Report on the Deliberation Results

May 10, 2018

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Xeljanz Tablets 5 mg
Non-proprietary Name	Tofacitinib Citrate (JAN*)
Applicant	Pfizer Japan Inc.
Date of Application	May 31, 2017

Results of Deliberation

In its meeting held on April 27, 2018, the First Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 4 years.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of patients included in Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until the data from the planned number of patients are accumulated, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product as early as possible, and taking necessary measures to ensure its proper use.

**Japanese Accepted Name (modified INN)*

Review Report

April 18, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Xeljanz Tablets 5 mg
Non-proprietary Name	Tofacitinib Citrate
Applicant	Pfizer Japan Inc.
Date of Application	May 31, 2017
Dosage Form/Strength	Each tablet contains Tofacitinib Citrate equivalent to 5 mg of tofacitinib.
Application Classification	Prescription drug; (4) Drug with a new indication, (6) Drug with a new dosage.
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the "induction and maintenance of remission in patients with moderate to severe ulcerative colitis (only patients who have not adequately responded to conventional treatments)," and that the product has acceptable safety in view of its benefits (see Attachment). The safety and efficacy of the product should be further investigated through post-marketing surveillance covering all patients treated with the product.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indications

Rheumatoid arthritis in patients who have not adequately responded to conventional treatments
<u>Induction and maintenance of remission in patients with moderate to severe ulcerative colitis (only patients who have not adequately responded to conventional treatments)</u>

(Underline denotes addition.)

Dosage and Administration

Rheumatoid arthritis

The usual dosage is 5 mg of tofacitinib given orally twice daily.

Ulcerative colitis

The usual adult dosage for induction therapy is 10 mg of tofacitinib given orally twice daily for 8 weeks. The induction therapy can be extended for an additional 8 weeks in patients who do not achieve an adequate response.

The usual adult dosage for maintenance therapy is 5 mg of tofacitinib given orally twice daily. The dose may be increased to 10 mg twice daily in patients experiencing a loss of response during maintenance therapy. The 10 mg twice-daily dose may be used in patients with ulcerative colitis refractory to prior drug treatment (e.g., those with tumor necrosis factor [TNF] inhibitor failure).

(Underline denotes additions.)

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of patients included in Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until the data from the planned number of patients are accumulated, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product as early as possible, and taking necessary measures to ensure its proper use.

Review Report (1)

March 28, 2018

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Xeljanz Tablets 5 mg
Non-proprietary Name	Tofacitinib Citrate
Applicant	Pfizer Japan Inc.
Date of Application	May 31, 2017
Dosage Form/Strength	Each tablet contains Tofacitinib Citrate equivalent to 5 mg of tofacitinib.
Proposed Indications	Rheumatoid arthritis in patients who have not adequately responded to conventional treatments Induction and maintenance of remission in patients with moderately to severely active ulcerative colitis (only patients who have not adequately responded to conventional treatments) (Underline denotes addition.)
Proposed Dosage and Administration	Rheumatoid arthritis The usual dosage is 5 mg of tofacitinib given orally twice daily. Ulcerative colitis The usual dosage for induction therapy is 10 mg of tofacitinib given orally twice daily. After remission is achieved, 5 mg of tofacitinib given orally twice daily is recommended, but the 10 mg twice-daily dose may be used in patients with ulcerative colitis who are refractory to prior drug treatment. If the patient experiences a loss of response on tofacitinib 5 mg twice daily for maintenance therapy, the dose may be increased to 10 mg twice daily. (Underline denotes additions.)

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Ulcerative colitis (UC) is a non-specific inflammatory bowel disease and its precise cause is unknown. UC primarily affects the colonic mucosa, leading to mucosal erosion and ulceration. In Japan, UC is classified as a designated intractable disease (No. 97, Ministerial Announcement No. 393 of the Ministry of Health, Labour and Welfare, dated October 21, 2014). The chronic clinical course of UC is characterized by repeated episodes of symptoms such as bloody stools and diarrhoea (the period of active disease), and remission in which such symptoms or lesions have resolved or improved.

Currently available therapies for UC include mesalazine, steroids, immunosuppressants, and biological products, and suitable drugs are selected depending on the degree of severity and other factors. Mesalazine is widely used for the treatment of patients with mildly to moderately active UC, and steroids or other medications for the treatment of patients with moderately to severely active UC. Agents such as tacrolimus or TNF inhibitors are used in patients with steroid-resistant UC. To maintain remission in UC, mesalazine is mainly used. Immunosuppressants such as azathioprine are recommended in patients with steroid-dependent UC, whereas patients whose disease activity has decreased with the use of TNF inhibitors need to remain on the same therapy ("Diagnostic Criteria and Treatment Guidelines for Ulcerative Colitis and Crohn's Disease: FY 2016 Revised Edition, dated March 31, 2017," FY 2016 Report [Supplementary volume]: "Research on Intractable Inflammatory Bowel Disease" [prepared by a study group led by Suzuki], Research on Policy Planning and Evaluation for Rare and Intractable Diseases, a research project funded by the Health and Labour Sciences Research Grants; hereinafter referred to as "the Treatment Guidelines").

Tofacitinib, a selective inhibitor of the Janus kinase (JAK) family, suppresses the production of inflammatory cytokines. In Japan, tofacitinib was approved in March 2013 for the treatment of rheumatoid arthritis in patients who have not adequately responded to conventional treatments. The applicant initiated the clinical development of tofacitinib because (i) its mechanism of action is different from that of other drugs approved for the treatment of moderately to severely active UC, and (ii) tofacitinib offers an option for oral therapy which will be more convenient for patients.

As of March 2018, tofacitinib has been approved in at least 80 countries including European countries and the United State for the treatment of patients with rheumatoid arthritis who have inadequately responded to conventional treatments or other conditions; however, no countries/regions have approved tofacitinib for the treatment of UC.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Because the present application is intended for the addition of a new indication and a new dosage, the submission data package did not include data relating to quality.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the present application is intended for the addition of a new indication and a new dosage, no new non-clinical pharmacology data were submitted because there were no animal models of the disease to evaluate

the pharmacological action of tofacitinib in an appropriate manner. Tofacitinib's mechanism of action to inhibit JAK family members (JAK1, JAK2, JAK3, and TYK2) and thereby suppress the production of inflammatory cytokines has already been evaluated at the time of initial approval.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is intended for the addition of a new indication and a new dosage, non-clinical pharmacokinetic data have already been evaluated at the time of initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application is intended for the addition of a new indication and a new dosage, no new non-clinical toxicity data were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Liquid chromatography with tandem mass spectrometry (LC-MS/MS) was used to measure plasma concentrations of tofacitinib in the foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), global phase III remission maintenance study (Study A3921096), and foreign phase III remission induction study (Study A3921095). The lower limit of quantitation was 0.1 ng/mL.

6.2 Clinical pharmacology

6.2.1 Foreign phase II study (CTD 5.3.5.1.1, Study A3921063 [January 2009 to September 2010])

This study investigated plasma tofacitinib concentrations following repeated oral administration of tofacitinib in non-Japanese patients aged ≥18 years with moderately to severely active UC. Subjects received tofacitinib 0.5, 3, 10, or 15 mg twice daily orally for 8 weeks. The outlines of the study and efficacy and safety results are described in Section 7.1.

Table 1 shows the pharmacokinetic parameters of tofacitinib in plasma at Day 1 and Week 8.

Table 1. Pharmacokinetic parameters[a)] of tofacitinib in plasma following repeated oral administration of tofacitinib to patients with UC[a)]

Dosage regimen of tofacitinib	Time point	Number of subjects	C_{max}[b)] (ng/mL)	t_{max}[c)] (h)
0.5 mg twice daily	Day 1	31	5.4 (15.7)	1.0 [0.5, 2.7]
	Week 8	23	6.3 (34.3)	0.6 [0.3, 2.2]
3 mg twice daily	Day 1	31	27.8 (31.4)	1.0 [0.3, 2.0]
	Week 8	26	29.3 (9.81)	1.0 [0.3, 2.3]
10 mg twice daily	Day 1	31	87.8 (15.2)	1.0 [0.3, 3.8]
	Week 8	25	80.8 (22.0)	0.5 [0.3, 3.1]
15 mg twice daily	Day 1	48	136 (12.5)	1.0 [0.3, 3.0]
	Week 8	41	112 (22.6)	1.0 [0.2, 2.8]

a) AUC and $t_{1/2}$ were not calculated because available data were not sufficient to calculate these parameters.
b) Geometric mean value (% variation coefficient)
c) Median value [minimum value, maximum value]

6.2.2 Global phase III remission induction study (CTD 5.3.5.1.2, Study A3921094 [April 2012 to May 2015])

This study investigated plasma tofacitinib concentrations following repeated oral administration of tofacitinib in Japanese and non-Japanese patients aged ≥18 years with moderately to severely active UC. Subjects received tofacitinib 10 mg twice daily orally for 9 weeks. The outlines of the study and efficacy and safety results are described in Section 7.2.1.

Table 2 shows the trough plasma concentrations of tofacitinib at Week 2 and Week 8.

Table 2. Plasma concentrations of tofacitinib in patients with UC (trough concentrations[a)] [ng/mL])

Dosage regimen of tofacitinib	Time point	Non-Japanese		Japanese	
		Number of subjects	Plasma concentration of tofacitinib	Number of subjects	Plasma concentration of tofacitinib
10 mg twice daily	Week 2	391	5.07 [0.00, 199]	46	4.78 [0.45, 21.9]
	Week 8	388	4.78 [0.00, 133]	46	4.46 [0.00, 112]

Median value [Minimum value, maximum value]
a) The plasma concentration prior to the first dose of the study drug for the day

6.2.3 Global phase III remission maintenance study (CTD 5.3.5.1.4, Study A3921096 [July 2012 to May 2016])

This study investigated plasma tofacitinib concentrations following repeated oral administration of tofacitinib in Japanese and non-Japanese patients aged ≥18 years with moderately to severely active UC. Subjects received tofacitinib 5 or 10 mg twice daily orally for 53 weeks. The outlines of the study and efficacy and safety results are described in Section 7.2.3.

Table 3 shows the trough plasma concentrations of tofacitinib at Weeks 8, 24, and 52.

Table 3. Plasma concentrations of tofacitinib in patients with UC (trough concentrations[a)] [ng/mL])

Dosage regimen of tofacitinib	Time point	Non-Japanese		Japanese	
		Number of subjects	Plasma concentration of tofacitinib	Number of subjects	Plasma concentration of tofacitinib
5 mg twice daily	Week 8	162	3.17 [0.00, 48.2]	15	2.60 [0.80, 8.74]
	Week 24	123	2.59 [0.00, 46.2]	12	2.63 [0.86, 39.0]
	Week 52	98	2.18 [0.00, 21.0]	11	3.81 [0.56, 9.18]
10 mg twice daily	Week 8	167	5.44 [0.00, 130]	11	8.94 [1.00, 120]
	Week 24	135	4.77 [0.00, 93.7]	10	5.58 [1.90, 9.81]
	Week 52	113	3.92 [0.00, 90.8]	10	8.16 [2.37, 25.7]

Median value [Minimum value, maximum value]
a) The plasma concentration prior to the first dose of the study drug for the day

6.2.4 Foreign phase III remission induction study (CTD 5.3.5.1.3, Study A3921095 [June 2012 to June 2015])

This study investigated plasma tofacitinib concentrations following repeated oral administration of tofacitinib in non-Japanese patients aged ≥18 years with moderately to severely active UC. Subjects received tofacitinib 10 mg twice daily orally for 9 weeks. The outlines of the study and efficacy and safety results are described in Section 7.2.2.

Table 4 shows the trough plasma concentrations of tofacitinib at Week 2 and Week 8.

Table 4. Plasma concentrations of tofacitinib in patients with UC (trough concentrations[a)] [ng/mL])

Dosage regimen of tofacitinib	Time point	Number of subjects	Plasma concentration of tofacitinib
10 mg twice daily	Week 2	389	5.46 [0.00, 127]
	Week 8	389	4.88 [0.00, 114]

Median value [Minimum value, maximum value]
a) The plasma concentration prior to the first dose of the study drug for the day

6.R Outline of the review conducted by PMDA

6.R.1 Differences in pharmacokinetics between Japanese and non-Japanese patients with UC

The applicant's explanation about the pharmacokinetics of tofacitinib in Japanese and non-Japanese patients with UC:

In the global phase III remission induction study (Study A3921094), Japanese and non-Japanese patients with UC received tofacitinib 10 mg twice daily, and the plasma concentrations of tofacitinib (n = 43-46) at Week 2 or Week 8 were analyzed for the subgroups. The results were similar between Japanese and non-Japanese patients at both time points (Table 2). On the other hand, in the global phase III remission maintenance study (Study A3921096) in Japanese and non-Japanese patients with UC, the median plasma tofacitinib concentration (n = 10-11) following administration of tofacitinib 10 mg twice daily was slightly higher in Japanese patients than in non-Japanese patients (Table 3). However, the difference in the pharmacokinetics of tofacitinib between Japanese and non-Japanese patients with UC is not considered significant enough to pose any clinical problems, for the following reasons.

- In healthy Japanese adults receiving tofacitinib 15 mg twice daily for 5 days, the plasma tofacitinib concentrations reached steady state within 24 hours of repeated administration of tofacitinib ("Review Report on Xeljanz Tablets 5 mg" dated February 28, 2013). These results suggest that the plasma tofacitinib concentrations at Week 2 in patients with UC receiving tofacitinib 10 mg twice daily in the global phase III remission induction study (Study A3921094) are the steady state values of the concentrations.
- In the global phase III remission maintenance study (Study A3921096) in Japanese and non-Japanese patients with UC, the median plasma tofacitinib concentration following administration of tofacitinib 10 mg twice daily was slightly higher in Japanese patients than in non-Japanese patients (Table 3). However, the data consist of as few as 10 Japanese patients, and are therefore unlikely to provide sufficient information (e.g., median value) to make a meaningful comparison of plasma tofacitinib concentrations between Japanese patients with UC and non-Japanese patients with UC.

- All pharmacokinetic parameters (e.g., C_{max}, t_{max}, AUC, and $t_{1/2}$) following administration of tofacitinib 1 to 30 mg to healthy Japanese and non-Japanese adults were similar between Japanese and non-Japanese subjects. The data suggested no ethnic difference in the pharmacokinetics of tofacitinib ("Review Report on Xeljanz Tablets 5 mg" dated February 28, 2013).

PMDA accepted the applicant's explanation.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from 5 global and foreign clinical studies in Japanese and non-Japanese patients with UC (Table 5). Mayo scores and the Mayo score-based efficacy endpoints used for efficacy assessment in the clinical studies are presented in Tables 6 and 7, respectively. When adverse event data were tabulated, aggravated cases of UC were also included in "colitis ulcerative."

Table 5. Outline of efficacy and safety evaluation data

Phase	Study Identifier	Target population	Study design	Treatment duration	Group[a)] (Number of subjects)	Major endpoints
Foreign phase II	A3921063	Patients with moderately to severely active UC	Double-blind parallel-group	8 weeks	Placebo: 48 subjects Tofacitinib 0.5 mg: 31 subjects Tofacitinib 3 mg: 33 subjects Tofacitinib 10 mg: 33 subjects Tofacitinib 15 mg: 49 subjects	Clinical response rate at Week 8 Placebo: 47.5% Tofacitinib 0.5 mg: 29.6% Tofacitinib 3 mg: 51.6% Tofacitinib 10 mg: 63.3% Tofacitinib 15 mg: 80.0%
Global phase III	A3921094	Patients with moderately to severely active UC	Double-blind parallel-group remission induction	9 weeks	Placebo: 122 subjects (13 Japanese subjects) Tofacitinib 10 mg: 476 subjects (49 Japanese subjects)	Remission rate at Week 8 Placebo: 8.2% Tofacitinib 10 mg: 18.5%
Foreign phase III	A3921095	Patients with moderately to severely active UC	Double-blind parallel-group remission induction	9 weeks	Placebo: 112 subjects Tofacitinib 10 mg: 429 subjects	Remission rate at Week 8 Placebo: 3.6% Tofacitinib 10 mg: 16.6%
Global phase III	A3921096	Patients with UC who completed Study A3921094 or A3921095	Double-blind parallel-group remission maintenance	53 weeks	Placebo: 198 subjects (11 Japanese subjects) Tofacitinib 5 mg: 198 subjects (16 Japanese subjects) Tofacitinib 10 mg: 196 subjects (12 Japanese subjects)	Remission rate at Week 52 Placebo: 11.1% Tofacitinib 5 mg: 34.3% Tofacitinib 10 mg: 40.6%
Global phase III	A3921139	Patients with UC who completed and failed to achieve response in Study A3921094 or A3921095, or who completed or discontinued Study A3921096	Open-label uncontrolled	Until approval[b)]	Tofacitinib 5 mg: 156 subjects (10 Japanese subjects) Tofacitinib 10 mg: 758 subjects (40 Japanese subjects)	Safety

a) The study drug was administered orally twice daily in all groups
b) The study will continue until the first marketing approval is granted on a major global market.

Table 6. Mayo score

Mayo score: total of subscores of the 4 categories shown below (0-12) Partial Mayo score: total of subscores of 3 categories, excluding endoscopic subscore (0-9)	
Stool frequency	0: Normal number of stools of the patient 1: 1-2 stools/day more than normal 2: 3-4 stools/day more than normal 3: ≥5 stools/day more than normal
Rectal bleeding	0: No bleed 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
Endoscopy[a)]	0: Normal or inactive disease 1: Mild disease (erythema, decreased vascular pattern, mild friability[b)]) 2: Moderate disease (significant erythema, absent vascular pattern, friability, erosions) 3: Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment	0: Normal 1: Mild 2: Moderate 3: Severe

a) While results of endoscopic image read by each study site investigator were used in the foreign phase II study (Study A3921063), results of endoscopic image read centrally were used in the foreign phase III study (Study A3921095) and global phase III studies (Studies A3921094, A3921096, and A3921139).
b) In the foreign phase II study (Study A3921063), "mild friability" was defined as score 1, and "moderate friability" as score 2. In the foreign phase III study (Study A3921095) and global phase III studies (Studies A3921094, A3921096, and A3921139), all degrees of friability were defined as score 2.

Table 7. Mayo score-based efficacy endpoints

Remission	Mayo score ≤2, with no individual subscore >1, and rectal bleeding subscore of 0
Clinical remission	Mayo score ≤2, with no individual subscore >1
Mucosal healing	Endoscopic subscore of 0 or 1
Clinical response	Decrease from baseline in the Mayo score of ≥3 points and ≥30%, with a decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1.

7.1 Phase II studies

7.1.1 Foreign phase II study (CTD 5.3.5.1.1, Study A3921063 [January 2009 to September 2010])

A multicenter, placebo-controlled, randomized, double-blind, parallel-group study was conducted at 51 centers in 17 countries overseas to investigate the efficacy and safety of tofacitinib in non-Japanese patients aged ≥18 years with moderately to severely active UC (Table 8; target sample size, 192 subjects).

Table 8. Key inclusion and exclusion criteria

Key inclusion criteria
- Patients with UC defined by Mayo score of ≥6 at baseline, with endoscopic subscore of ≥2

Key exclusion criteria
- Treatment-naïve patients who have not had previous exposure to treatment for UC, or patients who have received any of the following therapies in the specified period:
  - Oral administration of azathioprine (AZA), 6-mercaptopurine (6-MP), or aethotrexate (MTX) within 7 days of baseline
  - Intravenous or intrarectal administration of steroids, or intrarectal administration of 5-aminosalicylic acid (5-ASA) within 2 weeks of baseline
  - Oral administration of ciclosporin, mycophenolic acid, or tacrolimus within 4 weeks of baseline
  - Administration of a TNF inhibitor or interferon within 8 weeks of baseline

Subjects received placebo or tofacitinib 0.5, 3, 10, or 15 mg twice daily orally for 8 weeks. Patients who had been on oral 5-ASA, oral sulfasalazine, or oral steroid (≤30 mg/day of prednisone or its equivalent) for the treatment of UC were allowed to continue the therapy unless the dose was changed.

Of the 195 subjects randomized (49 in the placebo group, 31 in the tofacitinib 0.5 mg group, 33 in the tofacitinib 3 mg group, 33 in the tofacitinib 10 mg group, and 49 in the tofacitinib 15 mg group), 1 subject in the placebo group was withdrawn from the study before receiving the study drug. The remaining 194 subjects (48 in the placebo group, 31 in the tofacitinib 0.5 mg group, 33 in the tofacitinib 3 mg group, 33 in the tofacitinib 10 mg group, and 49 in the tofacitinib 15 mg group) received the study drug, and were included in the full analysis set (FAS) and safety analysis set. The FAS was used for the primary efficacy analysis. Treatment was discontinued in 37 subjects (13 in the placebo group, 11 in the tofacitinib 0.5 mg group, 7 in the tofacitinib 3 mg group, 2 in the tofacitinib 10 mg group, and 4 in the tofacitinib 15 mg group). The reasons for discontinuation were "insufficient clinical response" in 19 subjects (5 in the placebo group, 6 in the tofacitinib 0.5 mg group, 5 in the tofacitinib 3 mg group, 2 in the tofacitinib 10 mg group, and 1 in the tofacitinib 15 mg group), "adverse events" in 7 subjects (3 in the placebo group, 2 in the tofacitinib 0.5 mg group, and 2 in the tofacitinib 15 mg group), "withdrawal of consent" in 6 subjects (2 in the placebo group, 2 in the tofacitinib 0.5 mg group, and 2 in the tofacitinib 3 mg group), "protocol deviation" in 4 subjects (2 in the placebo group, 1 in the tofacitinib 0.5 mg group, and 1 in the tofacitinib 15 mg group), and "lost to follow-up" in 1 subject (1 in the placebo group).

Efficacy analysis was performed. The clinical response rate at Week 8, the primary endpoint, was 47.5% (19 of 40 subjects) in the placebo group, 29.6% (8 of 27 subjects) in the tofacitinib 0.5 mg group, 51.6% (16 of 31 subjects) in the tofacitinib 3 mg group, 63.3% (19 of 30 subjects) in the tofacitinib 10 mg group, and 80.0% (36 of 45 subjects) in the tofacitinib 15 mg group.

Safety analysis was performed. The incidence of adverse events was 47.9% (23 of 48 subjects) in the placebo group, 61.3% (19 of 31 subjects) in the tofacitinib 0.5 mg group, 33.3% (11 of 33 subjects) in the tofacitinib 3 mg group, 42.4% (14 of 33 subjects) in the tofacitinib 10 mg group, and 40.8% (20 of 49 subjects) in the tofacitinib 15 mg group. Table 9 shows adverse events occurring in ≥5.0% of subjects in any group. The incidence of adverse drug reactions was 16.7% (8 of 48 subjects) in the placebo group, 19.4% (6 of 31 subjects) in the tofacitinib 0.5 mg group, 12.1% (4 of 33 subjects) in the tofacitinib 3 mg group, 24.2% (8 of 33 subjects) in the tofacitinib 10 mg group, and 16.3% (8 of 49 subjects) in the tofacitinib 15 mg group. Adverse drug reactions occurring in ≥5.0% in any group were colitis ulcerative (6.3% [3 of 48 subjects] in the placebo group, 3.2% [1 of 31 subjects] in the tofacitinib 0.5 mg group, 6.1% [2 of 33 subjects] in the tofacitinib 3 mg group, 0% [0 of 33 subjects] in the tofacitinib 10 mg group, and 0% [0 of 49 subjects] in the tofacitinib 15 mg group), and headache (0% [0 of 48 subjects] in the placebo group, 3.2% [1 of 31 subjects] in the tofacitinib 0.5 mg group, 3.0% [1 of 33 subjects] in the tofacitinib 3 mg group, 6.1% [2 of 33 subjects] in the tofacitinib 10 mg group, and 4.1% [2 of 49 subjects] in the tofacitinib 15 mg group.

