Simponi® golimumab

COMPETITOR GUIDE

XELJANZ®
[tofacitinib citrate]
5 mg tablets

SPC SUMMARY

ISSUE RESPONSE GUIDE

HQ-GOL-00001 2/2019

SPC SUMMARY FOR XELJANZ*

THERAPEUTIC INDICATIONS

Rheumatoid arthritis

Xeljanz in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Xeljanz can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

Psoriatic arthritis

Xeljanz in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

Ulcerative colitis

Xeljanz is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Combination with other therapies

Xeljanz has not been studied and its use should be avoided in combination with biologics such as TNF antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, anti-integrins, selective co-stimulation modulators and potent immunosuppressants such as azathioprine, 6-mercaptopurine, ciclosporine and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

Serious infections

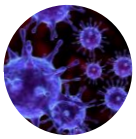
Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving Xeljanz. Xeljanz should not be initiated in patients with active infections, including localised infections. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Xeljanz.

The risks and benefits of treatment should be considered prior to initiating Xeljanz in patients who have been exposed to tuberculosis (TB) or who have resided or travelled in areas of endemic TB. Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of Xeljanz. Patients with latent TB who test positive should be treated with standard antimycobacterial therapy before administering Xeljanz.

*Select information from the SPC for Xeljanz dated November 26, 2018.
The full SPC should be consulted for additional information.

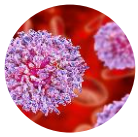
SPC SUMMARY FOR XELJANZ*

SPECIAL WARNINGS AND PRECAUTIONS FOR USE (cont.)



Viral reactivation

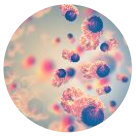
Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with Xeljanz. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with Xeljanz.



Malignancy and lymphoproliferative disorder

The risks and benefits of Xeljanz treatment should be considered prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing Xeljanz in patients who develop a malignancy. The possibility exists for Xeljanz to affect host defences against malignancies.

Lymphomas have been observed in patients treated with Xeljanz. Patients with RA, particularly those with highly active disease, may be at a higher risk (up to several-fold) than the general population for the development of lymphoma.

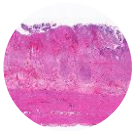


Non-melanoma skin cancer

NMSCs have been reported in patients treated with Xeljanz. The risk of NMSC may be higher in patients treated with Xeljanz 10 mg twice daily than in patients treated with 5 mg twice daily. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Interstitial lung disease

Caution is also recommended in patients with a history of chronic lung disease as they may be more prone to infections. Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with Xeljanz in RA clinical trials and in the post-marketing setting although the role of Janus kinase (JAK) inhibition in these events is not known.



Gastrointestinal perforations

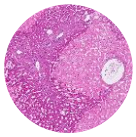
Events of gastrointestinal perforation have been reported in clinical trials although the role of JAK inhibition in these events is not known. Xeljanz should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis, patients with concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory drugs). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Cardiovascular risk

Patients with RA and PsA have an increased risk for cardiovascular disorders. Patients treated with Xeljanz should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care.

SPC SUMMARY FOR XELJANZ*

SPECIAL WARNINGS AND PRECAUTIONS FOR USE (cont.)



Liver enzymes

Treatment with Xeljanz was associated with an increased incidence of liver enzyme elevation in some patients. Caution should be exercised when considering initiation of Xeljanz treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST), particularly when initiated in combination with potentially hepatotoxic medicinal products such as MTX. Following initiation, routine monitoring of liver tests and prompt investigation of the causes of any observed liver enzyme elevations are recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of Xeljanz should be interrupted until this diagnosis has been excluded.

Hypersensitivity

In post-marketing experience, cases of drug hypersensitivity associated with Xeljanz administration have been reported. Allergic reactions included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Xeljanz should be discontinued immediately.

Laboratory parameters

Lymphocytes

Treatment with Xeljanz was associated with an increased incidence of lymphopenia compared to placebo. Lymphocyte counts less than 750 cells/mm^3 were associated with an increased incidence of serious infections. It is not recommended to initiate or continue Xeljanz treatment in patients with a confirmed lymphocyte count less than 750 cells/mm^3. Lymphocytes should be monitored at baseline and every 3 months thereafter.

Neutrophils

Treatment with Xeljanz was associated with an increased incidence of neutropenia (<2,000 cells/mm^3) compared to placebo. It is not recommended to initiate Xeljanz treatment in patients with an ANC <1,000 cells/mm^3. ANC should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter.

Haemoglobin

Treatment with Xeljanz has been associated with decreases in haemoglobin levels. It is not recommended to initiate tofacitinib treatment in patients with a haemoglobin value <9 g/dL. Haemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter.

