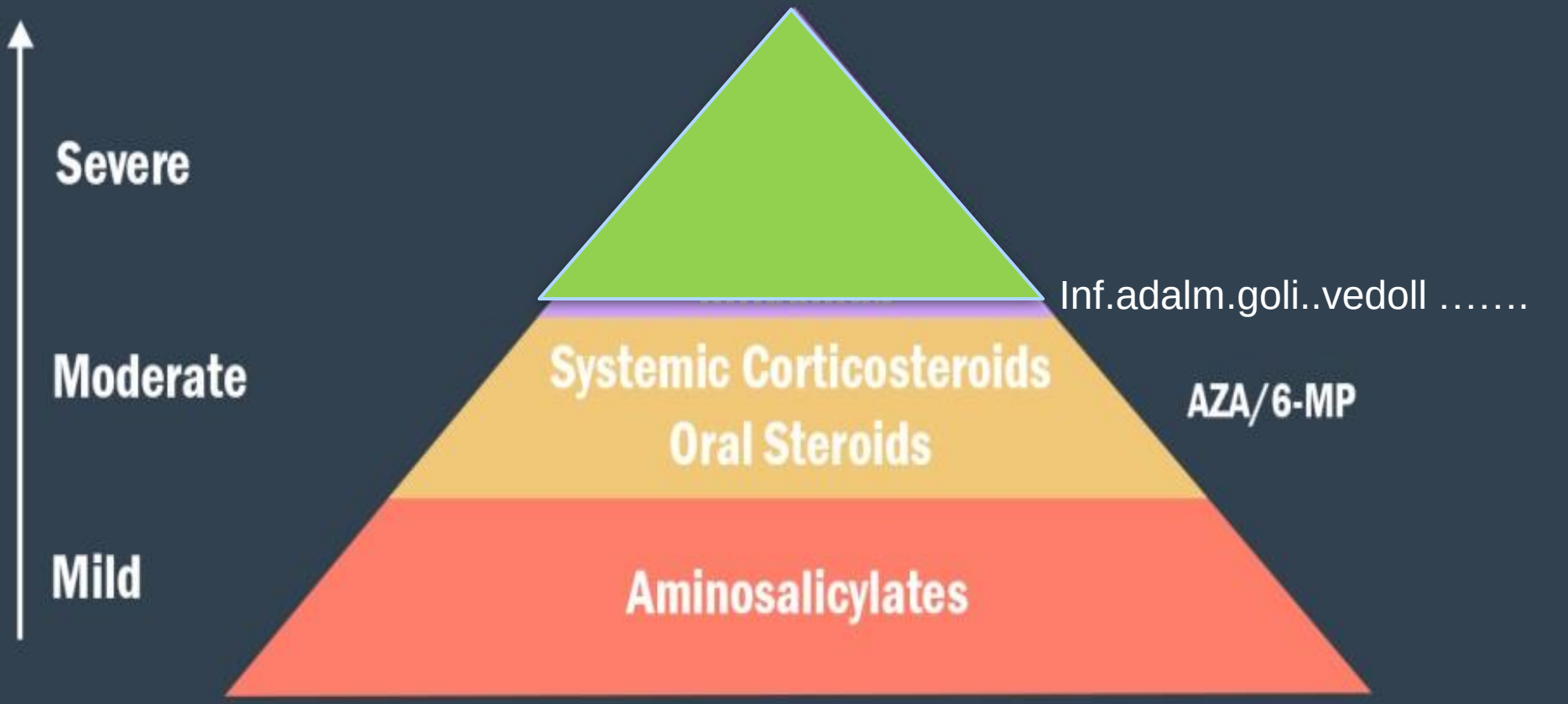
Simponi® in UC
The PURSUIT Trial

Dr. **KHALED CHIHA**
Head of G.I department
Headmaster of internal medicine
Damascus hospital
18-10-2018

Goals of Therapy for UC

- Inducing remission
- Maintaining remission
- Restoring and maintaining nutrition
- Maintaining paitient's quality of life
- Surgical intervention (selection of optimal time for surgery)

Therapeutic Pyramid for avtive UC



Biological Agents

INFLIXIMAB
ANTI TNF -α

ADALIMUMAB
ANTI TNF -α

GOLIMUMAB
ANTI TNF -α

ORAL TOFACITINIB
JANUS KINASE 3
INHIBITOR

VEDOLIZUMAB
α4β7 INTEGRIN
BLOCKER

Golimumab

- A novel, completely human IgG1 anti- TNF-α antagonist – administered subcutaneously Approved for use in RA, psoriatic arthritis, and AS patients.

- Greater affinity than those of INFLIXIMAB and ADALIMUMAB (2.4-fold and 7.1-fold, respectively) , similar to that of ETANERCEPT .

- Two large, double-blinded RCTs have been conducted :

THE PROGRAM OF UC RESEARCH STUDIES UTILIZING AN INVESTIGATION TREATMENT (PURSUIT)

which was divided into

SUBCUTANEOUS (PURSUIT- SC)

MAINTENANCE PHASES (PURSUIT-M)

Simponi is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Outline

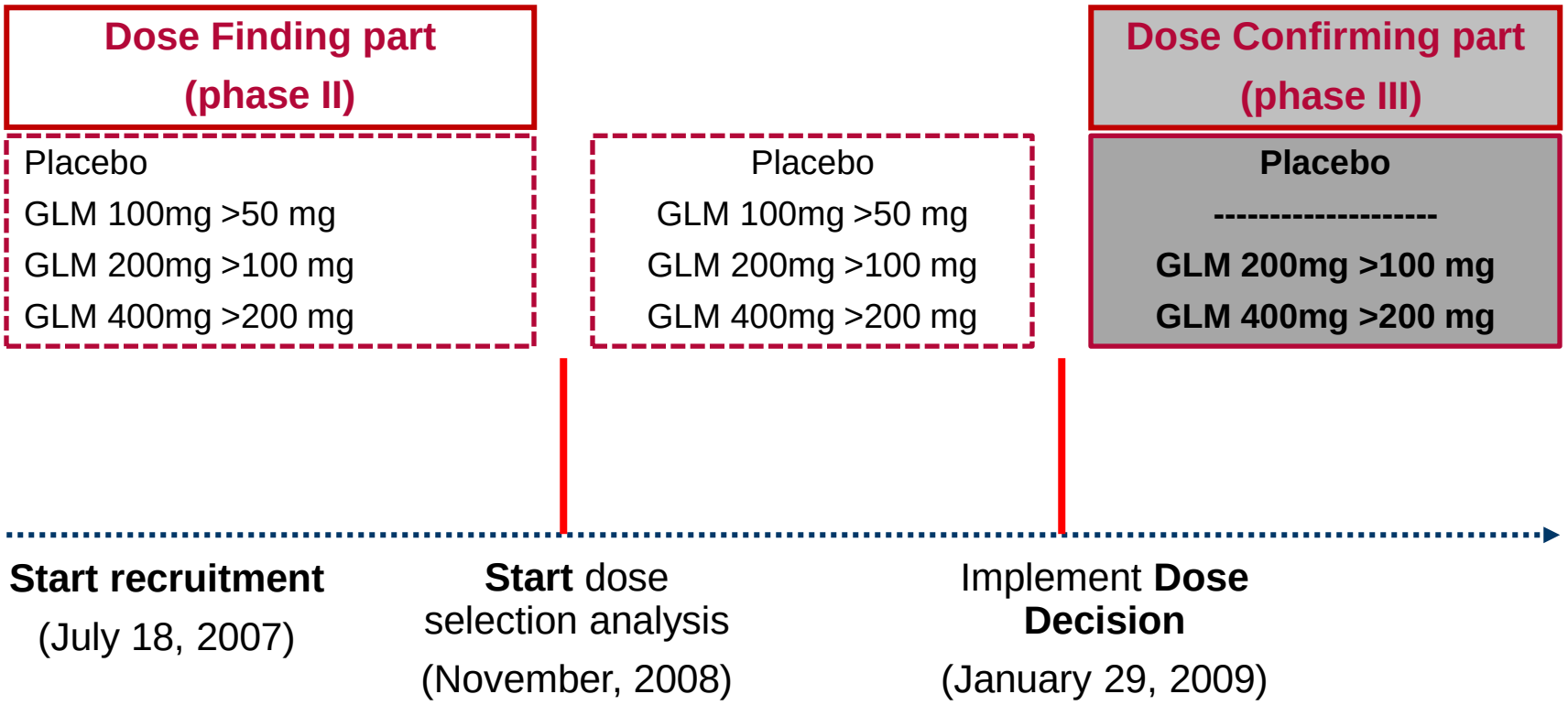
- **Induction Study (GLM SC induction)**
  - Study endpoints
  - Trial design
  - Main results
- **Maintenance Study (GLM SC maintenance)**
  - Study endpoints
  - Trial design
  - Main results

