SUPPORTING INFORMATION

CONTENTS

Supplementary Methods

1. Criteria for dose de-escalation from tofacitinib 10 mg to 5 mg twice daily (b.d.)

For patients receiving tofacitinib 10 mg b.d., tofacitinib dose could be adjusted to 5 mg b.d. if the patients met any of the following laboratory criteria (repeated and confirmed within 7 days): any single haemoglobin value that dropped >2 g/dL below baseline of OCTAVE Open; an absolute neutrophil count <1200 neutrophils/mm^3; an absolute lymphocyte count <750 lymphocytes/mm^3; a platelet count <100,000 platelets/mm^3.

In addition, for patients receiving tofacitinib 10 mg b.d., the dose could be adjusted to 5 mg b.d. if the patient was in remission (based on total Mayo score) or in partial Mayo score (PMS) remission (defined as a PMS ≤2 with no individual subscore >1) at Month 24 or at any visit beyond Month 24, after discussion with the sponsor.

2. Risk factor check for pulmonary embolism

If a patient had any of the risk factors listed below and was receiving tofacitinib 10 mg b.d., the patient's tofacitinib dose was reduced to 5 mg b.d. If a patient had any newly developed risk factors for pulmonary embolism identified during the study, they were not permitted to receive tofacitinib 10 mg b.d.

A patient may be at high risk for pulmonary embolism if he/she:

- has heart failure;
- has inherited coagulation disorders;
- has had venous thromboembolism, either deep venous thrombosis or pulmonary embolism;
- is taking combined hormonal contraceptives or hormone replacement therapy;
- has malignancy (association is strongest with cancers other than non-melanoma skin cancers);
- is undergoing major surgery.

3. Concomitant and prohibited concomitant medications in OCTAVE Open

3.1 Concomitant medications

The following therapies for the treatment of ulcerative colitis were allowed providing their doses were not changed (reduced or increased), with the exception of oral 5-aminosalicylates or sulfasalazine, and oral corticosteroids (see below), during the study treatment period:

- Oral 5-aminosalicylates or sulfasalazine dose modifications during the study were permitted
- Chronic treatment for ulcerative colitis with antibiotics (e.g. metronidazole, rifaximin) if continued from the preceding study
- Oral corticosteroids were allowed for patients entering OCTAVE Open on oral corticosteroids (maximum dose of 25 mg/day of oral prednisone or equivalent) and tapering was required to commence starting the first week of the study
    - The daily dose of oral prednisone or equivalent was decreased at a rate of 5 mg/week until the dose reached 20 mg/day, then reduced by 2.5 to 5.0 mg/week until the dose reached 0 mg
    - If a patient experienced worsening of ulcerative colitis symptoms during the corticosteroid taper, or symptoms related to chronic corticosteroid therapy that in the opinion of the investigator are attributable to the corticosteroid taper, then the investigator could instruct the patient to revert back to the preceding dose in the taper schedule (i.e. “step up”). Study patients with signs or symptoms attributed to corticosteroid taper are permitted to “step up” their corticosteroid dosage one time during the study and then resume corticosteroid taper to achieve steroid-free status
    - If a patient was unable to tolerate tapering their corticosteroid dose below 10 mg/day, the patient was permitted to remain in the study provided their dose did not exceed 10 mg/day. However, efforts were made to taper corticosteroids completely
    - Re-initiation of oral corticosteroid therapy above 10 mg/day of prednisone or equivalent for the treatment of ulcerative colitis, after a patient had achieved

steroid-free status during either OCTAVE Sustain or OCTAVE Open, was considered rescue therapy and the patient was discontinued from the study

- Initiation of oral corticosteroids during OCTAVE Open for the treatment of non-ulcerative colitis indications (e.g. allergic reaction, asthma, etc.) may be permitted and the sponsor should be notified.