Lipid Monitoring

Treatment with Xeljanz was associated with increases in lipid parameters such as total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. Assessment of lipid parameters should be performed after 8 weeks following initiation of Xeljanz therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia. Increases in total and LDL cholesterol associated with Xeljanz may be decreased to pretreatment levels with statin therapy.

SPC SUMMARY FOR XELJANZ*

SPECIAL WARNINGS AND PRECAUTIONS FOR USE (cont.)

Vaccinations

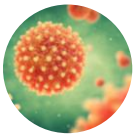
Prior to initiating Xeljanz, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines. It is recommended that live vaccines not be given concurrently with Xeljanz. The decision to use live vaccines prior to Xeljanz treatment should take into account the pre-existing immunosuppression in a given patient.

Vaccination with live vaccines should occur at least 2 weeks but preferably 4 weeks prior to initiation of Xeljanz or in accordance with current vaccination guidelines regarding immunomodulatory medicinal products.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

CONTRAINDICATIONS



- Hypersensitivity to the active substance or to any of its excipients
- Active TB, serious infections such as sepsis, or opportunistic infections
- Severe hepatic impairment
- Pregnancy and lactation

POSOLOGY AND METHOD OF ADMINISTRATION

Rheumatoid arthritis and psoriatic arthritis

The recommended dose is 5 mg administered twice daily.

Dose adjustment

No dose adjustment is required when used in combination with MTX.

Ulcerative colitis

The recommended dose is 10 mg given orally twice daily for induction for 8 weeks and 5 mg given twice daily for maintenance.

UNDESIRABLE EFFECTS

Rheumatoid arthritis

The most common serious adverse reactions were serious infections. The most commonly reported adverse reactions during the first 3 months in controlled clinical trials were headache, upper respiratory tract infections, nasopharyngitis, diarrhoea, nausea, and hypertension.

Psoriatic arthritis

Overall, the safety profile observed in patients with active PsA treated with Xeljanz was consistent with the safety profile observed in patients with RA treated with Xeljanz.

SPC SUMMARY FOR XELJANZ*

UNDESIRABLE EFFECTS (cont.)

Ulcerative colitis

The most commonly reported adverse reactions in patients receiving Xeljanz 10 mg twice daily in the induction studies were headache, nasopharyngitis, nausea, and arthralgia.

SPECIAL POPULATIONS

Elderly

No dose adjustment is required in patients aged 65 years and older. There are limited data in patients aged 75 years and older.

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (Classification–Child Pugh A). In moderate hepatic impairment (Classification–Child Pugh B), the dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal hepatic function is 5 mg twice daily. The dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal hepatic function is 10 mg twice daily. Xeljanz should not be used in patients with severe hepatic impairment (Classification–Child Pugh C).

Renal impairment

No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance 50–80 mL/min to 30–49 mL/min, respectively). In severe renal impairment (creatinine clearance <30 mL/min) the dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal renal function is 5 mg twice daily. The dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal renal function is 10 mg twice daily. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis.

Paediatric population

The safety and efficacy of Xeljanz in children aged 0 to less than 18 years have not been established. No data are available.

CLINICAL EFFICACY IN ULCERATIVE COLITIS

The efficacy and safety of Xeljanz for the treatment of adult patients with moderately to severely active UC (Mayo score 6 to 12 with endoscopy subscore ≥2 and rectal bleeding subscore ≥1) were assessed in 3 multicentre, double-blind, randomised, placebo-controlled studies: 2 identical induction studies (OCTAVE Induction 1 and OCTAVE Induction 2) followed by 1 maintenance study (OCTAVE Sustain). Patients enrolled in the study had failed at least 1 conventional therapy, including corticosteroids, immunomodulators, and/or a TNF inhibitor. Concomitant stable doses of oral aminosalicylates and corticosteroids (prednisone or equivalent daily dose up to 25 mg) were permitted with taper of corticosteroids to discontinuation mandated within 15 weeks of entering the maintenance study. Xeljanz was administered as monotherapy (i.e., without concomitant use of biologics and immunosuppressants) for UC.

SPC SUMMARY FOR XELJANZ*

CLINICAL EFFICACY IN ULCERATIVE COLITIS (cont.)

Table 1 provides information regarding the pertinent study design and population characteristics of the UC studies for Xeljanz.

