ACTIVE TUBERCULOSIS AND OPPORTUNISTIC INFECTIONS: POOLED SAFETY ANALYSIS OF USTEKINUMAB THROUGH UP TO 5 YEARS ACROSS ALL APPROVED INDICATIONS

B0379

E.V. Loftus,[1] M. Long,[2] E. Ott,[3] C. Gasink,[3] T. Baker,[4] B. Godwin,[3] Y. Miao,[4] S. Ghosh[5]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, MN, USA; [2]University of North Carolina at Chapel Hill, Division of Gastroenterology and Hepatology, Chapel Hill, NC, USA; [3]Janssen Scientific Affairs, LLC, Horsham, PA, USA; [4]Janssen Research & Development, LLC, Spring House, PA, USA; [5]College of Medicine and Health, University College Cork, Ireland

BACKGROUND/OBJECTIVE

- Ustekinumab (UST), a human monoclonal IL-12/23p40 antibody, is an approved treatment for adults with inflammatory bowel disease (IBD: Crohn's disease [CD] and ulcerative colitis [UC]), psoriasis (PsO), and psoriatic arthritis (PsA)
- Biologic treatments inhibit cytokines and therefore, may increase the risk for infections including opportunistic infections (OIs)
  - Patients who lack the IL-12/23 receptor β1 subunit have been shown to be at increased risk for mycobacterial infections[1]
- **Pooled safety analyses in approved indications for OIs (including active tuberculosis [TB]) and herpes zoster (HZ) through up to 5 years of UST treatment are presented**

CONCLUSIONS

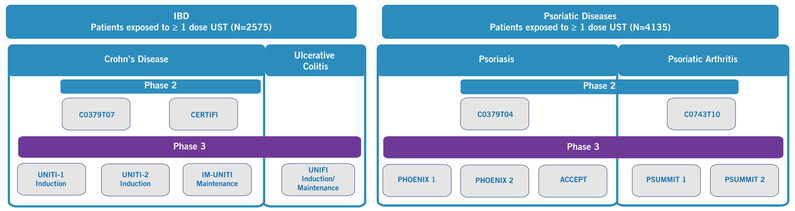
- **OIs, including active TB, in UST-treated patients were infrequently reported across approved indications through up to 5 years with 13807 PYs of follow-up**
- **Rates of OIs and HZ were not higher in UST patients compared with PBO, suggesting no increased risk with long-term UST treatment**
- **These data continue to support the well-established safety profile of UST in IBD and psoriatic indications**

METHODS/RESULTS

Methods

- Pooled data included 13 Phase 2/3 UST studies through 5 years of CD and PsO, 2 years of UC, and 1 year of PsA (**Figure 1**)
- OIs, including active TB, were identified through sponsor clinical review guided by consensus recommendations in Winthrop et al.[2]
- HZ was evaluated separately; all HZ events (disseminated [OI] or non-disseminated) were identified by MedDRA preferred terms for "varicella" or "zoster" and indicated by investigator as an infection
- Concomitant immunomodulators/corticosteroids were permitted in IBD and PsA studies
- Safety outcomes were presented as events per 100 patient years (PYs) of follow-up and 95% confidence intervals (CIs); 95% CIs based on an exact method assuming that the observed number of events follows a Poisson distribution
- In IBD, placebo (PBO) patients included data up to the first UST dose for patients initially treated with PBO, or >16 weeks after the last UST dose for UST patients who switched to PBO
- 6710 patients were exposed to ≥1 UST dose; 13807 PYs of exposure in UST Phase 2 and 3 clinical trials

Figure 1. Study Design



Results

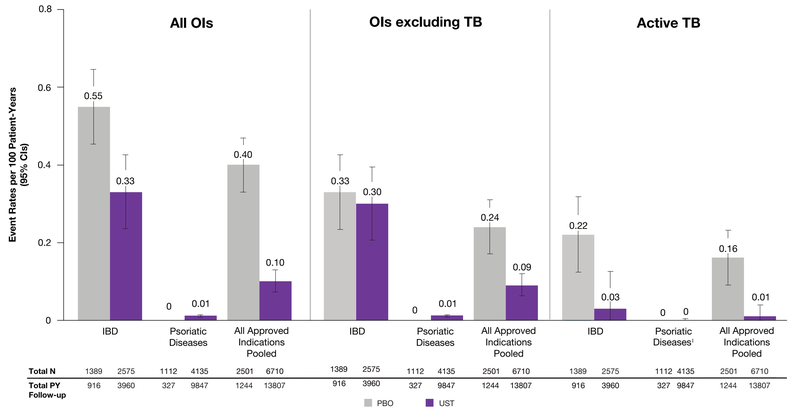
All Opportunistic Infections, Including Tuberculosis

- Rates of OIs, including active TB, were low in UST-treated patients across approved indications through up to 5 years
- Overall, 19 OIs were reported across all approved indications
  - 18 OIs occurred in IBD patients and 1 OI occurred in a PsO patient
- Rates of OIs were 0.40 in PBO patients and 0.10 in UST patients across indications through 5 years (**Figure 2**)