Studies Endpoints

- **Primary endpoint**
  - Proportion of subjects in clinical response at Week 6
- **Major secondary efficacy endpoints**
  - Proportions of subjects in clinical remission at Week 6
  - Proportion of subjects with mucosal healing at Week 6
  - Change from baseline in the IBDQ scores at Week 6
- **Other secondary efficacy endpoints**
  - Proportion of patients with normal or inactive mucosal disease (complete mucosal healing) at Week 6
  - Partial Mayo scores through week 6

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Study Design



SC doses administered at week 0 and 2
PE assessed at week 6

Target population for efficacy analysis: **only** subjects randomized after dose decision implementation

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Baseline Characteristics

		Golimumab			
	Placebo	100/50mg	200/100mg	400/200mg	Total
Subjects randomized	331	72	331	331	1065
Sex, Male	52.9%	55.6%	54.4%	60.7%	56.0%
Race, Caucasian	79.5%	90.3%	81.9%	83.1%	82.1%
Median age (years)	37.0	40.0	39.0	38.0	38.0
Median weight (kg)	70.0	75.0	72.3	72.8	72.0
Median UC disease duration (yrs)	4.0	4.1	4.5	4.3	4.2
Extensive disease	43.0%	40.3%	41.7%	42.3%	42.2%
Median Mayo score	8.0	8.0	9.0	8.0	8.0
Median CRP (mg/L)	4.5	4.3	4.9	4.9	4.8

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Baseline UC Medication

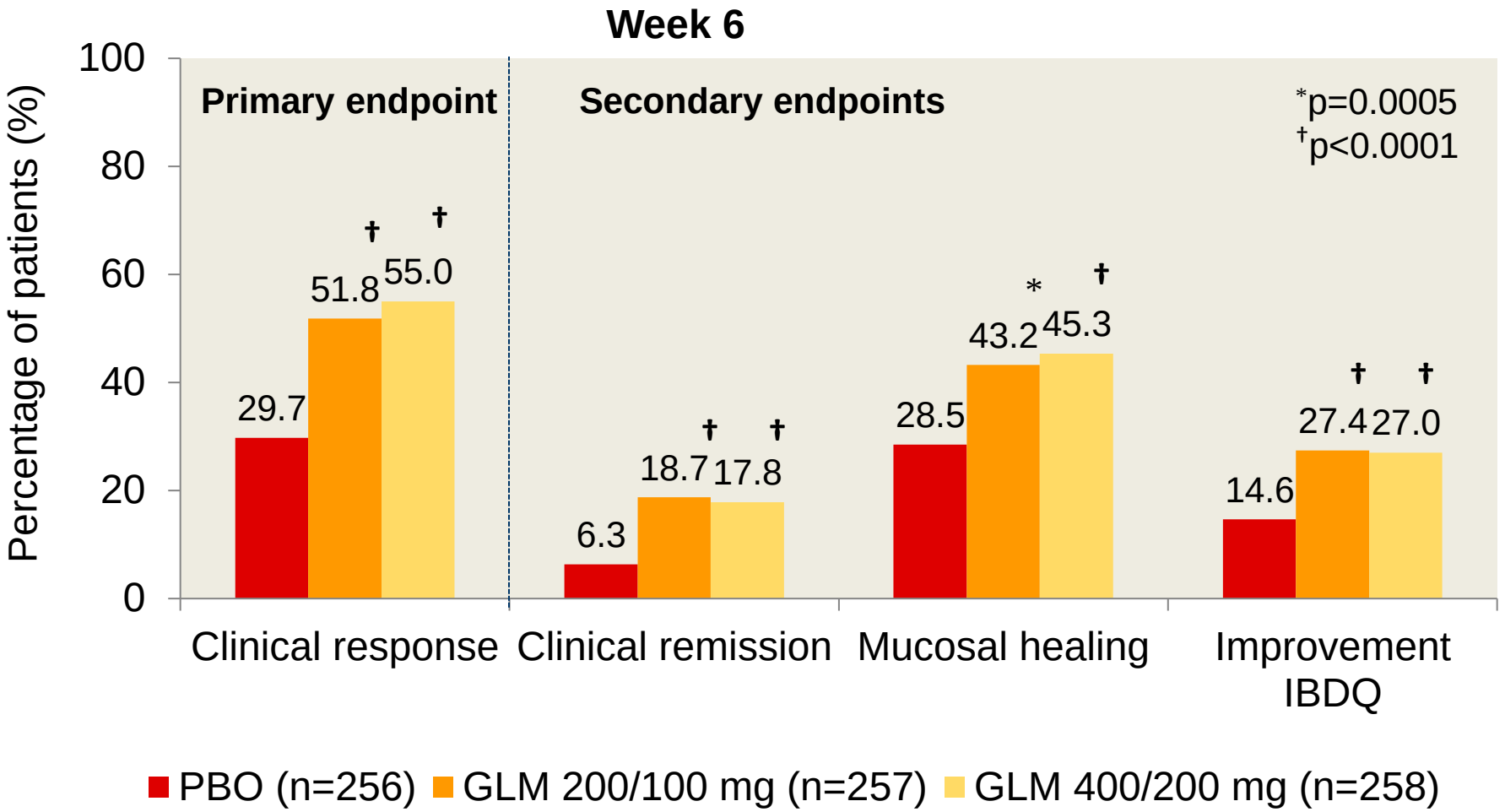
		Golimumab			
	Placebo	100/50mg	200/100mg	400/200mg	Total
Subjects randomized	331	72	331	331	1065
Any UC medication	93.7%	97.2%	91.2%	93.1%	93.0%
Corticosteroids	40.5%	48.6%	42.9%	43.8%	42.8%
Budesonide	2.4%	2.8%	1.8%	2.7%	2.3%
Immunomodulatory drugs	32.0%	37.5%	31.7%	32.3%	32.4%
Aminosalicylates	83.4%	81.9%	81.6%	80.7%	81.9%

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Primary and major secondary efficacy analyses

