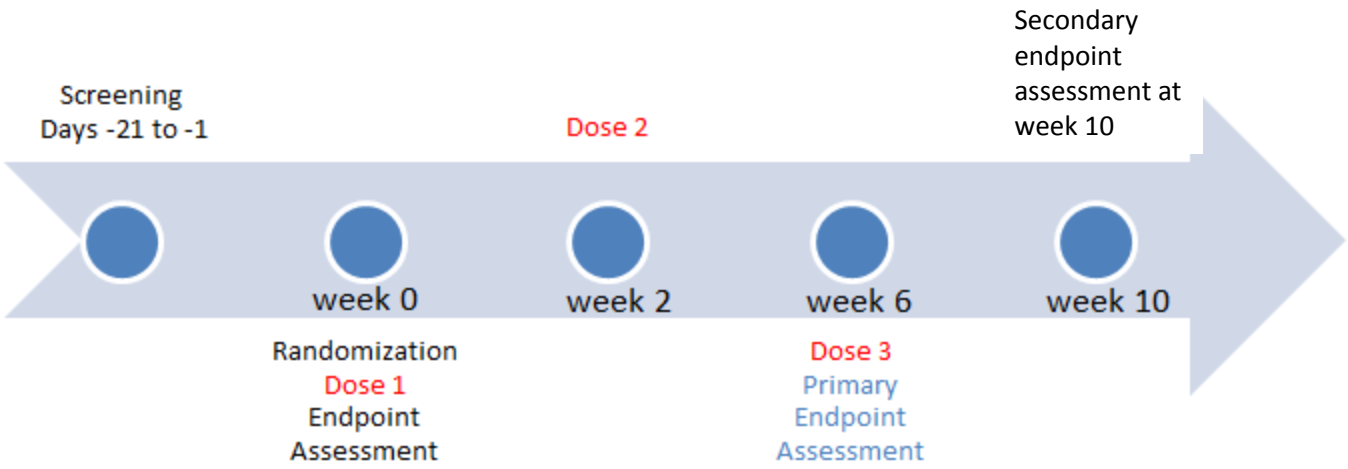
	Baseline	Week 6	Change
CRP PLA n=147	23.6	19.9	-3.6
CRP VDZ n=220	24.1	21.2	-2.9

Secondary Endpoint:
Change from baseline CRP
-p=0.93

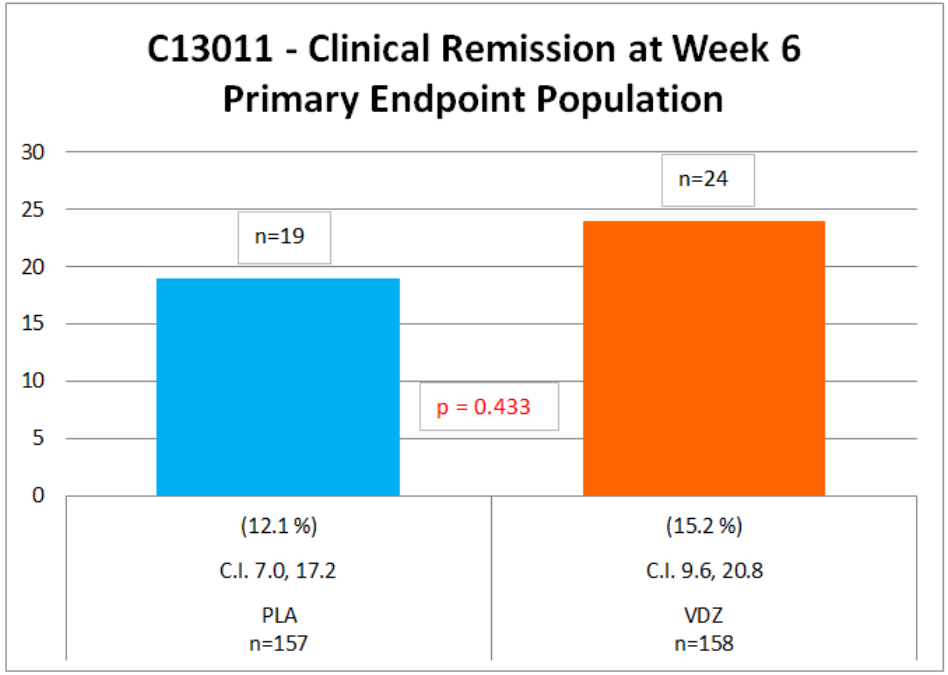
Summary Induction C13007

- Primary:
  - Clinical Remission p= 0.0206 (adjusted p-value 0.0412)
  - CDAI-100 - not significant p=0.232
  - *Relationship of Clinical Remission to CDAI-100 Response complicated by protocol violators*
- Secondary:
  - CRP change from baseline – not significant

C13011- Treatment Overview



C13011
Primary Endpoint Not Met



Doses at 0, 2 and 6 weeks (doses at 0 and 2 weeks used for primary efficacy analysis)

