European Crohn's and Colitis Organisation

TOFACITINIB FOR THE TREATMENT OF ULCERATIVE COLITIS: UP TO 4.4 YEARS OF SAFETY DATA FROM GLOBAL CLINICAL TRIALS

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Background

- Tofacitinib is an oral, small molecule JAK inhibitor that is being investigated for UC
- The safety of tofacitinib for the treatment of moderate to severe UC was evaluated in:
  - An 8-week induction Phase 2 study[1]
  - Two identical 8-week induction Phase 3 studies[2]
  - A 52-week maintenance Phase 3 study[2]
  - An ongoing, open-label LTE study (OCTAVE Open)[3]

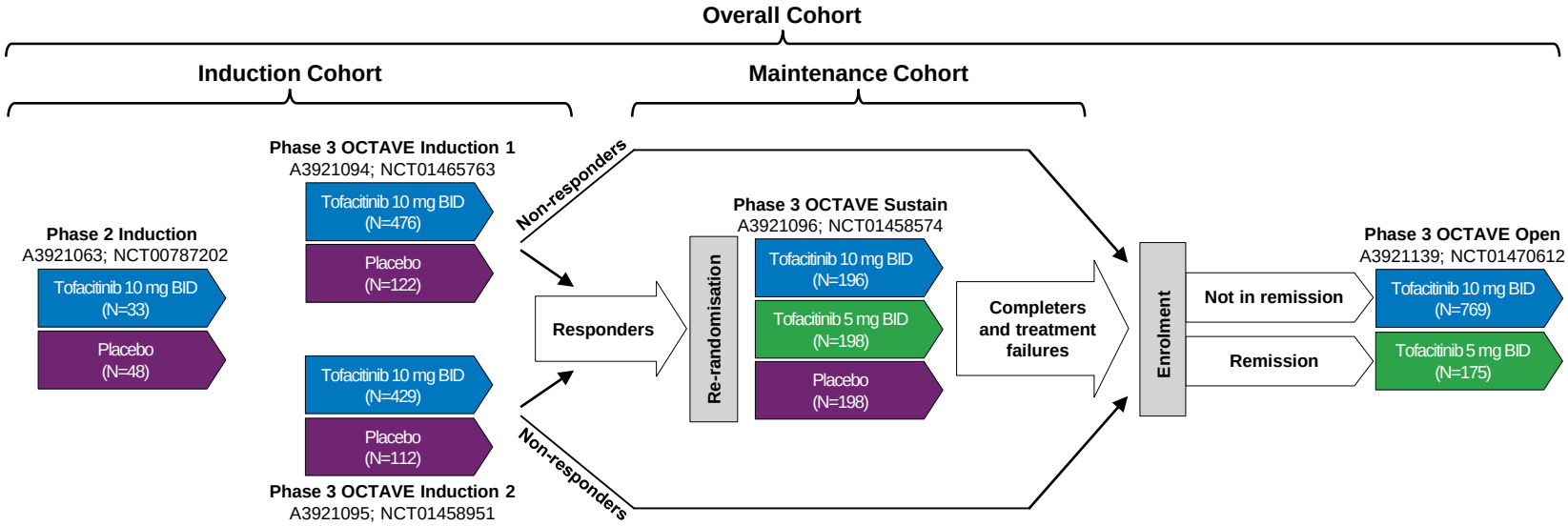
Objective: To describe an updated analysis of safety data from the tofacitinib clinical development programme in patients with moderately to severely active UC with tofacitinib exposure up to 4.4 years

Induction Phase 2 study (NCT00787202); 8-week induction Phase 3 studies (NCT01465763 and NCT01458951); maintenance Phase 3 study (NCT01458574); ongoing, open-label LTE study (OCTAVE Open, NCT01470612)

1. Sandborn WJ et al. N Engl J Med 2012;367:616-624. 2. Sandborn WJ et al. N Engl J Med 2017;376:1723-1736;
3. Lichtenstein GR et al. Am J Gastroenterol 2017;112(S1):Abstract 714

JAK, Janus kinase; LTE, long-term extension; UC, ulcerative colitis

Methods



- Select AEs of special interest (including OIs, malignancies, MACE and GI perforation) were adjudicated by independent committees blinded to treatment
- IRs for safety events of special interest were calculated for unique patients with events per 100 PY of exposure, with 95% CI computed using an exact method
- Events occurring >28 days after the last dose of study treatment were not included in the primary IR calculations
- For death and malignancy (excluding NMSC), events occurring >28 days after the last study treatment were included in sensitivity analyses IR calculations
- Data from the ongoing LTE study are as of 16 December 2016, from the unlocked database

