Presentation Number
3043 - A0202

Modeling to Inform Dose Selection for a Phase 2b Trial Investigating TOUR006, a Fully Human Anti-IL-6 Antibody, for Treatment of Thyroid Eye Disease

Kristine Erickson, Craig M. Comisar,* Swati Debroy, Stuart R. Seiff, Yung Chyung, Ryan Iarrobino, Emil DeGoma and Paul Martin*

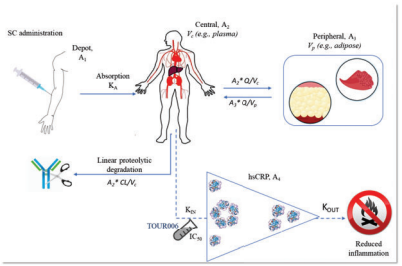
BACKGROUND

- IL-6 is a pleiotropic cytokine that plays a role in inflammation, and its production is readily induced by infectious stimuli or inflammatory cytokines. IL-6-mediated inflammation has been implicated in many autoimmune diseases. IL-6 pathway activation is thought to occur in TED as IL-6 levels are elevated in patients with this disorder [1, 2]. Further, several biomarkers that are hallmarks of IL-6 mediated inflammation, including C-reactive protein (CRP), red blood cell distribution width, and neutrophil-to-lymphocyte ratio are also elevated in patients with TED [3-6].
- Multiple lines of evidence support the investigation of IL-6 blockade in treating TED [7-28]. TOUR006 (previously known as PF-04236921), a selective fully human IgG2 monoclonal antibody (mAb), binds IL-6 with high affinity and has a long terminal half-life.
- TOUR006 has shown anti-inflammatory activity in other IL-6 driven indications including RA, CD, and SLE [29-31] and has been dosed in >400 subjects to date. TOUR006 is under development for the treatment of TED utilizing treatment regimens of subcutaneous (SC) administration every 8 weeks. Effective dosing regimens of TOUR006 for TED are predicted using a population PK/PD model of CRP, with the intention of robust blockade of the IL-6 pathway.

METHODS

A pharmacokinetic (PK) and pharmacodynamic (PKPD) model for TOUR006 was developed based on 5 clinical studies conducted with PF-04236921 in healthy volunteers and patients with autoimmune conditions other than TED [31]. Serum CRP, widely used as a surrogate for IL-6 pathway activity was selected as a biomarker.

Figure 1. Schematic diagram of PKPD model for effect of TOUR006 treatment



The mathematical model is 2-compartments with linear elimination and includes an indirect response of TOUR006 on CRP concentration using Hill equation (Figure 1). Dosing frequencies Q4W or Q8W, and dose levels 10 to 50 mg were evaluated.

Assumptions of simulation:

- Sampling used subset of actual participants with baseline serum CRP of >2 mg/L to 10 mg/L, comparable to most TED patients,
- The virtual TED population has inflammatory behavior like RA,
- *Target reduction* is defined as ≥90% CRP suppression from baseline or <2 mg/L CRP

This simulation was also conducted for a subset of actual participants with baseline CRP >10mg/L (not presented here). An exploratory analysis (not presented here) estimated CRP reduction for a population with higher baseline bodyweight median = 102.3 kg and IQR [98.5 kg, 115.1 kg].

***Commercial Interest:** Kristine Erickson (kerickson@tourmalinebio.com), Yung Chyung, Ryan Iarrobino, Emil DeGoma are employed by Tourmaline Bio; Craig Comisar (craig.comisar@certara.com), Swati Debroy, Stuart R. Seiff and Paul Martin are consultants for Tourmaline Bio.

RESULTS

- The baseline characteristics of the virtual subjects used for treatment simulations is given in Table 1.
- Over 90% of virtual subjects achieved the target reduction in CRP over time (Table 2).
- The time course of CRP suppression is summarized in Figure 2 and the time course of TOUR006 concentration over time is summarized in Figure 3.
- Baseline CRP of virtual subjects who achieved target reduction in CRP is significantly lower than subjects who did not achieve this milestone, as seen in Figure 4.

