Tofacitinib exposure-response modelling of partial Mayo score in ulcerative colitis patients in Phase 3 induction studies

IV-58

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Introduction

- Tofacitinib is an oral, small molecule Janus kinase inhibitor being investigated for ulcerative colitis (UC). Two completed identical Phase 3 induction studies (OCTAVE Induction 1, NCT01465763; OCTAVE Induction 2, NCT01458951) demonstrated efficacy of tofacitinib 10 mg twice daily (BID) for 8 weeks as an induction therapy in patients with moderately to severely active UC.[1]
- This analysis aimed to characterise the relationship between tofacitinib exposures and partial Mayo score (PMS) over time, and to identify covariates that may impact exposure-response (ER) of tofacitinib as induction therapy.

Methods

- Two Phase 3 induction studies (OCTAVE Induction 1 and 2) were analysed. Categorical PMS (range 0–9) from patients receiving tofacitinib 10 or 15 mg BID or placebo were analysed using first-order conditional estimation with LAPLACE in NONMEM.
- A proportional odds model was used to describe the probability of each PMS.
- Pharmacokinetics exposure, steady-state average concentration (C_{avg}), was calculated based on a one-compartment pharmacokinetics model using pooled Phase 2 and 3 data.[2]
- Exponential equation was applied to investigate the time course of placebo and drug effect separately, to detect whether there was onset of placebo and drug effect.
- The following characteristics were tested as covariates on tofacitinib efficacy, using a stepwise covariate modelling approach: race, age, sex, baseline albumin (BALB), baseline body mass index, concomitant medication (oral steroid, immunosuppressant or 5-aminosalicylic acid), Mayo score at baseline and prior tumour necrosis inhibitor (TNFi) failure and non-failure.
- Likelihood ratio tests and simulation approaches such as visual predictive checks (VPCs) were applied for model selection and evaluation.

Results

Observed data

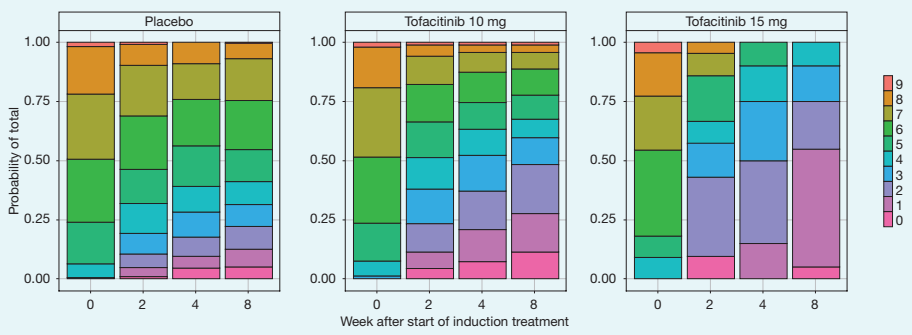
- 4487 PMS records from 1161 patients randomised in the induction studies were included in the ER analysis. Of these, PMS were obtained from 234 patients given placebo BID, from 905 patients given tofacitinib 10 mg BID and from 22 patients given tofacitinib 15 mg BID (Table 1). PMS distribution at each visit is shown in Figure 1.

Table 1. Summary of PMS data for combined induction studies

Visit	Placebo	Tofacitinib 10 mg BID	Tofacitinib 15 mg BID	Total
Baseline	233	903	22	1158
Visit 2	229	878	21	1128
Visit 4	220	873	20	1113
Visit 8	216	847	20	1083
Early termination visit	–	5	–	5
$Total_{records}$	898	3506	83	4487
$Total_{patients}$	234	905	22	1161

BID, twice daily; PMS, partial Mayo score; Visit, week from start of induction study

Figure 1. Distribution of PMS versus time for different treatments across induction studies