Main Results PURSUIT SC Induction

Subjects randomized after dose selection



Clinical response: Defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1
Clinical remission: Defined as Mayo score ≤ 2 points, with no individual subscore >1
Mucosal healing: Defined as a Mayo endoscopy score of 0 (normal) or 1 (mild)

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, Pages 85–95, January 2014

Summary of Efficacy

- The primary endpoint of clinical response at Week 6, for both groups: GLM SC 200/100 and 400/200 mg, was:
  - Highly statistically significant ($p<0.0001$)
  - Consistent across predefined sub-groups and analysis populations
- The major secondary endpoints of clinical remission, mucosal healing and IBDQ at Week 6 were:
  - Highly statistically significant ($p<0.0001$)
  - Consistent across analysis populations

Adapted from Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, Pages 85–95, January 2014

Safety

Summary of Key Safety Findings through Week 6

		Golimumab				
	Placebo	100/50 mg	200/100 mg	400/200 mg	Combined	All GLM
Subjects treated	330	71	331	332	663	734
Avg duration of follow-up (weeks)	6.05	5.95	6.08	6.09	6.09	6.07
Avg exposure (number of administrations)	1.98	1.97	1.99	1.99	1.99	1.99
Subjects who discontinued study agent because of 1 or more adverse events	3 (0.9%)	2 (2.8%)	1 (0.3%)	1 (0.3%)	2(0.3%)	4 (0.5%)
Subjects with 1 or more:						
Adverse events	126 (38.2%)	34 (47.9%)	124 (37.5%)	129 (38.9%)	253 (38.2%)	287 (39.1%)
Serious adverse events	**20 (6.1%)**	2 (2.8%)	9 (2.7%)	11 (3.3%)	**20 (3.0%)**	22 (3.0%)
Infections	40 (12.1%)	8 (11.3%)	39 (11.8%)	41 (12.3%)	80 (12.10%)	88 (12.0%)
Serious infections	**6 (1.8%)**	0 (0.0%)	1 (0.3%)	3 (0.9%)	**4 (0.6%)**	4 (0.5%)
Neoplasms (malignant)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)	1 (0.1%)
Injection site reactions	**5 (1.5%)**	4 (5.6%)	11 (3.3%)	10 (3.0%)	**21 (3.2%)**	25 (3.4%)

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

AEs of Special Interest

- **One death** due to peritonitis and sepsis following multiple surgeries for an ischiorectal abscess: 400/200 mg
- **Two malignancies**, neither of them attributable to Golimumab
  - Thyroid cancer: placebo
  - Colon cancer/carcinoma in situ identified in screening biopsies: 400/200 mg
- Non-serious **opportunistic infections** (OIs), cases of active TB or cases of possible anaphylaxis or delayed type hypersensitivity through Week 6
  - Two non-serious OIs, (1) oesophageal candidiasis; 400/200 mg and (1) cytomegalovirus (CMV); placebo
- Through final safety visit: 2 additional cases of CMV; 100/50 mg (serious) and 200/100 mg
- **Demyelination**; 1 case in 400/200 mg reported after Week 6 (subject randomized to placebo maintenance)
  - High enhancing lesion at MRI identified after complaint of right sided facial weakness and numbness.
  - Asymptomatic at follow-up a year later, no signs of multiple sclerosis

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Summary of Safety

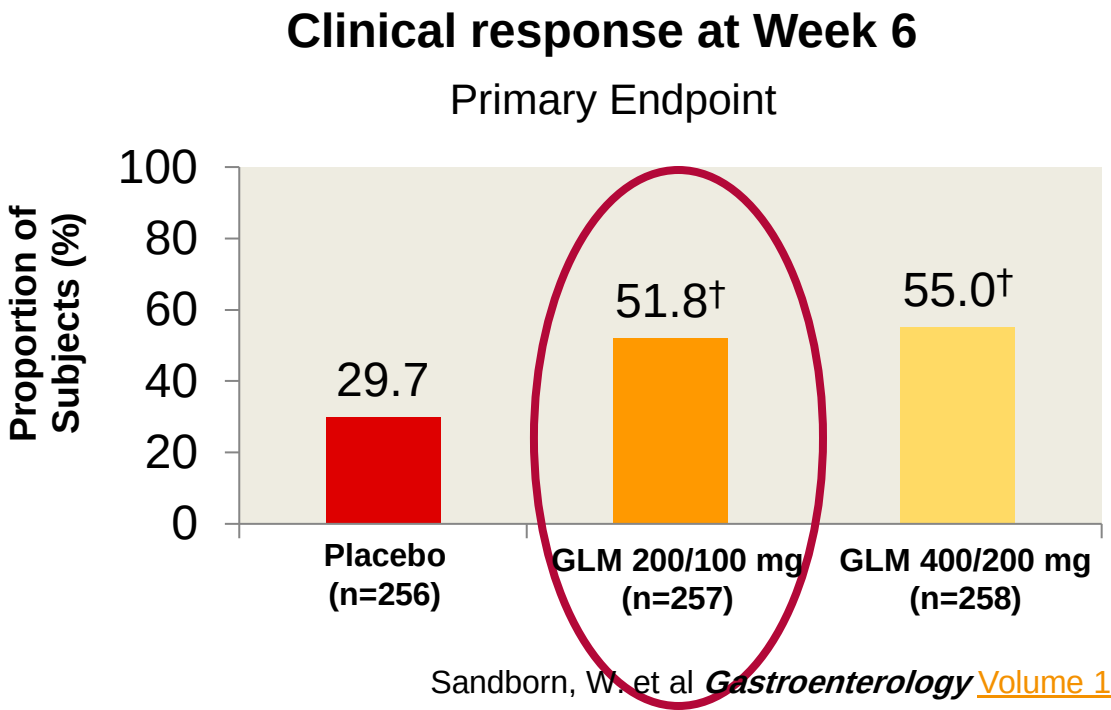
GLM was generally well tolerated in this population of adult subjects with moderately to severely active UC. The safety profile was similar to that observed with other anti-TNF therapies as well as with that of GLM in other indications

- Overall rates of AEs similar across treatment groups
- SAEs uncommon
  - Most frequent reported SAE was (worsening of) ulcerative colitis
- Rates of infection similar across treatment groups
  - More SAEs of infection reported for PBO vs. GLM treatment groups
- Injection site reactions uncommon and not serious
  - Injection site erythema was the most frequently reported reaction across GLM treatment groups

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Dosing Recommendation

- Based on overall safety and efficacy considerations, the following dosing strategy will be recommended:
  - Induction doses of GLM 200 mg at Week 0 followed by GLM 100 mg at Week 2



Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Outline

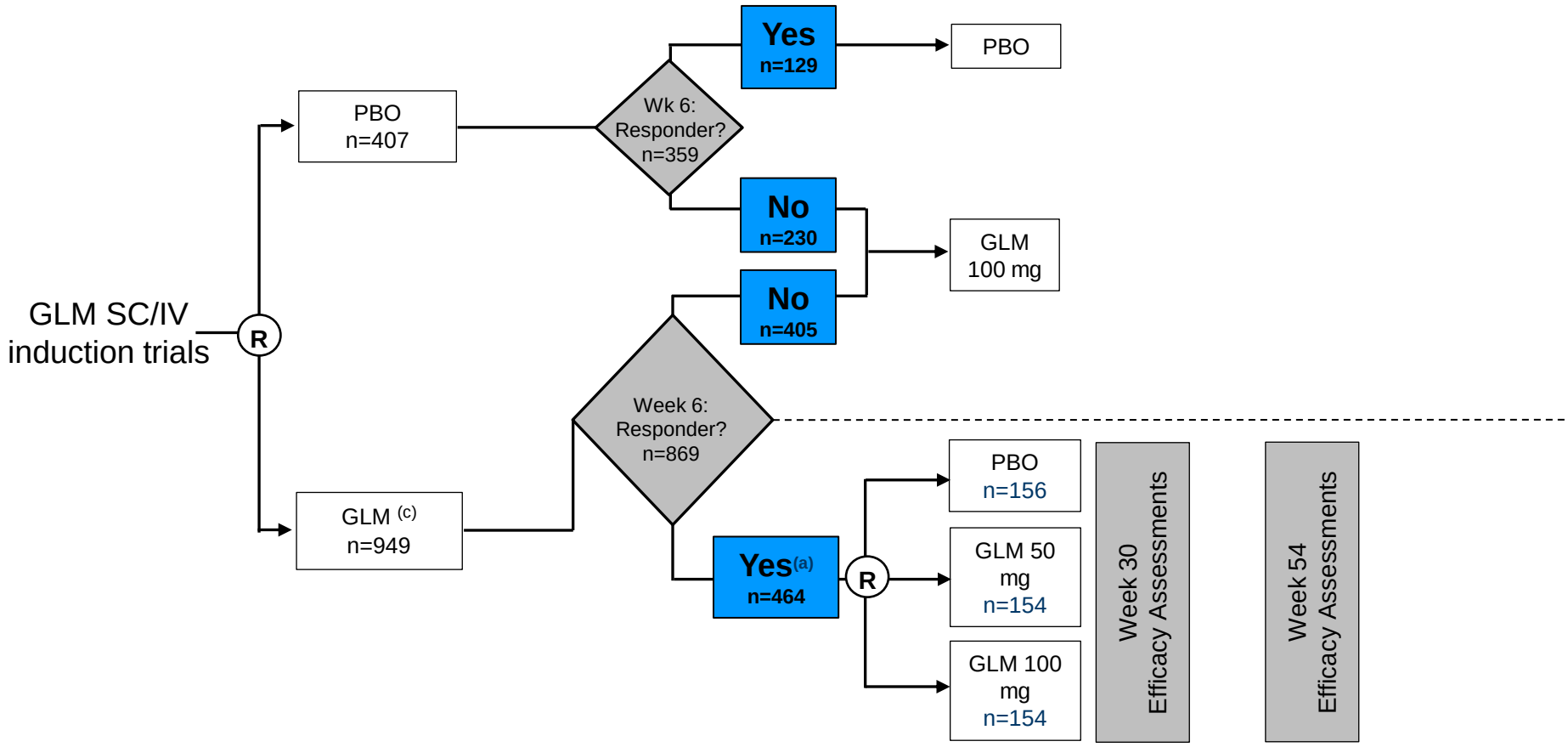
- **Induction Studies (GLM SC induction)**
  - Study endpoints
  - Trial design
  - Main results
- **Maintenance Study (GLM SC maintenance)**
  - Study endpoints
  - Trial design
  - Main results

Study Endpoints

- **Primary Endpoint:**
  - Clinical response through Wk 54: continuous clinical response among GLM induction responders
- **Major Secondary Endpoints:**
  - Clinical remission at both Wks 30 and 54 among GLM induction responders
  - Mucosal healing at both Wks 30 and 54 among GLM induction responders
  - Clinical remission at both Wks 30 and 54 among subjects in clinical remission at Wk 0
  - CS-free clinical remission at Wk 54 among subjects receiving concomitant CSs at Wk 0 of maintenance study (Wk 6 induction studies)

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Study Design PURSUIT



a. ~ 78% of patients randomized at maintenance came from SC induction trial, since IV induction trial was prematurely terminated
b. Week 54 maintenance = Week 60 from induction
c. Various tested doses

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

* required by protocol for patients in response

Full Mayo Score (range: 0-12)

Stool frequency (patient diary)

0 = Normal number stools for this patient

1 = 1-2 stools more than normal

2 = 3-4 stools more than normal

3 = 5 or more stools than normal

Rectal bleeding (patient diary)

0 = No blood seen

1 = Streaks of blood with stool less than half the time

2 = Obvious blood with stool most of the time

3 = Blood alone passed

Findings of endoscopy

0 = Normal or inactive disease

1 = Mild disease

2 = Moderate disease

3 = Severe disease

Physician's global assessment

0 = Normal

1 = Mild disease

2 = Moderate disease

3 = Severe disease

Rutgeerts P et al. N Engl J Med 2005;353(23):2462-76.

Partial Mayo Score (range: 0-9)

Stool frequency (patient diary)

0 = Normal number stools for this patient

1 = 1-2 stools more than normal

2 = 3-4 stools more than normal

3 = 5 or more stools than normal

Findings of endoscopy

0 = Normal or inactive disease

1 = Mild disease

2 = Moderate disease

3 = Severe disease

Rectal bleeding (patient diary)

0 = No blood seen

1 = Streaks of blood with stool less than half the time

2 = Obvious blood with stool most of the time

3 = Blood alone passed

Physician's global assessment

0 = Normal

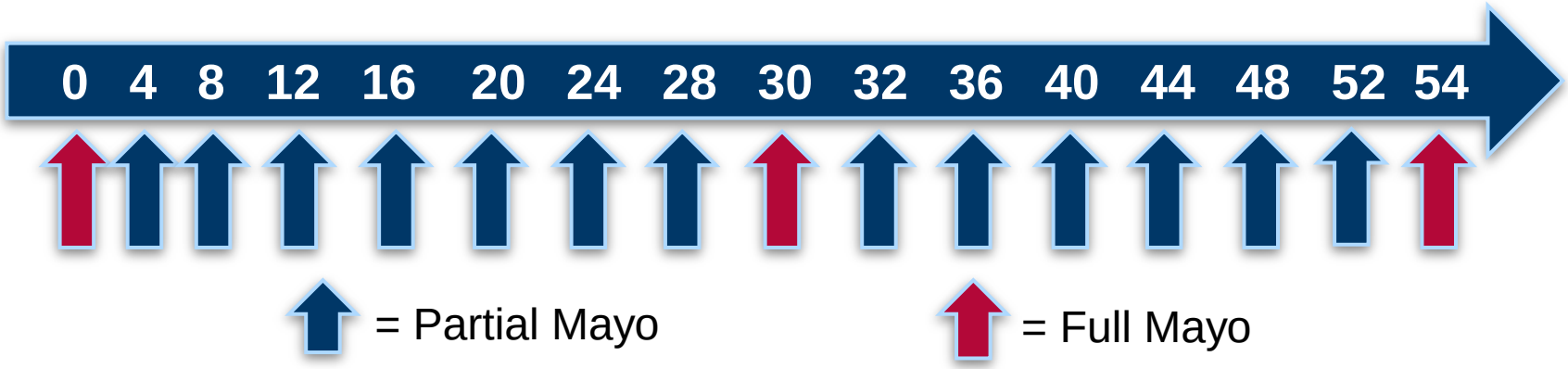
1 = Mild disease

2 = Moderate disease

3 = Severe disease

Rutgeerts P et al. N Engl J Med 2005;353(23):2462-76.