Table 9. Adverse events occurring in ≥5.0% of subjects in any group

	Placebo (N = 48)	Tofacitinib			
		0.5 mg (N = 31)	3 mg (N = 33)	10 mg (N = 33)	15 mg (N = 49)
Any adverse event	47.9 (23)	61.3 (19)	33.3 (11)	42.4 (14)	40.8 (20)
Headache	4.2 (2)	6.5 (2)	9.1 (3)	9.1 (3)	8.2 (4)
Colitis ulcerative	18.8 (9)	16.1 (5)	9.1 (3)	6.1 (2)	6.1 (3)
Abdominal pain	2.1 (1)	3.2 (1)	0 (0)	0 (0)	6.1 (3)
Arthralgia	0 (0)	0 (0)	0 (0)	6.1 (2)	4.1 (2)
Dizziness	2.1 (1)	6.5 (2)	0 (0)	3.0 (1)	4.1 (2)
Nasopharyngitis	2.1 (1)	6.5 (2)	3.0 (1)	3.0 (1)	2.0 (1)
Influenza	6.3 (3)	6.5 (2)	0 (0)	0 (0)	2.0 (1)
Pain in extremity	0 (0)	3.2 (1)	0 (0)	6.1 (2)	0 (0)
Rash	0 (0)	0 (0)	6.1 (2)	3.0 (1)	0 (0)
Dyspepsia	0 (0)	6.5 (2)	3.0 (1)	0 (0)	0 (0)
Sinusitis	0 (0)	6.5 (2)	0 (0)	0 (0)	0 (0)

MedDRA/J ver.13.0; incidence, % (n)

No deaths occurred. The incidence of serious adverse events was 8.3% (4 of 48 subjects) in the placebo group ("colitis ulcerative" [3] and "ischaemic stroke" [1]), 3.2% (1 of 31 subjects) in the tofacitinib 0.5 mg group ("general physical health deterioration"), 3.0% (1 of 33 subjects) in the tofacitinib 3 mg group ("colitis ulcerative"), 6.1% (2 of 33 subjects) in the tofacitinib 10 mg group ("drug hypersensitivity/colitis ulcerative/abdominal abscess" [1] and "anal abscess" [1]), and 4.1% (2 of 49 subjects) in the tofacitinib 15 mg group ("colitis ulcerative" [2]). Among these events, "colitis ulcerative" in 1 subject in the placebo group, "general physical health deterioration" in 1 subject in the tofacitinib 0.5 mg group, and "colitis ulcerative" in 1 subject in the tofacitinib 3 mg group were considered adverse drug reactions. Among the serious adverse drug reactions, the outcomes of "colitis ulcerative" in 1 subject in the placebo group and "general physical health deterioration" in 1 subject in the tofacitinib 0.5 mg group were reported as resolved, while the outcome of "colitis ulcerative" in 1 subject[1)] in the tofacitinib 3 mg group was reported as resolved with sequelae.

The incidence of adverse events leading to treatment discontinuation was 8.3% (4 of 48 subjects) in the placebo group ("colitis ulcerative" [3] and "ischaemic stroke" [1]), 6.5% (2 of 31 subjects) in the tofacitinib 0.5 mg group ("colitis ulcerative" [2]), 0% (0 of 33 subjects) in the tofacitinib 3 mg group, 3.0% (1 of 33 subjects) in the tofacitinib 10 mg group ("anal abscess"), and 4.1% (2 of 49 subjects) in the tofacitinib 15 mg group ("colitis ulcerative/vomiting" [1] and "colitis ulcerative" [1]). Among these events, "colitis ulcerative" in 1 subject in the placebo group was considered an adverse drug reaction, the outcome of which was reported as resolved.

7.2 Phase III studies

7.2.1 Global phase III remission induction study (CTD 5.3.5.1.2, Study A3921094 [April 2012 to May 2015])

A multicenter, placebo-controlled, randomized, double-blind, parallel-group study was conducted at 113 enters (including 23 centers in Japan) in 28 countries including Japan to investigate the efficacy and safety of

1) A white male aged 48 years. Colitis ulcerative worsened 11 days after the completion of study treatment. Total colectomy, prophylactic ileal pouch anal anastomosis, and temporary ileostomy were performed. Although a sequela developed, colitis ulcerative resolved.

tofacitinib in Japanese and non-Japanese patients aged ≥18 years with moderately to severely active UC (Table 10; target sample size, 545 subjects).

Table 10. Key inclusion and exclusion criteria

Key inclusion criteria
• Patients with UC defined by Mayo score of ≥6 at baseline, with rectal bleeding subscore of ≥1 and endoscopic subscore of ≥2
• Patients who responded inadequately or were intolerant to at least one of the following therapies: oral or intravenous steroids, AZA, 6-MP, and TNF inhibitor
 	
Key exclusion criteria
• Treatment-naïve patients who have not had previous exposure to treatment for UC, or patients who have received any of the following therapies in the specified period:
  • Oral administration of AZA, 6-MP, or MTX, intravenous or intrarectal administration of steroids, or intrarectal administration of 5-ASA within 2 weeks of baseline
  • Oral administration of ciclosporin, mycophenolate mofetil/mycophenolic acid, or tacrolimus within 4 weeks of baseline
  • Administration of a TNF inhibitor or interferon within 8 weeks of baseline

Subjects received placebo or tofacitinib 10 mg twice daily orally for 9 weeks.[2)] Patients who had been on oral 5-ASA, oral sulfasalazine, oral steroid (≤25 mg/day of prednisone or its equivalent, or ≤9 mg/day of budesonide), or an antibiotic for the treatment of UC were allowed to continue the therapy unless the dose was changed.

All 598 subjects randomized (122 subjects [including 13 Japanese subjects] in the placebo group, and 476 subjects [including 49 Japanese subjects] in the tofacitinib 10 mg group) received the study drug and were included in the FAS and safety analysis set. The FAS was used for the primary efficacy analysis. Treatment was discontinued in 35 subjects (4 in the placebo group and 31 in the tofacitinib 10 mg group). The reasons for discontinuation were "insufficient clinical response" in 12 subjects (1 in the placebo group and 11 in the tofacitinib 10 mg group), "adverse events" in 10 subjects (1 in the placebo group and 9 in the tofacitinib 10 mg group), "withdrawal of consent" in 5 subjects (1 in the placebo group and 4 in the tofacitinib 10 mg group), "protocol deviation" in 5 subjects (1 in the placebo group and 4 in the tofacitinib 10 mg group), "death" in 1 subject (1 in the tofacitinib 10 mg group), and "other reasons" in 2 subjects (2 in the tofacitinib 10 mg group).

Efficacy analysis was performed. Table 11 shows the "remission rate at Week 8," the primary endpoint. The difference in remission rate between the tofacitinib 10 mg group and the placebo group was statistically significant ($P = 0.007$, Cochran-Mantel-Haenszel χ^2 test, a two-sided significance level of 5%).

2) At the start of the study, subjects were originally to receive tofacitinib 10 mg or 15 mg twice daily orally for 9 weeks. However, in the foreign phase II study (Study A3921063), clinical response in the tofacitinib 10 mg group was found to be similar to that in the tofacitinib 15 mg group. For this reason and others, the protocol was revised in November 2012 to remove the tofacitinib 15 mg group and increase the number of subjects in the 10 mg group, instead, in order to clarify the risks and benefits of tofacitinib 10 mg compared with placebo. Sixteen subjects were assigned to tofacitinib 15 mg. The incidence of adverse events was 75.0% (12 of 16 subjects) for the overall study population, and 100% (3 of 3 subjects) for the Japanese subpopulation. There were no serious adverse events or adverse events leading to treatment discontinuation.

Table 11. Remission rate at Week 8 (FAS)

	Placebo (N = 122)	Tofacitinib 10 mg (N = 476)
Remission rate at Week 8 (n)[a)]	8.2% (10)	18.5% (88)
Between-group difference (Tofacitinib vs. placebo) [95%CI][b)]	10.3% [4.3, 16.3]	
P-value[c) d)]	0.007	

a) Subjects with missing data were treated as subjects who failed to achieve remission (non-responders).
b) 95% confidence interval (CI) was calculated using normal approximation for the difference.
c) Calculated using Cochran-Mantel-Haenszel $\chi 2$ test stratified by prior TNF inhibitor exposure, steroid use at baseline, and geographic region.
d) A two-sided significance level of 5%

According to safety analyses for the overall study population, the incidence of adverse events was 59.8% (73 of 122 subjects) in the placebo group and 56.5% (269 of 476 subjects) in the tofacitinib 10 mg group, and the incidence of adverse drug reactions was 26.2% (32 of 122 subjects) in the placebo group and 30.3% (144 of 476 subjects) in the tofacitinib 10 mg group. According to safety analyses for the Japanese subpopulation, the incidence of adverse events was 69.2% (9 of 13 subjects) in the placebo group and 55.1% (27 of 49 subjects) in the tofacitinib 10 mg group, and the incidence of adverse drug reactions was 30.8% (4 of 13 subjects) in the placebo group and 28.6% (14 of 49 subjects) in the tofacitinib 10 mg group. Tables 12 shows adverse events occurring in ≥2.0% of subjects in either group in the overall study population, or those occurring in ≥2 subjects in either group in the Japanese subpopulation. Table 13 shows and adverse drug reactions occurring in ≥2.0% of subjects in either group in the overall study population, or those occurring in ≥2 subjects in either group in the Japanese subpopulation.

Table 12. Adverse events occurring in ≥2.0% of subjects in either group in the overall study population, or those occurring in ≥2 subjects in either group in the Japanese subpopulation

Adverse event	Overall study population		Japanese subpopulation	
	Placebo (N = 122)	Tofacitinib 10 mg (N = 476)	Placebo (N = 13)	Tofacitinib 10 mg (N = 49)
Any adverse event	59.8 (73)	56.5 (269)	69.2 (9)	55.1 (27)
Headache	6.6 (8)	7.8 (37)	0 (0)	4.1 (2)
Nasopharyngitis	7.4 (9)	7.1 (34)	23.1 (3)	12.2 (6)
Abdominal pain	3.3 (4)	3.4 (16)	0 (0)	2.0 (1)
Nausea	4.1 (5)	3.2 (15)	7.7 (1)	2.0 (1)
Upper respiratory tract infection	0.8 (1)	3.2 (15)	0 (0)	2.0 (1)
Arthralgia	4.9 (6)	2.9 (14)	0 (0)	0 (0)
Pyrexia	2.5 (3)	2.9 (14)	0 (0)	2.0 (1)
Anaemia	4.9 (6)	2.3 (11)	7.7 (1)	2.0 (1)
Colitis ulcerative	4.1 (5)	2.3 (11)	0 (0)	2.0 (1)
Blood CK increased	0 (0)	2.5 (12)	0 (0)	0 (0)
Fatigue	3.3 (4)	2.1 (10)	0 (0)	0 (0)
Blood cholesterol increased	0 (0)	2.1 (10)	0 (0)	6.1 (3)
Acne	0 (0)	2.1 (10)	0 (0)	4.1 (2)
Cough	2.5 (3)	1.5 (7)	15.4 (2)	2.0 (1)
Abdominal pain upper	1.6 (2)	1.5 (7)	7.7 (1)	4.1 (2)
Gastroenteritis	1.6 (2)	1.5 (7)	0 (0)	4.1 (2)
Back pain	2.5 (3)	1.3 (6)	0 (0)	0 (0)
Herpes simplex	0 (0)	0.4 (2)	0 (0)	4.1 (2)
Metrorrhagia	2.2 (1)	0 (0)	33.3 (1)	0 (0)
Vulvovaginal candidiasis	2.2 (1)	0 (0)	0 (0)	0 (0)
Vulva cyst	2.2 (1)	0 (0)	0 (0)	0 (0)

MedDRA/J ver.18.0; incidence, % (n)

Table 13. Adverse drug reactions occurring in ≥2.0% of subjects in either group in the overall study population, or those occurring in ≥2 subjects in either group in the Japanese subpopulation

Adverse drug reaction	Overall study population		Japanese subpopulation	
	Placebo (N = 122)	Tofacitinib 10 mg (N = 476)	Placebo (N = 13)	Tofacitinib 10 mg (N = 49)
Any adverse drug reaction	26.2 (32)	30.3 (144)	30.8 (4)	28.6 (14)
Headache	3.3 (4)	4.4 (21)	0 (0)	4.1 (2)
Nausea	2.5 (3)	1.9 (9)	7.7 (1)	2.0 (1)
Blood cholesterol increased	0 (0)	1.9 (9)	0 (0)	6.1 (3)
Nasopharyngitis	3.3 (4)	1.7 (8)	7.7 (1)	4.1 (2)
Fatigue	2.5 (3)	1.3 (6)	0 (0)	0 (0)
Herpes simplex	0 (0)	0.4 (2)	0 (0)	4.1 (2)
Vulvovaginal candidiasis	2.2 (1)	0 (0)	0 (0)	0 (0)

MedDRA/J ver.18.0; incidence, % (n)

In the overall study population, 1 subject in the tofacitinib 10 mg group died due to "aortic dissection."[3)] This event was considered unrelated to the study drug. The incidence of serious adverse events was 4.1% (5 of 122 subjects) in the placebo group ("colitis ulcerative" [2], "vulva cyst" [1], "animal bite" [1], and "pulmonary

3) A white male aged 39 years. The onset of aortic dissection occurred on Day 24 after the start of study drug treatment. The subject died of aggravated acute cardiovascular insufficiency due to aortic dissection, aortic aneurysm rupture, and cardiac tamponade on Day 31. A causal relationship to the study drug was ruled out.

embolism" [1]) and 3.4% (16 of 476 subjects) in the tofacitinib 10 mg group ("colitis ulcerative" [4], "otitis externa" [1], "malaise" [1], "acute coronary syndrome" [1], "pneumonia" [1], "joint injury" [1], "intestinal perforation" [1], "aortic dissection" [1], "febrile infection" [1], "colitis ulcerative/drug eruption/arthralgia/drug hypersensitivity/cellulitis" [1], "*Clostridium difficile* infection" [1], "anal abscess" [1], and "temporal arteritis" [1]). Among these events, "pulmonary embolism" (1) in the placebo group, and "colitis ulcerative" (1), "pneumonia" (1), "intestinal perforation" (1), "febrile infection" (1), and "temporal arteritis" (1) in the tofacitinib 10 mg group were considered adverse drug reactions, the outcomes of which were all reported as resolved.

The incidence of adverse events leading to treatment discontinuation was 1.6% (2 of 122 subjects) in the placebo group ("hepatic enzyme increased" [1] and "colitis ulcerative" [1]) and 3.8% (18 of 476 subjects) in the tofacitinib 10 mg group ("colitis ulcerative" [8], "lymphopenia" [1], "intestinal perforation" [1], "abdominal pain upper" [1], "pneumonia" [1], "febrile infection" [1], "anal abscess" [1], "blood creatine kinase (CK) increased" [1], "hypertriglyceridaemia" [1], "alopecia" [1], and "temporal arteritis" [1]). "Hepatic enzyme increased" (1) in the placebo group, and "colitis ulcerative" (1), "lymphopenia" (1), "intestinal perforation" (1), "abdominal pain upper" (1), "pneumonia" (1), "febrile infection" (1), "blood CK increased" (1), "hypertriglyceridaemia" (1), "alopecia" (1), and "temporal arteritis" (1) in the tofacitinib 10 mg group were considered adverse drug reactions. The outcomes of "hepatic enzyme increased" in 1 subject in the placebo group and "blood CK increased" in 1 subject[4)] in the tofacitinib 10 mg group were reported as not resolved, while the outcomes of adverse drug reactions in the remaining 9 subjects were reported as resolved.

No deaths occurred in the Japanese subpopulation. In the Japanese subpopulation, no serious adverse events occurred in the placebo group, while serious adverse events occurred in 4.1% (2 of 49) of subjects in the tofacitinib 10 mg group ("*Clostridium difficile* infection" [1] and "colitis ulcerative" [1]). Both events were considered unrelated to tofacitinib. In the Japanese subpopulation, no adverse events led to treatment discontinuation in the placebo group, while adverse events leading to treatment discontinuation occurred in 2.0% (1 of 49) of subjects in the tofacitinib 10 mg group ("lymphopenia"). This event was considered an adverse drug reaction, the outcome of which was reported as resolved.

7.2.2 Foreign phase III remission induction study (CTD 5.3.5.1.3, Study A3921095 [June 2012 to June 2015])

A multicenter, placebo-controlled, randomized, double-blind, parallel-group study was conducted at 124 centers in 29 countries overseas to investigate the efficacy and safety of tofacitinib in non-Japanese patients aged ≥18 years with moderately to severely active UC (Table 10; target sample size, 545 subjects).

Subjects received placebo or 10 mg tofacitinib twice daily orally for 9 weeks. Patients who had been on oral 5-ASA, oral sulfasalazine, oral steroid (≤25 mg/day of prednisone or equivalent, or ≤9 mg/day of budesonide), or an antibiotic for the treatment of UC were allowed to continue the therapy unless the dose was changed.

4) A white male aged 24 years. The subject was assigned to the tofacitinib 10 mg group. Blood CK increased occurred on Day 30, and study treatment was discontinued on Day 37. The event was persistent on Day 43, according to the final report.

All 541 subjects randomized (112 in the placebo group and 429 in the tofacitinib 10 mg group) received the study drug and were included in the FAS and safety analysis set. The FAS was used for the primary efficacy analysis. Treatment was discontinued in 47 subjects (15 in the placebo group and 32 in the tofacitinib 10 mg group). The reasons for discontinuation were "insufficient clinical response" in 28 subjects (11 in the placebo group and 17 in the tofacitinib 10 mg group), "adverse events" in 9 subjects (2 in the placebo group and 7 in the tofacitinib 10 mg group), "protocol deviation" in 5 subjects (5 in the tofacitinib 10 mg group), "withdrawal of consent" in 4 subjects (2 in the placebo group and 2 in the tofacitinib 10 mg group), and "other reasons" in 1 subject (the tofacitinib 10 mg group).

Efficacy analysis was performed. Table 14 shows the "remission rate at Week 8," the primary endpoint. The difference in remission rate between the tofacitinib 10 mg group and the placebo group was statistically significant ($P = 0.0005$, Cochran-Mantel-Haenszel χ^2 test, a two-sided significance level of 5%).

Table 14. Remission rate at Week 8 (FAS)

	Placebo (N = 112)	Tofacitinib 10 mg (N = 429)
Remission rate at Week 8 (n)[a)]	3.6% (4)	16.6% (71)
Between-group difference (tofacitinib vs. placebo) [95%CI][b)]	13.0% [8.1, 17.9]	
P-value[c) d)]	0.0005	

a) Subjects with missing data were treated as those who failed to achieve remission (non-responders).
b) 95% CI was calculated using normal approximation for the difference.
c) Calculated using Cochran-Mantel-Haenszel χ2 test stratified by prior TNF inhibitor exposure, steroid use at baseline, and geographic region.
d) A two-sided significance level of 5%

Safety analysis was performed. The incidence of adverse events was 52.7% (59 of 112 subjects) in the placebo group and 54.1% (232 of 429 subjects)[5)] in the tofacitinib 10 mg group. Table 15 shows adverse events occurring in ≥2.0% of subjects in either group. The incidence of adverse drug reactions was 22.3% (25 of 112 subjects) in the placebo group and 26.8% (115 of 429 subjects) in the tofacitinib 10 mg group. Adverse drug reactions occurring in ≥2.0% of subjects in either group were "headache" (5.4% [6 of 112 subjects] in the placebo group and 6.1% [26 of 429 subjects] in the tofacitinib 10 mg group), "blood CK increased" (1.8% [2 of 112 subjects] in the placebo group and 2.6% [11 of 429 subjects] in the tofacitinib 10 mg group), and "nasopharyngitis" (1.8% [2 of 112 subjects] in the placebo group and 2.1% [9 of 429 subjects] in the tofacitinib 10 mg group).

5) A severe case of colitis ulcerative in 1 subject in the tofacitinib 10 mg group was reported as a serious adverse event after administration of the study drug. However, because severe colitis ulcerative had been noted prior to assignment, it was not classified as an adverse event. This case of colitis ulcerative was thus not included in the analysis of adverse events.

Table 15. Adverse events with an incidence of ≥2.0% in any group

Adverse event	Placebo (N = 112)	Tofacitinib 10 mg (N = 429)
Any adverse events	52.7 (59)	54.1 (232)
Headache	8.0 (9)	7.7 (33)
Nasopharyngitis	3.6 (4)	4.9 (21)
Acne	0.9 (1)	3.5 (15)
Colitis ulcerative	5.4 (6)	3.0 (13)
Blood CK increased	2.7 (3)	3.0 (13)
Dizziness	2.7 (3)	3.0 (13)
Nausea	3.6 (4)	2.8 (12)
Arthralgia	5.4 (6)	2.6 (11)
Anaemia	2.7 (3)	2.6 (11)
Upper respiratory tract infection	4.5 (5)	2.3 (10)
Pyrexia	0.9 (1)	2.3 (10)
Abdominal pain	5.4 (6)	2.1 (9)
Oedema peripheral	3.6 (4)	1.4 (6)
Cough	2.7 (3)	1.4 (6)
Oropharyngeal pain	2.7 (3)	0.7 (3)
Erythema nodosum	2.7 (3)	0.5 (2)
Hot flush	3.6 (4)	0 (0)

MedDRA/J ver. 18.0; incidence, % (n)

No deaths occurred. The incidence of serious adverse events was 8.0% (9 of 112 subjects) in the placebo group ("colitis ulcerative" [4], "anaemia" [1], "anal fistula" [1], "dehydration" [1], "intestinal perforation" [1], and "colon neoplasm" [1]), 4.2% (18 of 429 subjects[6)]) in the tofacitinib 10 mg group ("colitis ulcerative" [9], "asthenia" [1], "cardiac failure congestive" [1], "chills" [1], "Crohn's disease/furuncle" [1], "femur fracture" [1], "proctalgia" [1], "hypertension" [1], "colon adenoma" [1], "hip fracture/abdominal pain/constipation" [1], and "abdominal pain" [1]). Among these events, "colitis ulcerative" (2), "cardiac failure congestive" (1), and "furuncle" (1) in the tofacitinib 10 mg group were considered adverse drug reactions, and the outcomes of these adverse drug reactions were reported as resolved. The incidence of adverse events leading to treatment discontinuation was 7.1% (8 of 112 subjects) in the placebo group ("colitis ulcerative" [6], "intestinal perforation" [1], "asthenia/chest pain/blood CK increased/dyspnoea exertional" [1]) and 4.0% (17 of 429 subjects) in the tofacitinib 10 mg group ("colitis ulcerative" [8], "anaemia" [1], "cardiac failure congestive" [1], "asthenia" [1], "face oedema" [1], "furuncle" [1], "femur fracture" [1], "liver function test abnormal" [1], "lymphocyte count decreased" [1], and "colon adenoma" [1]). Among these events, "blood CK increased" (1) in the placebo group, and "colitis ulcerative" (2), "anaemia" (1), "cardiac failure congestive" (1), "face oedema" (1), "furuncle" (1), and "lymphocyte count decreased" (1) in the tofacitinib 10 mg group were considered adverse drug reactions. The outcomes of these adverse drug reactions were reported as resolved except for the case of blood CK increased in 1 subject in the placebo group.

6) A severe case of colitis ulcerative in 1 subject in the tofacitinib 10 mg group was reported as a serious adverse event after administration of the study drug. However, because severe colitis ulcerative had been noted prior to assignment, it was not classified as an adverse event. This case of colitis ulcerative was thus not included in the analysis of adverse events.

7.2.3 Global phase III remission maintenance study (CTD 5.3.5.1.4, Study A3921096 [July 2012 to May 2016])

A multicenter, placebo-controlled, randomized, double-blind, parallel-group study was conducted at 195 centers (including 20 centers in Japan) in 31 countries including Japan to investigate the efficacy and safety of tofacitinib as the maintenance therapy in patients with UC who had completed either the global phase III remission induction study (Study A3921094) or the foreign phase III remission induction study (Study A3921095) and achieved clinical response (target sample size, 654 subjects).