Primary analysis populations: patients who had previously failed TNFα antagonists (approx. 75 % of patients)

p = 0.433
Endpoint not met

All subsequent analyses are exploratory only

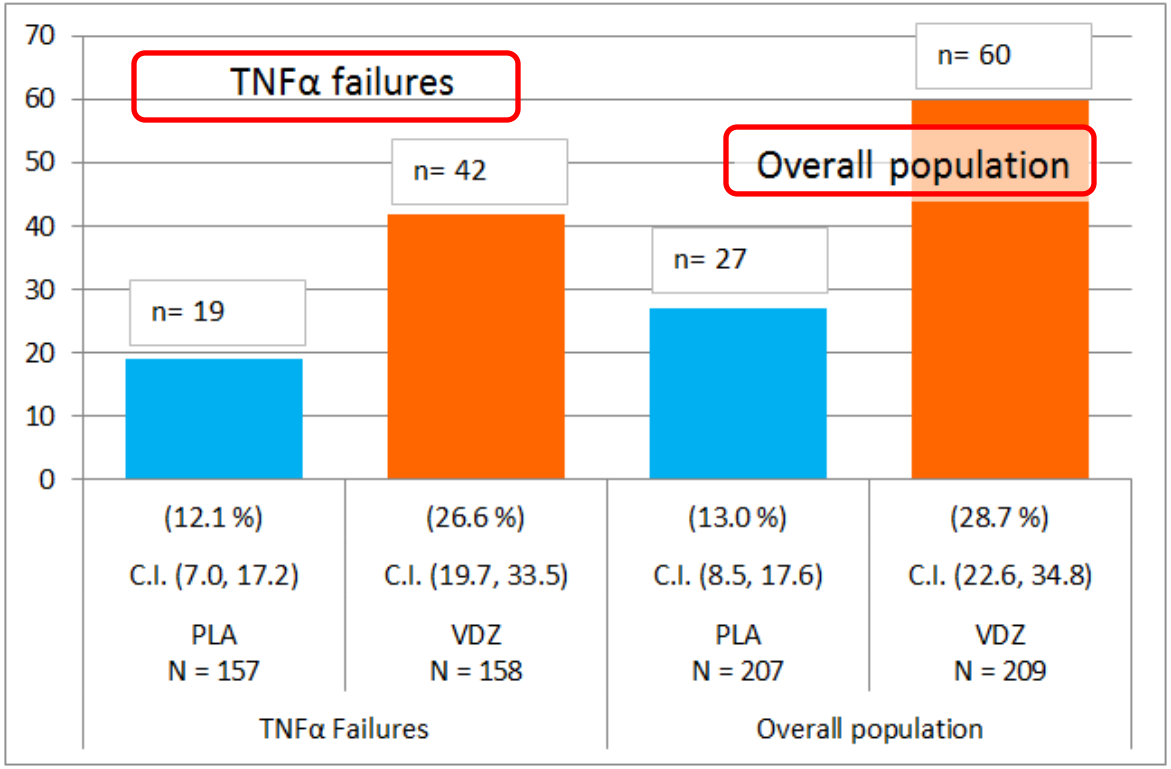
The Third Dose in C13011

Applicant: "Since the primary efficacy endpoint did not reach statistical significance, formal hypothesis testing could not be performed for the ranked secondary endpoints. Analyses of the secondary endpoints were performed, but should be considered exploratory in nature and for informational purposes only. These analyses suggest a potential treatment benefit in the TNF α Antagonist Failure ITT Subpopulation may be achieved beyond the 6-week treatment and evaluation period used to evaluate the primary endpoint."

Vedolizumab (MLN0002) Clinical Study Report C13011. Takeda Pharmaceuticals U.S.A., Inc. p. 98

C13011 Analysis at Week 10 (after a third dose at week 6)

Clinical Remission at week 10 – Exploratory Analysis



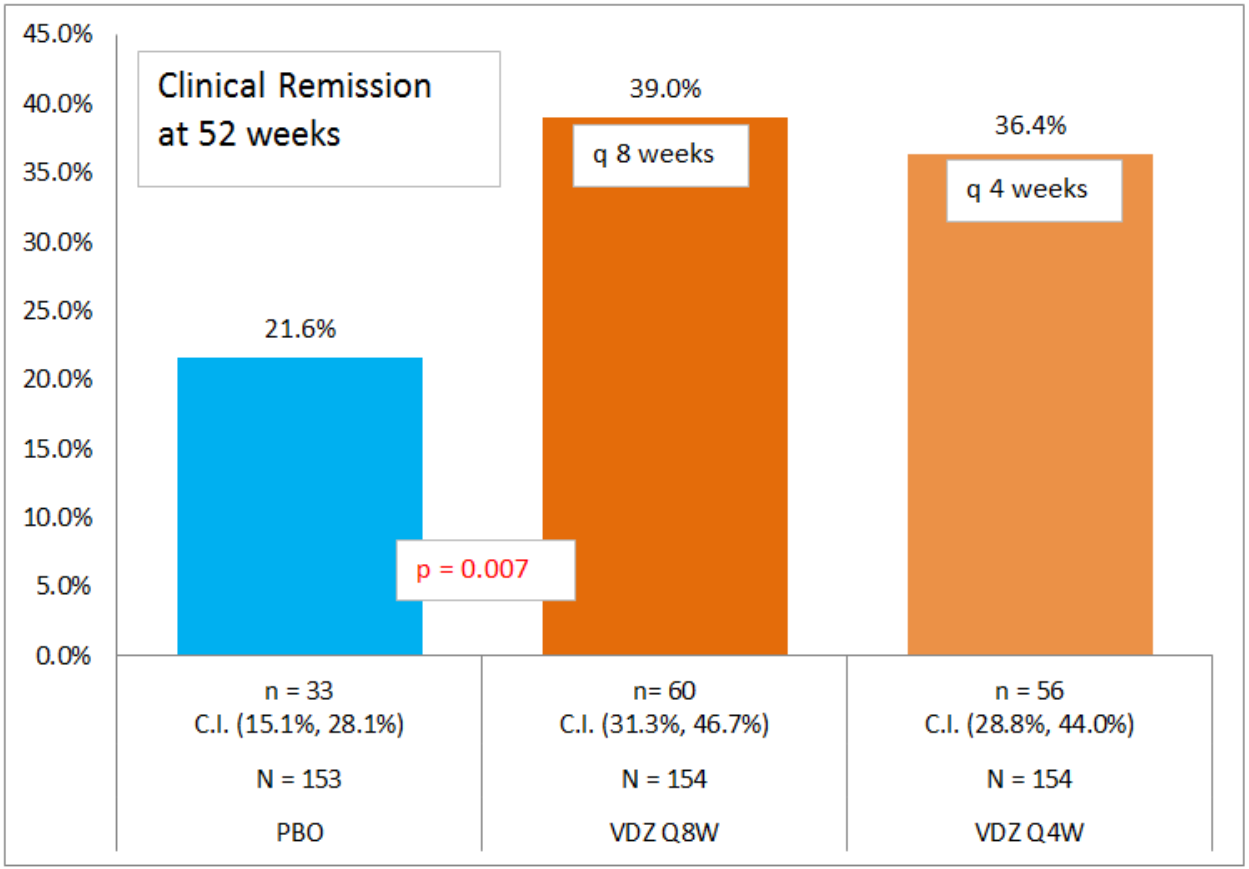
"A potential treatment benefit may be achieved…"

