

# Using PBPK-QSP model to move the boundaries of transthyretin stabilization understanding

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## PBPK-QSP model can be utilized to critically assess biomarkers of TTR amyloidosis treatment

### Introduction

Destabilized transthyretin (TTR – transport protein involved in thyroxine and retinol circulation) can misfold and form amyloid fibrils with ATTR cardiomyopathy and neuropathy being the most prominent clinical effects. TTR tetramer stabilizers, tafamidis and acoramidis, prevent tetramer dissociation and clinical data show indeed increase in TTR levels after treatment. However, mechanism of this effect is still not known and an effect our study seeks to explain the mechanism of this effect.

### Objectives

- utilize combination of PBPK (Physiologically Based Pharmacokinetics) model describing tafamidis disposition in human body after oral application and phenomenological QSP (Quantitative Systems Pharmacology) model describing TTR dynamics to simulate tafamidis disposition and effect
- simulate virtual clinical scenarios for various doses and dosing regimens
- analyse influence of dosing parameters on clinical effect, expressed as TTR plasma level modification after tafamidis application

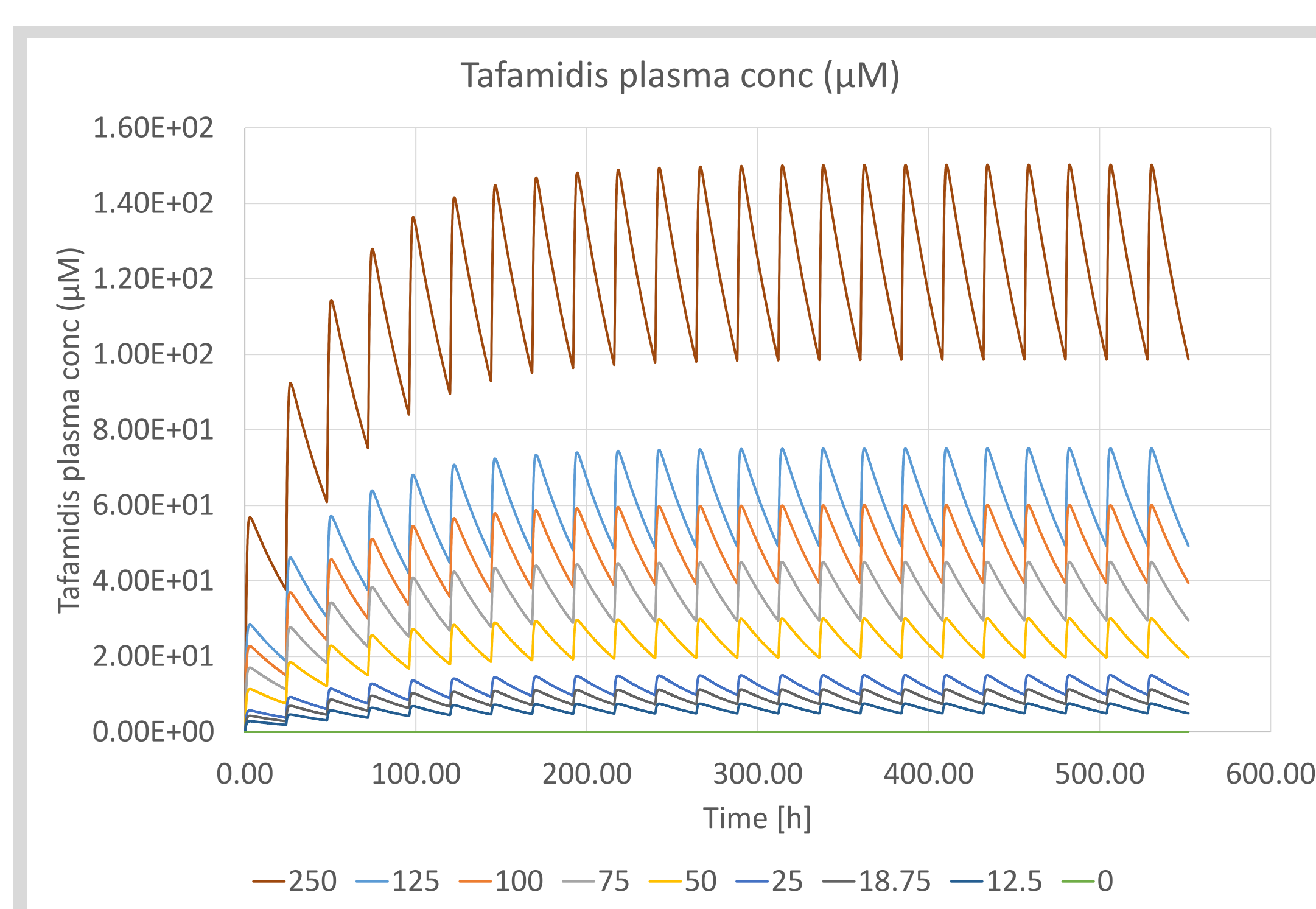
### Methods

Simcyp Simulator (V23, Certara, Sheffield, UK) was used to develop a PBPK-QSP (Physiologically Based Pharmacokinetic – Quantitative Systems Pharmacology) model by combining drug, system (population), and trial related data [1]. The Simcyp embedded tool for custom models' development, which employs LUA programming language, was used. Model development included the following steps: 1) parametrisation, verification and validation (with the use of experimental clinical data of plasma tafamidis concentration after oral application [2-4]) of PBPK model; 2) addition of age dependent TTR baseline concentration to the target population (based on the available literature data [5]); 3) development of a QSP ligand-protein binding model accounting for drug presence-dependent effects rates-dependent concentration transthyretin levels [6-7]. Simulation results were analysed for correlation between tafamidis plasma concentration and clinical effect expressed e.g. as total TTR plasma level.

### Results

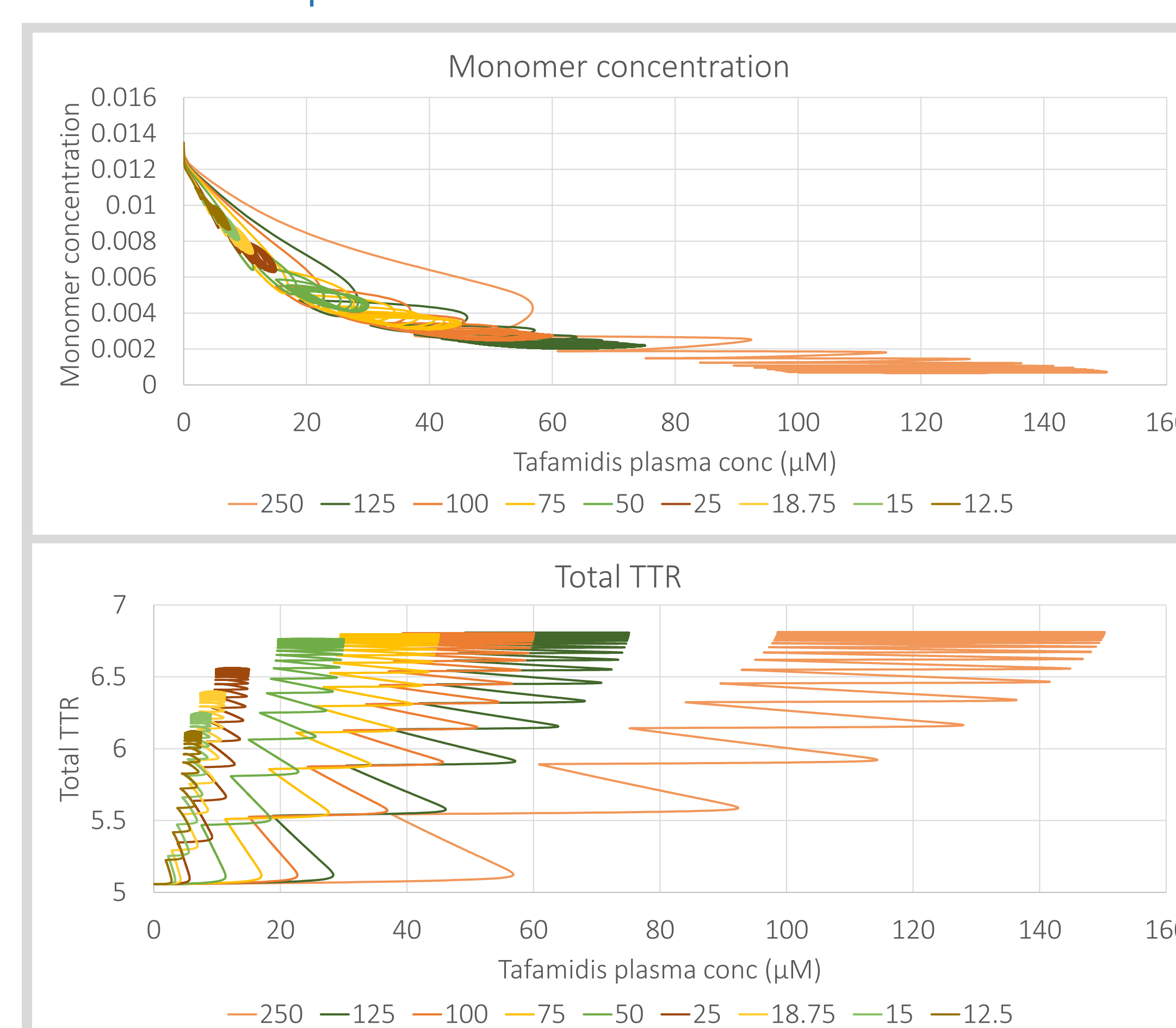
Figure 1 presents PBPK simulated Tafamidis plasma concentration ( $\mu\text{M}$ ) for eight various tested doses (12.5-250 mg).

