# Simulations to Inform Dose Selection for a Phase 2b Trial Investigating TOUR006, a Fully Human Anti-IL6 Antibody, for Treatment of Thyroid Eye Disease

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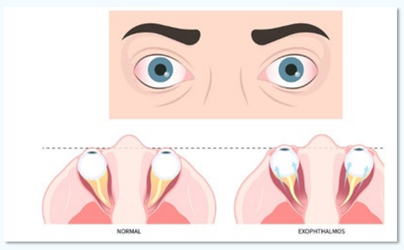
## BACKGROUND

Thyroid eye disease (TED) is an autoimmune disease in which the eye muscles and fatty tissue surrounding the eye become inflamed leading to bulging of eyes (proptosis) (Figure 1) 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].

**Figure 1: TED induced (proptosis) of eyes**



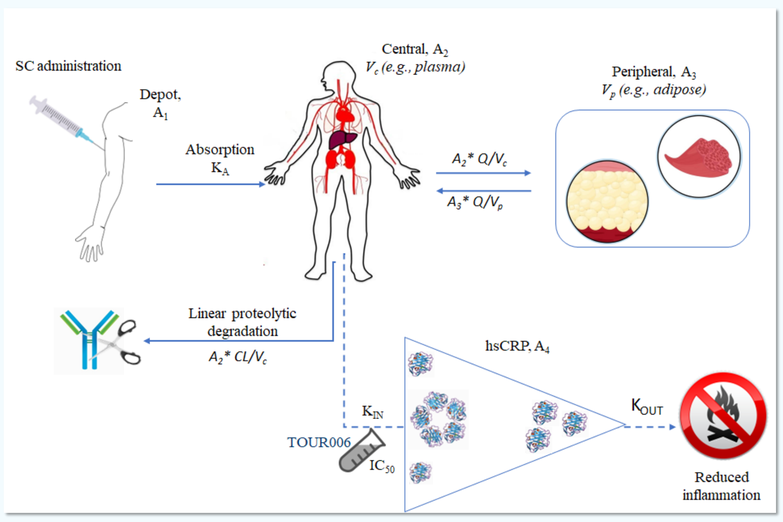

Further, several biomarkers that are hallmarks of IL-6 mediated inflammation, including C-reactive protein, red blood cell distribution width, and neutrophil-to-lymphocyte ratio are also elevated in patients with TED [3-6]. Multiple lines of evidence support the investigation of IL-6 blockade in treating 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 rheumatoid arthritis (RA), Chron's disease (CD), and systemic lupus erythematosus (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 highly sensitive C-reactive protein (hs-CRP), with the intention of robust blockade of the IL-6 pathway.

## METHODS

A pharmacokinetic 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 hs-CRP, widely used as a surrogate for IL-6 pathway activity was selected as an inflammatory biomarker. Figure 2 shows a schematic diagram of the model. Dosing frequencies Q4W or Q8W, and dose levels 10 to 50 mg were evaluated.

**Figure 2: Schematic diagram of PKPD model for effect of TOUR006 treatment**




Assumptions of simulation:

- Sampling used actual participants with baseline serum hs-CRP of >2 mg/L to 10 mg/L, comparable to most TED patients.
- Virtual TED population has inflammatory behavior like RA.
- *Target reduction* is defined as ≥90% hs-CRP suppression from baseline or <2 mg/L hs-CRP.
- Exploratory analysis was performed to estimate response to treatment for population with higher baseline bodyweight median = 102.3kg and IQR [98.5 kg, 115.1 kg] (results not presented here).

## RESULTS

**Equation Set 1: PK structural model**

$$\frac{dA_1}{dt} = -k_a A_1$$

$$\frac{dA_2}{dt} = k_a A_1 - k_{20} A_2 - k_{23} A_2 + k_{32} A_3$$

$$\frac{dA_3}{dt} = k_{23} A_2 - k_{32} A_3$$

**Equation Set 2: Indirect response PD Model**

$$\frac{dR}{dt} = K_{in} \times u(t) - K_{out} \times R$$

$$u(t) = \left(1 - \frac{I_{max} \times C(t)^{\gamma}}{IC_{50}^{\gamma} + C(t)^{\gamma}}\right)$$

$$R(t=0) = BLCRP = \frac{K_{in}}{K_{out}}$$

The previously developed structural model is 2-compartments with linear elimination (Equation Set 1) and includes an indirect response of TOUR006 on hs-CRP concentration using the Hill equation (Equation Set 2).