Subjects received placebo, or tofacitinib 5 or 10 mg twice daily orally for 53 weeks. Patients who had been on oral 5-ASA, oral sulfasalazine, or an antibiotic for the treatment of UC were allowed to continue the therapy unless the dose was changed. Patients who had been on oral steroids (≤25 mg/day of prednisone or its equivalent, or ≤9 mg/day of budesonide) are required to taper off steroid as follows: The dose of prednisone (or its equivalent) was tapered by 5 mg every week to 20 mg/day, then by 2.5 to 5.0 mg at weekly intervals to 10 mg/day, and then by 2.5 mg every week to 0 mg (patients who had been on oral budesonide [≤9 mg/day] were required to taper the dose by 3 mg every 3 weeks).

All 593 subjects randomized (198 subjects [including 11 Japanese subjects] in the placebo group, 198 subjects [including 16 Japanese subjects] in the tofacitinib 5 mg group, and 197 subjects [including 12 Japanese subjects] in the tofacitinib 10 mg group) were included in the FAS, which was used for the primary efficacy analysis.[7)] All 592 subjects who received at least 1 dose of the study drug (198 subjects [including 11 Japanese subjects] in the placebo group, 198 subjects [including 16 Japanese subjects] in the tofacitinib 5 mg group, and 196 subjects [including 12 Japanese subjects] in the tofacitinib 10 mg group[8)]) were included in the safety analysis set. Treatment was discontinued in 303 subjects (145 in the placebo group, 87 in the tofacitinib 5 mg group, and 71 in the tofacitinib 10 mg group). The reasons for discontinuation were "insufficient clinical response" in 255 subjects (132 in the placebo group, 70 in the tofacitinib 5 mg group, and 53 in the tofacitinib 10 mg group), "adverse events" in 21 subjects (7 in the placebo group, 5 in the tofacitinib 5 mg group, and 9 in the tofacitinib 10 mg group), "withdrawal of consent" in 15 subjects (5 in the placebo group, 6 in the tofacitinib 5 mg group, and 4 in the tofacitinib 10 mg group), "lost to follow-up" in 6 subjects (1 in the placebo group, 3 in the tofacitinib 5 mg group, and 2 in the tofacitinib 10 mg group), "pregnancy" in 2 subjects (1 each in the tofacitinib 5 mg and 10 mg groups), "protocol deviation" in 1 subjects (1 in the tofacitinib 10 mg group), and "other reasons" in 3 subjects (2 in the tofacitinib 5 mg group and 1 in the tofacitinib 10 mg group).

Table 16 shows the "remission rate at Week 52" as the primary endpoint. Statistically significant differences were observed both in the tofacitinib 5 mg and 10 mg groups compared with the placebo group (P <0.0001 in both groups, Cochran-Mantel-Haenszel χ^2 test, a two-sided significance level of 5%).

7) A subject who had not achieved clinical response in the remission induction study was assigned to the tofacitinib 5 mg group by mistake. The assignment was canceled on Day 2. This patient was not included in the FAS. No adverse event was reported by this patient.

8) A subject who was assigned to the tofacitinib 10 mg group withdrew consent, and did not receive the study drug.

Table 16. Remission rate at Week 52 (FAS)

	Placebo (N = 198)	Tofacitinib	
		5 mg (N = 198)	10 mg (N = 197)
Remission rate at Week 52 (n)[a)]	11.1% (22)	34.3% (68)	40.6% (80)
Between-group difference (Tofacitinib vs. placebo) [95%CI][b)]	–	23.2% [15.3, 31.2]	29.5% [21.4, 37.6]
P-value[c) d)]	–	<0.0001	<0.0001

a) Subjects with missing data were treated as those who failed to achieve remission (non-responders).
b) 95% CI was calculated using normal approximation for the difference.
c) Calculated using Cochran-Mantel-Haenszel $\chi 2$ test stratified by treatment group (i.e., the tofacitinib 10 mg group and placebo group) in the global phase III (Study A3921094) and foreign phase III (Study A3921095) studies for remission induction and achievement/non-achievement of remission at baseline.
d) A two-sided significance level of 5%; multiplicity adjustment was applied using graphical approaches including a closed testing procedure in which the test for the 5 mg group was performed only if the results for the 10 mg were statistically significant.

According to safety analyses for the overall study population, the incidence of adverse events was 75.3% (149 of 198 subjects) in the placebo group, 72.2% (143 of 198 subjects) in the tofacitinib 5 mg group, and 79.6% (156 of 196 subjects) in the tofacitinib 10 mg group, while the incidence of adverse drug reactions was 31.8% (63 of 198 subjects) in the placebo group, 36.9% (73 of 198 subjects) in the tofacitinib 5 mg group, and 49.5% (97 of 196 subjects) in the tofacitinib 10 mg group. According to safety analysis for the Japanese subpopulation, the incidence of adverse events was 72.7% (8 of 11 subjects) in the placebo group, 87.5% (14 of 16 subjects) in the tofacitinib 5 mg group, and 100% (12 of 12 subjects) in the tofacitinib 10 mg group, while the incidence of adverse drug reactions was 45.5% (5 of 11 subjects) in the placebo group, 50.0% (8 of 16 subjects) in the tofacitinib 5 mg group, and 58.3% (7 of 12 subjects) in the tofacitinib 10 mg group. Table 17 shows adverse events occurring in ≥5.0% of subjects in any group in the overall study population or those occurring in ≥2 subjects in any group in the Japanese subpopulation. Table 18 shows adverse drug reactions occurring in ≥5.0% of subjects in any group in the overall study population or those occurring in ≥2 subjects in any group in the Japanese subpopulation.

Table 17. Adverse events occurring in ≥5.0% of subjects in any group in the overall study population or those occurring in ≥2 subjects in any group in the Japanese subpopulation

Adverse event	Overall study population			Japanese subpopulation		
	Placebo (N = 198)	Tofacitinib		Placebo (N = 11)	Tofacitinib	
		5 mg (N = 198)	10 mg (N = 196)		5 mg (N = 16)	10 mg (N = 12)
Any adverse event	75.3 (149)	72.2 (143)	79.6 (156)	72.7 (8)	87.5 (14)	100 (12)
Colitis ulcerative	35.9 (71)	18.2 (36)	14.8 (29)	36.4 (4)	31.3 (5)	0 (0)
Nasopharyngitis	5.6 (11)	9.6 (19)	13.8 (27)	18.2 (2)	25.0 (4)	41.7 (5)
Arthralgia	9.6 (19)	8.6 (17)	8.7 (17)	18.2 (2)	0 (0)	0 (0)
Blood CK increased	2.0 (4)	3.0 (6)	6.6 (13)	0 (0)	0 (0)	16.7 (2)
Upper respiratory tract infection	3.5 (7)	6.6 (13)	6.1 (12)	0 (0)	6.3 (1)	0 (0)
Rash	4.0 (8)	3.0 (6)	5.6 (11)	0 (0)	0 (0)	16.7 (2)
Hypercholesterolaemia	1.0 (2)	2.0 (4)	5.6 (11)	0 (0)	0 (0)	8.3 (1)
Herpes zoster	0.5 (1)	1.0 (2)	5.1 (10)	0 (0)	0 (0)	0 (0)
Abdominal pain	5.6 (11)	2.5 (5)	3.6 (7)	0 (0)	0 (0)	0 (0)
Headache	6.1 (12)	8.6 (17)	3.1 (6)	0 (0)	12.5 (2)	0 (0)
Fatigue	5.6 (11)	4.0 (8)	2.0 (4)	0 (0)	6.3 (1)	0 (0)
Insomnia	0.5 (1)	1.5 (3)	0.5 (1)	0 (0)	12.5 (2)	8.3 (1)
Blood cholesterol increased	0 (0)	1.5 (3)	0.5 (1)	0 (0)	12.5 (2)	8.3 (1)
Restless legs syndrome	0 (0)	1.0 (2)	0 (0)	0 (0)	12.5 (2)	0 (0)

MedDRA/J ver. 19.0; incidence, % (n)

Table 18. Adverse drug reactions occurring in ≥5.0% of subjects in any group in the overall study population, or those occurring in ≥2 subjects in any group in the Japanese subpopulation

Adverse drug reaction	Overall study population			Japanese subpopulation		
	Placebo (N = 198)	Tofacitinib		Placebo (N = 11)	Tofacitinib	
		5 mg (N = 198)	10 mg (N = 196)		5 mg (N = 16)	10 mg (N = 12)
Any adverse drug reaction	31.8 (63)	36.9 (73)	49.5 (97)	45.5 (5)	50.0 (8)	58.3 (7)
Hypercholesterolaemia	0.5 (1)	2.0 (4)	5.1 (10)	0 (0)	0 (0)	8.3 (1)
Nasopharyngitis	1.5 (3)	4.5 (9)	4.6 (9)	0 (0)	12.5 (2)	0 (0)
Colitis ulcerative	5.1 (10)	4.0 (8)	3.6 (7)	18.2 (2)	0 (0)	0 (0)
Blood cholesterol increased	0 (0)	1.5 (3)	0.5 (1)	0 (0)	12.5 (2)	8.3 (1)

MedDRA/J ver. 19.0; incidence, % (n)

No deaths occurred. The incidence of serious adverse events was 6.6% (13 of 198 subjects) in the placebo group (“colitis ulcerative” [7], “malaise” [1], “colitis ulcerative/subcutaneous abscess” [1], “pancreatitis” [1], “embolism venous” [1], “diverticulitis” [1], and “invasive ductal breast carcinoma” [1]), 5.1% (10 of 198 subjects) in the tofacitinib 5 mg group (“colitis ulcerative” [2], “peritonsillar abscess” [1], “spondylolisthesis” [1], “lower limb fracture” [1], “lumbar vertebral fracture” [1], “chest pain” [1], “abortion spontaneous” [1], “myocardial infarction/gastrointestinal haemorrhage” [1], and “urinary tract infection” [1]), and 5.6% (11 of 196 subjects) in the tofacitinib 10 mg group (“diarrhoea” [1], “Bowen’s disease/squamous cell carcinoma of skin” [1], “bacterial diarrhoea” [1], “haemorrhagic stroke” [1], “sciatica” [1], “dermatitis acneiform” [1], “seizure/generalised tonic-clonic seizure/rash maculo-papular” [1], “cholecystitis acute/osteoarthritis/disease progression” [1], “spinal compression fracture” [1], “colitis ulcerative” [1], and “abdominal pain” [1]). Among these events, “subcutaneous abscess” (1) and “diverticulitis” (1) in the placebo group, “peritonsillar abscess” (1) in the tofacitinib 5 mg group, and “Bowen’s disease/squamous cell carcinoma of skin” (1), “generalised tonic-clonic seizure” (1), “bacterial diarrhoea” (1), “haemorrhagic stroke” (1), “dermatitis acneiform” (1), and

"seizure/generalised tonic-clonic seizure" (1) in the tofacitinib 10 mg group were considered adverse drug reactions. In the tofacitinib 10 mg group, the outcome of "dermatitis acneiform"[9] in 1 subject was reported as not resolved, and that of "haemorrhagic stroke"[10] in 1 subject was resolved with sequelae while the outcomes of adverse drug reactions in the remaining 7 subjects were reported either as resolved or resolving. The incidence of adverse events leading to treatment discontinuation was 18.7% (37 of 198 subjects) in the placebo group ("colitis ulcerative" [30], "arthralgia/myalgia" [1], "arthralgia" [1], "blood CK increased" [1], "pancreatitis" [1], "peripheral swelling" [1], "diverticulitis" [1], and "invasive ductal breast carcinoma" [1]), 9.1% (18 of 198 subjects) in the tofacitinib 5 mg group ("colitis ulcerative" [13], "dermatitis" [1], "peritonsillar abscess" [1], "urinary tract infection" [1], "myalgia" [1], and "fatigue" [1]), and 9.7% (19 of 196 subjects) in the 10 mg group ("colitis ulcerative" [10], "squamous cell carcinoma of skin" [1], "bacterial diarrhoea" [1], "haemorrhagic stroke" [1], "generalised tonic-clonic seizure" [1], "dermatitis acneiform" [1], "colon dysplasia" [1], "anaemia" [1], "alanine aminotransferase (ALT) increased/aspartate aminotransferase (AST) increased/blood alkaline phosphatase (ALP) increased/gamma-glutamyltransferase (GGT) increased" [1], and "blood CK increased" [1]). Among these events other than "colitis ulcerative", "blood CK increased" (1), and "diverticulitis" (1) in the placebo group, "dermatitis" (1), "peritonsillar abscess" (1), "myalgia" (1), and "fatigue" (1) in the tofacitinib 5 mg group, and "squamous cell carcinoma of skin" (1), "bacterial diarrhoea" (1), "haemorrhagic stroke" (1), "generalised tonic-clonic seizure" (1), "dermatitis acneiform" (1), "anaemia" (1), "AST increased/ALT increased/blood ALP increased/GGT increased" (1), and "blood CK increased" (1) in the tofacitinib 10 mg group were considered adverse drug reactions. The outcomes were reported as not resolved for the following events: "blood CK increased" (1) in the placebo group, "dermatitis"[11] (1), and "myalgia"[12] (1) in the tofacitinib 5 mg group, and "haemorrhagic stroke"[10] (1), "anaemia"[13] (1), "AST increased/ALT increased/blood ALP increased/GGT increased"[14] (1), and "blood CK increased"[15] (1) in the

9) A white female aged 31 years. The subject was assigned to the tofacitinib 10 mg group in the global phase III remission induction study (Study A3921094) and in the global phase III remission maintenance study (Study A3921096). In the global phase III remission maintenance study (Study A3921096), mild facial rash developed on Day 91, and swelling of the eyelids on Day 112; study treatment was discontinued on Day 281. In the global phase III remission maintenance study (Study A3921096), serious dermatitis acneiform developed on Day 283. On Day 292, this subject was withdrawn from the study. This event resolved on Day 311.

10) A white female aged 56 years. The subject was assigned to the tofacitinib 10 mg group in the global phase III remission induction study (Study A3921094) and in the global phase III remission maintenance study (Study A3921096). In the global phase III remission maintenance study (Study A3921096), haemorrhagic stroke with a primary symptom of right-sided paresis developed on Day 85, and the subject was withdrawn from the study. The event was determined as resolved with sequelae on Day 101.

11) A white female aged 47 years. The subject was assigned to the tofacitinib 10 mg group in the global phase III remission induction study (Study A3921094), and in the tofacitinib 5 mg group in the global phase III remission maintenance study (Study A3921096). In the global phase III remission induction study (Study A3921094), mild dermatitis in the periocular area developed on Day 62 (Day −2 in Study A3921096), and study treatment was discontinued on Day 48 in the global phase III remission maintenance study (Study A3921096). The event was persistent on Day 55, according to the final report.

12) A white female aged 44 years. The subject was assigned to the tofacitinib 10 mg group in the foreign phase III remission induction study (Study A3921095), and to the 5 mg group in the global phase III remission maintenance study (Study A3921096). In the global phase III remission maintenance study (Study A3921096), myalgia developed on Day 355, and study treatment was discontinued on Day 357. The event was persistent on Day 393, according to the final report.

13) A white female aged 18 years. The subject was assigned to the tofacitinib 10 mg group in the foreign phase III remission induction study (Study A3921095) and in the global phase III remission maintenance study (Study A3921096). Anaemia developed on Day 300 in the remission maintenance study, and study treatment was discontinued on Day 320. The event was persistent on Day 356, according to the final report.

14) A white female aged 54 years. The subject was assigned to the tofacitinib 10 mg group in the foreign phase III remission induction study (Study A3921095) and in the global phase III remission maintenance study (Study A3921096). In the remission maintenance study, AST increased/ALT increased/blood ALP increased/GGT increased developed on Day 123, and study treatment was discontinued on Day 237. The event was persistent on Day 267, according to the final report.

15) A male aged 65 years (unknown race). The subject was assigned to the tofacitinib 10 mg group in the foreign phase III remission induction study (Study A3921095) and in the global phase III remission maintenance study (Study A3921096). Moderate blood CK increased developed on Day 26 in the remission maintenance study. Because blood CK increased became severe on Day 283, study treatment was discontinued on Day 290. The event was persistent on Day 326, according to the final report.

tofacitinib 10 mg group. The outcomes of the remaining adverse drug reactions in 7 subjects were reported as resolved.

In the Japanese subpopulation, the incidence of serious adverse events was 18.2% (2 of 11 subjects) in the placebo group ("embolism venous" [1] and "diverticulitis" [1]), 0% in the tofacitinib 5 mg group (0 of 16 subjects), and 0% in the 10 mg group (0 of 12 subjects). The case of "diverticulitis" (1) in the placebo group was considered a serious adverse drug reaction, with its outcome being reported as resolved.

In the Japanese subpopulation, the incidence of adverse events leading to treatment discontinuation was 36.4% (4 of 11 subjects) in the placebo group, 25.0% (4 of 16 subjects) in the tofacitinib 5 mg group, and 0% (0 of 12 subjects) in the tofacitinib 10 mg group. After exclusion of the cases of "colitis ulcerative" from the analysis, the incidence of adverse events leading to treatment discontinuation in the Japanese subpopulation is 9.1% (1 of 11 subjects) in the placebo group ("diverticulitis"), 0% (0 of 16 subjects) in the tofacitinib 5 mg group, and 0% (0 of 12 subjects) in the tofacitinib 10 mg group. The adverse event in the placebo group was considered an adverse drug reaction, and categorized as serious adverse event. The outcome the event was reported as resolved.

7.2.4 Global long-term extension study (CTD 5.3.5.2.1, Study A3921139 [October 2012 to July 2016 (ongoing until approval date,[16] planned)])

A multicenter, open-label, uncontrolled study was conducted at 215 centers (including 21 centers in Japan) in 31 countries including Japan to investigate the long-term safety and other aspects of tofacitinib in the following patients (Table 19): patients who were non-responders after completing either the global phase III remission induction study (Study A3921094) or the foreign phase III remission induction study (Study A3921095); patients who demonstrated treatment failure and then discontinued treatment in the global phase III remission maintenance study (Study A3921096); and patients who completed the global remission maintenance study (Study A3921096).

Table 19. Key inclusion criteria[a)]

Patients who meet either of the following criteria: • Patients who completed a 52-week maintenance therapy, or patients who demonstrated treatment failure and then discontinued treatment, in the global phase III remission maintenance study (Study A3921096). Treatment failure: After ≥8 weeks of treatment with the study drug, an increase from baseline in Mayo score of ≥3 points, an increase in rectal bleeding subscore of ≥1 point, an increase in endoscopic subscore of ≥1 point, and the absolute endoscopic subscore of ≥2[b)] • Patients who were non-responders after completing 8-week treatment and whose endoscopic subscore at Week 8 was greater than the baseline value in the global phase III remission induction study (Study A3921094) or the foreign phase III remission induction study (Study A3921095).

a) The eligibility of patients to participate in the extension study was evaluated at the Week 8/Week 9 visit in the phase III remission induction studies (Studies A3921094 and A3921095) for non-responders, at the Week 52 or Week 53 visit in the global phase III remission maintenance study (Study A3921096) for those who completed the study, or at the visit for discontinuation for those who discontinued study treatment due to treatment failure.
b) After the protocol amendment dated August 6, 2015, patients who had an endoscopic subscore of 3 (maximum value) and had an endoscopic subscore of 3 also at baseline were defined as "treatment failure" as long as all the criteria except endoscopic subscore were met.

The dosage regimen for this study is shown in Table 20. Subjects who were in remission at baseline of this study received tofacitinib 5 mg twice daily orally (tofacitinib 5 mg group), and subjects who were not in

16) The study will continue until the first marketing approval is acquired in a major global market.

remission at baseline received tofacitinib 10 mg twice daily orally (tofacitinib 10 mg group). The dose was allowed to be adjusted in subjects meeting the dose adjustment criteria.[17] Patients who had been on oral 5-ASA, oral sulfasalazine, or an antibiotic for the treatment of UC were allowed to continue the therapy unless the dose was changed. Patients who had been on oral steroids (≤25 mg/day of prednisone or its equivalents, or ≤9 mg/day of budesonide) were required to taper their steroid dose as follows: The dose of prednisone (or its equivalents) was tapered off by 5 mg every week to 20 mg/day, then by 2.5 to 5.0 mg every week to 10 mg/day, and then by 2.5 mg every week to 0 mg (patients who had been on oral budesonide [≤9 mg/day] were required to taper the steroid dose by 3 mg every 3 weeks).

Table 20. Dosage regimen of tofacitinib in the global long-term extension study (Study A3921139)

Starting dose	Based on the remission status at baseline of the study, the starting dose was determined as follows: **Tofacitinib 5 mg: patients in remission at baseline of the study** • Patients who achieved remission at Week 52 of the global phase III remission maintenance study (Study A3921096) **Tofacitinib 10 mg: patients not in remission at baseline of the study** • Patients who failed to achieve remission at Week 52, or who discontinued study treatment due to treatment failure, in the global phase III remission maintenance study (Study A3921096) • Patients who were non-responders after completing the phase III remission induction study (Study A3921094 or A3921095).
Method of dose adjustment	For patients who received tofacitinib for ≥8 weeks in this study, dose adjustment is allowed once only during the study period, as follows: **Increasing the tofacitinib dose from 5 mg to 10 mg** If a loss of clinical response is noted and relapse is confirmed by endoscopic examination, the tofacitinib dose may be increased from 5 mg to 10 mg. **Decreasing the tofacitinib dose from 10 mg to 5 mg** If any safety and tolerability concerns arise, the tofacitinib dose may be decreased from 10 mg to 5 mg.

All 914 subjects participating in this study (156 subjects [including 10 Japanese subjects] in the tofacitinib 5 mg group and 758 subjects [including 40 Japanese subjects] in the tofacitinib 10 mg group) received the study drug, and were included in the FAS and the safety analysis set. Treatment was discontinued in 381 subjects (17 subjects in the tofacitinib 5 mg group and 364 subjects in the tofacitinib 10 mg group). The reasons for discontinuation were “insufficient clinical response” in 283 subjects (7 subjects in the tofacitinib 5 mg group and 276 subjects in the tofacitinib 10 mg group), “withdrawal of consent” in 42 subjects (2 subjects in the tofacitinib 5 mg group and 40 subjects in the tofacitinib 10 mg group), “adverse events” in 39 subjects (6 subjects in the tofacitinib 5 mg and 33 subjects in the tofacitinib 10 mg group), “protocol deviation” in 5 subjects (1 subject in the tofacitinib 5 mg group and 4 subjects in the tofacitinib 10 mg group), “lost to follow-up” in 4 subjects (1 subject in the tofacitinib 5 mg group and 3 subjects in the tofacitinib 10 mg group), “pregnancy” (4 subjects in the tofacitinib 10 mg group), and “other reasons” in 4 subjects (4 subjects in the tofacitinib 10 mg group).

Efficacy analysis was performed. The “remission rate at Month 24” was 46.7% (7 of 15 subjects) in the tofacitinib 5 mg group and 27.5% (93 of 338 subjects) in the tofacitinib 10 mg group.

17) When the clinical study was initiated, dose adjustment was allowed once only. After the protocol amendment dated August 6, 2015, dose adjustment was allowed more than once. Investigators were required to discuss with the sponsor if dose adjustment was needed 3 times or more.

According to safety analyses for the overall study population, the incidence of adverse events was 64.7% (101 of 156 subjects) in the tofacitinib 5 mg group and 74.1% (562 of 758 subjects) in the tofacitinib 10 mg group. The incidence of adverse drug reactions was 37.2% (58 of 156 subjects) in the tofacitinib 5 mg group and 44.2% (335 of 758 subjects) in the tofacitinib 10 mg group. According to safety analyses for the Japanese subpopulation, the incidence of adverse events was 80.0% (8 of 10 subjects) in the tofacitinib 5 mg group and 82.5% (33 of 40 subjects) in the tofacitinib 10 mg group, while the incidence of adverse drug reactions was 60.0% (6 of 10 subjects) in the tofacitinib 5 mg group and 47.5% (19 of 40 subjects) in the tofacitinib 10 mg group.