3.2. Prohibited concomitant medications

The following medications were prohibited:

- Azathioprine, 6-mercaptopurine and methotrexate;
- Cyclosporine, mycophenolate mofetil/mycophenolic acid and tacrolimus;
- Interferon;
- Tumour necrosis factor inhibitor therapy (e.g. infliximab, adalimumab, golimumab or certolizumab);
- Intravenous corticosteroids;
- Rectally administered formulation of corticosteroids or 5-aminosalicylates;
- Natalizumab, vedolizumab or other anti-adhesion molecule therapy (including investigational agents);
- Other investigational or marketed immunosuppressants or biologics with immunomodulatory properties;
- Leukocyte apheresis, including selective lymphocyte, monocyte or granulocyte apheresis (e.g. Cellsorba®) or plasma exchange;
- Moderate to potent CYP3A inducers or inhibitors due to potential for drug interactions or confounding of data interpretation;

4. Trial locations

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Non-State Healthcare Institution "Road Clinical Hospital at the station Samara"

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Supplementary Tables

TABLE S1 Additional reasons for discontinuation in OCTAVE Open

	Tofacitinib 5 mg b.d. (N = 175)	**Tofacitinib 10 mg b.d. (N = 769)**[†]	**Tofacitinib All (N = 944)**
Discontinuations, n (%)	84 (48.0)	665 (86.5)	749 (79.3)
No longer willing to participate in study	24 (13.7)	79 (10.3)	103 (10.9)
Withdrawn due to pregnancy	2 (1.1)	10 (1.3)	12 (1.3)
Due to protocol violation	2 (1.1)	7 (0.9)	9 (1.0)
Lost to follow-up	2 (1.1)	5 (0.7)	7 (0.7)
Due to not meeting entrance criteria	0 (0.0)	1 (0.1)	1 (0.1)
Due to another reason[‡]	3 (1.7)	13 (1.7)	16 (1.7)

[†]All patients underwent endoscopy at Month 2; induction non-responders were mandated to discontinue if they failed to achieve clinical response by Month 2.

[‡]Includes all the other reasons for withdrawal from OCTAVE Open.

b.d., twice daily; N, number of patients in the treatment group; n, number of unique patients with a particular adverse event.

TABLE S2 Summary of deaths in OCTAVE Open

Cause of death **Preferred term (verbatim term)**	**Tofacitinib dose**	**Therapy stop date**	**Date of death**
Hepatic angiosarcoma (liver infiltration of angiosarcoma epithelioid)[†]	10 mg b.d.	June 26, 2015	August 9, 2015
Adenocarcinoma metastatic (metastatic adenocarcinoma)[‡]	10 mg b.d.	March 28, 2019	December 24, 2019
Acute myeloid leukaemia (acute myeloid leukaemia)[‡]	10 mg b.d.	December 17, 2015	February 6, 2016
Pulmonary embolism (pulmonary embolism)[‡,§]	10 mg b.d.	July 20, 2014	July 26, 2014
Cardiac arrest (cardiac arrest)[‡,¶]	10 mg b.d.	June 10, 2019	February 1, 2020
Multiple organ dysfunction syndrome (multiple organ failure as a result of the cancer [malignant melanoma])[‡]	10 mg b.d.	September 29, 2016	March 7, 2017

[†]The investigator assessed this serious adverse event as related to study drug.

[‡]The investigator assessed this serious adverse event as unrelated to study drug.

[§]This event occurred in a patient who had also experienced a cholangiocarcinoma and a serious adverse event of metastases to the peritoneum.

[¶]Death occurred in the setting of lung cancer and pneumothorax post lung biopsy.

b.d., twice daily.

TABLE S3 Listing of adjudicated malignancy (excluding NMSC) events in OCTAVE Open