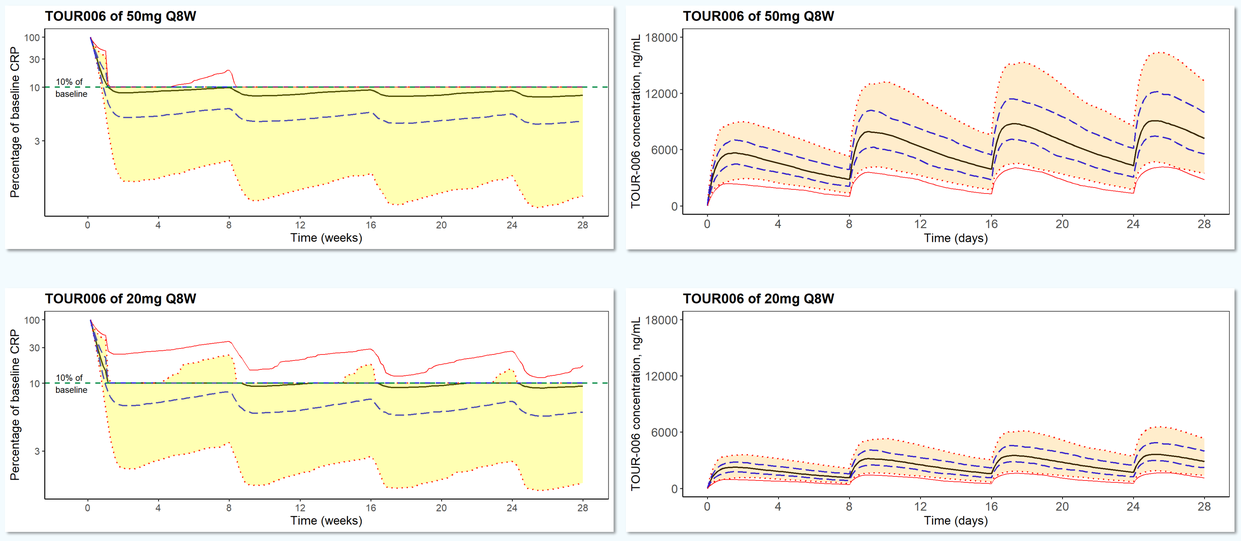
The model describes covariate impacts as follows:

- Separate clearance is estimated for HV and each disease indication.
- Fixed allometry for bodyweight on all clearance and volume parameters
- Baseline albumin negatively impacts CL
- Baseline hs-CRP, creatinine clearance and sex positively impacts CL
- Baseline hs-CRP (BLCRP), maximum inhibition ($I_{max}$), concentration for 50% of maximum inhibition ($IC_{50}$) is estimated separately for HV and each disease indication.
- Hill coefficient γ was fixed to 1 for HV, RA, CD and estimated for SLE only

## RESULTS

**Figure 3: Time course of hs-CRP suppression from baseline in virtual subjects under TOUR006 treatment**

**Figure 4: Time course of TOUR006 concentration over time in virtual subjects**




*Legend for Figures 3 & 4: 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 2: Percentage of virtual population achieving target hs-CRP resuction 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% |

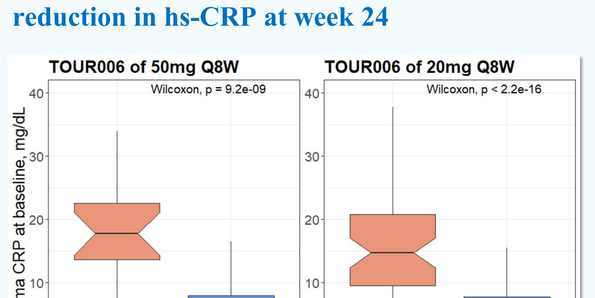
### Summary of Results:

- The baseline characteristics of the virtual subjects used for treatment simulations is given in Table 1.
- Over 90% of virtual subjects achieved target reduction in hs-CRP over time (Table 2).
- The time course of hs-CRP suppression is summarized in Figure 3 and the time course of TOUR006 concentration over time is summarized in Figure 4.
- Baseline hs-CRP of virtual subjects who achieved target reduction in hs-CRP is significantly lower than subjects who did not achieve this milestone, as seen in Figure 5.

**Table 1: Baseline characteristics of virtual population**

| Covariates | Median [IQR*] |
|---|---|
| Bodyweight at baseline (kg) | 58.8 [53.0, 67.8] |
| hs-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% |

**Figure 5: Distribution of baseline hs-CRP in virtual subjects based on achievement of target reduction in hs-CRP at week 24**




## DISCUSSION & CONCLUSION

- Simulations predict that most virtual participants with TED will achieve (≥90% hs-CRP suppression from baseline or <2 mg/L) target reduction in hs-CRP with dosing schedule of 20 mg SC Q8W and 50 mg SC Q8W.
- The 20 mg Q8W regimen may achieve the targeted reduction in hs-CRP in participants with moderate levels of IL-6 pathway activation (baseline hs-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.
- At week 24, the difference between the percentage of virtual subjects who achieved the target reduction in hs-CRP in the main simulation and the exploratory analysis population (with higher baseline bodyweight) is 2% or less.
- **Conclusion:** The simulations for 20 mg and 50 mg Q8W of SC TOUR006 predict that most TED subjects will reach the target reduction in hs-CRP, thus producing an expected robust reduction in inflammation. Further exploration suggests that fixed subcutaneous dosing for TOUR006 without weight-based adjustment is appropriate.

**Key References:** *Additional References are available upon request.*

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.