AEs, adverse events; BID, twice daily; CI, confidence interval; GI, gastrointestinal; IR, incidence rate; LTE, long-term extension; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; OIs, opportunistic infections; PY, patient-years

Summary of safety events

	Induction Cohort		Maintenance Cohort			Overall Cohort
	Placebo (N=282)	Tofacitinib 10 mg BID (N=938)	Placebo (N=198)	Tofacitinib 5 mg BID (N=198)	Tofacitinib 10 mg BID (N=196)	Tofacitinib All (N=1157)
Total PY of exposure	44.8	156.2	100.4	146.2	154.3	1612.8
Treatment duration (days), median (range)	62 (7–80)	63 (1–96)	138 (14–382)	364 (22–420)	368 (1–399)	514 (1–1606)
Patients with AEs, n (%)	155 (55.0)	515 (54.9)	149 (75.3)	143 (72.2)	156 (79.6)	950 (82.1)
Patients with SAEs, n (%)	18 (6.4)	36 (3.8)	13 (6.6)	10 (5.1)	11 (5.6)	169 (14.6)
Discontinuations due to AEs, n (%)[a]	14 (5.0)	36 (3.8)	37 (18.7)	18 (9.1)	19 (9.7)	78 (6.7)[b]
AEs occurring in ≥15% of patients, any treatment group, any cohort, n (%)						
Worsening UC	20 (7.1)	26 (2.8)	71 (35.9)	36 (18.2)	29 (14.8)	224 (19.4)
Nasopharyngitis	14 (5.0)	56 (6.0)	11 (5.6)	19 (9.6)	27 (13.8)	211 (18.2)

[a]Includes discontinuations due to worsening UC

[b]Data for the Overall Cohort are n (%) of patients with dose reduction or temporary discontinuation due to an AE

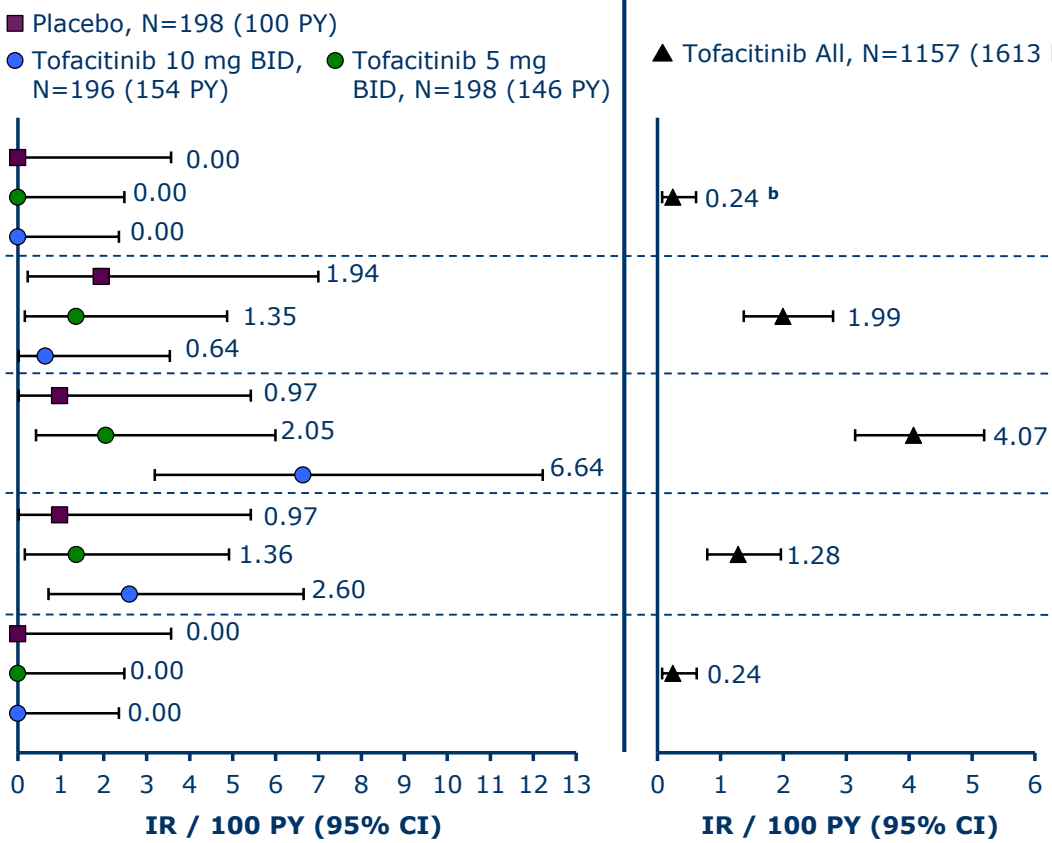
Only events occurring within 28 days after the last study treatment are included for calculation of proportion