All Opportunistic Infections, Excluding Tuberculosis

- Overall, 14/16 patients with OIs, excluding TB, were also receiving confounding concomitant medications (**Table 1**)
- The most common OIs were esophageal candidiasis (UST n=3; PBO n=2) and cytomegalovirus (CMV) colitis (UST n=3; PBO n=1)
  - All patients with events of esophageal candidiasis were taking other confounding concomitant medications
  - All UST-treated patients with events of CMV colitis had concomitant steroid use

Figure 2. Overall Rates of OIs in IBD and Psoriatic Studies Through 5 Years



[1]A previous reported case of active TB in a regional PsO study (Tsai T-F, et al. *J Dermatol Sci.* 2011;63:154-163) was not included with the global study data presented here

Table 1. Information Related to Patients With Reported OIs, Excluding TB

Indication	Age / Gender	Treatment	OI Diagnosis	Notes[1]
CD	33 / F	UST	Disseminated histoplasmosis	Fever 2 days prior to first UST dose; received IFX 3 months prior; prednisone, azathioprine
CD	54 / F	UST	Oesophageal candidiasis	Inhaled fluticasone propionate and mesalazine
CD	36 / M	UST	Oesophageal candidiasis	Corticosteroids and oral budesonide
CD	39 / M	PBO	Oesophageal candidiasis	Corticosteroids
CD	28 / F	UST	Cryptosporidiosis infection	Corticosteroids
CD	33 / M	UST	Meningitis listeria	Corticosteroids; field worker
CD	67 / F	PBO	Oesophageal candidiasis	Corticosteroids, methotrexate
CD	31 / F	UST	Oesophageal candidiasis	IFX 2 weeks after last UST and prior to OI diagnosis
CD	31 / M	PBO	CMV colitis	None
PsO	53 / F	UST	Disseminated herpes zoster	Back pain preceded first UST dose by 1 day; disseminated based on 19 vesicles outside of primary dermatome
UC	49 / F	UST	Pneumonia legionella	Symptoms 3 weeks after last UST dose; IFX and intravenous methylprednisolone 4 days prior to OI diagnosis
UC	51 / F	UST	CMV colitis	Corticosteroids
UC	31 / M	UST	CMV colitis	Corticosteroids, azathioprine
UC	29 / M	UST	Ophthalmic herpes simplex and oral herpes simplex	Corticosteroids
UC	71 / M	UST	CMV colitis	Corticosteroids, rectal mesalazine
UC	84 / F	UST	Listeriosis	Prednisolone, azathioprine; OI led to colectomy due to worsening of colitis, and complicated hospital stay including DIC, intubation, and multiple other infections

CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; IFX, infliximab
[1]All listed treatments were confounding concomitant medications

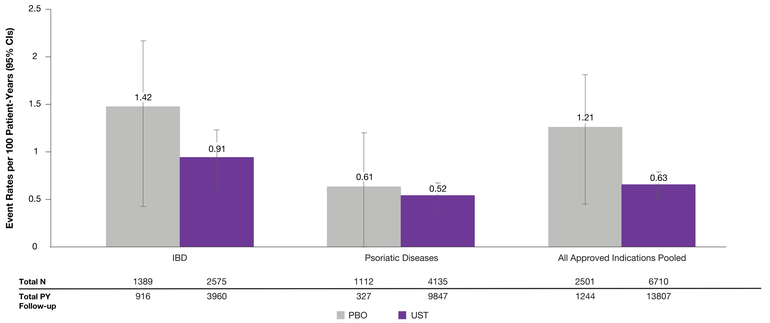
Tuberculosis

- A total of 3 active TB cases were reported in IBD patients: 1 in the UST group (0.03 events per 100 PYs) and 2 in the PBO group (0.22 events per 100 PYs:
- UST group
  - Asymptomatic 45-year-old South African CD patient treated with UST every 8 weeks during the long-term extension, who had a positive QuantiFERON®-TB Gold test on routine screening and bronchial brushings positive for M. *tuberculosis*[3]
- PBO group
  - 32-year-old Hungarian CD patient, 10 months after receiving last UST dose[4]
  - 52-year-old Korean UC patient with pulmonary TB who received PBO and never received UST[4]
- Both CD patients completed TB treatment with full disease resolution

All Herpes Zoster

- Rates of HZ, including disseminated HZ, were low and similar between treatment groups
- Overall rates of HZ across indications were 1.21 (PBO) and 0.63 (UST) per 100 PYs of follow-up through up to 5 years (**Figure 3**)
- Only 1 case of HZ was considered to be disseminated and also counted as an OI:
  - A 53-year-old patient with PsO treated with UST was reported to have left-sided flank pain 1 day prior to first UST dose and 4 days later was diagnosed with disseminated cutaneous HZ based on the presence of 19 cutaneous vesicles outside the primary dermatome (left T8), which resolved with treatment[5]

Figure 3. Overall Rates of HZ in IBD and Psoriatic Studies Through 5 Years



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