Table 21 shows adverse events occurring in ≥5.0% of subjects in either group in the overall study population or those occurring in ≥2 subjects in either group in the Japanese subpopulation. Table 22 shows adverse drug reactions occurring in ≥5.0% of subjects in either group in the overall study population or those occurring in ≥2 subjects in either group in the Japanese subpopulation.

Table 21. Adverse events occurring in ≥5.0% of subjects in either group in the overall study population or those occurring in ≥2 subjects in either group in the Japanese subpopulation

Adverse event	Overall study population		Japanese subpopulation	
	Tofacitinib 5 mg (N = 156)	Tofacitinib 10 mg (N = 758)	Tofacitinib 5 mg (N = 10)	Tofacitinib 10 mg (N = 40)
Any adverse event	64.7 (101)	74.1 (562)	80.0 (8)	82.5 (33)
Nasopharyngitis	11.5 (18)	14.5 (110)	30.0 (3)	42.5 (17)
Colitis ulcerative	12.2 (19)	13.9 (105)	10.0 (1)	10.0 (4)
Blood CK increased	5.1 (8)	7.7 (58)	0 (0)	5.0 (2)
Upper respiratory tract infection	4.5 (7)	7.0 (53)	0 (0)	0 (0)
Arthralgia	4.5 (7)	6.7 (51)	0 (0)	5.0 (2)
Abdominal pain	2.6 (4)	5.1 (39)	0 (0)	0 (0)
Influenza	6.4 (10)	4.4 (33)	0 (0)	5.0 (2)
Herpes zoster	4.5 (7)	4.1 (31)	10.0 (1)	12.5 (5)
Gastroenteritis	2.6 (4)	4.1 (31)	0 (0)	5.0 (2)
Oral herpes	0.6 (1)	2.2 (17)	10.0 (1)	7.5 (3)
Haemorrhoids	0.6 (1)	2.1 (16)	10.0 (1)	5.0 (2)
Abdominal pain upper	0 (0)	2.1 (16)	0 (0)	5.0 (2)
Insomnia	0 (0)	1.8 (14)	0 (0)	5.0 (2)
Blood cholesterol increased	0 (0)	1.7 (13)	0 (0)	12.5 (5)
Pharyngitis	2.6 (4)	1.1 (8)	20.0 (2)	0 (0)
Abdominal distension	0 (0)	1.1 (8)	0 (0)	5.0 (2)
Dental caries	0.6 (1)	0.9 (7)	0 (0)	10.0 (4)
Cataract	0 (0)	0.5 (4)	0 (0)	5.0 (2)
Herpes simplex	0 (0)	0.5 (4)	0 (0)	5.0 (2)
Asthma	0.6 (1)	0.4 (3)	10.0 (1)	5.0 (2)

MedDRA/J ver. 19.0; incidence, % (n)

Table 22. Adverse drug reactions occurring in ≥5.0% of subjects in either group in the overall study population, or those occurring in ≥2 subjects in either group in the Japanese subpopulation

Adverse drug reaction	Overall study population		Japanese subpopulation	
	Tofacitinib 5 mg (N = 156)	Tofacitinib 10 mg (N = 758)	Tofacitinib 5 mg (N = 10)	Tofacitinib 10 mg (N = 40)
Any adverse drug reaction	37.2 (58)	44.2 (335)	60.0 (6)	47.5 (19)
Nasopharyngitis	4.5 (7)	5.9 (45)	10.0 (1)	12.5 (5)
Blood CK increased	3.8 (6)	5.7 (43)	0 (0)	2.5 (1)
Herpes zoster	3.2 (5)	2.9 (22)	10.0 (1)	12.5 (5)
Oral herpes	0.6 (1)	2.0 (15)	10.0 (1)	5.0 (2)
Blood cholesterol increased	0 (0)	1.3 (10)	0 (0)	12.5 (5)
Herpes simplex	0 (0)	0.5 (4)	0 (0)	5.0 (2)

MedDRA/J ver. 19.0; incidence, % (n)

Death occurred in 3 subjects in the tofacitinib 10 mg group ("acute myeloid leukaemia,"[18)] "hepatic angiosarcoma,"[19)] and "pulmonary embolism"[20)]), and among these events, "hepatic angiosarcoma" in 1 subject was considered an adverse drug reaction. The incidence of serious adverse events was 7.1% (11 of 156 subjects) in the tofacitinib 5 mg group and 11.1% (84 of 758 subjects[21)]) in the tofacitinib 10 mg group. Serious adverse events occurring in ≥2 subjects in either group were "colitis ulcerative" (1.3% [2 of 156 subjects] in the tofacitinib 5 mg group and 4.1% [31 of 758 subjects] in the tofacitinib 10 mg group), "pulmonary embolism" (0% [0 of 156 subjects] in the tofacitinib 5 mg group and 0.5% [4 of 758 subjects] in the tofacitinib 10 mg group), "appendicitis" (0.6% [1 of 156 subjects] in the tofacitinib 5 mg group and 0.3% [2 of 758 subjects] in the tofacitinib 10 mg group) as well as the following events: "anaemia," "abdominal pain," "proctitis," "renal colic," and "ureterolithiasis" (each adverse event occurred in 0% [0 of 156] of subjects in the tofacitinib 5 mg group and 0.3% [2 of 758] of subjects in the tofacitinib 10 mg group). The incidence of serious adverse drug reactions was 1.3% (2 of 156 subjects) in the tofacitinib 5 mg group ("tonsillitis/myocarditis" [1] and "pulmonary mass" [1]) and 2.1% (16 of 758 subjects) in the tofacitinib 10 mg group ("colitis ulcerative" [2], "calculus urinary/ureteric obstruction/thrombosis" [1], "lower respiratory tract infection" [1], "chest pain" [1], "hepatic angiosarcoma" [1], "arthritis bacterial" [1], "tuberculosis" [1], "cholangiocarcinoma/metastases to peritoneum" [1], "squamous cell carcinoma" [1], "leiomyosarcoma" [1], "Epstein-Barr-virus [EBV] associated lymphoma" [1], "cytomegalovirus hepatitis" [1], "renal cell carcinoma" [1], "atypical pneumonia" [1], and

18) A white male aged 52 years. The subject was assigned to the tofacitinib 10 mg group in the foreign phase III remission induction study (Study A3921095), the placebo group in the global phase III remission maintenance study (Study A3921096), and the tofacitinib 10 mg group in the global long-term extension study (Study A3921139). In the long-term extension study, leukopenia and neutropenia developed on Day 267, and study treatment was discontinued on Day 283 due to the events. Acute myeloid leukaemia developed 27 days after the end of treatment, and the subject died of the event 51 days after the end of treatment. The event was considered unrelated to the study drug.

19) A white male aged 53 years. The subject was assigned to the tofacitinib 10 mg group in the global phase III remission induction study (Study A3921094), the placebo group in the global phase III remission maintenance study (Study A3921096), and the tofacitinib 10 mg group in the global long-term extension study (Study A3921139). In the long-term extension study, hepatic angiosarcoma was noted on Day 120, and study treatment was discontinued on Day 123 due to the event. On Day 164, a liver biopsy was performed, and subsequently haemoperitoneum occurred. The subject died of hepatic angiosarcoma on Day 168. The possibility of a causal relationship between the event and the study drug could not be ruled out.

20) A white male aged 68 years. The subject was assigned to the tofacitinib 15 mg group in the global phase III remission induction study (Study A3921094), the placebo group in the global phase III remission maintenance study (Study A3921096), and the tofacitinib 10 mg group in the global long-term extension study (Study A3921139). In the long-term extension study, cholangiocarcinoma was noted on Day 368. On Day 378, the subject was hospitalized with a complaint of abdominal pain, and study treatment was discontinued. Metastasis of cholangiocarcinoma to peritoneum and pulmonary embolism were noted on Day 383. The subject died of pulmonary embolism on Day 384. The events were considered unrelated to the study drug.

21) A severe case of colitis ulcerative in 1 subject in the tofacitinib 10 mg group was reported as a serious adverse event after administration of the study drug. However, because severe colitis ulcerative had been noted prior to assignment, it was not classified as an adverse event observed during the clinical study. This case of colitis ulcerative was thus not included in the adverse event data.

"histoplasmosis" [1]). The outcome of "hepatic angiosarcoma"[19] (1) in the tofacitinib 10 mg group was reported as death, and the outcomes of "pulmonary mass"[22] (1) in the 5 mg group and "tuberculosis"[23] (1) and "cholangiocarcinoma/metastases to peritoneum"[24] (1) in the tofacitinib 10 mg group were reported as not resolved. The outcomes of the remaining adverse drug reactions in 14 subjects were reported as either resolved or resolving. The incidence of adverse events leading to treatment discontinuation was 4.5% (7 of 156 subjects) in the tofacitinib 5 mg group and 12.1% (92 of 758 subjects) in the tofacitinib 10 mg group. Adverse events leading to treatment discontinuation in ≥2 subjects in either group were "colitis ulcerative" (0.6% [1 of 156 subjects] in the tofacitinib 5 mg group and 7.8% [59 of 758 subjects] in the tofacitinib 10 mg group), "fatigue" (0% [0 of 156 subjects] in the tofacitinib 5 mg group and 0.4% [3 of 758 subjects] in the tofacitinib 10 mg group), "anaemia" (0% [0 of 156 subjects] in the tofacitinib 5 mg group and 0.3% [2 of 758 subjects] in the tofacitinib 10 mg group), "abdominal pain" (0% [0 of 156 subjects] in the tofacitinib 5 mg group and 0.3% [2 of 758 subjects] in the tofacitinib 10 mg group), and "blood CK increased" (0% [0 of 156 subjects] in the tofacitinib 5 mg group and 0.3% [2 of 758 subjects] in the tofacitinib 10 mg group). The incidence of adverse drug reactions leading to treatment discontinuation was 2.6% (4 of 156 subjects) in the tofacitinib 5 mg group and 3.8% (29 of 758 subjects) in the tofacitinib 10 mg group. Adverse drug reactions leading to treatment discontinuation in ≥2 subjects in either group were "colitis ulcerative" (0% [0 of 156 subjects] in the tofacitinib 5 mg group and 1.5% [11 of 758 subjects] in the tofacitinib 10 mg group), "fatigue" (0% [0 of 156 subjects] in the tofacitinib 5 mg group and 0.3% [2 of 758 subjects] in the tofacitinib 10 mg group), and "blood CK increased" (0% [0 of 156 subjects] in the tofacitinib 5 mg group and 0.3% [2 of 758 subjects] in the tofacitinib 10 mg group).

In the Japanese subpopulation, the incidence of serious adverse events was 10.0% (1 of 10 subjects) in the tofacitinib 5 mg group ("tonsillitis/myocarditis/colitis ulcerative") and 12.5% (5 of 40 subjects) in the 10 mg group ("colitis ulcerative" [2], "prerenal failure" [1], "enteritis infectious" [1], and "cataract" [1]). "Tonsillitis/myocarditis" (1) in the tofacitinib 5 mg group and "colitis ulcerative" (1) in the 10 mg group were considered serious adverse drug reactions. The outcomes of both events were reported as resolved. In the Japanese subpopulation, the incidence of adverse events leading to treatment discontinuation was 10.0% (1 of 10 subjects) in the tofacitinib 5 mg group ("myocarditis/colitis ulcerative") and 12.5% (5 of 40 subjects) in the tofacitinib 10 mg group ("colitis ulcerative" [3], "enteritis infectious" [1], and "hypoaesthesia" [1]). Among these events, "myocarditis" (1) in the tofacitinib 5 mg group and "hypoaesthesia" (1) in the tofacitinib 10 mg

22) A white male aged 74 years. The subject was assigned to the tofacitinib 10 mg group in the foreign phase III remission induction study (Study A3921095), the tofacitinib 10 mg group in the global phase III remission maintenance study (Study A3921096), and the tofacitinib 5 mg group in the global long-term extension study (Study A3921139). In the long-term extension study, multiple pulmonary nodules were noted on Day 226, and study treatment was discontinued on Day 237. On Day 269, the subject underwent a lung biopsy, which revealed poorly differentiated carcinoma and lymphatic invasion. The events were persistent on Day 274, according to the final report.

23) A white male aged 57 years. The subject was assigned to the placebo group in the global phase III remission induction study (Study A3921094), and the tofacitinib 10 mg group in the global long-term extension study (Study A3921139). In the long-term extension study, abdominal pain, vomiting, and pyrexia developed on Day 391. The subject had a positive result of the Quantiferon TB Gold test on Day 434, and study treatment was discontinued on Day 435. The subject had a diagnosis of tuberculosis on Day 451. The outcome of this event was reported as not resolved.

24) A white male aged 68 years. The subject was assigned to the tofacitinib 15 mg group in the global phase III remission induction study (Study A3921094), the placebo group in the global phase III remission maintenance study (Study A3921096), and the tofacitinib 10 mg group in the global long-term extension study (Study A3921139). In the long-term extension study, cholangiocarcinoma was noted on Day 368, and study drug treatment was discontinued on Day 378. Metastasis of cholangiocarcinoma to peritoneum and pulmonary embolism were noted on Day 383, and the subject died of pulmonary embolism on Day 384. Cholangiocarcinoma and its metastasis to peritoneum were considered related to the study drug, whereas the pulmonary embolism was considered unrelated to the study drug.

group were considered adverse drug reactions. The outcomes of “myocarditis” and “hypoaesthesia” were reported as resolved and not resolved, respectively.

7.R Outline of the review conducted by PMDA

7.R.1 Enrollment of Japanese patients in global phase III studies conducted in patients with UC

The applicant’s explanation about the enrollment of Japanese patients in global phase III studies:
Intrinsic ethnic factors were addressed at the review of the initial application for tofacitinib, and the results of clinical studies in healthy Japanese and non-Japanese adults showed no clinically significant differences in the pharmacokinetics of tofacitinib (See “Review Report on Xeljanz Tablets 5 mg,” dated on February 28, 2013). Nor were there any clinically significant differences in the pharmacokinetics of tofacitinib in Japanese and non-Japanese patients with UC [See Section 6.R.1]. As for extrinsic ethnic factors, the approach to the medical treatment of UC in Japan is similar to that in Europe/the US. In addition, the Mayo score, which was used as an efficacy outcome measure, is a UC activity index used widely around the world. Because the Mayo score system has been used in clinical trials for new drug development, there is no particular problem with using the Mayo score system to evaluate the efficacy of tofacitinib. Based on the above, the enrollment of Japanese patients in the global phase III studies poses no concerns.

PMDA’s view:
It is acceptable that Japanese patients were enrolled in the global phase III studies in patients with UC.

7.R.2 Efficacy

PMDA’s view:
Based on the consideration and confirmation in Sections 7.R.2.1 and 7.R.2.2, the effects of tofacitinib in inducing and maintaining remission in patients with moderately to severely active UC who had not adequately responded to conventional treatments were demonstrated by the data submitted.

The final decision on the efficacy of tofacitinib will be made, taking account of comments from the Expert Discussion.

7.R.2.1 Treatment of active UC

7.R.2.1.1 Primary endpoint

The applicant’s explanation about the primary endpoint results from both the global phase III remission induction study (Study A3921094) and the foreign phase III remission induction study (Study A3921095):
The “remission rate at Week 8” was the primary endpoint of both the global phase III remission induction study (Study A3921094) and the foreign phase III remission induction study (Study A3921095). The primary endpoint results demonstrated the superiority of tofacitinib 10 mg over placebo in both studies [See Sections 7.2.1 and 7.2.2]. The results for the primary endpoint in the overall study population and Japanese subpopulation in the global phase III remission induction study (Study A3921094) are presented in Table 23. The results showed that there were no significant differences between the overall study population and the Japanese subpopulation. In the global phase III remission induction study (Study A3921094), there was a

concern over the possibility that blindness was not maintained in 3 Japanese patients.[25)] The 3 patients in question were therefore excluded from the FAS, and the resulting population was defined as the modified FAS (mFAS), which was used for an additional efficacy analysis (sensitivity analysis). Table 24 shows the results for the "remission rate at Week 8" in the mFAS of the global phase III remission induction study (Study A3921094), indicating that the results were similar to those in the FAS.

Based on the above findings, the remission-inducing effect of tofacitinib in patients with moderately to severely active UC was demonstrated.

Table 23. Remission rate at Week 8 in the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095) (FAS)

	Global phase III remission induction study (Study A3921094)				Foreign phase III remission induction study (Study A3921095)	
	Overall study population		Japanese subpopulation		Overall study population	
	Placebo (N = 122)	Tofacitinib 10 mg (N = 476)	Placebo (N = 13)	Tofacitinib 10 mg (N = 49)	Placebo (N = 112)	Tofacitinib 10 mg (N = 429)
Remission rate at Week 8 (n)[a)]	8.2% (10)	18.5% (88)	7.7% (1)	22.4% (11)	3.6% (4)	16.6% (71)
Between group difference (Tofacitinib vs. placebo) [95%CI][b)]	–	10.3% [4.3, 16.3]	–	14.8% [−3.9, 33.4]	–	13.0% [8.1, 17.9]

a) Subjects with missing data were treated as those who failed to achieve remission (non-responders).
b) 95% CI was calculated using normal approximation for the difference.

Table 24. Remission rate at Week 8 in the global phase III remission induction study (Study A3921094) (mFAS)

	Overall study population		Japanese subpopulation	
	Placebo (N = 122)	Tofacitinib 10 mg (N = 473)	Placebo (N = 13)	Tofacitinib 10 mg (N = 46)
Remission rate at Week 8 (n)[a)]	8.2% (10)	18.6% (88)	7.7% (1)	23.9% (11)
Between group difference (Tofacitinib vs. placebo) [95%CI][b)]	–	10.4% [4.4, 16.4]	–	16.2% [−2.8, 35.2]

a) Subjects with missing data were treated as those who failed to achieve remission (non-responders).
b) 95% CI was calculated using normal approximation for the difference.

7.R.2.1.2 Major secondary endpoints

The applicant's explanation about the major secondary endpoint results from the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095):

Table 25 shows the "mucosal healing rate at Week 8" and the "clinical response rate at Week 8," which were the major secondary endpoints in the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095). The results tended to be higher in the tofacitinib 10 mg group than in the placebo group for both endpoints. The trend in the Japanese subpopulation were similar to that in the overall study population, and the results tended to be higher in the tofacitinib 10 mg group than in the placebo group for both endpoints.

25) The right to access unblinded information was mistakenly given for a certain period of time to a monitor who was in charge of clinical trial sites in Japan. During that period, the monitor was engaged in monitoring data from 3 subjects, and blindness was potentially not maintained for these subjects. For this reason, the sponsor, before unblinding, decided to exclude the 3 subjects in question from the FAS, define the resulting population as the mFAS, and perform an additional efficacy analysis (sensitivity analysis).

Table 25. Mucosal healing rate or clinical response rate at Week 8 in the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095) (FAS)

	Global phase III remission induction study (Study A3921094)				Foreign phase III remission induction study (Study A3921095)	
	Overall study population		Japanese subpopulation		Overall study population	
	Placebo (N = 122)	Tofacitinib 10 mg (N = 476)	Placebo (N = 13)	Tofacitinib 10 mg (N = 49)	Placebo (N = 112)	Tofacitinib 10 mg (N = 429)
Mucosal healing rate at Week 8 (n)[a)]	15.6% (19)	31.3% (149)	15.4% (2)	30.6% (15)	11.6% (13)	28.4% (122)
Between group difference (Tofacitinib vs. placebo) [95%CI][b)]	–	15.7% [8.1, 23.4]	–	15.2% [−8.2, 38.7]	–	16.8% [9.5, 24.1]
Clinical response rate at Week 8 (n)[a)]	32.8% (40)	59.9% (285)	23.1% (3)	69.4% (34)	28.6% (32)	55.0% (236)
Between group difference (Tofacitinib vs. placebo) [95%CI][b)]	–	27.1% [17.7, 36.5]	–	46.3% [20.0, 72.6]	–	26.4% [16.8, 36.0]

a) Subjects with missing data were treated as those who failed to achieve mucosal healing or improved clinical response (non-responders).
b) 95% CI was calculated using normal approximation for the difference.

7.R.2.1.3 Efficacy by baseline demographics and disease characteristics of patients

The applicant's explanation about the remission rate by baseline demographics and disease characteristics of patients in the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095):

Table 26 shows the "remission rate at Week 8" by major baseline demographics and disease characteristics of patients in the pooled data from the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095). In all subgroups, the remission rate tended to be higher in the tofacitinib 10 mg group than in the placebo group.

Table 26. Remission rate at Week 8 by major baseline demographics and disease characteristics of patients (pooled data from the global phase III remission induction study [Study A3921094] and foreign phase III remission induction study [Study A3921095]) (FAS)

Baseline demographics and disease characteristics of patients	Placebo (N = 234)	Tofacitinib 10 mg (N = 905)	Between group difference (Tofacitinib vs. placebo) [95%CI]
Sex			
Male	5.3 (7/132)	15.3 (82/536)	10.0 [5.1, 14.9]
Female	6.9 (7/102)	20.9 (77/369)	14.0 [7.6, 20.4]
Disease duration			
<6 years	8.7 (10/115)	19.0 (83/437)	10.3 [4.0, 16.6]
≥6 years	3.4 (4/119)	16.2 (76/468)	12.9 [8.2, 17.5]
Disease type			
Proctosigmoiditis	14.3 (5/35)	19.7 (26/132)	5.4 [−8.0, 18.8]
Left-sided colitis	7.9 (6/76)	19.9 (61/307)	12.0 [4.4, 19.5]
Universal colitis/pancolitis	2.5 (3/122)	15.6 (72/463)	13.1 [8.8, 17.4]
Mayo score at baseline			
<8	7.5 (3/40)	33.6 (48/143)	26.1 [14.8, 37.3]
≥8 and <11	7.2 (11/152)	16.2 (100/618)	8.9 [3.9, 14.0]
≥11	0.0 (0/41)	7.7 (11/142)	7.7 [3.3, 12.1]
Oral steroid use at baseline			
No	5.0 (6/121)	18.1 (89/493)	13.1 [7.9, 18.2]
Yes	7.1 (8/113)	17.0 (70/412)	9.9 [4.0, 15.9]
Prior TNF inhibitor exposure			
No	12.5 (13/104)	23.7 (99/417)	11.2 [3.7, 18.8]
Yes	0.8 (1/130)	12.3 (60/488)	11.5 [8.2, 14.8]
Prior TNF inhibitor failure[a)]			
No	11.8 (13/110)	24.1 (106/440)	12.3 [5.0, 19.5]
Yes	0.8 (1/124)	11.4 (53/465)	10.6 [7.3, 13.9]
Reason for TNF inhibitor failure			
Primary non-responder[b)]	1.4 (1/74)	7.5 (19/253)	6.2 [2.0, 10.3]
Secondary non-responder[c)]	0.0 (0/43)	16.6 (31/187)	16.6 [11.2, 21.9]

Remission rate, % (n/N)

a) Includes patients who failed to achieve clinical response to ≥2 TNF inhibitors and patients who were primary non-responder to TNF inhibitors.
b) Patients who had an inadequate clinical response to TNF inhibitor induction therapy or who failed to achieve clinical response due to poor tolerability.
c) Patients who had clinical response to TNF inhibitor therapy, but subsequently had reduced response, a loss of response, or intolerance to the TNF inhibitor in the maintenance therapy.