Table 1. Phase 3 Clinical Trials of Xeljanz 5 mg and 10 mg Twice Daily Doses in Patients with UC

	OCTAVE Induction 1	OCTAVE Induction 2	OCTAVE Sustain
Treatment groups (Randomisation ratio)	Xeljanz 10 mg Twice Daily Placebo (4:1)	Xeljanz 10 mg Twice Daily Placebo (4:1)	Xeljanz 5 mg Twice Daily Xeljanz 10 mg Twice Daily Placebo (1:1:1)
Number of patients enrolled	598	541	593
Study duration	8 weeks	8 weeks	52 weeks
Primary efficacy endpoint	Remission	Remission	Remission
Key secondary efficacy endpoints	Improvement of endoscopic appearance of the mucosa	Improvement of endoscopic appearance of the mucosa	Improvement of endoscopic appearance of the mucosa Sustained corticosteroid-free remission among patients in remission at Baseline
Prior TNFi failure	51.3%	52.1%	44.7%
Prior corticosteroid failure	74.9%	71.3%	75.0%
Prior immunosuppressant failure	74.1%	69.5%	69.6%
Baseline corticosteroid use	45.5%	46.8%	50.3%

TNFi = tumour necrosis factor inhibitor; UC = ulcerative colitis.

In addition, safety and efficacy of Xeljanz were assessed in an open-label long-term extension study (OCTAVE Open). Patients who completed 1 of the induction studies (OCTAVE Induction 1 or OCTAVE Induction 2) but did not achieve clinical response or patients who completed or withdrew early due to treatment failure in the maintenance study (OCTAVE Sustain) were eligible for OCTAVE Open. Patients from OCTAVE Induction 1 or OCTAVE Induction 2 who did not achieve clinical response after 8 weeks in OCTAVE Open were to be discontinued from OCTAVE Open. Corticosteroid tapering was also required upon entrance into OCTAVE Open.

SPC SUMMARY FOR XELJANZ*

CLINICAL EFFICACY IN ULCERATIVE COLITIS (cont.)

Induction efficacy data (OCTAVE Induction 1 and OCTAVE Induction 2)

The primary endpoint of OCTAVE Induction 1 and OCTAVE Induction 2 was the proportion of patients in remission at week 8; the key secondary endpoint was the proportion of patients with improvement of endoscopic appearance of the mucosa at week 8. Remission was defined as clinical remission (a total Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0. Improvement of endoscopic appearance of the mucosa was defined as endoscopy subscore of 0 or 1.

A significantly greater proportion of patients treated with Xeljanz 10 mg twice daily achieved remission, improvement of endoscopic appearance of the mucosa, and clinical response at week 8 compared to placebo in both studies, as shown in Table 2.

Table 2. Proportion of Patients Meeting Efficacy Endpoints at Week 8 (OCTAVE Induction Study 1 and OCTAVE Induction Study 2)

	OCTAVE Induction Study 1			
	Central Endoscopy Read		Local Endoscopy Read	
Endpoint	Placebo	Xeljanz 10 mg Twice Daily	Placebo	Xeljanz 10 mg Twice Daily
	N = 122	N = 476	N = 122	N = 476
Remission[a]	8.2%	18.5%‡	11.5%	24.8%‡
Improvement of endoscopic appearance of the mucosa[b]	15.6%	31.3%†	23.0%	42.4%*
Normalization of endoscopic appearance of the mucosa[c]	1.6%	6.7%‡	2.5%	10.9%‡
Clinical response[d]	32.8%	59.9%*	34.4%	60.7%*

	OCTAVE Induction Study 2			
	Central Endoscopy Read		Local Endoscopy Read	
Endpoint	Placebo	Xeljanz 10 mg Twice Daily	Placebo	Xeljanz 10 mg Twice Daily
	N = 122	N = 429	N = 112	N = 429
Remission[a]	3.6%	16.6%†	5.4%	20.7%†
Improvement of endoscopic appearance of the mucosa[b]	11.6%	28.4%†	15.2%	36.4%*
Normalization of endoscopic appearance of the mucosa[c]	1.8%	7.0%‡	0.0%	9.1%‡
Clinical response[d]	28.6%	55.0%*	29.5%	58.0%*

* $P < 0.0001$; † $P < 0.001$; ‡ $P < 0.05$.
N = number of patients in the analysis set.
[a] Primary endpoint: Remission was defined as clinical remission (a Mayo score ≤ 2 with no individual subscore > 1) and rectal bleeding subscore of 0.
[b] Key secondary endpoint: Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).
[c] Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0.
[d] Clinical response was defined as a decrease from baseline in Mayo score of ≥ 3 points and ≥ 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥ 1 point or absolute subscore for rectal bleeding of 0 or 1.

SPC SUMMARY FOR XELJANZ*

CLINICAL EFFICACY IN ULCERATIVE COLITIS (cont.)

Induction efficacy data (OCTAVE Induction 1 and OCTAVE Induction 2) (cont.)

In both subgroups of patients with or without prior TNF inhibitor failure, a greater proportion of patients treated with Xeljanz 10 mg twice daily achieved remission and improvement of endoscopic appearance of the mucosa at week 8 as compared to placebo. This treatment difference was consistent between the 2 subgroups (Table 3).