Vedolizumab (MLN0002) Clinical Study Report C13011. Takeda Pharmaceuticals U.S.A., Inc. p. 98

Study C13007 "Maintenance" Phase Design

- Randomized Clinical Responders (CDAI-70) from
  - Cohort 1 Induction Phase VDZ group
  - Cohort 2
- Primary Endpoint = Clinical Remission by 52 weeks
- Secondary Endpoint "Durable Clinical Remission" = Clinical Remission in ≥80% of the study visits in the maintenance phase, including Week 52

"Maintenance" Phase Results C13007



Durable Remission/Maintenance of Remission

n (%) achieving endpoint at Week 52	PBO N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154
Durable Clinical Remission	22 (14.4%)	33 (21.4%)	25 (16.2%)
Difference from PBO		7.2%	2.0%
95% CI		(-1.5%, 16.0%)	(-6.3%, 10.2%)
CMH P-value		NS	NS

Providing "Substantial Evidence" of Clinical Effectiveness

- Generally at least 2 adequate and well-controlled studies
- A single adequate and well-controlled efficacy study may be adequate if:
  - Multicenter study
    - No single site with large fraction of patients or disproportionately responsible for a favorable effect
  - Excellent design
  - Statistically strong
  - Internal consistency across subgroups, centers, and multiple endpoints

Guidance for Industry, May 1998, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*

Maintenance Phase of C13007 Not Supported by Induction Studies

- Induction results in C13007 needs support by a second trial
- Induction results in C13011 did not meet primary endpoint
- "Maintenance" Phase results in C13007 are promising but difficult to operationalize due to
  - entry criteria, i.e., in CDAI-70 response from VDZ
  - Induction study results

Summary

- Results in C13007 are statistically significant for the primary analysis but are not supported by CDAI-100 or CRP results
- The primary endpoint in C13011 was not met. Exploratory analyses suggest a potential benefit with a third dose
- If an effect on induction has not been demonstrated, it is difficult to interpret the observed effect in “Maintenance” Phase
- Durable Remission/Maintenance of Remission analysis failed
- A future induction study that explicitly evaluates a third dose in the primary endpoint assessment may be needed