Assessment of Response



- PURSUIT Maintenance patients were assessed every 4 weeks (15 times) to ensure their response was maintained over time

- Subjects who met the criteria for a clinical flare* (compared to baseline at maintenance) received an endoscopy to confirm loss of response** (compared to baseline at induction)

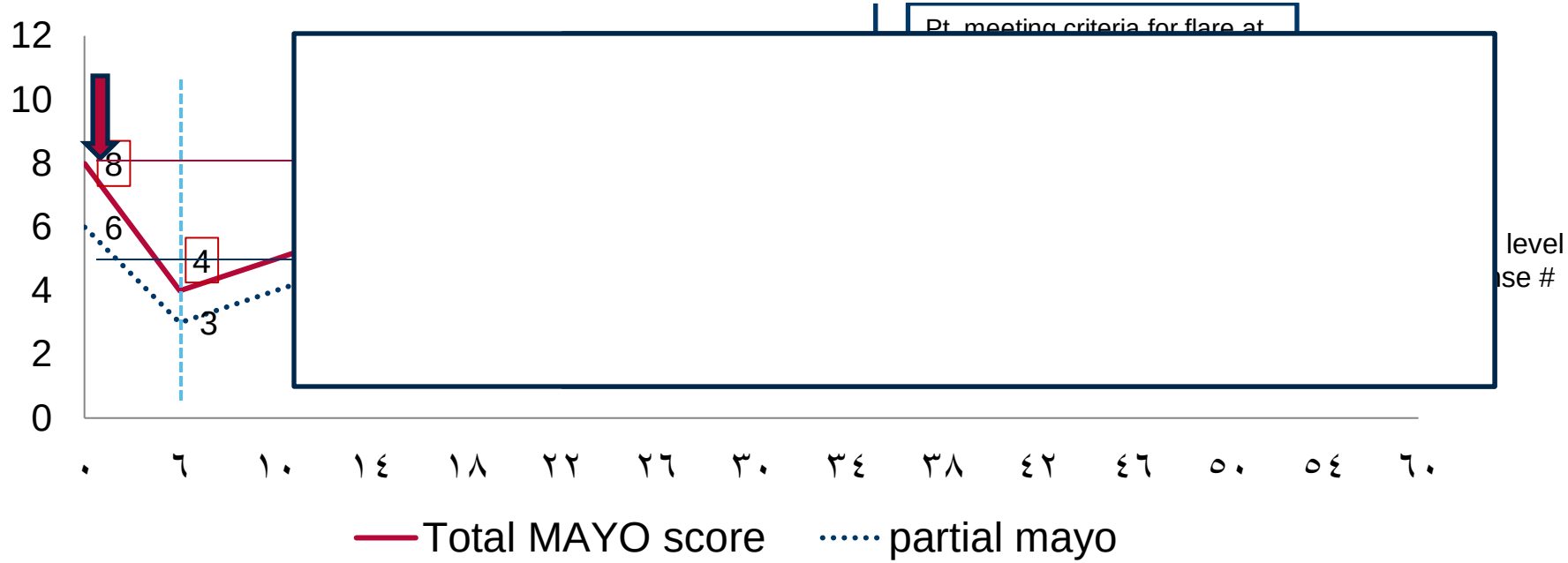
Loss of response at any assessment = Treatment failure

***Clinical flare defined as an increase from baseline (Week 0 of maintenance study) in the partial Mayo score of at least 2 points with an absolute partial Mayo score of ≥ 4, OR an absolute partial Mayo score ≥ 7 points**
****Minimum level of response: Decrease in the Mayo score by ≥30% & ≥3 points and a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1**

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Example of assessment of patient response: PURSUIT criteria

Illustrative only: graph is not based in real patient data



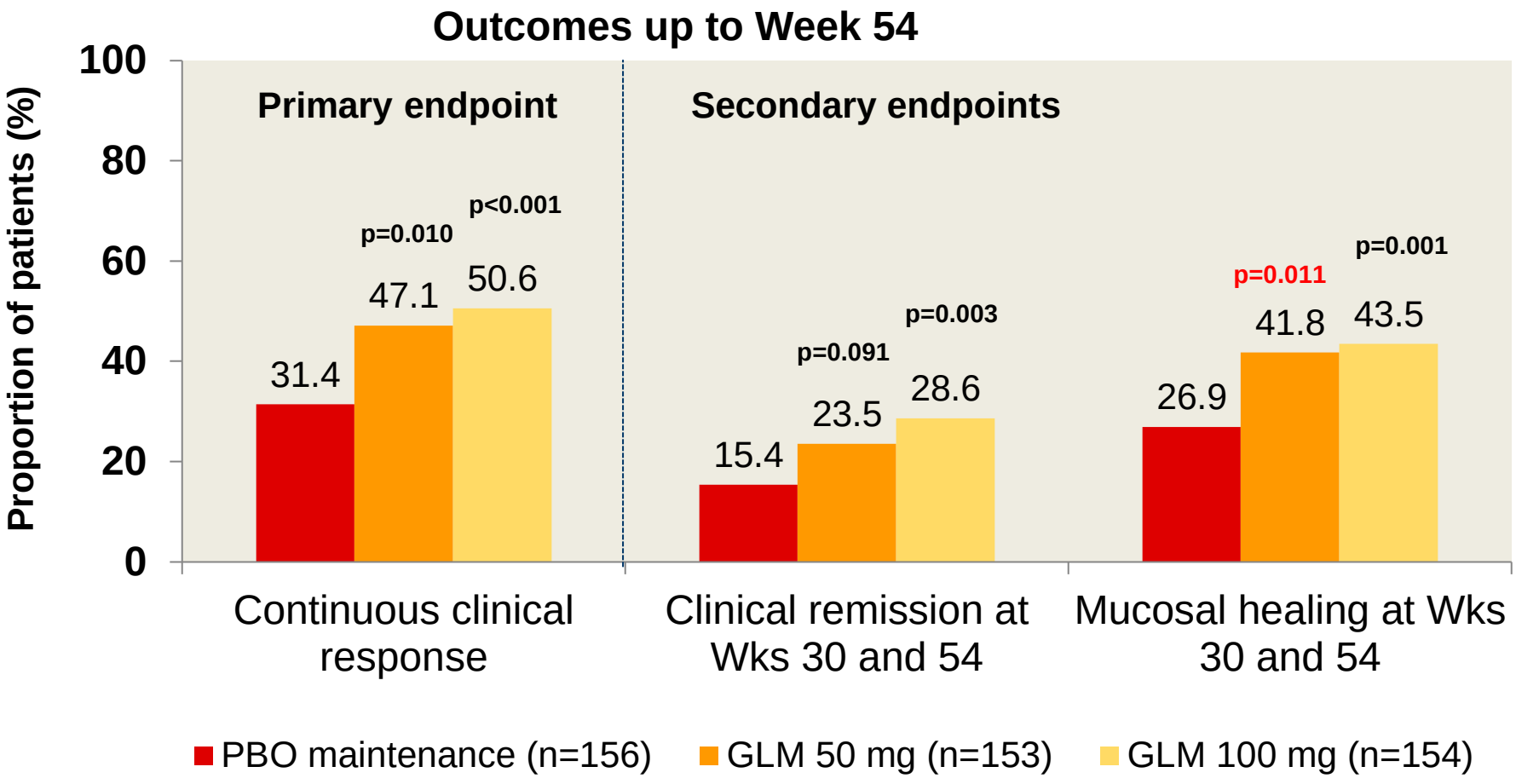
Definitions of flare in PURSUIT:
An increase from baseline (Week 0 of maintenance study) in the partial Mayo score of at least 2 points with an absolute partial Mayo score of ≥4, OR an absolute partial Mayo score ≥7 points
Loss of response is confirmed by Full Mayo Score