Table 3. Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 8 by TNF Inhibitor Therapy Subgroups (OCTAVE Induction Study 1 and OCTAVE Induction Study 2, Central Endoscopy Read)

	OCTAVE Induction Study 1	
Endpoint	**Placebo N = 122**	**Xeljanz 10 mg Twice Daily N = 476**
Remission[a]		
With prior TNF inhibitor failure	1.6% (1/64)	11.1% (27/243)
Without prior TNF inhibitor failure[b]	15.5% (9/58)	26.2% (61/233)
Improvement of endoscopic appearance of the mucosa[c]		
With prior TNF inhibitor failure	6.3% (4/64)	22.6% (55/243)
Without prior TNF inhibitor failure[b]	25.9% (15/58)	40.3% (94/233)
	OCTAVE Induction Study 2	
Endpoint	**Placebo N = 112**	**Xeljanz 10 mg Twice Daily N = 429**
Remission[a]		
With prior TNF inhibitor failure	0.0% (0/60)	11.7% (26/222)
Without prior TNF inhibitor failure[b]	7.7% (4/52)	21.7% (45/207)
Improvement of endoscopic appearance of the mucosa[c]		
With prior TNF inhibitor failure	6.7% (4/60)	21.6% (48/222)
Without prior TNF inhibitor failure[b]	17.3% (9/52)	35.7% (74/207)

TNF = tumour necrosis factor; N = number of patients in the analysis set.

[a] Remission was defined as clinical remission (a Mayo score ≤ 2 with no individual subscore > 1) and rectal bleeding subscore of 0.

[b] Included TNF inhibitor naïve patients.

[c] Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).

SPC SUMMARY FOR XELJANZ*

CLINICAL EFFICACY IN ULCERATIVE COLITIS (cont.)

Maintenance (OCTAVE Sustain)

Patients who completed 8 weeks in 1 of the induction studies and achieved clinical response were re-randomised into OCTAVE Sustain; 179 out of 593 (30.2%) patients were in remission at baseline of OCTAVE Sustain.

The primary endpoint in OCTAVE Sustain was the proportion of patients in remission at week 52. The 2 key secondary endpoints were the proportion of patients with improvement of endoscopic appearance at week 52, and the proportion of patients with sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline of OCTAVE Sustain.

A significantly greater proportion of patients in both the Xeljanz 5 mg twice daily and Xeljanz 10 mg twice daily treatment groups achieved the following endpoints at week 52 as compared to placebo: remission, improvement of endoscopic appearance of the mucosa, normalization of endoscopic appearance of the mucosa, maintenance of clinical response, remission among patients in remission at baseline, and sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline, as shown in Table 4.

SPC SUMMARY FOR XELJANZ*

CLINICAL EFFICACY IN ULCERATIVE COLITIS (cont.)

Maintenance (OCTAVE Sustain) (cont.)

Table 4. Proportion of Patients Meeting Efficacy Endpoints at Week 52 (OCTAVE Sustain)

	Central Endoscopy Read			Local Endoscopy Read		
Endpoint	Placebo N = 198	Xeljanz 5 mg Twice Daily N = 198	Xeljanz 10 mg Twice Daily N = 197	Placebo N = 198	Xeljanz 5 mg Twice Daily N = 198	Xeljanz 10 mg Twice Daily N = 197
Remission[a]	11.1%	34.3%*	40.6%*	13.1%	39.4%*	47.7%*
Improvement of endoscopic appearance of the mucosa[b]	13.1%	37.4%*	45.7%*	15.7%	44.9%*	53.8%*
Normalization of endoscopic appearance of the mucosa[c]	4.0%	14.6%**	16.8%*	5.6%	22.2%*	29.4%*
Maintenance of clinical response[d]	20.2%	51.5%*	61.9%*	20.7%	51.0%*	61.4%*
Remission among patients in remission at baseline[a,f]	10.2%	46.2%*	56.4%*	11.9%	50.8%*	65.5%*
Sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline[e,f]	5.1%	35.4%*	47.3%*	11.9%	47.7%*	58.2%*
Corticosteroid-free remission among patients taking corticosteroids at baseline[a,g]	10.9%	27.7%†	27.6%†	13.9%	32.7%†	31.0%†

* $P < 0.0001$; ** $P < 0.001$; † $P < 0.05$ for Xeljanz versus placebo.
N = number of patients in the analysis set.
[a] Remission was defined as clinical remission (a Mayo score ≤ 2 with no individual subscore > 1) and rectal bleeding subscore of 0.
[b] Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).
[c] Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0.
[d] Maintenance of clinical response was defined by a decrease from the induction study (OCTAVE Induction 1, OCTAVE Induction 2) baseline Mayo score of ≥ 3 points and ≥ 30%, with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or rectal bleeding subscore of 0 or 1. Patients were to be in clinical response at baseline of the maintenance study OCTAVE Sustain.
[e] Sustained corticosteroid-free remission was defined as being in remission and not taking corticosteroids for at least 4 weeks prior to the visit at both week 24 and week 52.
[f] N = 59 for placebo, N = 65 for Xeljanz 5 mg twice daily, N = 55 for Xeljanz 10 mg twice daily.
[g] N = 101 for placebo, N = 101 for Xeljanz 5 mg twice daily, N = 87 for Xeljanz 10 mg twice daily.