Figure 2. Time course of CRP suppression from baseline in virtual subjects under TOUR006 treatment

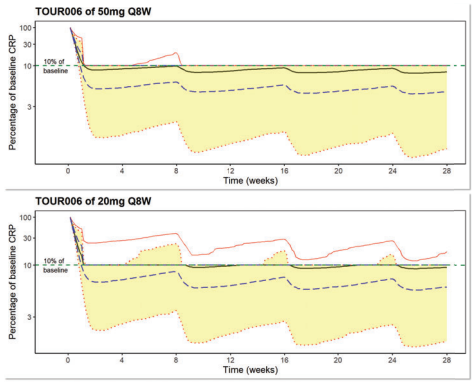
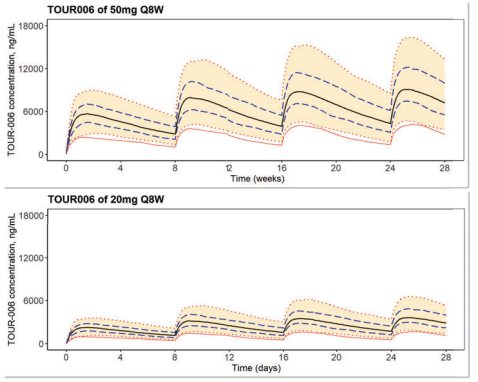


Figure 3. Time course of TOUR006 concentration over time in virtual subjects



Legend for Figures 2 and 3: Red dotted line= 5th and 95th percentile; blue dashed lines = 25th and 75th percentile; solid black line= median; red solid line= percentile with minimum exposure and weakest response to treatment.

Table 1. Baseline characteristics of virtual population

Covariates	Median [IQR*]
Bodyweight at baseline (kg)	58.8 [53.0, 67.8]
CRP at baseline (mg/L)	4.1 [3.4, 7.1]
Creatinine Clearance at baseline (mL/min)	89.3 [69.7, 100.5]
Albumin at baseline (g/dL)	4.3 [4.1, 4.5]
Female	86.0%

* IQR=Inter-quartile range

Figure 4. Distribution of baseline CRP in virtual subjects based on achievement of target reduction in CRP at week 24

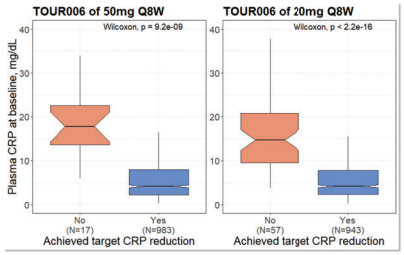


Table 2. Percentage of virtual population achieving success over treatment period

Dosing	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
50 mg Q8W	98.3%	96.6%	98.9%	98.0%	99.1%	98.3%
20 mg Q8W	95.0%	92.0%	96.3%	93.5%	96.8%	94.3%

DISCUSSION & CONCLUSION

- Simulations predict that most virtual participants with TED will achieve target reduction in CRP (≥90% CRP suppression from baseline or <2 mg/L) with a dosing regimen of 20 mg SC Q8W and 50 mg SC Q8W. Investigation of virtual subjects with baseline CRP>10mg/L (not presented here) confirms this finding for 50 mg SC Q8W.
- The 20 mg Q8W regimen may achieve the targeted efficacy in participants with moderate levels of IL-6 pathway activation (baseline CRP of 2 to 10 mg/L).
- The 50 mg Q8W regimen may be needed if IL-6 pathway activation is greater in TED or there are participants with relatively higher levels of IL-6-driven inflammation (baseline CRP > 10 mg/L).
- At week 24, the difference between percentage of subjects who achieved target reduction in CRP in the main simulation and the exploratory analysis cohort is 2% or less.
- **Conclusion:** The simulations for 20 mg and 50 mg Q8W of SC TOUR006 predict success in most TED subjects, thus producing a robust anti-inflammatory effect. Further exploration suggests that fixed subcutaneous dosing for TOUR006 without weight-based adjustment is appropriate.

Key References

2. Ueland HO, et al. Novel inflammatory biomarkers in thyroid eye disease. *Eur J Endocrinol.* 2022;187(2):293-300.
3. Czarnywojtek A, et al. The Role of Serum C-reactive Protein Measured by High- sensitive Method in Thyroid Disease. *Arch Immunol Ther Exp* (Warsz). 2014;62(6):501-509.
31. Li C, et al. Pharmacokinetics and C-reactive protein modelling of anti-interleukin-6 antibody (PF-04236921) in healthy volunteers and patients with autoimmune disease. *Br J Clin Pharmacol* (2018)84;2059–2074.

Additional References are available upon request.