 # Minimum level of response: Decrease in the Mayo score by ≥30% & ≥3 points and a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1

Primary and major secondary efficacy analyses

Main Results PURSUIT SC maintenance

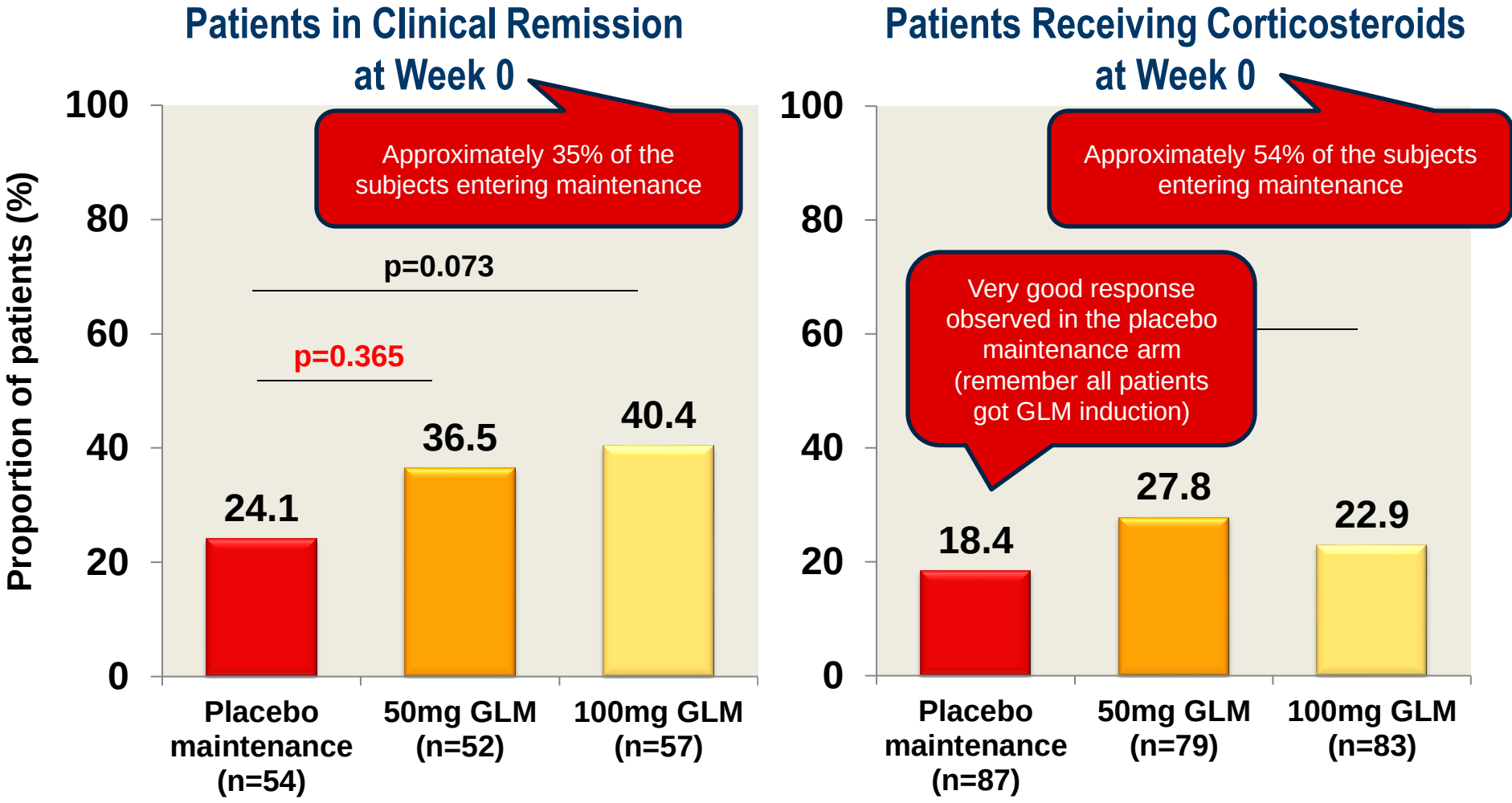
In GLM induction responders



p-values in red are nominal p-values

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

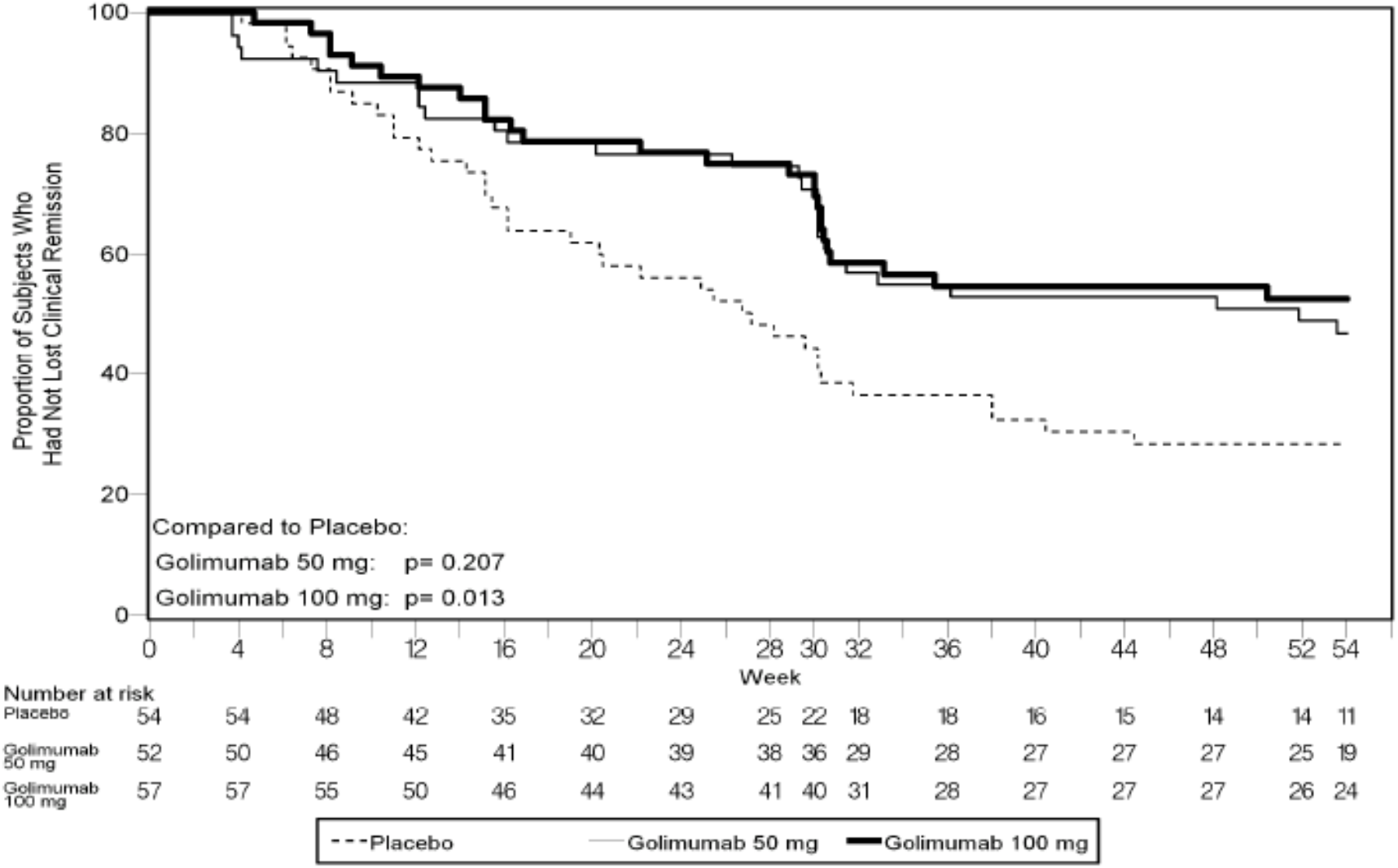
Maintenance of Clinical Remission at Both Wks 30 and 54 and Corticosteroid-Free Clinical Remission at Wk 54: Randomized Patients