SPC SUMMARY FOR XELJANZ*

CLINICAL EFFICACY IN ULCERATIVE COLITIS (cont.)

Maintenance (OCTAVE Sustain) (cont.)

In both subgroups of patients with or without prior TNF inhibitor failure, a greater proportion of patients treated with either Xeljanz 5 mg twice daily or Xeljanz 10 mg twice daily achieved the following endpoints at week 52 of OCTAVE Sustain as compared to placebo: remission, improvement of endoscopic appearance of the mucosa, or sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline (Table 5). This treatment difference from placebo was similar between Xeljanz 5 mg twice daily and Xeljanz 10 mg twice daily in the subgroup of patients without prior TNF inhibitor failure. In the subgroup of patients with prior TNF inhibitor failure, the observed treatment difference from placebo was numerically greater for Xeljanz 10 mg twice daily than Xeljanz 5 mg twice daily by 9.7 to 16.7 percentage points across the primary and key secondary endpoints.

Table 5. Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 52 by TNF Inhibitor Therapy Subgroup (OCTAVE Sustain, Central Endoscopy Read)

Endpoint	Placebo N = 198	Xeljanz 5 mg Twice Daily N = 198	Xeljanz 10 mg Twice Daily N = 197
Remission[a]			
With prior TNF inhibitor failure	10/89 (11.2%)	20/83 (24.1%)	34/93 (36.6%)
Without prior TNF inhibitor failure[b]	12/109 (11.0%)	48/115 (41.7%)	46/104 (44.2%)
Improvement of endoscopic appearance of the mucosa[c]			
With prior TNF inhibitor failure	11/89 (12.4%)	25/83 (30.1%)	37/93 (39.8%)
Without prior TNF inhibitor failure[b]	15/109 (13.8%)	49/115 (42.6%)	53/104 (51.0%)
Sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline[d]			
With prior TNF inhibitor failure	1/21 (4.8%)	4/18 (22.2%)	7/18 (38.9%)
Without prior TNF inhibitor failure[b]	2/38 (5.3%)	19/47 (40.4%)	19/37 (51.4%)

TNF = tumour necrosis factor; N = number of patients in the analysis set.
[a] Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0.
[b] Included TNF inhibitor naïve patients.
[c] Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).
[d] Sustained corticosteroid-free remission was defined as being in remission and not taking corticosteroids for at least 4 weeks prior to the visit at both week 24 and week 52.