PMS, partial Mayo score

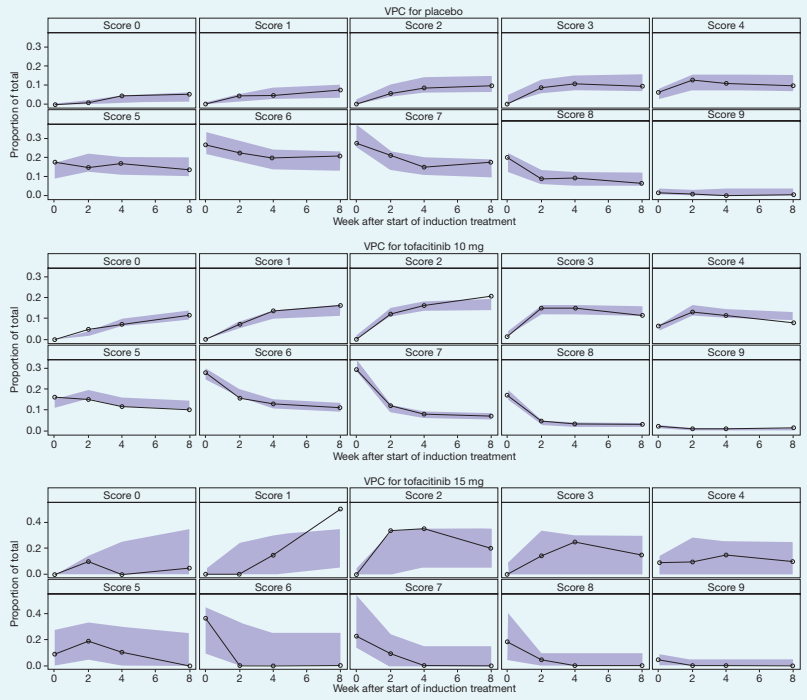
Base ER model

- The final base model was a longitudinal proportional odds model with exponential equation to describe the time course of placebo and drug effect.
- C_{avg} was used as an exposure metric describing linear drug effect. Inter-individual variability was estimated for baseline logit-transformation value (B1) and placebo maximum effect (PMAX). Population parameter estimates for base model are presented in Table 2.

Final covariate model

- Covariates were detected on parameters in base model using a stepwise covariate modelling approach to obtain the final model. BALB on baseline logit value and TNFi failure on placebo effect were found to be significant covariates and remained in the final model.
- VPC results of probability for each PMS, changing with time of the final model stratifying by dose, are shown in Figure 2.
- The parameter estimates for the final covariates model are presented in Table 2.
- The onsets of placebo and drug effect were rapid, with an equilibrium half-life of 1.29 weeks and 1.24 weeks, respectively.
- The maximum placebo effect was 2.35 decreasing in logit value. The linear drug effect in C_{avg} was estimated to be -0.0727, indicating a decrease in 7.27 logit value for C_{avg} of 100 mg/mL.
- BALB had a significant negative effect on B1, with a power factor of -0.497, suggesting that patients with low BALB have a higher probability to have Mayo score Y⩾1.
- Placebo response was estimated to increase for patients who did not previously fail TNFi (TNFNR=0) by 57.0%, compared to prior TNFi failures (TNFNR=1).
- The maximum placebo effects of logit value for Y⩾1 were estimated to be -2.35 and -3.69 for prior TNFi failure or no prior TNFi failure patients, respectively.
- Mean PMS versus time VPC results, and VPC plots of mean PMS change from baseline, grouped by dose, are presented in Figure 3. These model diagnostics and evaluation results suggest that the final model described data adequately, except underprediction of effect for the tofacitinib 15 mg BID group, due to the small sample size.

Figure 2. VPC of the proportion of PMS grouping by dose for the final model in the induction studies



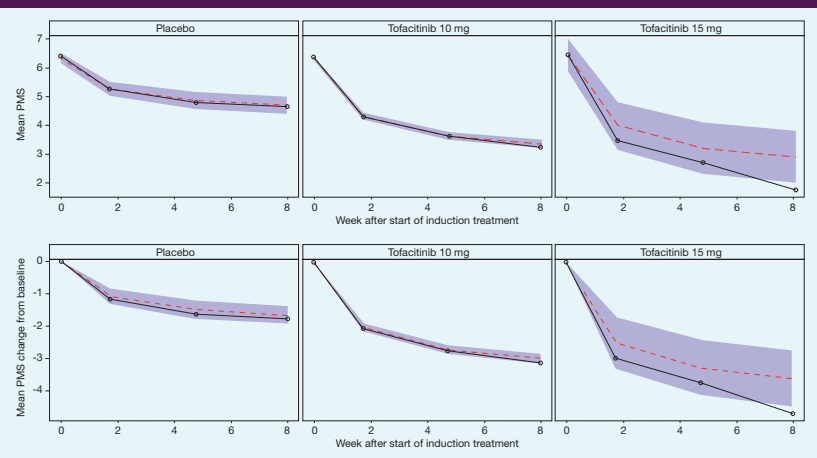
Symbols and black solid lines are the observed proportion for PMS. The shaded area is the predicted 95% confidence interval of simulated proportion for PMS
PMS, partial Mayo score; VPC, visual predictive check