Vedolizumab Clinical Trial Safety and Approach to Risk Assessment

Advisory Committee Meeting

December 9, 2013

Laurie Muldowney, MD

Medical Reviewer

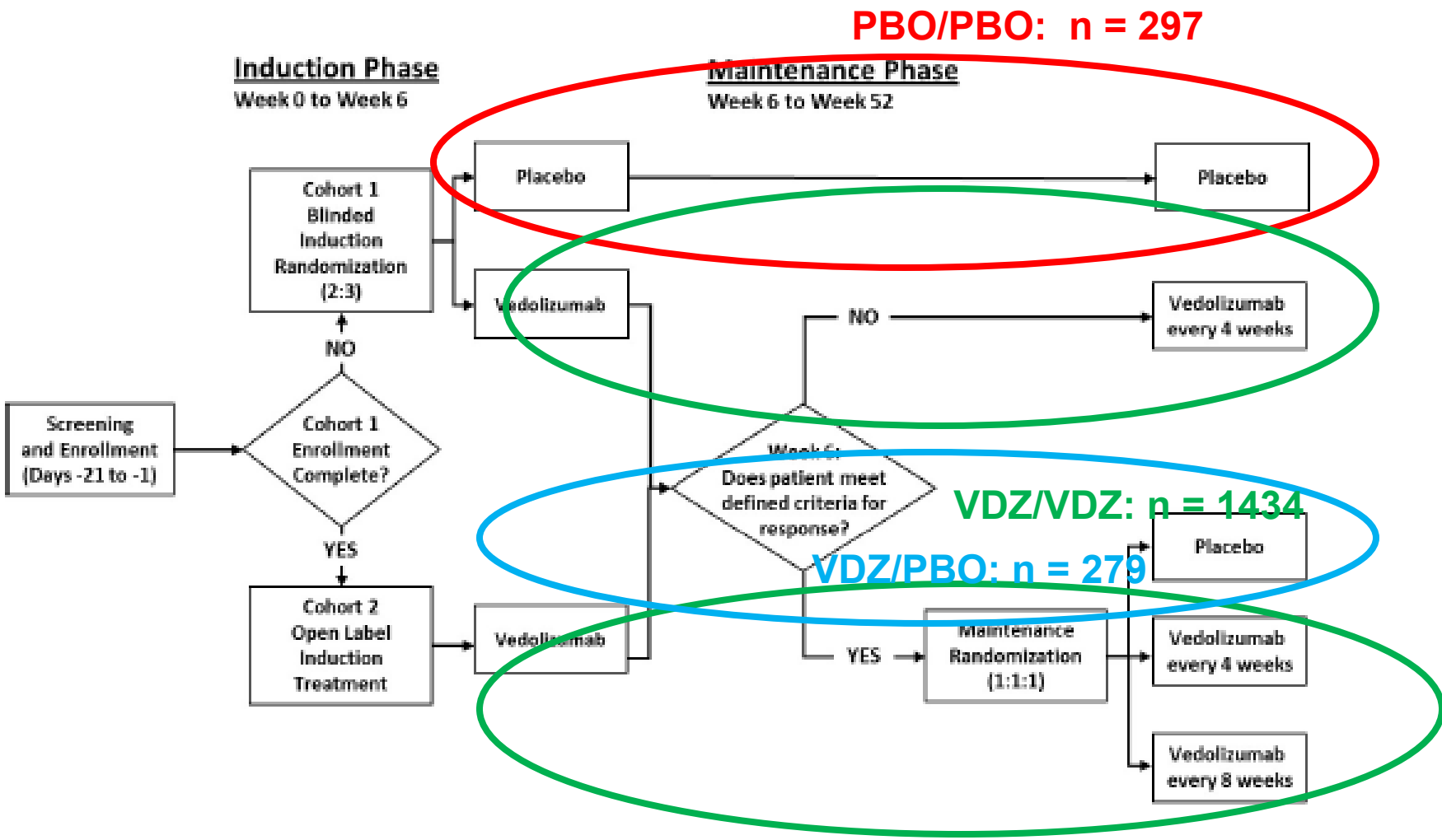
Division of Gastroenterology and Inborn Errors Products

CDER/FDA

Outline of Presentation

- Vedolizumab General Safety
  - Infection
  - Liver injury
- Vedolizumab and PML
  - Background and Relevant Regulatory History
  - Vedolizumab Clinical Development Program
  - Sample size and clinical trial findings
  - Statistical considerations

Safety Analyses Populations:



Infection AEs that occurred in ≥ 1% of VDZ/VDZ group by PT: C13006 and C13007

Preferred Term, n (%)	VDZ/PBO N = 279	PBO/PBO N = 297	VDZ/VDZ N = 1434
Pts with at least 1 AE	116 (42)	103 (35)	622 (43)
Nasopharyngitis	29 (10)	21 (7)	180 (13)
Upper Respiratory Tract Infection	19 (7)	19 (6)	106 (7)
Bronchitis	11 (4)	10 (3)	57 (4)
Influenza	10 (4)	5 (2)	51 (4)
Urinary Tract Infection	10 (4)	8 (3)	49 (3)
Sinusitis	10 (4)	3 (1)	44 (3)
Gastroenteritis	10 (4)	3 (1)	35 (2)
Anal Abscess	3 (1)	4 (1)	30 (2)
Pharyngitis	6 (2)	1 (<1)	24 (2)
Oral Herpes	6 (2)	4 (1)	20 (1)
Gastroenteritis, viral	2 (<1)	3 (1)	15 (1)

Source: Applicant Submission, Integrated Summary of Safety, Tables 18.2.2.2A and 18.2.2.16A

Serious Infection AEs: C13006 and C13007

- Overall SAEs of infection reported at similar rates across treatment groups
  - 3% VDZ/PBO, 3% PBO/PBO, 4% VDZ/VDZ
  - More reported in CD than UC
- Systemic infections from enteric pathogens occurred infrequently
- 51 Herpes viral infections
  - None serious

Long Term Safety: Serious Infections

Preferred Term, n (%)	*Ulcerative Colitis N = 894*	*Crohn's Disease N = 1349*	*Total N = 2243*
Patients with at least 1 serious infection adverse event	42 (5)	113 (8)	155 (7)
Gastroenteritis	3 (<1)	13 (<1)	16 (<1)
Pneumonia	7 (<1)	8 (<1)	15 (<1)
Clostridium difficile	7 (<1)	7 (<1)	14 (<1)
Appendicitis	4 (<1)	5 (<1)	9 (<1)
Cellulitis	3 (<1)	3 (<1)	6 (<1)
Diverticulitis	1 (<1)	3 (<1)	4 (<1)
Cytomegalovirus colitis	2 (<1)	1 (<1)	3 (<1)
Gastroenteritis viral	0	3 (<1)	3 (<1)
Pulmonary tuberculosis	1 (<1)	2 (<1)	3 (<1)
Urinary tract infection	1 (<1)	2 (<1)	3 (<1)

Source: Sponsor Submission, C13008 Complete Study Report: 120-day safety update
Note: Table includes infections which occurred in more than 2 patients enrolled in C13008. SAE could have occurred during C13008 or originating study. Abscesses occurring in CD patients were removed.