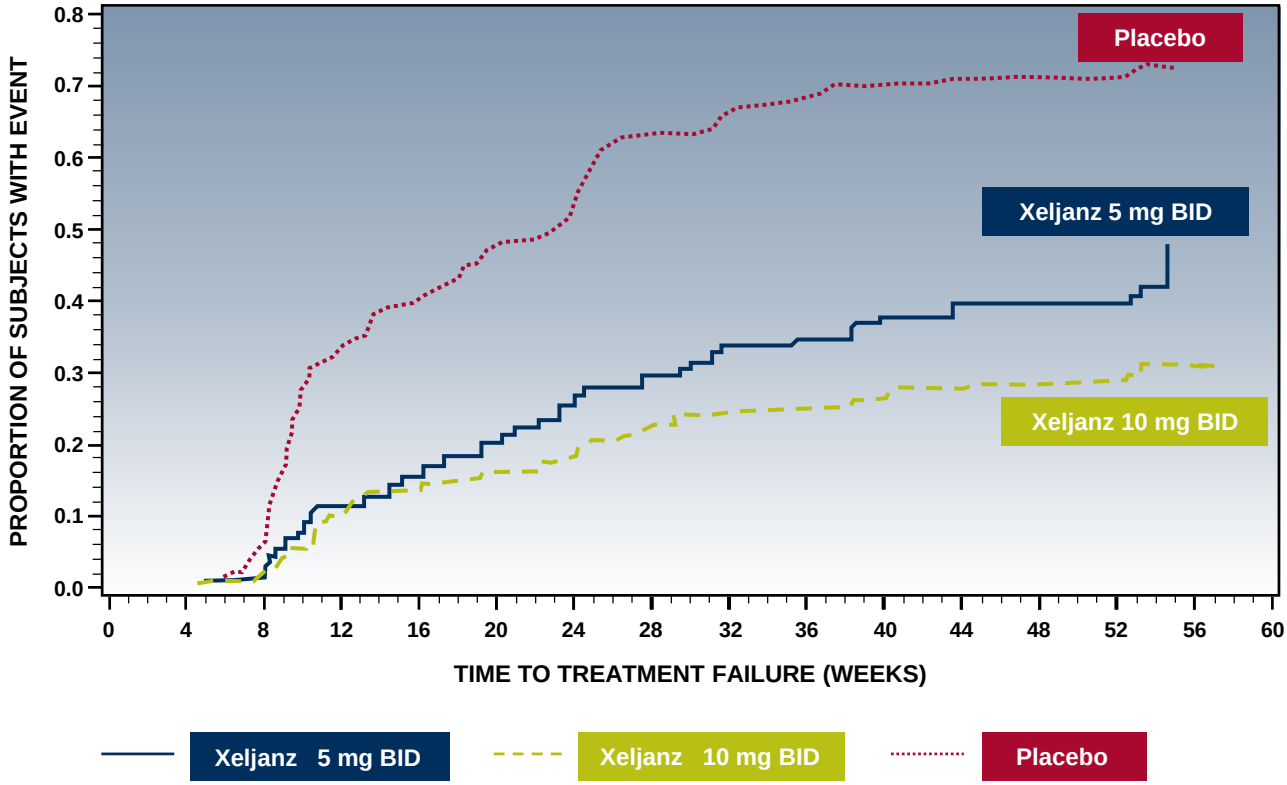
SPC SUMMARY FOR XELJANZ*

CLINICAL EFFICACY IN ULCERATIVE COLITIS (cont.)

Maintenance (OCTAVE Sustain) (cont.)

The proportion of patients in both Xeljanz groups who had treatment failure was lower compared to placebo at each time point as early as week 8, the first time point where treatment failure was assessed, as shown in Figure 1.

Figure 1. Time to Treatment Failure in Maintenance Study OCTAVE Sustain (Kaplan-Meier Curves)



P < 0.0001 for Xeljanz 5 mg twice daily versus placebo.
P < 0.0001 for Xeljanz 10 mg twice daily versus placebo.
BID = twice daily.
Treatment failure was defined as an increase in Mayo score of ≥3 points from maintenance study baseline, accompanied by an increase in rectal bleeding subscore by ≥1 point, and an increase of endoscopic subscore of ≥1 point yielding an absolute endoscopic subscore of ≥2 after a minimum treatment of 8 weeks in the study.

ISSUE RESPONSE GUIDE

Responding to Unsolicited Questions

When responding to a question, the important thing is to make sure that you understand the question and then provide the requested information.

The CRCT format – which stands for Clarify, Respond, Confirm, Transition – will help you to respond appropriately to a customer's question.

CLARIFY	If you are not sure what the customer wants to know, ask an open question. If you think that you understand the question, verify your understanding by paraphrasing it in a closed question.
RESPOND	If you know the answer, respond to the question by providing the requested information. If you do not know the answer, tell the customer you will get it.
CONFIRM	Confirm that you have addressed the issue to the customer's satisfaction.
TRANSITION	Transition back to the discussion using approved resources.

Responding to Unsolicited Concerns

In contrast to questions – which are a neutral request for information – concerns reflect some discomfort on the part of the customer. In general, concerns usually:

- are based on actual facts related to a product or service
- are related to a customer's doubts about the product
- seem to be an attempt to resolve or understand an issue
- are asked in a neutral manner

The process for responding to a concern is: Acknowledge, Clarify, Respond, Confirm, Transition.

ACKNOWLEDGE	When it is appropriate to the circumstances, acknowledge the customer's concern.
CLARIFY	If you are not sure what the customer wants to know, ask an open question. If you think that you understand the question, verify your understanding by paraphrasing it in a closed question.
RESPOND	If you know the answer, respond to the question by providing the requested information. If you do not know the answer, tell the customer you will get it.
CONFIRM	Confirm that you have addressed the issue to the customer's satisfaction.
TRANSITION	Transition back to the discussion using approved resources.

ISSUE RESPONSE GUIDE

Xeljanz | ISSUE 1

Xeljanz has demonstrated clinical efficacy on par with SIMPONI in UC. It's not clear to me why I should use SIMPONI in my UC patients.

ACKNOWLEDGE

Doctor, I understand that clinical efficacy is a driving factor when selecting an agent for your UC patients.

CLARIFY

Doctor, are you asking what additional clinical benefits SIMPONI can provide your patients with UC?

