2017. TOFA-CD

RCT/TOFA/ CD/Induction& Mainten

Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials

Two randomized, double-blind placebo-controlled, phase IIb trials.. Adult patients mod-severe CD were randomised to receive tofacitinib 10mg twice daily, TOFA 5 mg twice daily or placebo for 8 weeks.
Those achieving clinical response-100 or remission were re-randomised to maintenance with placebo or TOFA 5 or 10 mg twice daily for 26 weeks.

Primary endpoint: Clinical remission (CDAI<150) at week 8 and clinical response-100 (decrease in CDAI >100) or remission at the end of maintenance.

Results: N=280

- At w8 clinical remission 43.5 TOFA5, 43% TOFA10 and 36.7% placebo, p=0.325 and 0.392 for both doses vs placebo.
- At week 26, clinical response-100 or remission was 55.8% TOFA10, 39.5% TOFA 5 and 38.1% placebo, p=0.130.
- Compared to placebo TOFA10 significantly reduced CRP p<0.0001

Conclusion:
Primary efficacy endpoints were not significantly different from placebo, although there was evidence of a minor treatment effect. No new safety signals were observed for tofacitinib

(A) Induction study, week 8 (FAS)

	Placebo N=90	Tofacitinib 5 mg twice daily N=85	Tofacitinib 10 mg twice daily N=86
Clinical remission (NRI)			
n (%)†	33 (36.7)	37 (43.5)	37 (43.0)
Remission in TNFi-experienced patients (NRI)			
n/N (%)†	25/69 (36.2)	26/68 (38.2)	28/66 (42.4)
Clinical response-100 or remission (NRI)			
n (%)†	50 (55.6)	61 (71.8)*	60 (69.8)
Clinical response-100 or remission in TNFi-experienced patients (NRI)			
n/N (%)†	38/69 (55.1)	46/68 (67.7)	48/66 (72.7)
Clinical response-100 (NRI)			
n (%)†	49 (54.4)	60 (70.6)*	59 (68.6)
Clinical response-70 (NRI)			
n (%)†	56 (62.2)	65 (76.5)*	64 (74.4)
PRO2-75 (NRI)			
n (%)‡	36 (40.0)	50 (58.8)*	48 (55.8)*
PRO3-80 (NRI)			
n (%)§	22 (24.4)	33 (38.8)*	31 (36.1)
CDAI score			
Adjusted estimate, change from baseline (SE)¶	−117.4 (10.3)	−149.7 (10.7)*	−157.3 (10.7)*
CRP levels (mg/L)			
Observed median (min–max)	5.9 (0.4–132.5)	3.2 (0.1–69.0)	2.4 (0.1–65.3)
Adjusted estimate, change from baseline in log-transformed value (SE)¶	0.12 (0.12)	−0.42 (0.12)**	−0.73 (0.12)***
FCP levels (mg/kg)			
Observed median (min–max)	266.0 (25.2–3578.0)	310.0 (25.2–1104.0)	302.5 (25.2–1251.0)
Adjusted estimate, change from baseline in log-transformed value (SE)¶	−0.02 (0.12)	−0.31 (0.14)	−0.30 (0.13)

(B) Maintenance study, week 26 (mFAS)

	Placebo N=42	Tofacitinib 5 mg twice daily N=43	Tofacitinib 10 mg twice daily N=43
Clinical response-100 or remission (NRI)			
n (%)†	16 (38.1)	17 (39.5)	24 (55.8)
Clinical remission (NRI)			
n (%)†	12 (28.6)	16 (37.2)	18 (41.9)
Clinical response-100 or remission in TNFi-experienced patients (NRI)			
n/N (%)†	11/27 (40.7)	13/35 (37.1)	17/35 (48.6)
Clinical remission in TNFi-experienced patients (NRI)			
n/N (%)†	8/27 (29.6)	12/35 (34.3)	12/35 (34.3)
Sustained remission at both week 20 and 26 (NRI)			
n (%)†	9 (21.4)	10 (23.3)	17 (39.5)
Clinical response-100 (NRI)			
n (%)†	15 (35.7)	16 (37.2)	24 (55.8)
CDAI score			
Adjusted estimate, change from baseline (SE)¶	69.5 (22.1)	63.5 (21.6)	19.1 (21.1)
CRP levels at week 26 (mg/L)			
Observed median (min–max)	9.8 (1.5–148.7)	9.4 (0.3–46.1)	2.5 (0.1–14.7)
Adjusted estimate, change from baseline in log-transformed value (SE)¶	1.73 (0.26)	1.12 (0.25)	0.11 (0.23)***
FCP levels at week 26 (mg/kg)			
Observed median (min–max)	689.5 (60.0–4100.0)	445.5 (59.0–999.0)	177.5 (25.2–707.0)
Adjusted estimate, change from baseline in log-transformed value (SE)¶	1.13 (0.21)	0.57 (0.19)*	−0.07 (0.18)***

†Statistical significance (p<0.05) based on the Cochran-Mantel-Haenszel test statistic stratified on prior use of TNFi treatments.
‡Clinical remission based on the sum of the first two components with multipliers (stool frequency score+abdominal pain score) <75.
§Clinical remission based on the sum of the first three components with multipliers (stool frequency score+abdominal pain score+general well-being score) <80.
¶Statistical significance based on a linear mixed-effects model for change in CDAI score, change in log-transformed CRP and FCP.
*p<0.05; **p<0.001; ***p<0.0001, vs placebo.
CDAI, Crohn's disease activity index; CRP, C-reactive protein; FAS, full analysis set; FCP, faecal calprotectin; mFAS, modified FAS (excluding placebo responders of the induction study); NRI, non-responder imputation; PRO, patient-reported outcomes; TNFi, tumour necrosis factor inhibitors.

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