PMDA's view on the efficacy of tofacitinib in the treatment of active UC, based on the discussions in Sections 7.R.2.1.1 through 7.R.2.1.3:

The results of the global phase III remission induction study (Study A3921094) demonstrated the superiority of tofacitinib 10 mg over placebo in terms of the "remission rate at Week 8" as the primary endpoint. In the Japanese subpopulation, the remission rate was higher in the tofacitinib 10 mg group than in the placebo group, indicating that there were no trends inconsistent with the results for the overall study population, though it should be noted that the results for the Japanese subpopulation are based on data from a limited number of patients (Tables 23 and 24). Further, data for the major secondary endpoints (mucosal healing rate and clinical response rate), and efficacy data by baseline demographics and disease characteristics of patients raised no particular concerns (Tables 25 and 26). Based on the above, the remission-inducing effect of tofacitinib in patients with moderately to severely active UC who had not adequately responded to conventional treatments was demonstrated by the data submitted, and tofacitinib can be expected to be effective in the Japanese

subpopulation. However, because only a very limited number of Japanese patients with UC participated in the global phase III remission induction study (Study A3921094), information on the efficacy of tofacitinib in Japanese patients with UC should continue to be collected through post-marketing surveillance.

7.R.2.2 Maintenance of remission in UC

7.R.2.2.1 Primary endpoint

The applicant's explanation about the primary endpoint results of the global phase III remission maintenance study (Study A3921096):

The "remission rate at Week 52" as the primary endpoint of the global phase III remission maintenance study (Study A3921096) demonstrated the superiority of both tofacitinib 5 mg and 10 mg over placebo [See Section 7.2.3]. The results of the Japanese subpopulation tended to be consistent with those of the overall study population (Table 27).

Subjects on placebo who had achieved a clinical response either in the global phase III remission induction study (Study A3921094) or the foreign phase III remission induction study (Study A3921095) also participated in the global phase III remission maintenance study (Study A3921096). The "remission rate at Week 52" was also analyzed for patients who had achieved clinical response in the tofacitinib 10 mg group in the global phase III remission induction study (Study A3921094) or the foreign phase III remission induction study (Study A3921095) before participating in the global phase III remission maintenance study (Study A3921096) (174 subjects in the placebo group, 176 subjects in the tofacitinib 5 mg group, and 173 subjects in the tofacitinib 10 mg group) (Table 28). In this patient subgroup, the remission rate was higher in the tofacitinib 5 mg and 10 mg groups than in the placebo group, which was consistent with the results in the FAS.

Based on the above, the data support the remission-maintaining effect of tofacitinib in patients with UC.

Table 27. Remission rate at Week 52 in the global phase III remission maintenance study (Study A3921096) (FAS)

	Overall study population			Japanese subpopulation		
	Placebo (N = 198)	Tofacitinib		Placebo (N = 11)	Tofacitinib	
		5 mg (N = 198)	10 mg (N = 197)		5 mg (N = 16)	10 mg (N = 12)
Remission rate (n)[a)]	11.1% (22)	34.3% (68)	40.6% (80)	9.1% (1)	31.3% (5)	66.7% (8)
Between group difference (Tofacitinib vs. placebo) [95%CI][b)]	–	23.2% [15.3, 31.2]	29.5% [21.4, 37.6]	–	22.2% [−6.2, 50.5]	57.6% [26.0, 89.2]

a) Subjects with missing data were treated as those who failed to achieve remission (non-responders).
b) 95% CI was calculated using normal approximation for the difference.

Table 28. Remission rate at Week 52 in patients who participated in the global phase III remission maintenance study (Study A3921096) after achieving clinical response to tofacitinib in the global phase III remission induction study (Study A3921094) or the foreign phase III remission induction study (Study A3921095)

	Overall study population			Japanese subpopulation		
	Placebo (N = 174)	Tofacitinib		Placebo (N = 11)	Tofacitinib	
		5 mg (N = 176)	10 mg (N = 173)		5 mg (N = 13)	10 mg (N = 12)
Remission rate (n)[a)]	10.3% (18)	32.4% (57)	41.0% (71)	9.1% (1)	38.5% (5)	66.7% (8)
Between group difference (Tofacitinib vs. placebo) [95%CI][b)]	–	22.0% [13.8, 30.3]	30.7% [22.1, 39.3]	–	29.4% [−2.1, 60.8]	57.6% [26.0, 89.2]

a) Subjects with missing data were treated as those who failed to achieve remission (non-responders).
b) 95% CI was calculated using normal approximation for the difference.

7.R.2.2.2 Major secondary endpoints

The applicant's explanation about the results for major secondary endpoints in the global phase III remission maintenance study (Study A3921096):

Table 29 shows the "mucosal healing rate at Week 52" and the "clinical response rate at Week 52," which were the major secondary endpoints in the global phase III remission maintenance study (Study A3921096). The results tended to be higher in the tofacitinib 5 mg and 10 mg groups than in the placebo group for both endpoints. The trend in the Japanese subpopulation was similar to that in the overall study population, and the results tended to be higher in the tofacitinib 5 mg and 10 mg groups than in the placebo group for both endpoints.

Table 29. Mucosal healing rate and clinical response rate at Week 52 in the global phase III remission maintenance study (Study A3921096) (FAS)

	Overall study population			Japanese subpopulation		
	Placebo (N = 198)	Tofacitinib		Placebo (N = 11)	Tofacitinib	
		5 mg (N = 198)	10 mg (N = 197)		5 mg (N =16)	10 mg (N = 12)
Mucosal healing rate at Week 52 (n)[a)]	13.1% (26)	37.4% (74)	45.7% (90)	18.2% (2)	31.3% (5)	66.7% (8)
Between group difference (Tofacitinib vs. placebo) [95%CI][b)]	–	24.2% [16.0, 32.5]	32.6% [24.2, 41.0]	–	13.1% [−19.1, 45.2]	48.5% [13.4, 83.6]
Clinical response rate at Week 52 (n)[a)]	20.2% (40)	51.5% (102)	61.9% (122)	27.3% (3)	56.3% (9)	83.3% (10)
Between group difference (Tofacitinib vs. placebo) [95%CI][b)]	–	31.3 [22.4, 40.2]	41.7 [32.9, 50.5]	–	29.0 [−6.8, 64.8]	56.1 [22.3, 89.8]

a) Subjects with missing data were treated as those who failed to achieve mucosal healing or improve clinical response (non-responders).
b) 95% CI was calculated using normal approximation for the difference.

7.R.2.2.3 Efficacy by baseline demographics and disease characteristics of patients

The applicant's explanation about the remission rate by baseline demographics and disease characteristics of patients in the global phase III remission maintenance study (Study A3921096):

Table 30 shows the "remission rate at Week 52" by major baseline demographics and disease characteristics of patients in the global phase III remission maintenance study (Study A3921096). In all subgroups, the remission rate tended to be higher in the tofacitinib 5 mg and 10 mg groups than in the placebo group.

Table 30. Remission rate at Week 52 by major baseline demographics and disease characteristics of patients in the global phase III remission maintenance study (Study A3921096) (FAS)

Baseline demographics and disease characteristics of patients	Placebo (N = 198)	Tofacitinib			
		5 mg (N = 198)		10 mg (N = 197)	
		Remission rate	Difference from placebo [95%CI]	Remission rate	Difference from placebo [95%CI]
Sex					
Male	9.5 (11/116)	38.8 (40/103)	29.4 [18.5, 40.2]	36.4 (40/110)	26.9 [16.4, 37.3]
Female	13.4 (11/82)	29.5 (28/95)	16.1 [4.3, 27.8]	46.0 (40/87)	32.6 [19.8, 45.4]
Disease duration[a)]					
<6 years	14.4 (13/90)	39.2 (38/97)	24.7 [12.6, 36.9]	41.3 (38/92)	26.9 [14.5, 39.3]
≥6 years	8.3 (9/108)	29.7 (30/101)	21.4 [11.0, 31.7]	40.0 (42/105)	31.7 [20.9, 42.4]
In remission at baseline[b)]					
No	11.5 (16/139)	28.6 (38/133)	17.1 [7.7, 26.4]	34.5 (49/142)	23.0 [13.5, 32.4]
Yes	10.2 (6/59)	46.2 (30/65)	36.0 [21.6, 50.3]	56.4 (31/55)	46.2 [31.0, 61.4]
Oral steroid use at baseline[b)]					
No	11.3 (11/97)	40.2 (39/97)	28.9 [17.2, 40.5]	50.0 (55/110)	38.7 [27.4, 49.9]
Yes	10.9 (11/101)	28.7 (29/101)	17.8 [7.1, 28.5]	28.7 (25/87)	17.8 [6.6, 29.1]
Prior TNF inhibitor exposure [a)]					
No	10.4 (11/106)	40.7 (44/108)	30.4 [19.4, 41.3]	44.8 (43/96)	34.4 [22.9, 45.9]
Yes	12.0 (11/92)	26.7 (24/90)	14.7 [3.4, 26.0]	36.6 (37/101)	24.7 [13.2, 36.2]
Prior TNF inhibitor failure[a) c)]					
No	11.0 (12/109)	41.7 (48/115)	30.7 [20.0, 41.5]	44.2 (46/104)	33.2 [22.0, 44.4]
Yes	11.2 (10/89)	24.1 (20/83)	12.9 [1.6, 24.2]	36.6 (34/93)	25.3 [13.5, 37.1]
Reason for TNF inhibitor failure[a)]					
Primary non-responder[d)]	10.9 (5/46)	23.1 (9/39)	12.2 [−3.8, 28.2]	30.6 (15/49)	19.7 [4.0, 35.5]
Secondary non-responder[e)]	11.8 (4/34)	25.0 (9/36)	13.2 [−4.6, 31.0]	41.5 (17/41)	29.7 [11.1, 48.3]

Remission rate, % (n/N)

a) Baseline data from the global phase III remission induction study (Study A3921094) or foreign phase III remission induction study (Study A3921095)

b) Baseline data from the global phase III remission maintenance study (Study A3921096)

c) Includes patients who failed to achieve clinical response to ≥2 TNF inhibitors and patients who were primary non-responders to TNF inhibitors.

d) Patients who had inadequate clinical response to TNF inhibitor remission induction therapy or who failed to achieve clinical response due to poor tolerability.

e) Patients who had clinical response to TNF inhibitor remission induction therapy, but subsequently had reduced response, a loss of response, or intolerance to the TNF inhibitor in the maintenance therapy.

PMDA's view on the efficacy of tofacitinib as maintenance therapy, based on the discussions in Sections 7.R.2.2.1 through 7.R.2.2.3:

The global phase III remission maintenance study (Study A3921096) demonstrated the superiority of both tofacitinib 5 mg and 10 mg over placebo for the "remission rate at Week 52" as the primary endpoint. In the Japanese subpopulation, the remission rate was higher in the tofacitinib 5 mg and 10 mg groups than in the placebo group, indicating that the results for the Japanese subpopulation tended to be consistent with the results for the overall study population, albeit data from a limited number of Japanese patients studied (Tables 27 and 28). Further, data for the major secondary endpoints (mucosal healing rate and clinical response rate at Week 52), and the efficacy by baseline demographics and disease characteristics of patients raised no particular concerns (Tables 29 and 30). Based on the above, the remission maintaining effect of tofacitinib in patients with UC was demonstrated by the data submitted, and tofacitinib can be expected to be effective in the Japanese subpopulation. However, because only a very limited number of Japanese patients with UC participated in the global phase III remission maintenance study (Study A3921096), information on the efficacy in Japanese patients with UC should continue to be collected through post-marketing surveillance.

7.R.3 Safety

Based on the consideration and confirmation in Sections 7.R.3.1 through 7.R.3.4, tofacitinib should be used with caution by a physician with sufficient knowledge of tofacitinib and experience in the treatment of UC while paying attention to safety aspects, as with the treatment of rheumatoid arthritis (RA) for which tofacitinib has already been approved. Further, the clinical studies evaluated data from only a limited number of Japanese patients. Given that the tofacitinib 10 mg twice-daily dose, in particular, has not been approved for the treatment of RA, information on long-term safety of tofacitinib 10 mg twice daily is only available from patients with UC participating the clinical studies; therefore, safety information should continue to be collected through post-marketing surveillance and by other means for investigation.

The final decision on the safety of tofacitinib will be made, taking account of comments from the Expert Discussion.

7.R.3.1 Safety of tofacitinib compared with placebo

7.R.3.1.1 Safety in overall study population

The applicant's explanation about the safety of tofacitinib in patients with active UC and those with UC in sustained remission:

The safety of tofacitinib in patients with active UC was evaluated based on the pooled data from the following 3 studies: foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), and foreign phase III remission induction study (Study A3921095). The incidences of adverse events and adverse drug reactions in the pooled data from the above studies are presented in Tables 31 and 32, respectively. The incidences of adverse events or adverse drug reactions in the tofacitinib 10 mg group did not tend to be clinically significantly different from those in the placebo group. No deaths occurred in the placebo group. One death occurred in the tofacitinib 10 mg group ("aortic dissection"),[3)] which was considered unrelated to tofacitinib. The incidences of serious adverse drug reactions and adverse drug reactions leading to treatment discontinuation in the tofacitinib 10 mg group were not clinically significantly different from those in the placebo group.

Table 31. Adverse events occurring in ≥2.0% of subjects in either group
(Pooled data from the foreign phase II study [Study A3921063], global phase III remission induction study [Study A3921094], and foreign phase III remission induction study [Study A3921095])

Adverse event	Placebo (N = 282)	Tofacitinib 10 mg (N = 938)
Any adverse event	55.0 (155)	54.9 (515)
Headache	6.7 (19)	7.8 (73)
Nasopharyngitis	5.0 (14)	6.0 (56)
Nausea	3.9 (11)	3.0 (28)
Arthralgia	4.3 (12)	2.9 (27)
Colitis ulcerative	7.1 (20)	2.8 (26)
Upper respiratory tract infection	2.1 (6)	2.8 (26)
Abdominal pain	3.9 (11)	2.7 (25)
Blood CK increased	1.1 (3)	2.7 (25)
Acne	0.4 (1)	2.7 (25)
Pyrexia	1.4 (4)	2.6 (24)
Anaemia	3.2 (9)	2.4 (22)
Cough	2.5 (7)	1.4 (13)

MedDRA/J ver. 19.0; incidence, % (n)

Table 32. Adverse drug reactions occurring in ≥2.0% of subjects in either group
(Pooled data from the foreign phase II study [Study A3921063], global phase III remission induction study [Study A3921094], and foreign phase III remission induction study [Study A3921095])

Adverse event	Placebo (N = 282)	Tofacitinib 10 mg (N = 938)
Any adverse drug reaction	23.0 (65)	28.5 (267)
Headache	3.5 (10)	5.2 (49)
Blood CK increased	0.7 (2)	2.1 (20)
Nasopharyngitis	2.1 (6)	1.8 (17)

MedDRA/J ver. 19.0; incidence, % (n)

The safety of tofacitinib in patients with UC in sustained remission was evaluated based on the data from the global phase III remission maintenance study (Study A3921096). The incidences of adverse events and adverse drug reactions in the global phase III remission maintenance study (Study A3921096) are shown in Tables 17 and 18, respectively. There were no clinically significant trends in the tofacitinib 5 mg or 10 mg group compared with the placebo group [See Section 7.2.3]. No deaths occurred in any of the groups. There were no clinically significant concerns raised by serious adverse drug reactions or adverse drug reactions leading to treatment discontinuation.

PMDA confirmed that there were no clinically significant trends in tofacitinib-treated patients with active UC or patients in sustained remission compared with patients on placebo. Adverse events of special interest, such as “infections,” “haemoglobin/neutrophils/lymphocytes decreased,” “major cardiovascular events,” and “malignancy” will be discussed in Section 7.R.3.3.

7.R.3.1.2 Safety in the Japanese subpopulation

The applicant’s explanation about the safety of tofacitinib in Japanese patients with active UC and those in sustained remission:

The safety of tofacitinib in Japanese patients with active UC was evaluated based on the data from the global phase III remission induction study (Study A3921094). The incidences of adverse events and adverse drug reactions in the global phase III remission induction study (Study A3921094) is shown in Tables 12 and 13, respectively. There were no significant differences in the incidence of adverse events between the tofacitinib 10 mg group and the placebo group in the Japanese subpopulation, nor was there any clinically significant difference between the overall study population and Japanese subpopulation [See Section 7.2.1].

The safety of tofacitinib in Japanese patients with UC in sustained remission was evaluated based on the data from the global phase III remission maintenance study (Study A3921096). The incidences of adverse events and adverse drug reactions in the global phase III remission maintenance study (Study A3921096) are shown in Tables 17 and 18, respectively. There were no clinically significant trends in the tofacitinib 5 mg or 10 mg group compared with the placebo group [See Section 7.2.3]. No deaths occurred in any of the groups. There were no significant clinically concerns raised by serious adverse drug reactions and adverse drug reactions leading to treatment discontinuation.

PMDA confirmed that there were no significant differences between the Japanese subpopulation and the overall study population in term of the trends of adverse events in patients with active UC and those in sustained remission. However, since data from only a limited number of Japanese patients with UC were evaluated in the clinical studies, the safety of tofacitinib in Japanese patients with UC should be further investigated by continuously collecting information through post-marketing surveillance.

7.R.3.2 Long-term safety of tofacitinib

The incidence of adverse events by treatment period in the global phase III remission maintenance study (Study A3921096) is presented in Table 33. No trends towards increased incidence of adverse events with increasing treatment duration were noted. There were no significant differences in the incidence of adverse events between the tofacitinib 5 mg and 10 mg groups.

Table 33. Incidence of adverse events by treatment period (global phase III remission maintenance study [Study A3921096])

Treatment group		Weeks 1-13 (N = 592)	Weeks 14-26 (N = 458)	Weeks 27-39 (N = 363)	Week ≥40 (N = 308)	Overall period (N = 592)
Placebo	Adverse event	63.1% (125/198)	50.0% (61/122)	31.3% (25/80)	25.9% (15/58)	75.3% (149/198)
	Infections[a)]	16.2% (32/198)	13.1% (16/122)	11.3% (9/80)	8.6% (5/58)	24.2% (48/198)
	Serious infections[b)]	0.5% (1/198)	0.0% (0/122)	0.0% (0/80)	1.7% (1/58)	1.0% (2/198)
Tofacitinib 5 mg	Adverse event	51.0% (101/198)	41.3% (71/172)	36.3% (49/135)	31.9% (37/116)	72.2% (143/198)
	Infections[a)]	17.7% (35/198)	15.1% (26/172)	14.8% (20/135)	12.9% (15/116)	35.9% (71/198)
	Serious infections[b)]	1.0% (2/198)	0.0% (0/172)	0.0% (0/135)	0.0% (0/116)	1.0% (2/198)
Tofacitinib 10 mg	Adverse event	57.7% (113/196)	43.9% (72/164)	44.6% (66/148)	36.6% (49/134)	79.6% (156/196)
	Infections[a)]	26.0% (51/196)	17.1% (28/164)	17.6% (26/148)	11.9% (16/134)	39.8% (78/196)
	Serious infections[b)]	0.5% (1/196)	0.0% (0/164)	0.0% (0/148)	0.0% (0/134)	0.5% (1/196)

MedDRA/J ver.19.0; incidence, % (n/N)
a) Adverse events coded to the preferred terms (PTs) of MedDRA "Infections and infestations (SOC)"
b) Adverse events coded to "Infections and infestations (SOC)" that met the reporting criteria for serious adverse events

The incidence of adverse events in the global long-term extension study (Study A3921139) is shown in Table 21. Compared with the global phase III remission maintenance study (Study 3921096), no adverse events that raised concerns were noted.

7.R.3.3 Adverse events of special interest

The applicant identified "infections," "malignancy," "haemoglobin/neutrophils/lymphocytes decreased," "major cardiovascular events," "interstitial lung disease," "gastrointestinal perforations," "hepatic dysfunction-related events," and "CK increased and rhabdomyolysis-related events" as adverse events of special interest, and investigated the incidence of them based on non-clinical data for tofacitinib and clinical data for indications including UC. The applicant's explanation is as follows:

In all clinical studies[26)] conducted in patients with UC, no interstitial lung disease occurred in patients who received tofacitinib 5 mg or 10 mg. The incidence of "gastrointestinal perforations" was as low as 0.3% (3 of 1123 subjects[27)]; "gastrointestinal perforation" [1], "intestinal perforation" [1], and "appendicitis" [1][28)]), and there were no cases of gastrointestinal perforations in the Japanese subpopulation.

An analysis was made for "hepatic dysfunction-related events" in all the clinical studies[26)] conducted in patients with UC, and no adverse events suggestive of hepatic failure occurred in patients who received tofacitinib 5 mg or 10 mg. Tables 34 and 35 show the proportions of patients with active UC and patients in sustained

26) Foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), foreign phase III remission induction study (Study A3921095), global phase III remission maintenance study (Study A3921096), and global long-term extension study (Study A3921139).
27) In the foreign phase II study (Study A3921063), adjudication committees were not established for "opportunistic infections," "malignancies (including non-melanoma skin cancer," "major cardiovascular events," and "gastrointestinal perforations"; therefore, data from the study were not included in the analyses of these events.
28) These events occurred in the following groups: "gastrointestinal perforation" in the tofacitinib 10 mg group in the global long-term extension study (Study A3921139), "intestinal perforation" in the tofacitinib 10 mg group in the global phase III remission induction study (Study A3921094), and "appendicitis" in the tofacitinib 5 mg group in the global long-term extension study (Study A3921139).

remission, respectively, whose ALT, AST, or total bilirubin increased to ≥2 times the upper limit of normal (ULN). There were no trends towards a significant increase in ALT, AST, or total bilirubin following administration of tofacitinib, nor was there any trend towards a significant increase in ALT, AST, or total bilirubin in the Japanese subpopulation following administration of tofacitinib.

Table 34. Proportion of subjects whose liver function test values increased to ≥2 × ULN in the foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), and foreign phase III remission induction study (Study A3921095)

Liver function test	Proportion of subjects whose liver function test values increased to ≥2 × ULN	
	Placebo (N = 282)	Tofacitinib 10 mg (N = 938)
ALT	2.5 (7)	1.5 (14)
AST	1.8 (5)	0.9 (8)
Total bilirubin	1.1 (3)	0.7 (7)

Proportion of subjects (n)

Table 35. Proportion of subjects whose liver function test values increased to ≥2 × ULN in the global phase III remission maintenance study (Study A3921096)

Liver function test	Proportion of subjects whose liver function test values increased to ≥2 × ULN		
	Placebo (N = 198)	Tofacitinib	
		5 mg (N = 198)	10 mg (N = 196)
ALT	0 (0)	2.5 (5)	3.6 (7)
AST	1.0 (2)	1.5 (3)	2.6 (5)
Total bilirubin	1.5 (3)	1.5 (3)	2.0 (4)

Percentage of subjects (n)

Data from the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095) were analyzed for "CK increased and rhabdomyolysis-related events." In the 2 studies, CK levels increased to ≥3 × ULN in 3.0% (7 of 234) of subjects in the placebo group and 4.3% (39 of 905) of subjects in the tofacitinib 10 mg group, indicating that there was no difference between these groups. In contrast, in the global phase III remission maintenance study (Study A3921096), CK levels increased to ≥3 × ULN in 5.1% (10 of 198) of subjects in the placebo group, 7.6% (15 of 198) of subjects in the tofacitinib 5 mg group, and 13.3% (26 of 196) of subjects in the tofacitinib 10 mg group, indicating that CK levels tended to increase in a dose-dependent manner. Data from the global phase III remission maintenance study (Study A3921096) were analyzed for "CK increased and rhabdomyolysis-related events." The incidence of "blood CK increased" was 2.0% (4 of 198 subjects) in the placebo group, 3.0% (6 of 198 subjects) in the tofacitinib 5 mg group, and 6.6% (13 of 196 subjects) in the tofacitinib 10 mg group, indicating a trend towards a dose-dependent increase in CK levels. In the Japanese subpopulation in the global phase III remission maintenance study (Study A3921096), the incidence of "blood CK increased" was 0% (0 of 11 subjects) in the placebo group, 0% (0 of 16 subjects) in the tofacitinib 5 mg group, and 16.7% (2 of 12 subjects) in the tofacitinib 10 mg group. As in the case of the overall study population, "blood CK increased" in the Japanese subpopulation occurred more frequently in the tofacitinib 10 mg group than in other groups. However, all cases of "blood CK increased" reported in the global phase III remission maintenance study (Study A3921096) were mild or

moderate in severity except for 1 severe case in 1 subject in the tofacitinib 10 mg group, which was reported as resolved after treatment discontinuation; therefore, "blood CK increased" is unlikely to pose significant clinical problems. Furthermore, no rhabdomyolysis/myopathy-related events occurred in patients who received tofacitinib in any of the clinical studies[26)] involving patients with UC.