RESPOND

Doctor, the efficacy and safety of SIMPONI for the treatment of UC have been established in two randomized placebo-controlled trials. In PURSUIT-SC, an integrated phase 2 and phase 3 trial of patients with UC at over 200 sites worldwide, SIMPONI-treated patients showed a significantly greater clinical response* than placebo-treated patients at week 6. In PURSUIT-M, a phase 3 trial of patients with UC at over 250 sites worldwide, SIMPONI-treated patients maintained clinical response* through week 54.

SIMPONI also delivered long-term clinical benefits in a real-world setting in a retrospective study of patients with UC. In this study, 64.8% of 142 patients with moderate to severe UC achieved clinical response† at week 8 (short-term primary endpoint). After a median follow-up of 12 months, 57.7% of all patients maintained sustained clinical benefit‡ (long-term co-primary endpoint)—with 46.5% achieving clinical response† and 35.2% in clinical remission.§ Eighty-five percent all patients avoided colectomy (long-term co-primary endpoint) and 33.8% patients were in corticosteroid-free clinical remission.§ Four of the 142 patients exposed to SIMPONI experienced adverse events that led to SIMPONI withdrawal.

Doctor, as you know, uncontrolled mucosal inflammation in UC can lead to a relapsing disease course that may result in bowel damage requiring colectomy. Early and continuous control of mucosal inflammation with clinical and endoscopic remission is identified as an important target of medical therapy in UC. In fact, continuous clinical response (CCR)—clinical response sustained without treatment failure—may be associated with a change in disease course and better clinical outcomes, including clinical remission and a corticosteroid-free state. SIMPONI is the only biologic shown versus placebo to deliver CCR, maintaining clinical response* at every 4-week assessment for 54 weeks in UC patients.

CONFIRM

Would you agree that long-term disease control and change in disease course are important attributes in selecting a UC therapy?

TRANSITION

Doctor, I'm sure you want to offer your UC patients a treatment that can deliver clinical benefit at week 6 as well as maintain sustained clinical benefit. Let me show you how SIMPONI can provide this. . .

*In PURSUIT-SC and PURSUIT-M, clinical response was defined as a decrease from baseline in the Mayo score ≥30% and ≥3 points, accompanied by either a rectal bleeding subscore of 0 or 1 or a decrease from baseline in the rectal bleeding subscore ≥1.

†In the study by Taxonera, et al, clinical response was defined as a 3-point decrease in the partial Mayo score or a decrease of ≥50% in the partial Mayo score and a final partial Mayo score of ≤2.

‡In Taxonera, et al, sustained clinical benefit was defined as the absence of golimumab failure.

§In Taxonera, et al, clinical remission was defined as a partial Mayo score of 0 or 1.

ISSUE RESPONSE GUIDE

Xeljanz | ISSUE 2

Xeljanz is an appealing new agent. Based on the data of OCTAVE clinical studies, it is efficacious in UC. Additionally, it is an oral agent, which is more convenient for my patients. I'm considering using it in my patients, even before SIMPONI.

ACKNOWLEDGE

Doctor, I realize that efficacy is a main decision criteria when selecting an agent for your UC patients.

CLARIFY

Note: Be sure to clarify which clinical outcomes the customer wants to achieve (i.e., mucosal healing, clinical remission, or corticosteroid-free remission). Then base your response on the data in the Respond section below that reflect the customer's specific need(s). For example:

Doctor, what are your expectations around clinical response and remission rates when choosing a UC agent?

RESPOND

Note: In this case the customer was interested in clinical remission and corticosteroid-free remission. A sample response could include the following:

The efficacy and safety profile of SIMPONI for the treatment of UC have been established in two randomized placebo-controlled trials. A retrospective study of 142 patients in a real-world clinical setting supports the efficacy of SIMPONI in moderate to severe UC. In this study, 64.8% of all anti-TNFα-naïve and anti-TNFα-experienced patients combined achieved clinical response† at week 8 (short-term primary endpoint). Specifically, in the anti-TNFα-naïve patient population, 75.4% achieved clinical response* and 43.9% were in clinical remission† at week 8. Rates of clinical response* and clinical remission†, respectively, at week 8 were 69.7% and 33.3% for patients who received SIMPONI as a second-line anti-TNFα biologic and 50% and 17.3% for those receiving SIMPONI as a third-line anti-TNFα biologic. After a median follow-up of 12 months, 57.7% of all patients maintained sustained clinical benefit‡ (long-term co-primary endpoint) with 46.5% achieving clinical response* and 35.2% in clinical remission†. Eighty-five percent of all patients avoided colectomy (long-term co-primary endpoint) and 33.8% patients were in corticosteroid-free remission. Four of the 142 patients exposed to SIMPONI experienced adverse events that led to SIMPONI withdrawal.