p-values in red are nominal p-values

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

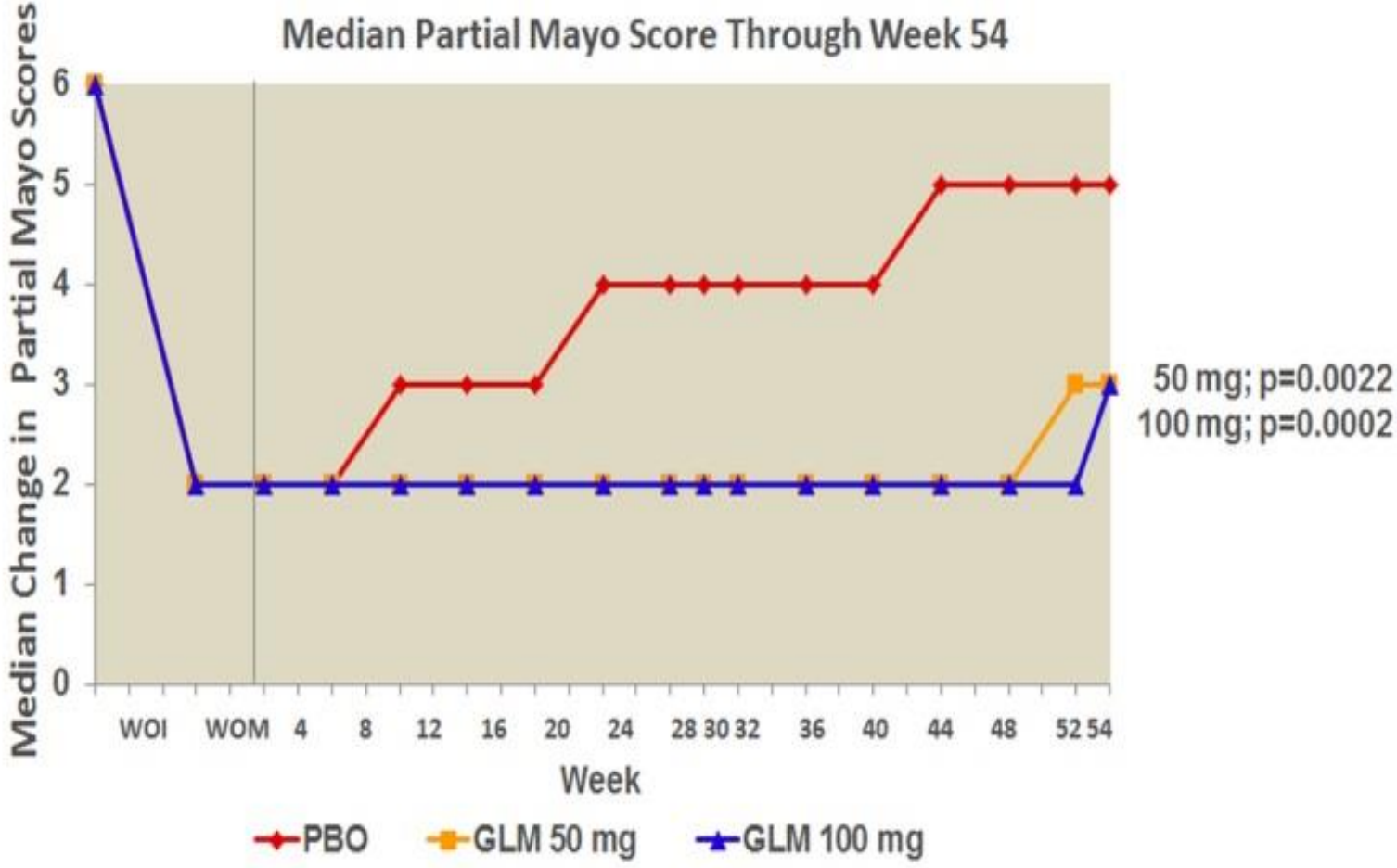
Kaplan-Meier Analysis*: Time to Loss of Clinical Remission Among Subjects in Clinical Remission at Wk 0



* Post hoc analysis

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Change in Partial Mayo Score Through Week 54



WOI: 1st week of induction phase
WOM: 1st week of maintenance phase

Safety

Summary of Key Safety Findings of Randomized Subjects

[a] Includes data up to the time of dose adjustment for those who increased dose

	Placebo Maintenance [a,b]	Golimumab 50 mg [a]	Golimumab 100 mg [a]
Subjects randomized	156	154	154
Avg duration of follow-up (weeks)	32.7	44.3	46.3
Avg exposure (number of administrations)	8.2	11.1	11.3
Subjects who discontinued study agent because of 1 or more adverse events	10 (6.4%)	8 (5.2%)	14 (9.1%)
Subjects who died	0 (0.0%)	0 (0.0%)	1 (0.6%)
Subjects with 1 or more:			
Adverse events	103 (66.0%)	112 (72.7%)	113 (73.4%)
Serious adverse events	12 (7.7%)	13 (8.4%)	22 (14.3%)
Infections	44 (28.2%)	60 (39.0%)	60 (39.0%)
Serious Infections	3 (1.9%)	5 (3.2%)	5 (3.2%)
Neoplasms (malignant)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Injection site reactions	3 (1.9%)	3 (1.9%)	11 (7.1%)

[B] Subjects who were in clinical response to GLM induction dosing and were randomized to PBO on entry into this maintenance study

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Summary of Key Safety Findings Per 100 PY's of FU of Randomized Subjects

[a] Includes data up to the time of dose adjustment for those who increased dose

	Placebo Maintenance [a,b]	Golimumab 50 mg [a]	Golimumab 100 mg [a]
Subjects randomized	156	154	154
Avg duration of follow-up (weeks)	32.7	44.3	46.3
Avg exposure (number of administrations)	8.2	11.1	11.3
Number of specified events per hundred subject years of follow-up			
Adverse events	211.22	187.16	172.68
Serious adverse events	12.62	10.41	17.09
Infections	55.09	61.06	60.39
Serious Infections	3.08	3.88	3.73
Adverse events leading to discontinuation of study agent	10.43	6.16	10.44

AE profile similar for all-treated patient analysis

[B] Subjects who were in clinical response to GLM induction dosing and were randomized to PBO on entry into this maintenance study

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

Summary of Safety

- Subcutaneously administered GLM 50 mg and GLM100 mg administered ever 4 weeks through Week 54 were generally well-tolerated

  Among randomized subjects:

  – The proportion of subjects with AE's were similar across the GLM treatment groups but were somewhat higher compared with the placebo group; however, when the safety data were normalized to 100 years of patient follow-up, incidence of AE's was comparable across treatment groups

  – Similar trends were observed for infections, serious infections and AE's leading to discontinuation of study agent

  – The proportion of subjects with 1 or more SAEs was higher in the GLM 100 mg group compared with the placebo and GLM 50 mg groups; these differences were less remarkable when corrected for subject years of follow-up

  – UC was the most frequently reported SAE across treatment groups (1.9%, 1.9%, and 3.9% of subjects in the placebo, GLM 50 mg, and GLM 100 mg groups). When summarizing events up to the time of dose adjustment, the incidence of colitis ulcerative was comparable across treatment groups: 1.9%, 0.6%, and 1.9%, respectively.