Based on the above analyses of data related to "interstitial lung disease," "gastrointestinal perforations," "hepatic dysfunction-related events," and "CK increased and rhabdomyolysis-related events," there were no clinically significant trends for those events in the clinical studies involving patients with UC.

Trends in "infections," "haemoglobin/neutrophils/lymphocytes decreased," "major cardiovascular events," and "malignancy" are discussed in the following Sections 7.R.3.3.1, 7.R.3.3.2, 7.R.3.3.3, and 7.R.3.3.4, respectively.

7.R.3.3.1 Infections

7.R.3.3.1.1 Incidence of infections

The applicant investigated the incidence of infections in the clinical studies conducted in patients with UC because of the immunosuppressive effect of tofacitinib. The applicant's explanation is as follows:

The incidence of infections in patients with active UC was determined using the pooled data from the foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), and foreign phase III remission induction study (Study A3921095). The incidence of infections in the overall study population and Japanese subpopulation are shown in Table 36. Both in the overall study population and the Japanese subpopulation, there were no clinically significant differences in the incidences of infections and serious infections between the tofacitinib 10 mg group and placebo group. Serious infections occurred in 8 subjects in the tofacitinib 10 mg group, but the outcomes were reported as either resolved or resolving.

Table 36. Incidence of infections in patient with active UC (Pooled data from the foreign phase II study [A3921063], global phase III remission induction study [Study A3921094], and foreign phase III remission induction study [Study A3921095])

	Overall study population		Japanese subpopulation	
	Placebo (N = 282)	Tofacitinib 10 mg (N = 938)	Placebo (N = 13)	Tofacitinib 10 mg (N = 49)
Infections	15.2 (43)	21.1 (198)	23.1 (3)	24.5 (12)
Serious infections	0 (0)	0.9 (8)[a)]	0 (0)	2.0 (1)
Anal abscess	0 (0)	0.2 (2)	0 (0)	0 (0)
Clostridium difficile infection	0 (0)	0.1 (1)	0 (0)	2.0 (1)
Febrile infection	0 (0)	0.1 (1)	0 (0)	0 (0)
Furuncle	0 (0)	0.1 (1)	0 (0)	0 (0)
Otitis externa	0 (0)	0.1 (1)	0 (0)	0 (0)
Pneumonia	0 (0)	0.1 (1)	0 (0)	0 (0)
Postoperative abscess	0 (0)	0.1 (1)	0 (0)	0 (0)

MedDRA/J ver. 19.0; incidence, % (n)

a) Serious infections were reported in 9 subjects in the tofacitinib 10 mg group. Of the 9 subjects, 1 discontinued study treatment after receiving tofacitinib for 1 day. Cellulitis was reported in this subject 61 days after the final dose. This subject was not included in the analysis of incidence of serious infections.

The incidence of infections in patients in sustained remission was determined using data from the global phase III remission maintenance study (Study A3921096). The incidence of infections in the overall study population and the Japanese subpopulation is shown in Table 37. Both in the overall study population and the Japanese subpopulation, infections tended to occur more frequently in the tofacitinib 5 mg and 10 mg groups than in the placebo group, whereas there were no significant differences in the incidence of serious infections between the groups.

Table 37. Incidence of infections in patients in sustained remission (Global phase III remission maintenance study [Study A3921096])

	Overall study population			Japanese subpopulation		
	Placebo (N = 198)	Tofacitinib		Placebo (N = 11)	Tofacitinib	
		5 mg (N = 198)	10 mg (N = 196)		5 mg (N = 16)	10 mg (N = 12)
Infection	24.2 (48)	35.9 (71)	39.8 (78)	36.4 (4)	50.0 (8)	66.7 (8)
Serious infection	1.0 (2)	1.0 (2)	0.5 (1)	9.1 (1)	0 (0)	0 (0)
Bacterial diarrhoea	0 (0)	0 (0)	0.5 (1)	0 (0)	0 (0)	0 (0)
Diverticulitis	0.5 (1)	0 (0)	0 (0)	9.1 (1)	0 (0)	0 (0)
Peritonsillar abscess	0 (0)	0.5 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Subcutaneous abscess	0.5 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urinary tract infection	0 (0)	0.5 (1)	0 (0)	0 (0)	0 (0)	0 (0)

MedDRA/J ver. 19.0; incidence, % (n)

Table 38 shows the incidence of serious infections by period in the pooled data from all the clinical studies[26)] conducted in patients with UC. Both in the overall study population and the Japanese subpopulation, no trends towards increased incidence of serious infections with increasing treatment duration were noted.

Table 38. Incidence of serious infections by period in the pooled data[a)] from all the clinical studies in patients with UC

Treatment period	Overall study population			Japanese subpopulation		
	Tofacitinib 5 mg (N = 172)	Tofacitinib 10 mg (N = 984)	Tofacitinib group total (N = 1156)	Tofacitinib 5 mg (N = 13)	Tofacitinib 10 mg (N = 52)	Tofacitinib group total (N = 65)
0-6 months	1.2 (2/172)	1.2 (12/984)	1.2 (14/1156)	0 (0/13)	1.9 (1/52)	1.5 (1/65)
6-12 months	0.6 (1/164)	0.7 (4/606)	0.6 (5/770)	0 (0/12)	3.0 (1/33)	2.2 (1/45)
12-18 months	0.7 (1/138)	0.8 (4/501)	0.8 (5/639)	0 (0/11)	0 (0/31)	0 (0/42)
18-24 months	0 (0/99)	0.3 (1/331)	0.2 (1/430)	0 (0/7)	0 (0/19)	0 (0/26)
>24 months	3.8 (2/52)	1.1 (2/183)	1.7 (4/235)	20.0 (1/5)	0 (0/15)	5.0 (1/20)

Incidence, % (n/N)

a) Pooled data from the foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), foreign phase III remission induction study (Study A3921095), global phase III remission maintenance study (Study A3921096), and global long-term extension study (Study A3921139). Subjects were classified based on the mean daily dose of tofacitinib (twice daily) over the treatment period, and those receiving <15 mg and those receiving ≥15 mg were defined as the tofacitinib 5 mg and 10 mg groups, respectively.

Next, the applicant provided the following explanation about the incidence of opportunistic infections in the clinical studies conducted in patients with UC:

Given that serious opportunistic infections were noted in the clinical studies in patients with RA (See "Review Report on Xeljanz Tablets 5 mg" dated on February 28, 2013), and that in some cases opportunistic infections potentially are life-threatening, the current package insert includes a cautionary statement to the effect that the patient's condition should be carefully monitored, with attention to the risk of opportunistic infections during treatment with tofacitinib.

The incidence of opportunistic infections in patients with active UC was determined using the pooled data from the global phase III remission induction study (Study A3921094) and the foreign phase III remission induction study (Study A3921095). The incidence of opportunistic infections was 0% (0 of 234 subjects) in the placebo group, 0.3% (3 of 905 subjects) in the tofacitinib 10 mg group ("herpes zoster" [2] and "cytomegalovirus infection" [1]), indicating that there were no clinically significant differences between the placebo group and the 10 mg group. No cases of opportunistic infections were reported in the Japanese subpopulation.

The incidence of opportunistic infections in patients in sustained remission was determined using data from the global phase III remission maintenance study (Study A3921096). The incidence of opportunistic infections was 0.5% (1 of 198 subjects) in the placebo group ("herpes zoster"), 1.0% (2 of 198 subjects) in the tofacitinib 5 mg group ("herpes zoster" [1] and "herpes zoster cutaneous disseminated" [1]), and 2.0% (4 of 196 subjects) in the 10 mg group ("herpes zoster" [4]), indicating that opportunistic infections tended to occur more frequently in the tofacitinib 5 mg and 10 mg groups than in the placebo group. No cases of opportunistic infections were reported in the Japanese subpopulation.

Table 39 shows the incidence of opportunistic infections by period in all the phase III clinical studies[29)] in patients with UC. No trends towards increased incidence of opportunistic infections with increasing treatment duration were noted.

Table 39. Incidence of opportunistic infections by period in the pooled data[a)] from all phase III studies in patients with UC

Treatment period	Overall study population			Japanese subpopulation		
	Tofacitinib 5 mg (N = 172)	Tofacitinib 10 mg (N = 951)	Tofacitinib group total (N = 1123)	Tofacitinib 5 mg (N = 13)	Tofacitinib 10 mg (N = 52)	Tofacitinib group total (N = 65)
0-6 months	2.3 (4/172)	0.7 (7/951)	1.0 (11/1123)	0 (0/13)	0 (0/52)	0 (0/65)
6-12 months	0 (0/162)	0.3 (2/604)	0.3 (2/766)	0 (0/12)	3.0 (1/33)	2.2 (1/45)
12-18 months	0 (0/134)	0.2 (1/500)	0.2 (1/634)	0 (0/11)	0 (0/30)	0 (0/41)
18-24 months	0 (0/95)	0.3 (1/331)	0.2 (1/426)	0 (0/7)	0 (0/18)	0 (0/25)
>24 months	2.0 (1/50)	0.5 (1/182)	0.9 (2/232)	0 (0/5)	0 (0/14)	0 (0/19)

Incidence, % (n/N)

a) Pooled data from the global phase III remission induction study (Study A3921094), foreign phase III remission induction study (Study A3921095), global phase III remission maintenance study (Study A3921096), and global long-term extension study (Study A3921139). Subjects were classified based on the mean daily dose of tofacitinib (twice daily) over the treatment period, and those receiving <15 mg and those receiving ≥15 mg were defined as the tofacitinib 5 mg and 10 mg groups, respectively.

The occurrence of tuberculosis was investigated in the patients with UC who received tofacitinib in all the clinical studies. Only 1 patient in the 10 mg group in the global long-term extension study (Study A3921139)

29) The global phase III remission induction study (Study A3921094), foreign phase III remission induction study (Study A3921095), global phase III remission maintenance study (Study A3921096), and global long-term extension study (Study A3921139).

was suspected of having active tuberculosis.[30)] No cases of tuberculosis were reported in the Japanese subpopulation.

7.R.3.3.1.2 Incidence of herpes zoster

The applicant's explanation about the incidence of herpes zoster in patients with UC:
Given that many of the cases of serious opportunistic infections that occurred in Japanese patients participating in the clinical studies involving patients with RA were "herpes zoster" (See "Review Report on Xeljanz Tablets 5 mg" dated on February 28, 2013), and that "herpes zoster disseminated" was also reported, the "Important Precautions" section of the current package insert includes a cautionary statement to the effect that the patient's condition should be carefully monitored for the risk of herpes zoster during treatment with tofacitinib. In addition, many cases of opportunistic infections that occurred in the clinical studies involving patients with UC were also "herpes zoster" [See Section 7.R.3.3.1.1].

The incidence of "herpes zoster" in patients with active UC was determined using the pooled data from the foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), and foreign phase III remission induction study (Study A3921095). The incidence of "herpes zoster" was 0.4% (1 of 282 subjects) in the placebo group and 0.6% (6 of 938 subjects) in the tofacitinib 10 mg group. There were no clinically significant differences between the tofacitinib 10 mg group and placebo group. No cases of "herpes zoster" occurred in the Japanese subpopulation.

The incidence of "herpes zoster" in patients in sustained remission was determined using data from the global phase III remission maintenance study (Study A3921096). The incidence of "herpes zoster" was 0.5% (1 of 198 subjects) in the placebo group, 1.5% (3 of 198 subjects) in the tofacitinib 5 mg group, and 5.1% (10 of 196 subjects) in the tofacitinib 10 mg group, indicating that "herpes zoster" tended to occur more frequently in the tofacitinib 5 mg and 10 mg groups than in the placebo group. No cases of "herpes zoster" occurred in the Japanese subpopulation.

Table 40 shows the incidence of "herpes zoster" by period in all the clinical studies[26)] in patients with UC. No trends towards increased incidence of "herpes zoster" with increasing treatment duration were noted in the overall study population. In the Japanese subpopulation, "herpes zoster" occurred in 6 subjects in the tofacitinib 10 mg group at ≥12 months, and all these cases were mild in severity. The lesions were limited to a single dermatome, or two adjacent dermatomes, and none of the events were related to post-herpetic neuralgia.

30) A Serbian male aged 57 years. The subject had a diagnosis of tuberculosis on Day 451 in the global long-term extension study (Study A3921139). At screening, the subject had a negative Quantiferon TB Gold test result. After receiving placebo for 74 days in the global remission induction study (Study A3921094), the subject participated in the global long-term extension study (Study A3921139) and received tofacitinib 10 mg. From Day 391 in the open-label, long-term extension study, abdominal pain, vomiting, and pyrexia were noted. On Day 406, the subject underwent a chest X-ray and a tuberculin skin test, which gave negative results. Ascites was noted on Day 416. Mycobacterium tuberculosis was not detected in the test of smear and culture of ascitic fluid. A positive result of the Quantiferon TB Gold test was confirmed on Day 434, and tofacitinib treatment was discontinued the next day. On Day 451, the subject received 4 drugs in accordance with the standard of care provided in Serbia. The event (tuberculosis) was reported as a serious adverse event, and was considered related to the study drug by the investigator. As of the data cut-off date (July 8, 2016), this case was still under review by the opportunistic infection adjudication committee.

Table 40. Incidence of herpes zoster by period in the pooled data[a)] from all the clinical studies in patients with UC

Treatment period	Overall study population			Japanese subpopulation		
	Tofacitinib 5 mg (N = 172)	Tofacitinib 10 mg (N = 984)	Tofacitinib group total (N = 1156)	Tofacitinib 5 mg (N = 13)	Tofacitinib 10 mg (N = 52)	Tofacitinib group total (N = 65)
0-6 months	4.1 (7/172)	1.4 (14/984)	1.8 (21/1156)	0 (0/13)	0 (0/52)	0 (0/65)
6-12 months	0.6 (1/159)	2.0 (12/599)	1.7 (13/758)	0 (0/12)	3.0 (1/33)	2.2 (1/45)
12-18 months	1.5 (2/130)	2.3 (11/485)	2.1 (13/615)	0 (0/11)	16.7 (5/30)	12.2 (5/41)
18-24 months	0 (0/91)	2.9 (9/315)	2.2 (9/406)	0 (0/7)	0 (0/14)	0 (0/21)
>24 months	2.2 (1/46)	1.2 (2/169)	1.4 (3/215)	0 (0/5)	9.1 (1/11)	6.3 (1/16)

Incidence, % (n/N)

a) Pooled data from the foreign phase II study (Study A3921063), phase III remission induction studies (Studies A3921094 and A3921095), phase III remission maintenance study (Study A3921096), and long-term extension study (Study A3921139). Subjects were classified based on the mean daily dose of tofacitinib (twice daily) over the treatment period, and those receiving <15 mg and those receiving ≥15 mg were defined as the tofacitinib 5 mg and 10 mg groups, respectively.

PMDA's view:

No significant clinical concerns have been raised so far in relation to serious infections and "herpes zoster" in the clinical studies in patients with UC. However, given that infections in the overall study population and the Japanese subpopulation tended to occur more frequently in the tofacitinib 5 mg and 10 mg groups than in the placebo group, and that "herpes zoster" occurred in 7 Japanese patients even though the events were mild or moderate in severity, the patient's condition should be carefully monitored for the risk of infections and "herpes zoster" in patients with UC during treatment with tofacitinib, as in the case of patients with RA. Data on the incidence of infections and herpes zoster should continue to be collected through post-marketing surveillance.

7.R.3.3.2 Haemoglobin/neutrophils/lymphocytes decreased

The applicant's explanation about the incidence of "haemoglobin/neutrophils/lymphocytes decreased" in patients with UC.

Since decreased blood cell counts may be caused by the pharmacological action of tofacitinib (See "Review Report on Xeljanz Tablets 5 mg" dated on February 28, 2013), the "Important Precautions" section of the package insert include a cautionary statement that haemoglobin levels and neutrophil and lymphocyte counts should be checked immediately before and during treatment with tofacitinib.

7.R.3.3.2.1 Incidence of haemoglobin decreased and anaemia

The applicant's explanation about the incidence of haemoglobin decreased and "anaemia":

The incidence of "anaemia" in patients with active UC was determined using the pooled data from the foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), and foreign phase III remission induction study (Study A3921095). The incidence of "anaemia" was 3.2% (9 of 282 subjects) in the placebo group and 2.3% (22 of 938 subjects) in the tofacitinib 10 mg group. All the cases were either mild or moderate in severity. In the Japanese subpopulation, the incidence of "anaemia" was 7.7% (1 of 13 subjects) in the placebo group and 2.0% (1 of 49 subjects) in the tofacitinib 10 mg group. All the cases were mild in severity.

The incidence of "anaemia" in patients in sustained remission was determined using data from the global phase III remission maintenance study (Study A3921096). The incidence of "anaemia" was 1.5% (3 of 198 subjects)

in the placebo group, 4.0% (8 of 198 subjects) in the tofacitinib 5 mg group, and 2.0% (4 of 196 subjects) in the tofacitinib 10 mg group. All the cases were either mild or moderate in severity, except for 1 case in 1 subject in the tofacitinib 10 mg group. The severe anaemia case in the tofacitinib 10 mg group was reported as an adverse drug reaction, and its outcome was reported as not resolved. Nevertheless, the event is unlikely to pose a significant clinical problem because (i) the event was non-serious, (ii) the platelet count was within the normal range, and (iii) no other anaemia-related adverse events were noted. In the Japanese subpopulation, no cases of "anaemia" occurred in the placebo group, tofacitinib 5 mg or 10 mg group.

Further, data from the global long-term extension study (Study A3921139) was analyzed, and the incidence of "anaemia" was 0.6% (1 of 156 subjects) in the tofacitinib 5 mg group and 3.7% (28 of 758 subjects) in the tofacitinib 10 mg group. All the cases were either mild or moderate in severity, except for cases in 2 subjects in the tofacitinib 10 mg group. The severe anaemia cases in the 2 subjects in the tofacitinib 10 mg group were considered unrelated to tofacitinib, and their outcomes were reported as resolved. In the Japanese subpopulation, no cases of "anaemia" occurred in the tofacitinib 5 mg group. A mild anaemia case occurred in 1 of 40 subjects (2.5%) in the tofacitinib 10 mg group.

No "erythropenia" occurred in any of the clinical studies[26)] in patients with UC.

7.R.3.3.2.2 Incidence of neutrophils decreased

The applicant's explanation about the incidence of "neutropenia" and "neutrophil count decreased" in patients with UC:

The pooled data from the foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), and foreign phase III remission induction study (Study A3921095) were analyzed for the incidence of "neutropenia" or "neutrophil count decreased" in patients with active UC. No "neutropenia" or "neutrophil count decreased" occurred in the placebo or tofacitinib 10 mg group.

Data from the global phase III remission maintenance study (Study A3921096) were analyzed for the incidence of "neutropenia" or "neutrophil count decreased" in patients in sustained remission. "Neutropenia" did not occurred in the placebo group, but occurred in 0.5% (1 of 198) of subjects in the tofacitinib 5 mg group. "Neutrophil count decreased" occurred in 0.5% (1 of 196) of subjects in the tofacitinib 10 mg group. These events were either mild or moderate in severity. In the Japanese subpopulation, no "neutropenia" or "neutrophil count decreased" occurred in any of the groups.

In the global long-term extension study (Study A3921139), "neutropenia" occurred in 0.6% (1 of 156) of subjects in the tofacitinib 5 mg group and 0.3% (2 of 758) of subjects in the tofacitinib 10 mg group. All cases were moderate in severity. In the Japanese subpopulation, no "neutropenia" or "neutrophil count decreased" occurred in any of the groups.

7.R.3.3.2.3 Incidence of lymphocytes decreased

The applicant's explanation about the incidence of "lymphopenia" and "lymphocyte count decreased" in patients with UC:

The incidence of "lymphopenia" or "lymphocyte count decreased" in patients with active UC was determined using the pooled data from the foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), and foreign phase III remission induction study (Study A3921095). The incidence of "lymphopenia" or "lymphocyte count decreased" was 0.4% (1 of 282 subjects) in the placebo group ("lymphocyte count decreased") and 0.3% (3 of 938 subjects) in the tofacitinib 10 mg group ("lymphopenia" [2] and "lymphocyte count decreased" [1]), and all events were mild in severity. In the Japanese subpopulation, mild lymphopenia occurred in 1 subject in the tofacitinib 10 mg group.

The incidence of "lymphopenia" or "lymphocyte count decreased" in patients in sustained remission was determined using data from the global phase III remission maintenance study (Study A3921096). No "lymphopenia" or "lymphocyte count decreased" occurred in the placebo group, tofacitinib 5 mg or 10 mg group.

In the global long-term extension study (Study A3921139), the incidence of "lymphopenia" or "lymphocyte count decreased" was 1.3% (2 of 156 subjects) in the tofacitinib 5 mg group ("lymphopenia" [1] and "lymphocyte count decreased" [1]) and 1.6% (12 of 758 subjects) in the tofacitinib 10 mg group ("lymphocyte count decreased" [9] and "lymphopenia" [3]). These events were either mild or moderate in severity, except for a severe case in 1 subject in the tofacitinib 10 mg group ("lymphocyte count decreased"). The severe case in the tofacitinib 10 mg group was reported as an adverse drug reaction, and its outcome was reported as resolved. In the Japanese subpopulation, "lymphocyte count decreased" occurred in 1 subject each in the tofacitinib 5 mg and 10 mg groups, and both events were mild in severity.

Based on the discussions in Sections 7.R.3.3.2.1 through 7.R.3.3.2.3, PMDA confirmed that there were no significant clinical concerns about "haemoglobin/neutrophils/lymphocytes decreased" in the clinical studies conducted in patients with UC. However, because currently available data from patients with UC are limited, data should continue to be collected through post-marketing surveillance.

7.R.3.3.3 Major cardiovascular events

The applicant investigated the incidence of "major cardiovascular events" in patients with UC, and explained as follows:

Given that serum lipids such as total cholesterol increased following administration of tofacitinib ("Review Report on Xeljanz Tablets 5 mg" dated on February 28, 2013), MedDRA PTs corresponding to the following categories were retrieved as major cardiovascular events, and they were evaluated: "cardiovascular deaths (death due to acute myocardial infarction, sudden cardiac death, death due to cardiac failure, death due to stroke, death due to cardiovascular procedure, death due to cardiovascular haemorrhage, and death due to other cardiovascular causes," "non-fatal myocardial infarction," and "non-fatal stroke of any category."

The incidence of “major cardiovascular events” in patients with active UC was determined using the pooled data from the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095). No “major cardiovascular events” occurred in the placebo group, and the incidence of “major cardiovascular events” was 0.2% (2 of 905 subjects) in the tofacitinib 10 mg group (“aortic dissection” [1] and “acute coronary” syndrome [1]). These events were considered unrelated to tofacitinib. In the Japanese subpopulation, no “major cardiovascular events” occurred in any group.

The incidence of “major cardiovascular events” in patients in sustained remission was determined using data from the global phase III remission maintenance study (Study A3921096). No “major cardiovascular events” occurred in the placebo group. The incidence of “major cardiovascular events” was 0.5% (1 of 198 subjects) in the tofacitinib 5 mg group (“myocardial infarction”) and 0.5% (1 of 196 subjects) in the 10 mg group (“haemorrhagic stroke”). While “myocardial infarction” in the tofacitinib 5 mg group was considered unrelated to tofacitinib, “haemorrhagic stroke”[10)] in the tofacitinib 10 mg group was reported as an adverse drug reaction, and its outcome was reported as resolved with sequelae. In the Japanese subpopulation, no “major cardiovascular events” occurred in any group.