Commonly Reported AEs by Baseline Concomitant Immunomodulators: Studies C13006 and C13007

Preferred Term, n (%)	No Concomitant Meds[a] at baseline		Concomitant immunomodulators[b] at baseline	
	PBO/PBO N = 99	VDZ/VDZ N = 445	PBO/PBO N = 95	VDZ/VDZ N = 483
Patients with at least 1 AE	74 (75)	363 (82)	78 (82)	418 (87)
Nasopharyngitis	8 (8)	67 (15)	7 (7)	61 (13)
Headache	11 (11)	54 (12)	11 (12)	60 (12)
Arthralgia	8 (8)	56 (13)	9 (9)	43 (9)
Nausea	6 (6)	44 (10)	10 (11)	32 (7)
Pyrexia	8 (8)	53 (12)	9 (9)	33 (7)
Abdominal pain	11 (11)	44 (10)	10 (11)	41 (8)
Upper respiratory tract infection	1 (1)	34 (8)	10 (11)	39 (8)
Fatigue	2 (2)	25 (6)	2 (2)	30 (6)
Vomiting	5 (5)	23 (5)	7 (7)	30 (6)
Anemia	4 (4)	21 (5)	8 (8)	22 (5)
Cough	4 (4)	28 (6)	2 (2)	20 (4)

Source: Adapted from Applicant Submission, Integrated Summary of Safety, Tables 7-14

[a]patients classified as “no concomitant meds” at baseline were not receiving concomitant immunomodulators or corticosteroids

[B] patients receiving concomitant immunomodulators, with or without corticosteroids at baseline

Liver Injury

- Tysabri (natalizumab) is causally associated with liver injury, including serious drug-induced hepatocellular liver injury
- Idiosyncratic mechanism not fully understood, however treatment with other biologic agents that modulate T cell activity and/or lymphocyte effector functions has resulted in a variety of forms of liver injury
- Cases of liver injury, including serious liver injury occurred during vedolizumab clinical development program

Bezabeh S et. al. *Aliment Pharmacol Ther* 2010;31:1028–1035.
Lisotti A et. al. *Dig and Liv Dis* 2012;44(4):356-357.

Clinical Laboratory Values: C13006 and C13007

- No imbalances of liver test abnormalities between randomized treatment groups in controlled Phase 3 Trials
- No clear difference in rates of marked abnormalities between treatment groups

Table: Marked[a] Abnormalities in Clinical Laboratory Values: C13006 and C13007

Analyte, n (%)	VDZ/PBO N = 279	PBO/PBO N = 297	VDZ/VDZ N = 1434
ALT > 3.0 x ULN	6 (2)	3 (1)	22 (2)
AST > 3.0 x ULN	7 (3)	0	16 (1)
Bilirubin > 2.0 x ULN	2 (<1)	2 (<1)	7 (<1)

Source: Sponsor Submission, Integrated Summary of Safety, Table 18.2.3.1
[a] Marked abnormalities were outside the pre-defined criteria for marked abnormality and had an on-treatment value more extreme than the baseline value

Hepatocellular Injury

- 4 patients reported SAEs
  - Acute hepatitis
  - Range of vedolizumab exposure from 2 – 35 doses
  - All discontinued treatment and were treated with IV corticosteroids
  - All recovered
- Spectrum of plausibility in terms of relatedness
  - 36yo female developed acute hepatitis after 35 doses (951 days after 1st dose), subsequently diagnosed with subacute cutaneous lupus erythematosus
  - 35yo female developed hepatitis 41 days after second dose and ~3 months after beginning sulfasalazine. Fever, eosinophilia, and liver biopsy consistent with hypersensitivity to sulfasalazine
  - 23yo female developed hepatitis 13 days after her 2nd dose. Case highly confounded (pneumonia, sepsis)

Case of Hepatocellular Injury

- 20 year old male with UC (Italy)
- 1st dose of vedolizumab November 26, 2009
- Acute hepatocellular injury noted March 4, 2010 at time of 5th dose of vedolizumab
- w/u for viral, autoimmune, liver storage diseases negative [except for a slight rise in smooth muscle antibodies (1 in 40)]
- Ultrasound and biopsy c/w drug-induced and/or autoimmune hepatitis

Date of Result	ALT (IU/L) [RR 10, 40]	AST (IU/L) [RR 10, 40]	Alkaline Phosphatase (IU/L) [RR 32, 92]	Bilirubin, total (mg/dL, [RR 1.20, 0.20] unless otherwise specified)
05Nov2009 (baseline)	18	20	73	5.0* µmol/L
08Mar2010	436	305	148	0.50
29Apr2010	622	458	174	1.47
10May2010	285	91	116	20* µmol/L
22Feb2011	15	19	134	0.60