Preferred term (malignancy classification)[†]	**Tofacitinib dose**	**Age**[‡]	**Event onset day**[§]	**Prior immunosuppressant use**	**Prior TNFi use**
Pulmonary mass (lung cancer)	5 mg b.d.	75	269	yes	no
Cervical dysplasia (cervical cancer)	5 mg b.d.	33	390	no	yes
Diffuse large B-cell lymphoma (non-Hodgkin lymphoma)	5 mg b.d.	54	624	no	yes
Breast cancer (breast cancer)	5 mg b.d.	54	640	yes	no
Breast cancer (breast cancer)	5 mg b.d.	83	1037	yes	no
Cholangiocarcinoma (liver cancer)	5 mg b.d.	40	1978	no	no
Penile dysplasia (cancer of the penis)	5 mg b.d.	73	766	yes	no
Cervical dysplasia (cervical cancer)	10 mg b.d.	38	489	yes	no
Malignant melanoma (melanoma of the skin)	10 mg b.d.	43	1569	yes	no
Malignant melanoma (melanoma of the skin)	10 mg b.d.	66	1345	no	no
Oesophageal adenocarcinoma (oesophagus/esophagogastric junction cancers)	10 mg b.d.	60	988	yes	no
Hepatic angiosarcoma (soft tissue sarcoma)	10 mg b.d.	54	164	yes	yes
Invasive ductal breast carcinoma (breast cancer)	10 mg b.d.	45	642	yes	no
Bowen’s disease (cancer of the penis)	10 mg b.d.	68	776	yes	yes
Essential thrombocythemia (myeloproliferative neoplasms)	10 mg b.d.	30	279	no	no

Acute myeloid leukaemia (acute myeloid leukaemia and related precursor neoplasms)	10 mg b.d.	53	310	yes	yes
Cholangiocarcinoma (gallbladder and extrahepatic bile duct cancer)	10 mg b.d.	70	381	yes	yes
Cutaneous leiomyosarcoma (soft tissue sarcoma)	10 mg b.d.	82	556	yes	yes
Epstein-Barr virus-associated lymphoma (non-Hodgkin lymphoma)	10 mg b.d.	52	45	yes	yes
Renal cell carcinoma (renal cancer)	10 mg b.d.	46	257	yes	yes
Adenocarcinoma of colon (colorectal cancer)	10 mg b.d.	35	745	yes	yes
Adenocarcinoma of colon (colorectal cancer)	10 mg b.d.	47	57	yes	yes
Adenocarcinoma metastatic (colorectal cancer)	10 mg b.d.	47	2035	yes	yes
Colorectal cancer metastatic (colorectal cancer)	10 mg b.d.	28	1550	yes	yes
Lung neoplasm malignant (lung cancer)	10 mg b.d.	73	1652	no	yes

[†]Malignancy classification was based on adjudication committee.

[‡]Age at the time of event onset.

[§]Day of study in relation to first day of study drug dosing.

b.d., twice daily; NMSC, non-melanoma skin cancer; TNFi, tumour necrosis factor inhibitor.

TABLE S4 Listing of adjudicated NMSC events in OCTAVE Open

Tofacitinib dose	Demographics			NMSC history	Prior immunosuppressant use	Prior TNFi use
	Race	Sex	Age[†]			
Basal cell carcinoma						
5 mg b.d.	White	Female	48	no	yes	yes
5 mg b.d.	White	Male	65	no	yes	no
5 mg b.d.	White	Female	58	no	no	no
5 mg b.d.	White[‡]	Male	71	yes	yes	no
5 mg b.d.	White	Female	46	yes	yes	yes
10 mg b.d.	[§]	Female	65	no	yes	yes
10 mg b.d.	White	Male	72	no	yes	yes
10 mg b.d.	White	Male	74	no	yes	no
10 mg b.d.	White	Male	68	no	yes	yes
10 mg b.d.	White	Male	68	yes	yes	yes
10 mg b.d.	White[‡]	Male	68	no	yes	yes
10 mg b.d.	White[‡]	Male	78	yes	yes	yes
10 mg b.d.	White	Male	61	no	yes	yes
Squamous cell carcinoma						
5 mg b.d.	White	Male	64	yes	yes	yes
5 mg b.d.	White[‡]	Male	71	yes	yes	no
5 mg b.d.	White[‡]	Female	46	yes	yes	yes

10 mg b.d.	White	Male	50	no	yes	no
10 mg b.d.	White	Male	69	no	yes	yes
10 mg b.d.	White[‡]	Male	66	no	yes	yes
10 mg b.d.	White[‡]	Male	78	yes	yes	yes
10 mg b.d.	White	Female	48	no	yes	yes
10 mg b.d.	White	Male	66	yes	yes	yes

[†]Age at the time of event onset.