Patient demographics and baseline characteristics, including mean total Mayo score and disease duration, were generally similar among groups within each cohort

AEs, adverse events; BID, twice daily; n, number of unique patients with a particular adverse event; N, number of patients in the treatment group; PY, patient-years; SAEs, serious adverse events; UC, ulcerative colitis

Events of special interest (1 / 2)

	Induction Cohort, n (%)		Maintenance Cohort, IR (95% CI)	Overall Cohort, IR (95% CI)
	Placebo, N=282	Tofacitinib 10 mg BID, N=938		
Deaths	0 (0.0)	1 (0.1) [a]	0.00 / 0.00 / 0.00	0.24 [b]
Serious infections	0 (0.0)	8 (0.9)	1.94 / 1.35 / 0.64	1.99
HZ (serious and non-serious)	1 (0.4)	6 (0.6)	0.97 / 2.05 / 6.64	4.07
OI[c]	0 (0.0)	3 (0.3)	0.97 / 1.36 / 2.60	1.28
Non-HZ OI[c]	0 (0.0)	1 (0.1)	0.00 / 0.00 / 0.00	0.24

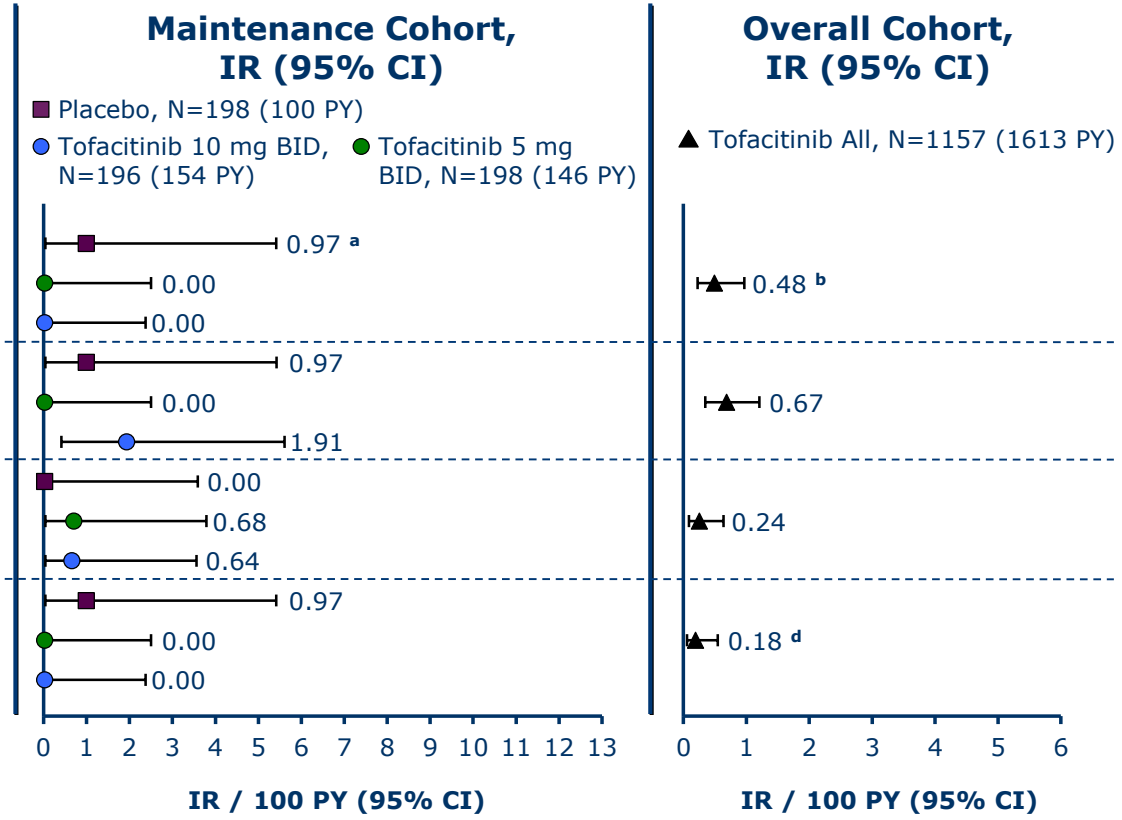


[a]Aortic dissection; [b]A total of four deaths: two occurred within 28 days of last study treatment (one aortic dissection [Induction Cohort] and one pulmonary embolism); two occurred >28 days following last study treatment (one hepatic angiosarcoma after 45 days and one acute myeloid leukaemia after 51 days); sensitivity analysis IR shown; [c]Adjudicated events. Percentage calculated based on patients with confirmed event, with adjudication as numerator; does not include data from the Phase 2 Induction study

BID, twice daily; CI, confidence interval; HZ, herpes zoster; IR, incidence rate; n, number of unique patients with a particular adverse event; N, number of patients in treatment group; OI, opportunistic infection; PY, patient-years

Events of special interest (2 / 2)

	Induction Cohort, n (%)	
	Placebo, N=282	Tofacitinib 10 mg BID, N=938
Malignancy (excl. NMSC)	0 (0.0)	0 (0.0)
NMSC	0 (0.0)	2 (0.2)
MACE	0 (0.0)	2 (0.2)
GI perforation[c]	1 (0.4)	1 (0.1)



[a]One case of breast cancer; [b]Eight cases within 28 days since last study treatment: one each of cervical cancer, cutaneous leiomyosarcoma, cholangiocarcinoma, EBV-associated lymphoma, essential thrombocythaemia, invasive ductal breast carcinoma, acute myeloid leukaemia and adenocarcinoma of the colon; three additional cases occurred >28 days after last study treatment: renal cell carcinoma, hepatic angiosarcoma and lung cancer; including these 11 patients in sensitivity analysis: IR 0.66 (95% CI 0.33, 1.19); [c]GI perforation excludes fistulae and abscesses below peritoneal reflection; [d]Three GI perforation serious adverse events: descending colon perforation, appendicitis adjudicated as GI perforation, and perforated sigmoid colon at site of EBV lymphoma