* No reference range provided for these lab values

Liver Injury, Summary

- Cases of acute hepatocellular injury occurred
- Mechanistic plausibility with biologics, and specifically with integrin antagonists
- Appropriate labeling and pharmacovigilance for liver events in the postmarketing setting will be needed

General Safety, Summary

- Higher proportion of infectious AEs in the vedolizumab arms of UC and CD trials
  - Serious infections were at similar rates across treatment groups
  - No increase in infections was observed with prolonged exposure
- Serious infections from enteric pathogens occurred infrequently
- No clinically significant differences were seen when comparing AEs between patients based on baseline concomitant immunomodulator use
- Postmarketing monitoring for drug induced liver injury will be needed

Vedolizumab and Progressive Multifocal Leukoencephalopathy (PML)

Natalizumab and PML

- Approved in 2004 for relapsing MS
- Market suspension in 2005 following PML
- Approved in 2008 for moderate to severe CD
- Risk factors for PML in natalizumab treated patients:
  - Prior immunosuppressants
  - JCV Ab status
  - Length of treatment
- Risk was not identified until after natalizumab was approved

Vedolizumab compared with Natalizumab

	Vedolizumab	Natalizumab
Integrin Receptor Binding and Distribution	binds α4β7	binds α4 subunit (α4β7 and α4β1)
Ligand Interaction	selectively inhibits the interaction of α4β7 with MAdCAM-1[a]	Also inhibits interaction of α4β1 with VCAM-1
Human PD data	no effect on CD4+ counts, CD8+ counts, or the CD4+:CD8+ lymphocyte ratio in the CSF of healthy subjects studied	shown to reduce the CSF CD4+:CD8+ lymphocyte ratio

[a] MAdCAM-1: mucosal addressin cell adhesion molecule-1; [b] VCAM-1: vascular adhesion molecule-1

Select Regulatory History

Date	Regulatory Activity
6/00	IND submitted
1/06	Clinical hold due to PML cases with natalizumab
7/06	Agency Internal Meeting re: integrin antagonists •Discuss path forward for development •Provide general principles for risk mitigation and assessment
7/07	Clinical hold removed with enhanced identification and assessment of neurologic AE's and suspected PML cases
6/08 – 7/10	Meetings to discuss phase 3 protocols for UC and CD
7/11	Closed advisory committee

Approach to Integrin Antagonists: General Principles

- Receptor binding and mechanism of action
- Appropriate study population
- Safety monitoring
- Safety database
- Informed consent

Approach to Vedolizumab: Clinical Trials

- Appropriate study population
  - Moderate to severely active disease
  - Immunosuppressant or TNFα treatment failures only
  - Immunosuppressants limited to induction (i.e., 6 weeks)
- Safety Monitoring
  - Risk Assessment and Minimization for PML (RAMP) program
  - 2 years of post-study follow up
- Safety database
  - Safety database of at least 3,000 patients for a mean duration of 18 months prior to filing

Joint GIDAC DSaRM Advisory Committee Meeting: July 20, 2011

Purpose: seek the committee's input regarding the design of phase 3 studies, in light of PML risk with natalizumab

Joint Advisory Committee Advice

- the available nonclinical and human PD data did not provide assurance of less risk of PML than natalizumab
- entry criteria should remain stringent for phase 3 studies
- restrictions on concomitant immunosuppressants use (prohibited beyond the induction phase of vedolizumab treatment) should continue
- no consensus was reached on an acceptable pre-approval safety database size, however,
  - duration of exposure is important; 24 months could be considered as the minimum duration timeframe
  - increasing the sample size has merit

Final Safety Database Recommendation

A safety database of at least 900 patients that received ≥ 24 infusions, with a minimum of 4 weeks of follow-up after the last infusion was eventually agreed upon to provide a reasonable pre-approval assessment of PML risk in patients with UC and CD (for purpose of presentation to AC)

Vedolizumab Exposure

Duration	Healthy Subjects	Ulcerative Colitis	Crohn's Disease	Total[a]
At least 1 dose[b]	197	1279	1850	3326
Months of exposure				
≥ 6	0	855	1167	2022
≥ 12	0	588	830	1418
≥ 18	0	485	677	1162
≥ 24	0	428	478	906
≥ 36	0	198	209	407
≥ 48	0	30	10	40
Number of infusions with 4-week follow-up				
≥ 1	193	1261	1826	3280
≥ 6	0	913	1283	2196
≥ 12	0	673	916	1589
≥ 18	0	498	730	1228
≥ 24	0	444	560	1004
≥ 36	0	254	278	532
≥ 48	0	63	53	116

Source: Applicant Submission, 120-day safety update

[a] Exposure from Studies C13013 and CPH-001 is not included

[b] dose is defined as administration of any amount of vedolizumab in phase ½ studies and as administration of ≥ 75% of volume in phase 3 studies

RAMP Algorithm Results: Phase 2 and 3 Studies

PML Checklist	Ulcerative Colitis	Crohn's Disease	Total
Number of patients, n (%)	**1146**	**1781**	**2927**
Subjective checklist administered[b]	1142 (> 99)	1771 (> 99)	2913 (> 99)
Positive subjective findings	97 (8)	193 (11)	290 (10)
Objective checklist administered	97 (8)	193 (11)	290 (10)
Abnormal finding on objective checklist	17 (1)	47 (3)	64 (2)
RAMP algorithm, n (%)			
Referred to a neurologist	24 (2)	61 (3)	85 (3)
MRI performed	15 (1)	43 (2)	58 (2)
IAC involved	24 (2)	62 (3)	86 (3)
Lumbar puncture	2 (<1)	3 (<1)	5 (<1)
CSF analysis for JCV by PCR	2 (<1)	3 (<1)	5 (<1)
JCV DNA detected by PCR in CSF	0	0	0
Diagnosed with PML by the IAC	0	0	0