[‡]Patient experienced both basal cell carcinoma and squamous cell carcinoma.

[§]Other (Middle Eastern).

b.d., twice daily; NMSC, non-melanoma skin cancer; TNFi, tumour necrosis factor inhibitor.

TABLE S5 Listing of adjudicated MACE in OCTAVE Open

	Adjudicated event type (preferred term)			
	Myocardial infarction (acute myocardial infarction)	Cerebrovascular accident (cerebellar haemorrhage)	Cerebrovascular accident (cerebrovascular accident)	Cardiac death (cardiac arrest)
Sex	Male	Male	Male	Male
Age (years)	64	55	56	67
Day of onset	1107	1004	786	1661
Tofacitinib dose at onset	5 mg b.d.	5 mg b.d.	10 mg b.d.	10 mg b.d.
Baseline CV risk factors				
Smoking status	Non-smoker	Non-smoker	Smoker	Ex-smoker
BMI (kg/m^2)	22.7	23.0	30.1	31.4
Medical history	No significant medical history	Left ventricular hypertrophy; hypertension	Diabetes mellitus; hypertension	Pulmonary embolism; dyslipidaemia
Concomitant medications				
Lipid-lowering	Yes	Yes	Yes	Yes
Anti-diabetic	No	No	Yes	No
Anti-hypertension	No	Yes	Yes	No
Baseline serum lipid concentrations[†]				
Total cholesterol, mg/dL	220	258	242	130
HDL-c, mg/dL	79	47	39	43
LDL-c, mg/dL	118	162	128	70
Triglycerides, mg/dL	116	246	373	84

Baseline CRP, mg/L	0.74	0.38	29.03	6.05
Outcome	Temporary discontinuation	Permanent discontinuation	Permanent discontinuation	Death

MACE were adjudicated by an independent review committee and defined as any myocardial infarction, stroke or CV death.

[†]Reference ranges: total cholesterol, 130-200 mg/dL; HDL-c, 40-80 mg/dL; LDL-c, 0-130 mg/dL; triglycerides, 45-250 mg/dL; CRP, 0-3 mg/L.

b.d., twice daily; CRP, C-reactive protein; CV, cardiovascular; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events.