In the global long-term extension study (Study A3921139), no “major cardiovascular events” occurred in the tofacitinib 5 mg or 10 mg group.

The above findings indicate that the incidence of “major cardiovascular events” was low in all the clinical studies in patients with UC, no events occurred in the Japanese subpopulation, and there was no difference in the incidence between the tofacitinib 5 mg and 10 mg groups; therefore, there seems to be no safety concerns about “major cardiovascular events.”

PMDA confirmed that there are currently no significant clinical concerns about “major cardiovascular events” in the clinical studies conducted in patients with UC. However, because currently available data from patients with UC are limited, data should continue to be collected through post-marketing surveillance.

7.R.3.3.4 Malignancy

The applicant’s explanation about the incidence of malignancy in patients with UC:
The review of tofacitinib in patients with RA concluded that the risk of malignancy associated with the use of tofacitinib cannot be ruled out (See “Review Report on Xeljanz Tablets 5 mg,” dated on February 28, 2013), and caution is advised in the “Warnings” and “Important precautions” sections of the package insert to the effect that the patient’s condition should be monitored for the risk of malignancy.

The incidence of malignancies in patients with active UC was determined using the pooled data from the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095). While no malignancies occurred in the placebo group, malignancies were noted in 0.2% (2 of 905) of subjects in the tofacitinib 10 mg group (“squamous cell carcinoma of skin” [1] and “basal cell carcinoma” [1]). In the Japanese subgroup, no malignancies occurred in any group.

The incidence of malignancies in patients in sustained remission was determined using data from the global phase III remission maintenance study (study A3921096). While no malignancies occurred in the tofacitinib 5 mg group, malignancies were noted in 1.0% (2 of 198) of subjects in the placebo group ("invasive ductal breast carcinoma" [1] and "basal cell carcinoma" [1]) and 1.5% (3 of 196 subjects) in the tofacitinib 10 mg group ("squamous cell carcinoma of skin" [1], "squamous cell carcinoma" [1], and "basal cell carcinoma" [1]). In the Japanese subgroup, no malignancies occurred in any group.

In the global long-term extension study (Study A3921139), the incidence of malignancies was 0.6% (1 of 156 subjects) in the tofacitinib 5 mg group ("basal cell carcinoma"), 1.8% (14 of 758 subjects) in the 10 mg group ("squamous cell carcinoma" [3], "basal cell carcinoma" [2], "cervical dysplasia" [1], "hepatic angiosarcoma" [1], "essential thrombocythaemia" [1], "acute myeloid leukaemia" [1], "cholangiocarcinoma" [1], "leiomyosarcoma" [1], "EBV associated lymphoma" [1], "renal cell carcinoma" [1], and "adenocarcinoma of colon" [1]). In the Japanese subgroup, no malignancies occurred in any group.

According to an analysis of data from patients who received at least 1 dose of tofacitinib 5 mg or 10 mg in any of the phase III clinical studies[29)] in patients with UC, malignancies occurred in 19 non-Japanese subjects. No malignancies were reported in the Japanese subpopulation. The reported 19 malignancies were analyzed. Non-melanoma skin cancer occurred in 10 subjects ("squamous cell carcinoma of skin" [1], "basal cell carcinoma" [3], "squamous cell carcinoma" [4], "squamous cell carcinoma of skin/basal cell carcinoma" [1], and "squamous cell carcinoma of skin/squamous cell carcinoma" [1]), solid tumour in 4 subjects ("cervical dysplasia" [1], "cholangiocarcinoma" [1], "renal cell carcinoma" [1], and "adenocarcinoma of colon" [1]), hematopoietic tumor in 3 subjects ("EBV associated lymphoma" [1], "essential thrombocythaemia" [1], and "acute myeloid leukaemia" [1]), and sarcoma in 2 subjects ("hepatic angiosarcoma" [1], and "leiomyosarcoma" [1]), indicating that the majority were non-melanoma skin cancers. Except for non-melanoma skin cancers, there were no trends towards an increase in the incidence of the specific types of carcinoma.

The incidence of non-melanoma skin cancers in the global phase III remission maintenance study (Study A3921096) was 1.0% (2 of 198 subjects) in the placebo group, 0% (0 of 198 subjects) in the tofacitinib 5 mg group, and 1.5% (3 of 196 subjects) in the 10 mg group, indicating no clear dose-response relationship. The incidence rate of non-melanoma skin cancers was 0.71/100 patient-years in the clinical studies in patients with UC, and 0.55/100 patient-years in the clinical studies in patients with RA, indicating that the incidence rate of non-melanoma skin cancers was similar between patients with UC and patients with RA.

The incidence rate of malignancies excluding non-melanoma skin cancers was 0.50/100 patient-years in the clinical studies in patients with UC, and 0.75/100 patient-years in the clinical studies in patients with RA, indicating that the incidence rate of malignancies excluding non-melanoma skin cancers was also similar between patients with UC and patients with RA.

As shown above, taking into consideration that there were no particular differences in the incidence of malignancies between patients with UC and patients with RA, at present, there should be no particular problems with the use of tofacitinib in patients with UC. However, the patient's condition should be monitored for the risk of malignancy in patients with UC during treatment with tofacitinib, as in the case of patients with RA.

PMDA's view:
There were no significant clinical concerns about the incidence of malignancies in the clinical studies conducted in patients with UC. However, currently available data from patients with UC are limited. When tofacitinib is used in patients with UC, the patient's condition should be closely monitored for the risk of malignancy, as in the case of patients with RA. Data on the incidence of malignancies when using tofacitinib in patients with UC should be continuously gathered through post-marketing surveillance.

7.R.3.4 Post-marketing safety information

The applicant's explanation about the post-marketing safety of tofacitinib:
Tofacitinib has been approved in and outside Japan for the treatment of RA in patients who have not adequately responded to conventional treatments. According to the latest Periodic Safety Update Report (covering period from November 6, 2012 to November 5, 2017), the estimated cumulative patient exposure from worldwide marketing experience of tofacitinib is approximately 105,385 patient-years. In the post-marketing setting, 14,745 serious adverse events were reported until November 5, 2017. Main adverse events reported were "drug ineffective" (14.3%), "arthralgia" (8.2%), "headache" (7.3%), "condition aggravated" (7.0%), "pain" (6.2%), "fatigue" (6.1%), "product use in unapproved indication" (6.1%), "pain in extremity" (4.9%), "diarrhoea" (4.7%), "nausea" (4.6%), "malaise" (4.2%), "joint swelling" (4.2%), "musculoskeletal stiffness" (3.9%), "nasopharyngitis" (3.8%), "peripheral swelling" (3.6%), "drug effect incomplete" (2.8%), "herpes zoster" (2.8%), "cough" (2.7%), "rheumatoid arthritis" (2.6%), "drug dose omission" (2.5%), "dizziness" (2.4%), "back pain" (2.3%), "abdominal discomfort" (2.3%), "abdominal pain upper" (2.3%), "weight increased" (2.2%), "sinusitis" (2.1%), "urinary tract infection" (2.1%), "pneumonia" (2.1%), "rash" (2.1%), and "dyspnoea" (2.0%). Main serious adverse events were "rheumatoid arthritis" (2.6%), "condition aggravated" (2.2%), and "pneumonia" (2.1%).

An analysis was performed using the data from the specified use-results survey in patients with RA that is currently underway in Japan. According to the latest Periodic Safety Update Report (covering the period from November 6, 2016 to November 5, 2017), 3929 patients were included in the safety analysis set (data gathered from July 30, 2013 to November 5, 2017), of whom 339 experienced serious adverse drug reactions (499 cases). Serious adverse drug reactions reported relatively frequently were "herpes zoster" (1.2%, 48 patients), "pneumonia" (1.0%, 39 patients), "interstitial lung disease" (0.7%, 28 patients), "pneumocystis jirovecii pneumonia" (0.5%, 20 patients), "pneumonia bacterial" (0.4%, 16 patients), "bronchitis" (0.3%, 13 patients), "cellulitis" (0.3%, 11 patients), "condition aggravated" (0.3%, 10 patients), "sepsis" (0.2%, 9 patients), "gastric cancer" (0.2%, 8 patients), "pyrexia" (0.2%, 8 patients), "arthritis bacterial" (0.2%, 6 patients), urinary tract infection (0.2%, 6 patients), disseminated intravascular coagulation (0.2%, 6 patients), "pyelonephritis" (0.1%, 5 patients), "breast cancer" (0.1%, 5 patients), and "lymphocyte count decreased" (0.1%, 5 patients).

Based on the above results, no particular safety concerns have been noted so far in post-marketing safety information about tofacitinib.

PMDA confirmed that there have been no particular safety concerns so far in post-marketing safety information about tofacitinib for the approved indication.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of tofacitinib in the treatment of UC:
In Japan, therapies used to treat patients with active UC in accordance with the Treatment Guidelines are 5-ASA agents, steroids, immunosuppressants, and TNF inhibitors, and suitable therapy are selected primarily depending on the degree of severity. In patients with UC in sustained remission, 5-ASA agents, immunosuppressants, and TNF inhibitors are used primarily based on the remission induction therapy and treatment resistance of each patient.

Tofacitinib should be used after the use of at least 1 of the conventional therapies (steroids, immunosuppressants, or biological products) is thoroughly considered. Tofacitinib is a JAK inhibitor which has a mechanism of action different from those of approved drugs; therefore, tofacitinib can offer a new treatment option for patients with moderately to severely active UC who have inadequately responded to conventional therapies.

PMDA's view:
Tofacitinib should be used after the use of at least 1 of the conventional therapies (steroids, immunosuppressants, or biological products) is thoroughly considered.

7.R.5 Indications

The remission-inducing and maintaining effects of tofacitinib were demonstrated in the global phase III remission induction study (Study A3921094) and global phase III remission maintenance study (Study A3921096) [See Section 7.R.2]. The safety profile of tofacitinib in the clinical studies involving patients with UC was acceptable [See Section 7.R.3]. Because patients enrolled in the global phase III remission induction study (Study A3921094) were those with moderately to severely active UC who have inadequately responded to conventional treatments, PMDA considers that the indication of tofacitinib should be "Induction and maintenance of remission in patients with moderately to severely active ulcerative colitis (only patients who have not adequately responded to conventional treatments)."

The final decision on the indication of tofacitinib will be made, taking account of comments from the Expert Discussion.

7.R.6 Dosage and administration

7.R.6.1 Dosage and administration of tofacitinib in patients with active UC and duration of remission induction therapy

7.R.6.1.1 Dosage and administration of tofacitinib in patients with active UC

The applicant's explanation about the dosage regimen for tofacitinib in patients with active UC:
In the foreign phase II study, "clinical response rate at Week 8," the primary endpoint of the study, was 47.5% (19 of 40 subjects) in the placebo group, 29.6% (8 of 27 subjects) in the tofacitinib 0.5 mg group, 51.6% (16 of 31 subjects) in the tofacitinib 3 mg group, 63.3% (19 of 30 subjects) in the tofacitinib 10 mg group, and 80.0% (36 of 45 subjects) in the 15 mg group. The "clinical remission rate at Week 8," one of the secondary endpoints, was 12.2% (5 of 41 subjects) in the placebo group, 7.4% (2 of 27 subjects) in the tofacitinib 0.5 mg group, 35.5% (11 of 31 subjects) in the tofacitinib 3 mg group, 50.0% (15 of 30 subjects) in the tofacitinib 10 mg group, and 42.2% (19 of 45 subjects) in the tofacitinib 15 mg group. Both the "clinical response rate at Week 8" and "clinical remission rate at Week 8" tended to be higher in the tofacitinib 10 mg and 15 mg groups than in the placebo group.

Safety analyses were performed. The incidence of adverse events was 47.9% (23 of 48 subjects) in the placebo group, 61.3% (19 of 31 subjects) in the tofacitinib 0.5 mg group, 33.3% (11 of 33 subjects) in the tofacitinib 3 mg group, 42.4% (14 of 33 subjects) in the tofacitinib 10 mg group, and 40.8% (20 of 49 subjects) in the tofacitinib 15 mg group. The incidence of adverse drug reactions was 16.7% (8 of 48 subjects) in the placebo group, 19.4% (6 of 31 subjects) in the tofacitinib 0.5 mg group, 12.1% (4 of 33 subjects) in the tofacitinib 3 mg group, 24.2% (8 of 33 subjects) in the tofacitinib 10 mg group, and 16.3% (8 of 49 subjects) in the tofacitinib 15 mg group. The incidence of adverse events and adverse drug reactions were not dose dependent.

Based on the above results, the applicant selected the oral dose of tofacitinib 10 mg twice daily for the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095). The results of these studies demonstrated the superiority of tofacitinib 10 mg over placebo, together with acceptable safety. The oral dose of tofacitinib 10 mg twice daily was considered appropriate as the dosage regimen for remission induction therapy with tofacitinib, because the same dosage regimen was employed in the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095).

7.R.6.1.2 Duration of remission induction therapy with tofacitinib

The applicant's explanation about the duration of remission induction therapy with tofacitinib:
In the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095), the treatment effect of the study drug was evaluated at Week 8, and patients who had achieved clinical response were allowed to participate in the global phase III remission maintenance study (Study A3921096). The assessment of clinical response at Week 8 was considered appropriate because 57.6% (521 of 905) of subjects who received tofacitinib 10 mg achieved clinical response at Week 8 in the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095).

In contrast, patients who had failed to achieve clinical response at Week 8 in the global phase III remission induction study (Study A3921094) or the foreign phase III remission induction study (Study A3921095) were allowed to participate in the global long-term extension study (Study A3921139) and to receive tofacitinib 10 mg. There were 295 patients who had failed to achieve clinical response at Week 8 after receiving tofacitinib 10 mg twice daily orally for 8 weeks in the global phase III remission induction study (Study A3921094) or the foreign phase III remission induction study (Study A3921095) and who then continued to receive tofacitinib 10 mg in the global long-term extension study (Study A3921139) (hereinafter referred to as "the extended tofacitinib 10 mg group"). Table 41 shows the "remission rate, mucosal healing rate, or clinical response rate at Week 8 (at 16 or 17 weeks of tofacitinib treatment)" of the global long-term extension study (Study A3921139) in the extended tofacitinib 10 mg group. An additional 8 weeks of treatment (up to 16 or 17 weeks of tofacitinib treatment) for patients who had failed to achieve clinical response in the global phase III remission induction study (Study A3921094) or foreign phase III remission induction study (Study A3921095) was considered to show therapeutic benefit.

Table 41. Remission rate, mucosal healing rate, or clinical response rate at Week 8 (at 16 or 17 weeks of tofacitinib treatment) of the global long-term extension study (Study A3921139) in the extended tofacitinib 10 mg group

Endpoint	Baseline[b)]	Week 8[c)]
Remission rate (n/N)[a) d)]	0% (0/293)	8.7% (25/289)
Mucosal healing rate (n/N)[a) d)]	2.4% (7/293)	13.8% (40/290)
Clinical response rate (n/N)[a) d)]	0% (0/293)	51.6% (149/289)

a) Subjects with missing data were treated as those who failed to achieve remission, clinical response, or mucosal healing (non-responders).
b) At entry into the global long-term extension study (Study A3921139)
c) Corresponding to 16 or 17 weeks after the start of treatment in the global phase III remission induction study (Study A3921094) or foreign phase III remission induction study (Study A3921095)
d) Number of subjects whose Mayo score was given (endoscopic subscore for mucosal healing data)

Table 42 shows the incidence of adverse events in the extended tofacitinib 10 mg group at Week 8 (at 8 or 9 weeks of tofacitinib treatment or at 16 or 17 weeks of tofacitinib treatment) of the global long-term extension study (Study A3921139). The results for the extended tofacitinib 10 mg group did not differ significantly from the results for the placebo or tofacitinib 10 mg group (up to 8 or 9 weeks of study drug treatment in both groups) in the pooled data from the foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), and foreign phase III remission induction study (Study A3921095).

Table 42. Summary of adverse events at Week 8 (at 8 or 9 weeks of tofacitinib treatment or at 16 or 17 weeks of tofacitinib treatment) in the extended tofacitinib 10 mg group in the global long-term extension study (Study A3921139)

	Pooled data from the foreign phase II study (Study A3921063), global phase III remission induction study (Study A3921094), and foreign phase III remission induction study (Study A3921095) (up to 8 or 9 weeks of study drug treatment)		Global long-term extension study (Study A3921139) (at 8 or 9 weeks of tofacitinib treatment or at 16 or 17 weeks of tofacitinib treatment)
	Placebo (N = 282)	Tofacitinib 10 mg (N = 938)	Extended tofacitinib 10 mg (N = 295)
Any adverse event	55.0 (155)	54.9 (515)	52.2 (154)
Serious adverse event	6.4 (18)	3.8 (36)	3.7 (11)
Adverse event leading to treatment discontinuation	5.0 (14)	3.8 (36)	2.4 (7)
Serious infection	0 (0)	0.9 (8)	0.7 (2)
Herpes zoster	0.4 (1)	0.6 (6)	0.3 (1)
Malignancy (excluding non-melanoma skin cancer)	0 (0)	0 (0)	0.3 (1)
Non-melanoma skin cancer	0 (0)	0.2 (2)	0 (0)
Major cardiovascular event	0 (0)	0.2 (2)	0 (0)
Gastrointestinal perforation	0.4 (1)	0.1 (1)	0.3 (1)

MedDRA/J ver. 19.0; incidence, % (n)

Based on the above, the applicant considered that the following measures should be taken: The 8-week treatment with tofacitinib is recommended as remission induction therapy, but an additional 8 weeks of treatment with tofacitinib 10 mg twice daily should be considered if clinical symptoms do not improve after 8 weeks of treatment with tofacitinib. If clinical response cannot be achieved, treatment with tofacitinib should be discontinued, and switching to other therapies should be considered.

PMDA asked the applicant to explain if there was any difference in baseline demographics and disease characteristics of patients or other factors between patients who had achieved clinical response and those who had not in the extended tofacitinib 10 mg group in the global long-term extension study (Study A3921139).

The applicant's response:
Factors such as baseline demographics and disease characteristics of patients (e.g., age, body weight, and sex), Mayo score at enrollment in the global phase III remission induction study (Study A3921094) or the foreign phase III remission induction study (Study A3921095), and prior therapies for UC were investigated in patients who had achieved clinical response and those who had not in the extended tofacitinib 10 mg group in the global long-term extension study (Study A3921139). The results showed no significant differences between the subgroups.

Subgroup analyses were performed for the subgroup of patients who had improved Mayo scores with failure to achieve clinical response and another subgroup of patients whose Mayo scores had remained unchanged or worsened at Week 8 from baseline in the global phase III remission induction study (Study A3921094) or foreign phase III remission induction study (Study A3921095). Table 43 shows remission rate, mucosal healing rate, and clinical response rate at Week 8 (at 16 or 17 weeks of tofacitinib treatment) of the global long-term extension study (Study A3921139). Of the 128 patients whose Mayo scores at Week 8 had remained unchanged or worsened from baseline in the global phase III remission induction study (Study A3921094) or foreign phase

III remission induction study (Study A3921095), 49 patients (38.3%) achieved clinical response; further, these patients inadequately responded to conventional treatments and thus their treatment options are limited. Therefore, if the patient's condition remained unchanged, or worsened after the 8-week treatment with tofacitinib 10 mg twice daily, an additional 8 weeks of tofacitinib 10 mg twice daily is considered clinically meaningful.

Table 43. Remission rate, mucosal healing rate, or clinical response rate at Week 8 (at 16 or 17 weeks of tofacitinib treatment) in the extended tofacitinib 10 mg group in the global long-term extension study (Study A3921139)

Endpoint	Patients who had failed to achieve clinical response but had improved scores in the global phase III remission induction study (Study A3921094) or foreign phase III remission induction study (Study A3921095)		Patients whose scores remained unchanged or worsened in the global phase III remission induction study (Study A3921094) or foreign phase III remission induction study (Study A3921095)	
	Baseline[b)]	Week 8[c)]	Baseline[b)]	Week 8[c)]
Remission rate (n/N)[a) d)]	0% (0/164)	10.6% (17/161)	0% (0/129)	6.3% (8/128)
Mucosal healing rate (n/N)[a) d)]	3.7% (6/164)	18.0% (29/161)	0.8% (1/129)	8.5% (11/129)
Clinical response rate (n/N)[a) d)]	0% (0/164)	62.1% (100/161)	0% (0/129)	38.3% (49/128)

a) Subjects with missing data were treated as those who failed to achieve remission, clinical response, or mucosal healing (non-responders)
b) At entry into the global long-term extension study (Study A3921139)
c) Corresponding to 16 or 17 weeks after the start of treatment in the global phase III remission induction study (Study A3921094) or foreign phase III remission induction study (Study A3921095)
d) Number of subjects whose Mayo score was given (endoscopic subscore for mucosal healing data)

Based on the discussions in Sections 7.R.6.1.1 and 7.R.6.1.2, PMDA considers the dosage regimen for tofacitinib in patients with active UC as follows:
There are no particular problems with specifying oral tofacitinib 10 mg twice daily as the dosage regimen in remission induction therapy with tofacitinib, based on the dosage regimen employed in the global phase III remission induction study (Study A3921094). It is also acceptable to administer an additional 8 weeks of tofacitinib to patients who had an inadequate response after oral administration of tofacitinib 10 mg twice daily for 8 weeks.

The final decision on the dosage and administration of tofacitinib as remission induction therapy, and the duration of remission induction therapy with tofacitinib will be made, taking account of comments from the Expert Discussion.

7.R.6.2 Dosage and administration of tofacitinib in patients with UC in sustained remission

The applicant's explanation about the dosage regimen for tofacitinib in patients with UC in sustained remission:
The dosage regimen for tofacitinib in the global phase III remission induction study (Study A3921094) and foreign phase III remission induction study (Study A3921095) was tofacitinib 10 mg twice daily. Because the applicant considered that the dosage regimen for tofacitinib in the global phase III remission maintenance study (Study A3921096) should not exceed the dosage for remission induction therapy, tofacitinib 5 mg or 10 mg twice daily was selected.

The global phase III remission maintenance study (Study A3921096) demonstrated the superiority of both tofacitinib 5 mg and 10 mg over placebo in terms of the "remission rate at Week 52" as the primary endpoint

for the study [See Section 7.R.2.2]. No clinically significant trends were noted in the tofacitinib 5 mg and 10 mg groups compared with the placebo group [See Section 7.R.3.2]. Because tofacitinib is likely to be administered to patients with UC in sustained remission for a prolonged period of time, tofacitinib 5 mg was considered to be more appropriate for the usual dosage, taking safety aspects into consideration.

In the global long-term extension study (Study A3921139), patients who were in remission at the completion of the global phase III remission maintenance study (Study A3921096) had to receive tofacitinib 5 mg twice daily. However, the dose increase from tofacitinib 5 mg to 10 mg was permitted in patients who experienced a loss of clinical response (defined by an increase in partial Mayo score of ≥2 points from baseline for 2 consecutive visits with at least 2 weeks apart), and relapse confirmed by endoscopic examination (defined by an increase in Mayo score of ≥3 points from baseline, an increase in rectal bleeding subscore by ≥1 point, and an increase in endoscopic subscore by ≥1 point) after receiving tofacitinib 5 mg twice daily for ≥8 weeks. In the global long-term extension study (Study A3921139), of the 144 patients who started tofacitinib at 5 mg, only 1 patient had his/her dose increased to 10 mg. Almost all of the patients remained on tofacitinib 5 mg.