Source: Applicant Integrated Summary of Safety and 120-day Safety Update (Table 6-1)
[a] includes Studies C13002, C13004, C13006, C13007, C13008, and C13011
[b] proportions are based on number of patients completing at least 1 subjective checklist

Comparisons of PML Risk

- Gold standard for comparative claims based upon multiple, randomized (natalizumab vs vedolizumab), controlled clinical trials
  - For rare event, this is exhaustive and often infeasible
- Absent at least *one* head-to-head, randomized controlled clinical trial, we do not accept direct comparisons of PML risk between vedolizumab and natalizumab
  - Different patient populations
  - Different exposure
  - Other unmeasured confounders

Patient Exposure

- Natalizumab:
  - 2 PML cases in 1,869 MS patients and 1 PML case in 1,043 CD patients.
  - overall mean duration of exposure was ~ 18 months
- Vedolizumab:
  - 3,326 subjects exposed
    - Overall mean duration of exposure 14.9 months/16.4 infusions
  - 2,830 part of the RAMP program
    - mean exposure 17.4 months/19.1 vedolizumab infusions
- The size of the vedolizumab safety database and duration of exposure is roughly similar to natalizumab when the first 3 cases of PML were observed

Estimating PML Risk: "The Rule of 3"

- Point estimate of PML incidence rate: 0 cases per 1,000 patients
- The "Rule of 3" provides a worst possible scenario by calculating the upper bound of the incidence rate
  - When zero events are observed, the 95% confidence upper bound for the true event rate is approximately 3/n, where n is the total sample size
  - If no events are observed in a study with 3,000, the true event rate will be lower than 3/3,000 (1 in a 1,000) with 95% confidence

- 95% upper bound of PML incidence rate for vedolizumab was 0.9 and 1.1 in 1,000 patients exposed and with RAMP assessments, respectively

Does not consider duration of treatment

PML Incidence Rates and Risk Estimates

Duration of Exposure	Point Estimate Natalizumab PML Rates[a]	Upper Bound 95% CI Rate for 0 Observed Vedolizumab PML Events (27June 2013 data cutoff)
≥ 12 months	3.15/1000	2.11/1000
≥ 18 months	3.40/1000	2.57/1000
≥ 24 months	3.76/1000	3.30/1000

Modified from Table 3.1 from Submission, Progressive Multifocal Leukoencephalopathy Risk Assessment for Vedolizumab

[a] Source: Bloomgren, et al. 2012

Applicant Provided Risk Estimates Based on Exposure Stratified by Natalizumab PML Risk Factors

Vedolizumab Exposure	Anti-JCV Antibody Positive	
	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1 – 24 months	0.19	2.13
25 – 48 months	0.42	4.02

Total Expected Cases of PML:	6.75
Probability of Observing Zero Cases:	0.0012

Modified from Table 3.5 from Submission, Progressive Multifocal Leukoencephalopathy Risk Assessment for Vedolizumab

Limitations to PML risk assessment

- Direct comparison cannot be made without head-to-head trials
- Different patient populations
- Different data sources for risk estimates/assessments
- Underlying assumptions

PML, Summary and Discussion

- 0 cases of PML observed in ~3,000 patients exposed to slightly less than 18 months of vedolizumab.
- Cannot conclude that PML risk for vedolizumab is lower than for natalizumab
  - Limitations to direct comparisons
- Rule of three estimates the worst case scenario of the true rate:
  - less than 0.9 – 1.1 cases per 1000 (considering all exposure)
  - less than 3.31 cases per 1,000 exposed for ≥ 24 months

What level of risk of PML are we comfortable with in the setting of moderately to severely active UC or CD?

Risk Management Considerations

Vedolizumab

BLA 125476/BLA125507

Gastrointestinal Drugs Advisory Committee (GIDAC) & Drug Safety and Risk Management Advisory Committee (DSaRM) Advisory Committee Meeting

December 9, 2013

George Neyarapally, Pharm.D., M.P.H.
Risk Management Analyst
Division of Risk Management
Office of Medication Error Prevention and Risk Management, OSE/CDER

Overview

- Benefit-risk assessment
- Potential risk of PML
- Risk management approaches
- REMS background
- Discussion of risk management strategies

Benefit-Risk Assessment Framework

- Analysis of condition
- Current treatment options
- Benefit
- Risk
- Risk Management[1]

1. FDA. Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making. Draft PDUFA V Implementation Plan - February 2013, Fiscal Years 2013-2013. February 2013.