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

GLM UC Program (PURSUIT): Summary of Induction and Maintenance

- Subcutaneous administration of GLM as both an induction and maintenance therapy to subjects with moderate to severe ulcerative colitis is generally well-tolerated with a safety profile consistent with other anti-TNFs

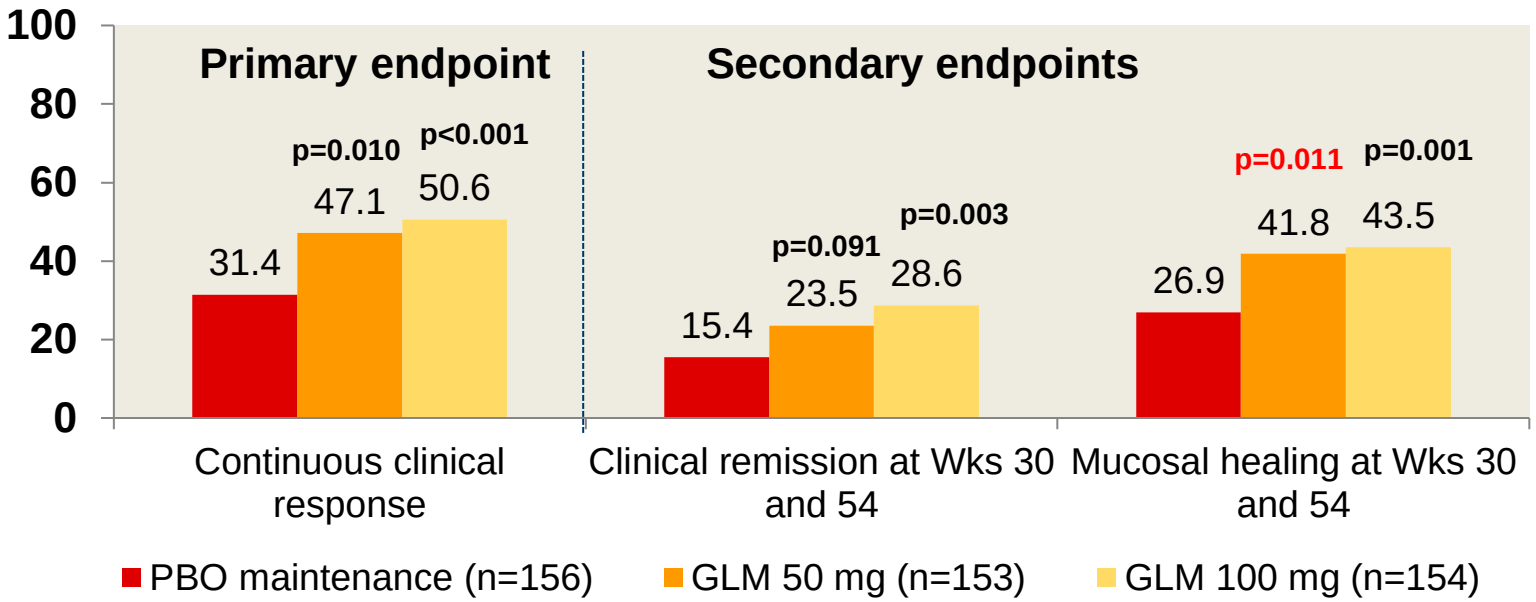
- GLM **induction therapy** administered subcutaneously at 200/100mg and 400/200 mg at Wks 0 and 2:
  - Induces clinical response
  - Induces clinical remission
  - Induces mucosal healing
  - Leads to improved quality of life

- GLM **maintenance therapy** of subjects induced into clinical response with GLM:
  - Maintains clinical response through Wk 54 (GLM 50 and GLM 100 mg)
  - Achieves clinical remission at both Wks 30 and 54 (GLM 100 mg)
  - Achieves mucosal healing at both Wks 30 and 54 (GLM 100 mg)

Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

GLM UC Program (PURSUIT): Dosing Recommendation

- Based on overall safety and efficacy considerations, the following dosing strategy will be recommended:
  - Induction doses of GLM 200 mg at Week 0 followed by GLM 100 mg at Week 2
  - Maintenance dose of GLM 100 mg every 4 weeks from Week 6 onward



Sandborn, W. et al ***Gastroenterology*** Volume 146, Issue 1, 96–109.e1, January 2014

What is Unique About PURSUIT?

- **The PURSUIT-Maintenance study is the first randomized withdrawal study of an anti-TNF in UC**
  - PURSUIT answered a previously unanswered question in UC on whether an induction only regimen is sufficient for maintaining long-term response
- **The PURSUIT-Maintenance study has a stringent definition of long term response**
  - Maintenance of response over a course of 15 prospective efficacy assessments without loss of response at any time
    - ACT 1 → 3 assessments
    - ACT 2 → 2 assessments
    - ULTRA 2 → 2 assessments

Danese et al. Nat Rev Gastroenterol Hepatol 2013;10:511-2.

Simponi Benefit-Risk

For full safety information, please review the full Simponi Summary of Product Characteristics

Simponi Contraindications

Simponi is contraindicated in patients with:

- Hypersensitivity to the active substance (GLM) or the excipients (Sorbitol [E420], L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injection)
- Active TB or other severe infections such as sepsis and opportunistic infections
- Moderate or severe heart failure (NYHA class III/IV)

Before Simponi Treatment

Before initiating Simponi therapy, patients should be screened for:

- Tuberculosis (TB): active and latent disease. Patients with active TB should not be treated with Simponi. If latent TB is detected, appropriate anti-tuberculosis treatment should be started prior to Simponi therapy.
- Hepatitis B virus (HBV) infection. For patients who test positive for HBV, expert physician consultation on the treatment of HBV is recommended. The value of anti-viral therapy to prevent HBV reactivation in patients treated with TNF-blocking therapy is unknown. Hepatitis B virus carrier patients should be closely monitored for HBV reactivation.

During Simponi Treatment

Monitoring should be performed on the following patients treated with Simponi:

- All patients with new infections, including sepsis, opportunistic infections and TB
- Carriers of HBV for signs and symptoms of active Hepatitis B
- Patients who develop new or worsening symptoms of heart failure
- All patients with malignancies and lymphomas, including melanoma
- All patients with anaphylactic or other serious allergic reactions

In case of an event, Simponi should be stopped and appropriate treatment should be started

Malignancies Including Lymphoma

- With the current knowledge, a risk for the development of malignancies and lymphoma in patients treated with TNF-blocking therapy cannot be excluded
- Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering the continuation of treatment in patients who develop a malignancy
- Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocking agents. Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer

Simponi Injections

- After proper training in subcutaneous injection technique, patients may self-inject with Simponi if their physician determines that this is appropriate, with medical follow-up as necessary.
- Patients should be instructed to inject the full amount of Simponi according to the comprehensive instructions for administration provided in the package leaflet.
- If multiple injections are required, the injections should be administered at different sites on the body.

Thank you!
Questions?