Table 2. Population parameter estimates for the base and final model

Parameter	Description	Base model		Final model	
		Estimate	SE	Estimate	SE
Blog1	Logit value of Pr(Y⩾1)	10.5	0.26	10.4	0.256
Dlog2	Logit value of Pr(Y⩾1) – Pr(Y⩾2)	-2.21	0.125	-2.21	0.126
Dlog3	Logit value of Pr(Y⩾2) – Pr(Y⩾3)	-1.93	0.0879	-1.93	0.0883
Dlog4	Logit value of Pr(Y⩾3) – Pr(Y⩾4)	-1.42	0.0698	-1.42	0.0699
Dlog5	Logit value of Pr(Y⩾4) – Pr(Y⩾5)	-1.23	0.0613	-1.23	0.0613
Dlog6	Logit value of Pr(Y⩾5) – Pr(Y⩾6)	-1.56	0.0689	-1.56	0.0689
Dlog7	Logit value of Pr(Y⩾6) – Pr(Y⩾7)	-2.06	0.0844	-2.05	0.0842
Dlog8	Logit value of Pr(Y⩾7) – Pr(Y⩾8)	-2.42	0.108	-2.4	0.107
Dlog9	Logit value of Pr(Y⩾8) – Pr(Y⩾9)	-3.41	0.232	-3.37	0.229
PMAX	Placebo maximum effect	-3.06	0.233	-2.35	0.251
Phalf	Half-life of placebo effect	1.3	0.146	1.29	0.148
Dslope	Coefficient of C_{avg}	-0.0706	0.00758	-0.0727	0.00751
Dhalf	Half-life of drug effect	1.23	0.24	1.24	0.237
LOG1BALB	Coefficient of BALB on B1	--	--	-0.497	0.0719
PMAXTNFNR	Coefficient of TNFNR=0 on PMAX	--	--	0.57	0.134
Inter-individual variability					
IIV_{B1}	Inter-individual variability of B1	2.14	0.102	2.03	0.103
IIV_{PMAX}	Inter-individual variability of PMAX	3.16	0.157	3.09	0.157

B1, baseline logit-transformation value; BALB, baseline albumin; IIV, inter-individual variability; PMAX, placebo maximum effect; Pr(Y≥n), cumulative probability for Y≥n; SE, standard error; TNFNR, prior TNFi failure

Figure 3. VPC of mean, and change from baseline PMS for the final model, grouped by dose



The upper panel shows VPC for mean PMS and the bottom panel shows PMS change from baseline. Symbols and black solid lines are the observed data. The red dashed line is the median of simulation. The shaded area is the predicted 95% confidence interval of median of simulation
PMS, partial Mayo score; VPC, visual predictive check

Discussion

- **The longitudinal data of PMS for the induction studies were adequately described by the proposed proportional odds models with linear C_{avg} drug effect.**
- **Onset of efficacy was achieved within 2 weeks of the start of induction therapy, with near-maximal effect by Week 8.**
- **The efficacy of placebo is more pronounced in patients who did not fail TNFi previously than in those with prior TNFi failure. Similar placebo-adjusted effect of tofacitinib treatment was detected for these two types of patients.**

References

1. Sandborn WJ et al. N Engl J Med 2017; 376: 1723-1736.
2. Vong C et al. PAGE Meeting (25) 2016; Poster 5960.

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Disclosure of interest

C Deng, R Xie, C Vong, SW Martin, C Su and A Mukherjee are employees and stockholders of Pfizer Inc.

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