Next, data were analyzed for patients in the tofacitinib 5 mg group in the global phase III remission maintenance study (Study A3921096) who had discontinued treatment due to lack of efficacy before receiving tofacitinib 10 mg twice daily in the global long-term extension study (Study A3921139). There were 58 patients who received tofacitinib 10 mg twice daily in the global phase III remission induction study (Study A3921094) or foreign phase III remission induction study (Study A3921095), and who were assigned to the tofacitinib 5 mg group in the global phase III remission maintenance study (Study A3921096) but discontinued treatment (administered for at least 8 weeks). These patients received tofacitinib 10 mg twice daily in the global long-term extension study (Study A3921139). The remission rate was 0% (0 of 58 subjects) at baseline, 34.5% (20 of 58 subjects) at Month 2, 52.1% (25 of 48 subjects) at Month 12, and 31.3% (5 of 16 subjects) at Month 24, suggesting the efficacy of tofacitinib 10 mg in patients who had had an inadequate response to tofacitinib 5 mg in the maintenance therapy (Table 44). Similar trends were observed for the mucosal healing rate and clinical response rate. Furthermore, there were no significant clinical concerns about the safety aspects in the tofacitinib 5 mg and 10 mg groups. Based on the above, a dose increase of tofacitinib from 5 mg to 10 mg twice daily is expected to produce some therapeutic benefits in patients who had an inadequate response to tofacitinib 5 mg twice daily in maintenance therapy.

Table 44. Remission rate, mucosal healing rate, and clinical response rate at each time point in patients who had discontinued treatment due to inadequate response to tofacitinib 5 mg in the global remission maintenance study (Study A3921096) before receiving tofacitinib 10 mg in the global long-term extension study (Study A3921139)

Endpoint	Baseline	Month 2	Month 12	Month 24
Remission rate (n/N)[a)]	0% (0/58)	34.5% (20/58)	52.1% (25/48)	31.3% (5/16)
Mucosal healing rate (n/N)[a)]	5.2% (3/58)	41.4% (24/58)	60.4% (29/48)	43.8% (7/16)
Clinical response rate (n/N)[a)]	5.2% (3/58)	58.6% (34/58)	68.8% (33/48)	50.0% (8/16)

a) Subjects with missing data were handled as those who failed to achieve remission, clinical response, and mucosal healing (non-responders)

For the treatment of patients with refractory UC with prior TNF inhibitor failure, physicians are required to choose a suitable therapy which is expected to achieve adequate response, though other treatment options are limited. Data from the global phase III remission maintenance study (Study A3921096) was analyzed for the "remission rate at Week 52" in patients with or without prior TNF inhibitor failure. The "remission rates at Week 52" in patients without and with prior TNF inhibitor failure in the tofacitinib 5 mg group were 41.7% (48 of 115 subjects) and 24.1% (20 of 83 subjects), respectively, and those in patients without and with prior TNF inhibitor failure in the 10 mg group were 44.2% (46 of 104 subjects) and 36.6% (34 of 93 subjects), respectively. While the results in the tofacitinib 10 mg group were similar to those in the overall study population regardless of prior TNF inhibitor failure, the therapeutic effect tended to be lower in patients with prior TNF inhibitor failure in the tofacitinib 5 mg group. Therefore, the continued use of tofacitinib 10 mg twice daily in patients with refractory UC with prior TNF inhibitor failure should be considered.

PMDA's view:
The global phase III remission maintenance study (Study A3921096) demonstrated the superiority of both tofacitinib 5 mg and10 mg over placebo [See Section 7.R.2.2]. The safety of tofacitinib was shown to be acceptable [See Section 7.R.3]. A lower dose level should be selected within the range at which tofacitinib is expected to be effective. For these reasons, there are no particular problems with selecting the oral administration of tofacitinib 5 mg twice daily as the usual dosage regimen for maintenance therapy. It is acceptable to specify that tofacitinib 10 mg may be administered twice daily to patients experiencing a loss of response on tofacitinib 5mg twice daily for maintenance therapy. Further, the use of tofacitinib 10 mg twice daily in patients who are refractory to prior drug treatment (e.g., those with TNF inhibitor failure) is also acceptable for maintenance therapy.

The final decision on the dosage regimen for tofacitinib in maintenance therapy (including tofacitinib 10 mg) will be made, taking account of comments from the Expert Discussion.

7.R.7 Use of tofacitinib in combination with conventional therapeutic drugs for UC

The applicant's explanation about the use of tofacitinib in combination with conventional therapeutic drugs for UC:
The protocols of the clinical studies in patients with UC prohibited the concomitant use of conventional biological products and immunosuppressants that might affect the evaluation of the efficacy and safety of tofacitinib. No data regarding the use of tofacitinib in combination with these drugs were available from clinical studies conducted in patients with RA. Because of the immunosuppressive effect of tofacitinib and taking the mechanism of action of tofacitinib into consideration, immunosuppressive effect may be intensified when used in combination with conventional biological products or immunosuppressants, which may increase the risk of infections. Therefore, the package insert should advise that tofacitinib should not be used in combination with conventional biological products or immunosuppressants.

PMDA's view:

The risk for infections or other events may be increased by the use of tofacitinib in combination with conventional therapeutic drugs for UC; therefore, the package insert should advise that tofacitinib should not be used in combination with conventional biological products (e.g., TNF inhibitors) or immunosuppressants (e.g., tacrolimus and azathioprine).

7.R.8 Post-marketing investigations

The applicant has planned to conduct a post-marketing, specified use-results survey as shown in Table 45.

Table 45. Outline of specified use-results survey plan (draft)

Objective	To evaluate the long-term safety and efficacy of tofacitinib in patients with UC in routine clinical practice
Survey method	All case surveillance
Population	Patients with moderately to severely active UC who did not adequately respond to conventional treatments
Planned sample size	All patients who received tofacitinib (target sample size, 470 patients)
Observation period	60 weeks
Main survey items	• Baseline demographics and disease characteristics of patients (age, sex, history of UC [disease duration, lesion range, degree of severity], complications, medical history, etc.) • Usage of tofacitinib (dose per administration, number of dose per day, treatment duration, etc.) • Concomitant medication for treatment of UC (name of drugs, route of administration, treatment duration) • Adverse events (onset date, seriousness, outcome, actions taken, causal relationship to tofacitinib, etc.) • Laboratory test values • Efficacy (partial Mayo subscore)

PMDA's view:

Given that the very limited number of Japanese patients participating in the clinical studies in patients with UC, and that tofacitinib is likely to be administered for a prolonged period of time, post-marketing surveillance should be conducted to evaluate the long-term safety and efficacy of tofacitinib, covering all patients treated with tofacitinib, as planned by the applicant. The details will be finalized, taking account of comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.2, CTD 5.3.5.1.4, and CTD 5.3.5.2.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection showed that the clinical studies as a whole were conducted in compliance with GCP; therefore, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents. However, the following issue was found at a study center albeit with no major impact on the overall study evaluation. The issue was identified as an area for improvement, and notified to the head of the medical institutions.

Finding requiring corrective action:

Study center

- Deviation from the protocol (error in registration of stratification factors)

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that tofacitinib has efficacy in the treatment of ulcerative colitis, and that tofacitinib has acceptable safety in view of its benefits. Ulcerative colitis is classified as a designated intractable disease. Given that treatment options for the disease are limited and that the mechanism of action of tofacitinib differs from that of existing UC drugs, tofacitinib offers a new treatment option for ulcerative colitis, and therefore is clinically meaningful. Further discussions are needed regarding efficacy, safety, indications, dosage and administration, and post-marketing investigations.

PMDA has concluded that tofacitinib may be approved if tofacitinib is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

April 17, 2018

Product Submitted for Approval

Brand Name	Xeljanz Tablets 5 mg
Non-proprietary Name	Tofacitinib Citrate
Applicant	Pfizer Japan Inc.
Date of Application	May 31, 2017

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/20 dated December 25, 2008).

1.1 Outline of review of tofacitinib 10 mg for treatment of RA

At the Expert Discussion, PMDA provided an explanation that summarized the review of tofacitinib 10 mg indicated for the treatment of RA as follows:

Tofacitinib has been approved in several countries including Japan, European countries and the US for the treatment of "rheumatoid arthritis in patients who have not adequately responded to conventional treatments," and in all countries/regions, the approved dosage for the treatment of RA is tofacitinib 5 mg twice daily. When an application for the treatment of RA was initially filed in the US and Japan, the dosage of tofacitinib 10 mg twice daily was also proposed. In the course of reviewing the application for the treatment of RA, the regulatory authorities of the US and Japan decided not to approve the dosage of tofacitinib 10 mg twice daily ("Review Report on Xeljanz Tablets 5 mg" dated on February 28, 2013), for the following reasons: (i) the incidence of adverse events associated with the use of tofacitinib increased in a dose-dependent manner; (ii) serious infections and malignancies as adverse events tended to occur more frequently in the tofacitinib 10 mg group than in the 5 mg group; (iii) tuberculosis and malignancies may be more common in in the tofacitinib 10 mg group than in the adalimumab (genetical recombination) group (Tables 46 through 49).

Table 46. Incidence of serious infections in the clinical studies conducted in patients with RA

	Phase III studies (up to Month 12)[a]				Long-term extension study[b]	
	Placebo (N = 681)	Tofacitinib		Adalimumab (genetical recombination) (N = 204)	Tofacitinib	
		5 mg (N = 1216)	10 mg (N = 1214)		5 mg (N = 1321)	10 mg (N = 1906)
Incidence (n)	0.4% (3)	2.4% (29)	2.2% (27)	1.5% (3)	3.8% (50)	2.3% (43)
Incidence rate (/100 patient-year) [95%CI]	1.48 [0.48, 4.59]	3.22 [2.24, 4.63]	2.97 [2.04, 4.33]	1.68 [0.54, 5.21]	2.25 [1.71, 2.97]	4.89 [3.63, 6.60]

a) Foreign phase III studies in patients with RA (Studies A3921032, A3921045, A3921046, and A3921064) and global phase III study in patients with RA (Study A3291044)
b) Foreign long-term extension study in patients with RA (Study A3921024) and Japanese long-term extension study in patients with RA (Study A3921041)

Table 47. Incidence of opportunistic infections in the clinical studies conducted in patients with RA

	Phase III studies (up to Month 12)[a]				Long-term extension study[b]	
	Placebo (N = 681)	Tofacitinib		Adalimumab (genetical recombination) (N = 204)	Tofacitinib	
		5 mg (N = 1216)	10 mg (N = 1214)		5 mg (N = 1321)	10 mg (N = 1906)
Incidence (n)	0% (0)	0.2% (3)	0.8% (10)	0% (0)	0.6% (8)	0.3% (5)
Incidence rate (/100 patient-year) [95%CI]	0	0.33 [0.11, 1.03]	1.10 [0.59, 2.04]	0	0.36 [0.18, 0.72]	0.57 [0.24, 1.36]

a) Foreign phase III studies in patients with RA (Studies A3921032, A3921045, A3921046, and A3921064) and global phase III study in patients with RA (Study A3291044)
b) Foreign long-term extension study in patients with RA (Study A3921024) and Japanese long-term extension study in patients with RA (Study A3921041)

Table 48. Incidence of tuberculosis in the clinical studies conducted in patients with RA

	Phase III studies (up to Month 12)[a]				Long-term extension study[b]	
	Placebo (N = 681)	Tofacitinib		Adalimumab (genetical recombination) (N = 204)	Tofacitinib	
		5 mg (N = 1216)	10 mg (N = 1214)		5 mg (N = 1321)	10 mg (N = 1906)
Incidence (n)	0% (0)	0% (0)	0.5% (6)	0% (0)	<0.1% (1)	<0.1% (1)
Incidence rate (/100 patients-year) [95%CI]	0	0	0.66 [0.30, 1.47]	0	0.05 [0.01, 0.32]	0.11 [0.02, 0.81]

a) Foreign phase III studies in patients with RA (Studies A3921032, A3921045, A3921046, and A3921064) and global phase III study in patients with RA (Study A3291044)
b) Foreign long-term extension study in patients with RA (Study A3921024) and Japanese long-term extension study in patients with RA (Study A3921041)

Table 49. Incidence of malignancies (excluding non-melanoma skin cancers) in the clinical studies conducted in patients with RA

	Phase III studies (up to Month 12)[a]				Long-term extension study[b]	
	Placebo (N = 681)	Tofacitinib		Adalimumab (genetical recombination) (N = 204)	Tofacitinib	
		5 mg (N = 1216)	10 mg (N = 1214)		5 mg (N = 1321)	10 mg (N = 1906)
Incidence (n)	0% (0)	0.4% (5)	0.7% (8)	0.5% (1)	1.7% (23)	0.6% (12)
Incidence rate (/100 patient-year) [95%CI]	0	0.55 [0.23, 1.33]	0.88 [0.44, 1.76]	0.56 [0.08, 3.97]	1.03 [0.68, 1.55]	1.36 [0.77, 2.40]

a) Foreign phase III studies in patients with RA (Studies A3921032, A3921045, A3921046, and A3921064) and global phase III study in patients with RA (Study A3291044)
b) Foreign long-term extension study in patients with RA (Study A3921024) and Japanese long-term extension study in patients with RA (Study A3921041)

In the past, the applicant also undertook a clinical development program of tofacitinib for [redacted] psoriasis [redacted], and filed a marketing application in the US [redacted] ([redacted]). The US Food and Drug Administration (US FDA) concluded that "[redacted] cannot be approved at that point in time." The applicant [redacted] and therefore withdrew the application in the US [redacted]. In February 2017, the applicant filed an application for the treatment of "psoriatic arthropathy" in the US, and Xeljanz (tofacitinib) was granted approval in December 2017. (The dosage and administration of the tofacitinib 5-mg tablet was tofacitinib 5 mg twice daily in combination with non-biologic disease-modifying anti-rheumatic drugs (DMARDs). The sustained-release formulation of tofacitinib was approved in the US at the same time. The dosage and administration for the sustained-release formulation is 11 mg once daily in combination with non-biologic DMARDs.)

The applicant has filed an application in the US for tofacitinib in the treatment of "patients with ulcerative colitis who have had inadequately responded to conventional treatments" in May 2017 (the proposed dosage and administration for the treatment of UC currently under review in and outside Japan is the same [redacted]).

On March 8, 2018, the US FDA held an Advisory Committee meeting concerning the review of the application for the treatment of UC and the Committee discussed the following issues regarding the dosage and administration of tofacitinib:

- The Advisory Committee discussed the benefit of an extended period of 16 weeks for induction therapy with tofacitinib 10 mg twice daily in adult patients with UC who have had an inadequate response to tofacitinib by Week 8 in induction therapy. Continuation of induction therapy with tofacitinib 10 mg for an additional 8 weeks was supported by the Advisory Committee (15 agreed/0 disagreed) for the following reasons: (i) Patients who participated in the global long-term extension study (Study A3921139) after completing the global phase III remission induction study (Study A3921094) or the foreign phase III remission induction study (Study A3921095) achieved clinical response to an additional 8 weeks of treatment, and (ii) there were no particular safety concerns associated with an additional 8 weeks of treatment.

- The Advisory Committee discussed the appropriateness of tofacitinib 10 mg twice daily as maintenance therapy in patients with prior TNF inhibitor failure. This decision was supported by the Advisory Committee (15 agreed / 0 disagreed) based on the following findings from the global phase III remission maintenance study (Study A3921096) in patients with UC: (i) An analysis of data from patients with prior TNF inhibitor failure indicated that the "remission rate at Week 52" would be higher in the tofacitinib 10 mg group than in the tofacitinib 5 mg group; (ii) herpes zoster raised no particular concerns in patients receiving tofacitinib 10 mg as maintenance therapy for UC [See Section 7.R.3.3.1.2]; and no dose-response relationship was observed between the tofacitinib 5 mg and 10 mg groups in terms of the incidence of malignancies in patients with UC [See Section 7.R.3.3.4].

1.2 Efficacy, safety, indications, and dosage and administration for treatment of UC

PMDA's conclusions presented in Sections "7.R.2 Efficacy," "7.R.3 Safety," "7.R.5 Indications," and "7.R.6 Dosage and Administration" in Review Report (1) were supported by the expert advisors at the Expert Discussion.

Based on the comments made in the Expert Discussion, PMDA asked the applicant to define the "Indications," "Dosage and Administration," and "Precautions for Indications" and "Precautions Concerning Dosage and Administration" in the package insert as shown below. The applicant responded to the request, and PMDA accepted.

Indications

Induction and maintenance of remission in patients with moderate to severe ulcerative colitis (only patients who have not adequately responded to conventional treatments)

Precautions for indications

Ulcerative colitis

Tofacitinib should be used in patients who have evidence of persistent clinical symptoms associated with ulcerative colitis despite an adequate course of other drug therapies (steroids, immunosuppressants, or biological products).

Dosage and Administration

The usual adult dosage for induction therapy is 10 mg of tofacitinib given orally twice daily for 8 weeks. The induction therapy can be extended for an additional 8 weeks in patients who do not achieve an adequate response.

The usual adult dosage for maintenance therapy is 5 mg of tofacitinib given orally twice daily. The dose may be increased to 10 mg twice daily in patients with a loss of response during maintenance therapy. The 10 mg twice-daily dose may be used in patients with ulcerative colitis who are refractory to prior drug treatment (e.g., those with TNF inhibitor failure).

Precautions Concerning Dosage and Administration

1. Consider switching to other therapies if clinical response is not confirmed by clinical symptoms or endoscopic findings at 16 weeks of induction therapy with tofacitinib.
2. Carefully examine whether tofacitinib is discontinued if no improvement in clinical symptoms is observed during maintenance therapy with tofacitinib 10 mg twice daily. Then, consider switching to other therapies.
3. Tofacitinib should be carefully administered to patients with UC with moderate to severe renal impairment and patients with UC with moderate hepatic impairment [See the "Pharmacokinetics" section]. Reduce the dose of tofacitinib in those patients (reduce the dose per administration. If the dose cannot be reduced, reduce the dose frequency).
4. Do not use tofacitinib in combination with biological products such as TNF inhibitors, or potent immunosuppressants such as tacrolimus and azathioprine (except for topical formulations). The immunosuppressive effect of tofacitinib may be intensified when used in combination with these agents, and this may result in an increased risk for infections. There is no clinical experience with the use of tofacitinib in combination with these biological products or immunosuppressants.

(Only the portions relating to the present application are presented)

1.3 Risk management plan (draft)

At the Expert Discussion, the following comment was made regarding the PMDA's conclusion provided in Section "7.R.8 Post-marketing investigations" in Review Report (1), and the conclusion was supported by the expert advisors.

- In the global phase III remission induction study (Study A3921094), foreign phase III remission induction study (Study A3921095), and global phase III remission maintenance study (Study A3921096), there were no significant differences in the incidence of malignancies between the tofacitinib 10 mg group and the placebo group [See Section7.R.3.3.4]. Because of this and for other reasons, at present there seem to be no significant clinical concerns about the risk of malignancy associated with the use of tofacitinib 10 mg. However, given that information about the long-term safety of tofacitinib 10 mg twice daily is only data from clinical studies conducted in patients with UC, that only a limited number of Japanese patients were enrolled in the global clinical studies, and that the dosage of tofacitinib 10 mg twice daily is not approved in patients with RA, the applicant should conduct a specified use-results survey in patients with UC to collect information regarding the incidence of malignancies in long-term treatment (especially for long-term treatment with tofacitinib 10 mg) by following up patients for >60 weeks, wherever possible.

In view of the discussion above, PMDA has concluded that the current risk management plan (draft) for tofacitinib should include the safety and efficacy specifications presented in Table 50, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 51 and specified use-results survey presented in Table 52.

Table 50. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious infections (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, opportunistic infections) • Herpes zoster • Neutrophils/lymphocytes/ haemoglobin decreased • Hepatic dysfunction • Activation of Hepatitis B virus • Gastrointestinal perforation • Interstitial lung disease	• Malignancies • Cardiovascular events • Rhabdomyolysis, myopathy	• Not applicable
Efficacy specification		
• Not applicable		

Table 51. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (UC) • Specified use-results survey (RA) • Specified use-results survey (UC) • Post-marketing clinical study (UC)[a)]	• Information provision through early post-marketing phase vigilance (UC) • Preparation and distribution of materials for healthcare professionals (guidelines for proper use) (RA, UC) • Preparation and provision of information materials for patients (for patients who will take Xeljanz and their families) (RA, UC) • Ensuring information provision regarding proper use of the drug prior to shipping

a) After approval of the present application for tofacitinib, the global long-term extension study (Study A3921139) will be switched to the post-marketing clinical study (UC). The study will continue until the commercial product become available for patients.

Table 52. Outline of specified use-results survey (draft)

Objective	To evaluate the long-term safety and efficacy of tofacitinib in patients with UC in routine clinical practice
Survey method	All case surveillance
Population	Patients with moderately to severely active UC who did not adequately respond to conventional treatments
Planned sample size	All patients who received tofacitinib (target sample size, 470 patients)
Observation period	60 weeks (Patients who continue to receive tofacitinib for more than 60 weeks will be monitored until the end of the survey period)
Main survey items	• Baseline demographics and disease characteristics of patients (age, sex, history of UC [disease duration, lesion range, degree of severity], complications, medical history, etc.) • Usage of tofacitinib (dose per administration, number of dose per day, treatment duration, etc.) • Concomitant medication for the treatment of UC (name of drugs, route of administration, treatment duration) • Adverse events (onset date, seriousness, outcome, actions taken, causal relationship to tofacitinib, etc.) • Laboratory test values • Efficacy (partial Mayo subscore)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indications, and dosage and administration as shown below, with the following conditions of approval. Since the present application is intended for the addition of a new indication and a new dosage, the re-examination period is 4 years for the indication and dosage and administration specified in the present application.

Indications

Rheumatoid arthritis in patients who have not adequately responded to conventional treatments

Induction and maintenance of remission in patients with moderate to severe ulcerative colitis (only patients who have not adequately responded to conventional treatments).

(Underline denotes addition.)

Dosage and Administration

Rheumatoid arthritis

The usual dosage is 5 mg of tofacitinib given orally twice daily.

Ulcerative colitis

The usual adult dosage for induction therapy is 10 mg of tofacitinib given orally twice daily for 8 weeks. The induction therapy can be extended for an additional 8 weeks in patients who do not achieve an adequate response

The usual adult dosage for maintenance therapy is 5 mg of tofacitinib given orally twice daily. The dose may be increased to 10 mg twice daily in patients experiencing a loss of response during maintenance therapy. The 10 mg twice-daily dose may be used in patients with ulcerative colitis who are refractory to prior drug treatment (e.g., those with TNF inhibitor failure).

(Underline denotes additions.)

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of patients included in Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until the data from the planned number of patients are accumulated, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product as early as possible, and taking necessary measures to ensure its proper use.

Appendix

List of Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADR	Adverse drug reaction
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
AZA	Azathioprine
CI	Confidence interval
CK	Creatine kinase
C_{max}	Maximum plasma concentration
EBV	Epstein-Barr-virus
FAS	Full analysis set
FDA	US Food and Drug Administration
GCP	Good clinical practice
GGT	γ-glutamyltransferase
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
JAK	Janus kinase
LC/MS/MS	Liquid chromatography / tandem mass spectrometry
MedDRA	Medical dictionary for regulatory activities
MedDRA/J	Medical dictionary for regulatory activities Japanese version
mFAS	Modified full analysis set
MTX	Methotrexate
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term
PSUR	Periodic safety update report
RA	Rheumatoid arthritis
SOC	System organ class
$t_{1/2}$	Terminal half-life
t_{max}	Time to maximum plasma concentration
TNF	Tumor necrosis factor
Treatment Guidelines	Diagnostic Criteria and Treatment Guidelines for Ulcerative Colitis and Crohn's Disease: FY 2016 Revised Edition, dated March 31, 2017, FY 2016 Report [Supplementary volume]: "Research on Intractable Inflammatory Bowel Disease" [prepared by a study group led by Suzuki], Research on Policy Planning and Evaluation for Rare and Intractable Diseases, a research project funded by the Health and Labour Sciences Research Grants
TYK2	Tyrosine kinase 2
UC	Ulcerative colitis