TABLE S6 Proportion of patients evaluated for drug-induced liver injury

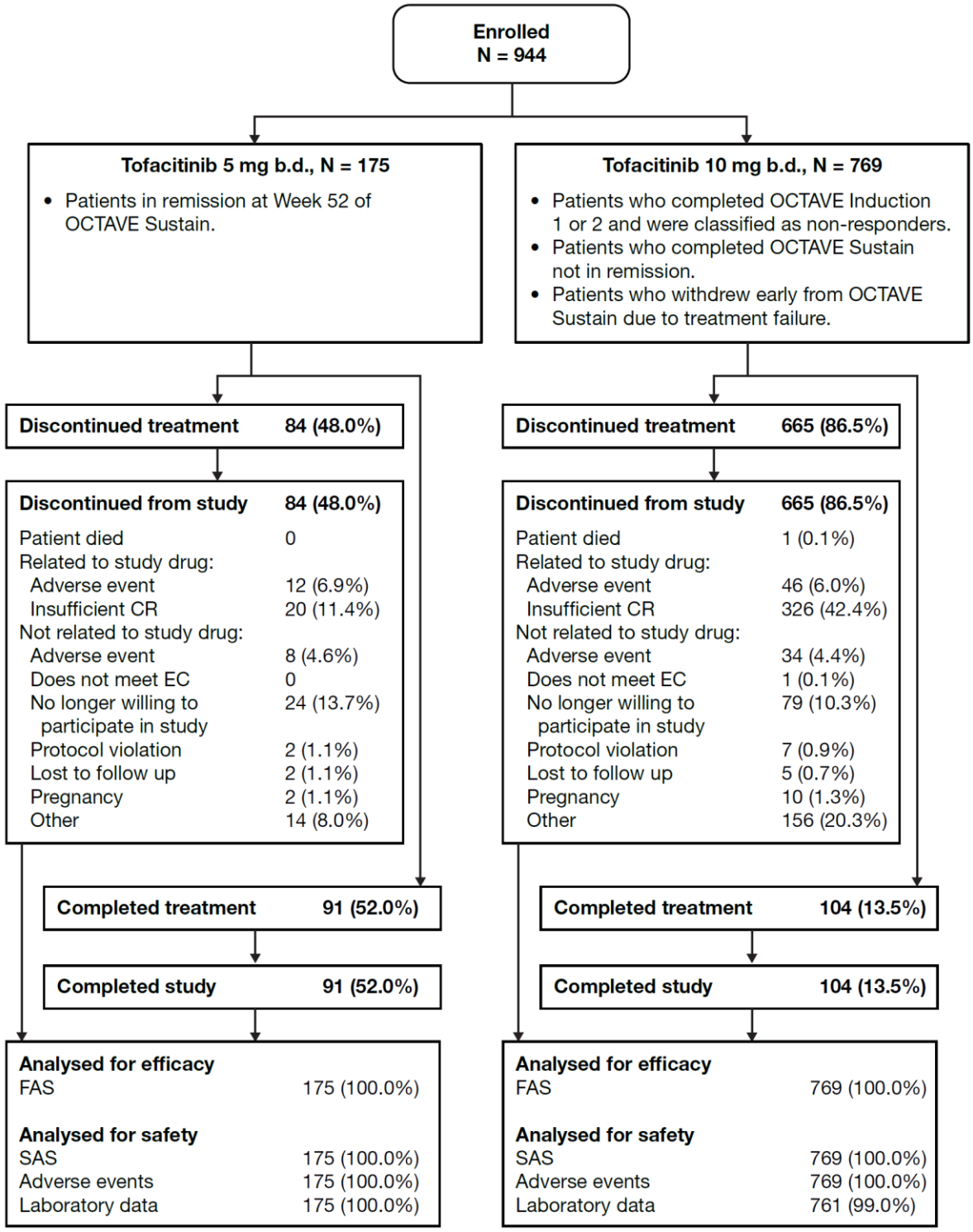
n (%)	**Tofacitinib 5 mg b.d. (N = 175)**	**Tofacitinib 10 mg b.d. (N = 769)**	**Tofacitinib All (N = 944)**
Drug-induced liver injury[†]	7 (4.0)	19 (2.5)	26 (2.8)
Possible	1 (0.6)	4 (0.5)	5 (0.5)
Unlikely	1 (0.6)	7 (0.9)	8 (0.8)
Unrelated	5 (2.9)	9 (1.2)	14 (1.5)
Severity of injury			
Mild	3 (1.7)	14 (1.8)	17 (1.8)
Moderate	3 (1.7)	2 (0.3)	5 (0.5)
Severe	0 (0.0)	2 (0.3)	2 (0.2)
Fatal or transplantation	0 (0.0)	1 (0.1)	1 (0.1)
Undetermined	1 (0.6)	0 (0.0)	1 (0.1)
Liver failure			
Yes	0 (0.0)	1 (0.1)	1 (0.1)
No	7 (4.0)	18 (2.3)	25 (2.6)

[†]There were no undetermined, probable, highly likely or definite drug-induced liver injury events.

b.d., twice daily.