Vedolizumab: Risk of PML

- Potential risk of progressive multifocal leukoencephalopathy (PML)
  - Upper bound of risk of PML: 3.31 cases/1,000 patients based on 906 patients exposed for ≥ 24 months

Risk Management Approaches

- Risk mitigation
  - Labeling +/- Medication Guide
  - Risk Evaluation and Mitigation Strategies (REMS)
- Risk assessment
  - Routine or enhanced pharmacovigilance
  - Registries
  - Pharmacoepidemiologic studies
  - Clinical trials
  - Other

Risk Evaluation and Mitigation Strategy (REMS)

- A risk management plan that utilizes strategies beyond labeling to ensure that the benefits of a drug outweigh the risks
- Designed to achieve specific goals to mitigate risks associated with use of a drug
- The Agency has authority to require a REMS pre-approval or post-approval[1]

1. The FDA Amendments Act of 2007 authorized FDA to require a REMS.

Elements of REMS

A REMS may include:

- Medication Guide or patient package insert
- Communication plan
- Elements to Assure Safe Use (ETASU)
- Implementation System

A REMS must include:

- Timetable for submission of assessments for New Drug Application (NDA) or Biological License Application (BLA) products

Types of ETASU

A. Certification and training of prescribers

B. Certification of dispensers

C. Requirement that a drug be dispensed to patients only in certain health care settings

D. Documentation of safe-use condition prior to dispensing a drug

E. Requirement for certain monitoring of a patient to receive a drug

F. Requirement that a patient enroll in a registry

REMS Considerations

- FDAAA-mandated REMS consideration factors
  - Estimated size of the population likely to use the drug
  - Seriousness of the disease/condition to be treated
  - Expected benefit of the drug with respect to such disease/condition
  - Expected/actual duration of treatment
  - Seriousness of any known/potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
  - Whether a drug is a new molecular entity

Considerations for ETASU REMS

- A product can be approved only if an ETASU is put in place to mitigate the risk
- ETASU must be commensurate with specific serious risk(s) listed in the labeling
- ETASU cannot be unduly burdensome on patient access to drug, considering in particular, patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing health care
- To minimize the burden on the healthcare delivery system, ETASU must, to the extent practicable, conform with elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs

To optimize the Risk Management Strategy for the Risk of PML

- Consider *uncertainty* about potential risk of PML
  - "Regulatory paradox…tension between aversion to uncertainty and willingness to accept certain unknowns about a drug before approval"[1]
- The selection of the evidentiary threshold to rule out the potential risk of PML with a reasonable level of certainty will drive the risk management strategy

1. Zineh, I and Woodcock, J. Clinical pharmacology and the catalysis of regulatory science: opportunities for the advancement of drug development and evaluation. Clin Pharmacol Ther. 2013;93(6):515-25.

FDA's Proposed Risk Management Strategy

- If the threshold to rule of the potential risk of PML with reasonable certainty has been met
  - Labeling
  - Enhanced pharmacovigilance
  - Completion of ongoing long term extension study
  - Consider requiring a voluntary long term observational safety study to assess the long term safety of vedolizumab, including characterizing the risks of PML, other infections, malignancies, and other safety issues
  - No REMS

FDA's Proposed Risk Management Strategy

- If the threshold to rule of the potential risk of PML with reasonable certainty has **NOT** been met
- Same as strategy as previous slide + an **ETASU REMS**

FDA's Proposed REMS Elements

- Medication Guide
  - To be provided prior to each infusion
- ETASU
  - Prescriber certification
  - Pharmacy and infusion site certification
  - Safe use conditions
    - A pre-infusion checklist must be completed before each infusion
    - A reauthorization questionnaire must be submitted periodically, along with a questionnaire 6 months after discontinuation

* Modeled on Tysabri REMS program and Vedolizumab RAMP program

Rationale for FDA's Proposed Risk Management Strategic Options

- If the threshold to rule out the potential risk of PML with reasonable certainty has been met
  - FDA's strategy would focus on assessing the long term safety of vedolizumab
- If the threshold to rule out the potential risk of PML with reasonable certainty has not been met
  - FDA's strategy would assure that: (1) patients and prescribers are informed about potential serious risk, (2) patients are periodically monitored to facilitate early PML detection, and (3) robust PML surveillance is effectuated; and
  - Minimize undue burden by re-assessing the need for a REMS in the postmarket setting once the threshold has been met

Applicant's Proposed Risk Management Strategy

- Labeling
- Enhanced pharmacovigilance for suspected cases of PML
- Completion of ongoing long term safety extension study
- Voluntary long term observational safety study

Applicant's Proposed Risk Management Strategy …cont.

- REMS with a Medication Guide and Communication Plan
- Goal: To inform health care professionals (HCPs) and patients regarding the "theoretical" risk of PML
- Communication Plan
  - Dear Healthcare Professional Letter
    - Gastroenterologists; other HCPs prescribing biologics for Crohn's Disease (CD) and Ulcerative Colitis (UC)
  - Dear Professional Society Letter
    - Gastroenterology societies, CD and UC society, nursing societies
  - HCP Brochure
  - REMS Program Website

Assessment of Applicant's Proposed Risk Management Strategy

- If the threshold to rule out the potential risk of PML has been met
  - The Applicant's proposed REMS could cause confusion because the risk of PML has been ruled out with reasonable certainty
- If the threshold to rule out the potential risk of PML has not been met
  - The Applicant's approach will not assure adequate patient monitoring and robust PML surveillance

Question for the Advisory Committee

- If vedolizumab is approved for the proposed UC or CD indication, what post-market risk mitigation strategies beyond labeling, if any, would be needed to ensure that the product's benefits outweigh its risks?