In terms of convenience, the GO-MORE study examined factors influencing injection patterns and patient evaluations of an autoinjector among biologic-naïve patients with active RA beginning treatment with SIMPONI. Study may result indicated that SIMPONI offers a favorable patient experience. In fact, after 6 months of autoinjector use, 92.1% of RA patients were satisfied or very satisfied with once-monthly self-administration frequency; 91.7% reported that the overall autoinjection experience was favorable or extremely favorable, and 94.4% of patients reported mild or no pain with autoinjector use.

CONFIRM

Doctor, would you agree that SIMPONI offers efficacy in a UC agent as well as favorable patient experience with its convenient once-monthly self-administration?

TRANSITION

Doctor, I'm sure you want to start your patients on a UC treatment they can stay on. Let me show you how patients taking SIMPONI…

*In Taxonera, et al, clinical response was defined as a 3-point decrease in the partial Mayo score or a decrease of ≥50% in the partial Mayo score and a final partial Mayo score of ≤2.

†In Taxonera, et al, sustained clinical benefit was defined as the absence of golimumab failure.

‡In Taxonera, et al, clinical remission was defined as a partial Mayo score of 0 or 1.

ISSUE RESPONSE GUIDE

Xeljanz | ISSUE 3

Xeljanz has demonstrated clinical efficacy in patients failing anti-TNF agent(s). I'm considering switching my patients to Xeljanz following failure on TNF-inhibitor therapy.

ACKNOWLEDGE

Doctor, I can understand that you want the best possible outcomes for your patients with UC.

CLARIFY

Doctor, would you share with me your reasons for not considering SIMPONI as first-line treatment for your patients with UC?

[If customer has not used SIMPONI as first-line treatment due to efficacy concerns, continue to RESPONSE A. If customer has not used SIMPONI as first-line treatment due to access issues, continue to RESPONSE B.]

RESPONSE A

Doctor, the efficacy and safety of SIMPONI for the treatment of UC have been established in two randomised controlled trials. In PURSUIT-SC, an integrated phase 2 and phase 3 trial of patients with UC at over 200 sites worldwide, SIMPONI-treated patients showed a significantly greater clinical response* than placebo-treated patients at week 6. In PURSUIT-M, a phase 3 trial of patients with UC at over 250 sites worldwide, SIMPONI-treated patients maintained clinical response* through week 54.

RESPONSE B

Doctor, a retrospective study of 142 patients in a real-world clinical setting supports the efficacy of SIMPONI in moderate to severe UC. In anti-TNFα-experienced patients, 69.7% of those treated with SIMPONI as a second-line anti-TNFα agent achieved clinical response† and 33.3% were in clinical remission‡ at week 8§. Fifty percent of patients treated with SIMPONI as a third-line anti-TNFα agent achieved clinical response† and 17.3% were in clinical remission‡ at week 8. There was no significant difference in the probability of sustained clinical benefit‖ between those who received SIMPONI as the first or second anti-TNF agent. Four of the 142 patients exposed to SIMPONI experienced adverse events that led to SIMPONI withdrawal.

CONFIRM

[For RESPONSE A]: Would you agree that SIMPONI is an effective choice as first-line treatment for your patients with UC?

[For RESPONSE B]: Would you agree that SIMPONI is an appropriate and effective next step for your UC patients following failure on another TNF inhibitor therapy?

TRANSITION

[For RESPONSE A]: Doctor, I'm sure you want to offer your UC patients a first-line treatment that can deliver clinical benefit at week 6 as well as maintain sustained clinical benefit. Let me show you how SIMPONI may provide this. . .

[For RESPONSE B]: Doctor, I'm sure you want to offer your UC patients who are failing anti-TNF therapy a chance to achieve clinical response and/or clinical remission. Let me show you how SIMPONI may provide this. . .

*In PURSUIT-SC and PURSUIT-M, clinical response was defined as a decrease from baseline in the Mayo score ≥30% and ≥3 points, accompanied by either a rectal bleeding subscore of 0 or 1 or a decrease from baseline in the rectal bleeding subscore ≥1.

†In Taxonera, et al, clinical response was defined as a 3-point decrease in the partial Mayo score or a decrease of ≥50% in the partial Mayo score and a final partial Mayo score of ≤2.

‡In Taxonera, et al, sustained clinical benefit was defined as the absence of golimumab failure.

§Primary endpoint data can be found in the Issue 1 response for this study.

‖In Taxonera, et al, clinical remission was defined as a partial Mayo score of 0 or 1.

ISSUE RESPONSE GUIDE

Note to countries: Local markets to ensure the insertion of the approved local short balance/indication (i.e., ISI) for SIMPONI along with any other requirements regarding the access and presentation of SSI.