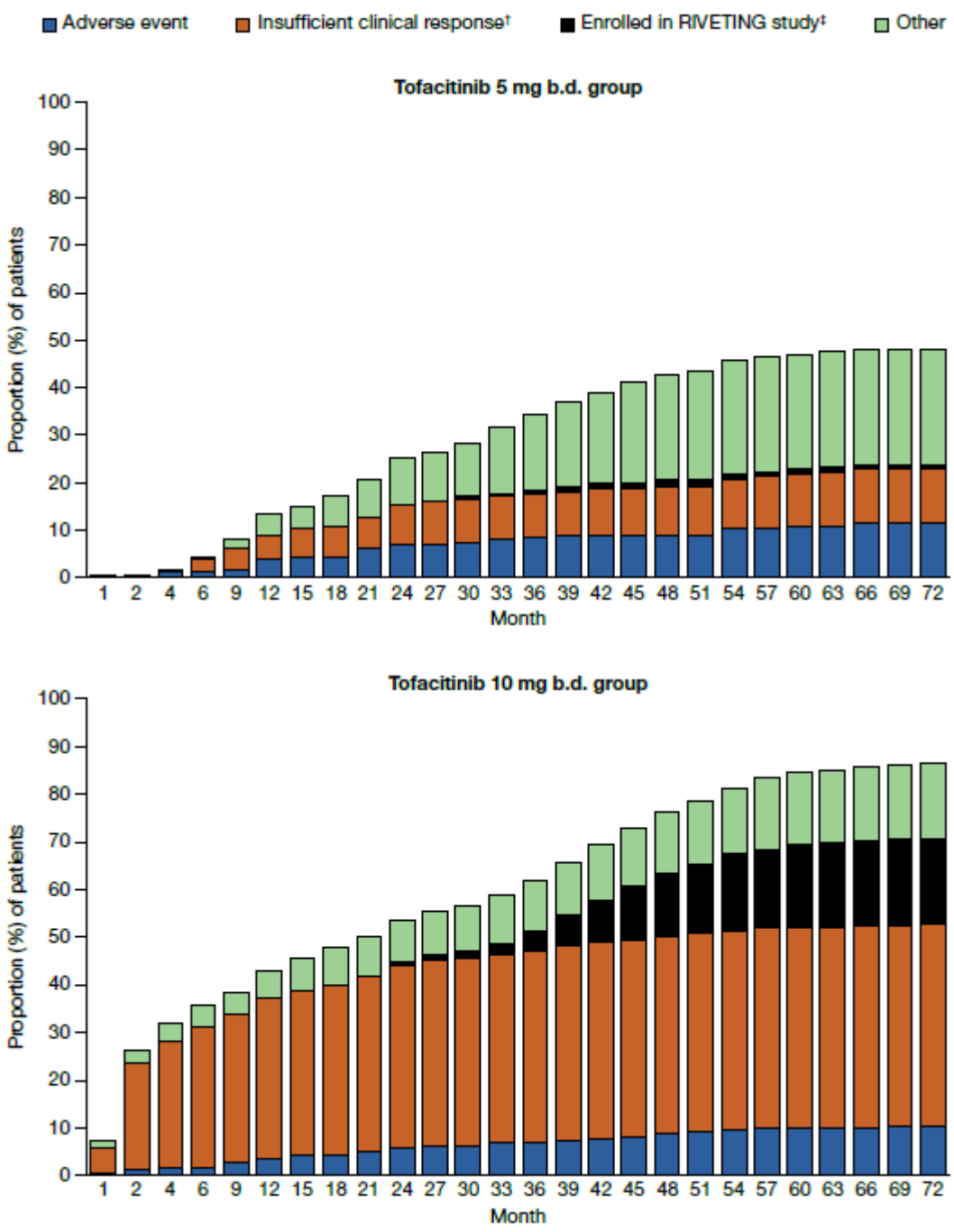
Supplementary Figures

Figure S1. Overall patient disposition.



b.d., twice daily; CR, clinical response; EC, enrolment criteria; FAS, full analysis set; N, number of patients in the analysis population; SAS, safety analysis set.

Figure S2. Patient discontinuation over time (SAS).



All patients underwent endoscopy at Month 2; induction non-responders (all assigned to tofacitinib 10 mg b.d.) were mandated to discontinue if they failed to achieve a clinical response by Month 2.

†Adverse events of worsening ulcerative colitis leading to discontinuation were designated as insufficient clinical response.

‡ClinicalTrials.gov number: NCT03281304.

b.d., twice daily; SAS, safety analysis set.