BID, twice daily; CI, confidence interval; EBV, Epstein-Barr virus; GI, gastrointestinal; IR, incidence rate; MACE, major adverse cardiovascular event; n, number of unique patients with a particular adverse event; N, number of patients in treatment group; NMSC, non-melanoma skin cancer; PY, patient-years

Limitations

- Short exposure time and small groups overall for tofacitinib treatment in patients with UC, compared with the larger tofacitinib database in RA of >6000 patients and >19,000 patient-years of exposure up to 8.5 years[1]
- Overall Cohort included patients who had switched tofacitinib doses, and so does not provide a clear evaluation of tofacitinib dose dependency

Conclusions

- Data from the Maintenance Cohort suggest dose dependency for the risk of HZ in patients with UC
- Based on the Maintenance and Overall Cohorts, the risk of serious infection, OI, HZ, malignancy excluding NMSC, NMSC, or MACE did not increase with longer duration of tofacitinib treatment, up to 4.4 years
- These data are consistent with previously presented integrated analysis of the safety cohorts up to 3.9 years, based on the July 2016 data cut[2]
- An overall manageable safety profile of tofacitinib 5 and 10 mg BID was observed, generally similar to that of the tofacitinib RA programme[1] and – with the exception of an increased HZ risk – that of other UC therapies, including biologics[3–7]

1. Cohen SB et al. Ann Rheum Dis 2017;76:1253-1262; 2. Sandborn WJ et al. Am J Gastroenterol 2017;112(S1):Abstract 731; 3. Rutgeerts P et al. N Engl J Med 2005;353:2462-2476; 4. Sandborn WJ et al. Gastroenterology 2012;142:257-265; 5. Sandborn WJ et al. Gastroenterology 2014;146:96-109; 6. Sandborn WJ et al. Gastroenterology 2014;146:85-95; 7. Feagan BG et al. N Engl J Med 2013;369:699-710

BID, twice daily; HZ, herpes zoster; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; OI, opportunistic infection; RA, rheumatoid arthritis; UC, ulcerative colitis

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