Figure 1. Simcyp PBPK model simulations for Tafamidis.



Analyzed PD effects included – among others – total TTR plasma concentration, TTR monomer plasma concentration (Figure 2).

Figure 2. Total TTR and TTR monomer plasma concentration versus tafamidis plasma concentration.



### References

- [1] <https://www.certara.com/software/simcyp-pbpbk/>
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- [3] K. J. Klamers, E. Watsky, R. Moller, R. Wang, and S. Riley, "The effect of tafamidis on the QTc interval in healthy subjects," Br. J. Clin. Pharmacol., vol. 79, no. 6, pp. 918–925, Jun. 2015, doi: 10.1111/bcp.12561.
- [4] Center for drug evaluation and research, "Application number 211996Orig1s000; 212161Orig1s000." Nov. 02, 2018.
- [5] Y. Ingenbleek, "Plasma Transthyretin Reflects the Fluctuations of Lean Body Mass in Health and Disease," in Recent Advances in Transthyretin Evolution, Structure and Biological Functions, S. J. Richardson and V. Cody, Eds., Berlin, Heidelberg: Springer Berlin Heidelberg, 2009, pp. 329–357. doi: 10.1007/978-3-642-00646-3\_20.
- [6] B. Lisowski et al. "Phenomenological model of transthyretin stabilization", submitted for publication.
- [7] S. Ulaszek et al. "Exploring Tafamidis Effects Through PBPK-QSP Modelling", submitted for publication.

### Model description

Equations describing TTR kinetics: Eq 1 - Single molecule of tafamidis-TTR complex, Eq 2 - Double molecule of tafamidis-TTR complex, Eq 3 - Free TTR concentration, Eq 4 - Dissociated monomers concentration, Eq 5 - Tafamidis-albumin complex concentration, Eq 6 - Free albumin concentration, Eq 7 - Free tafamidis concentration.

$$\frac{dC_{TTR1}}{dt} = -T_{bound,deg} * C_{TTR1} + k_{on1} * C_{Taf} * C_{TTRfree} - k_{off1} * C_{TTR1} + k_{off2} * C_{TTR2} - k_{on2} * C_{Taf} * C_{TTR1}$$

$$\frac{dC_{TTR2}}{dt} = -T_{bound,deg} * C_{TTR2} + k_{on2} * C_{Taf} * C_{TTR1} - k_{off2} * C_{TTR2}$$

$$\frac{dC_{TTRfree}}{dt} = r + k_a * C_{Monomer}^4 - (k_{diss} + T_{deg}) * C_{TTRfree} - k_{on1} * C_{Taf} * C_{TTRfree} + k_{off1} * C_{TTR1}$$

$$\frac{dC_{Monomer}}{dt} = 4k_{diss} * C_{TTR} - 4 * k_a * C_{Monomer}^4 - M_{deg} * C_{Monomer}$$

$$\frac{dC_{Alb1}}{dt} = k_{on,albumin} * C_{Taf} * C_{Alb,free} - k_{off,albumin} * C_{Alb1}$$

$$\frac{dC_{Alb,free}}{dt} = -k_{on,albumin} * C_{Taf} * C_{Alb,free} + k_{off,albumin} * C_{Alb1}$$

$$C_{Taf} = C_{total} - (C_{TTR1} + 2 * C_{TTR2} + C_{Alb1})$$

### Learning objectives

Study findings suggest that PBPK-QSP model can be utilized to critically assess biomarkers of TTR amyloidosis treatment. This is not limited to total TTR plasma concentration but also other potential biomarkers including TTR monomers plasma concentration. Simulations suggest that dose increase above 50 mg gives negligible increase in the effect.