# Coupling complex mechanistic PK/PD modelling with dynamic system analysis to obtain relevant clinical/biological insights

## Application to a gonadotropin hormone release agonist

Elba Romero, Nieves Vélez de Mendizábal, Josep María Cendrós, Concepción Peraire, Rosendo Obach, Iñaki F. Trocóniz

School of Pharmacy, University of Navarra/ Pamplona
Ipsen Pharma/ Barcelona
Spain

# Aim

- Develop a predictive receptor-based pharmacokinetic-pharmacodynamic (PK/PD) model for the testosterone (TST) effects of triptorelin (TRT).

- To extract relevant clinical PK properties of the sustained release (SR) formulations through a formal mathematical analysis of the model.

# Outline

- Brief introduction to the pharmacological treatment of prostate cancer
- Study design
- Description of the semi-mechanistic model developed
- Model evaluation
- Search of important clinical descriptors for the development of new SR formulations
  - Model based simulations
  - Model based system analyses

# Pharmacological treatment of prostate cancer

- Prostate tumors are highly sensitive to testosterone hormone (TST) levels
- Therapeutic strategies to achieve and maintain TST plasma levels below the castration limit (0.5 ng/mL)
  - Gonadotropin Release Hormone agonist
    - Triptorelin (TRT) , goserelin, nafarelin, leuprorelin
  - Gonadotropin Release Hormone antagonist
    - Cetrorelix, degarelix, ganirelix
- Sustained release forms have proven their efficacy on hormonal treatment
  - Protection against hydrolysis mechanisms
  - Reduction of toxicity
  - Increase of bioavailability
  - Several types of systems: Microtubules (MT), microparticles (MP), microspheres (MS)

# Study design

| | | | | | |
|---|---|---|---|---|---|
| No. studies | 1 | 2 | 3 | 4 | 5 |
| Type of population | Patients/healthy | Patients | Patients | Patients | Patients |
| No. subjects | 19 | 12 | 12 | 24 | 15 |
| Dose (mg) | 3,6,9 | 6 | 15 | 6 | 22.5 twice |
| Formulation | $Microtubules_A$ | $Microtubules_B$ | Microparticles | $Microtubules_C$ | Microspheres |
| Type of administration | SC | SC | SC | IM | IM |
| Triptorelin data | 409 (14%) | 307 | 220 | 379 | 526 |
| Testosterone data | 438 (2%) | 333 (57%) | 230 (47%) | 263 (3%) | 299 (3%) |

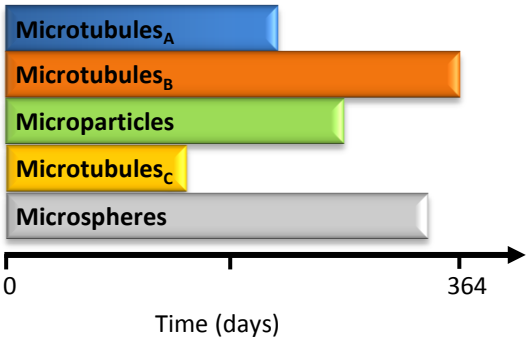
BQL observations

Blood samples were taken until effect was observed (over a period of 4 months)

## Fundamental data characteristic to develop predictive complex semi-mechanistic models

***High degree of system perturbation***

- Magnitude of exposure
  - Doses of 3,6,9 and 22.5 mg
  - Single and multiple administrations
- Duration of exposure
- Profile of exposure
  - SC and IM administration
  - MT, MS,MP



# Details of the model developed

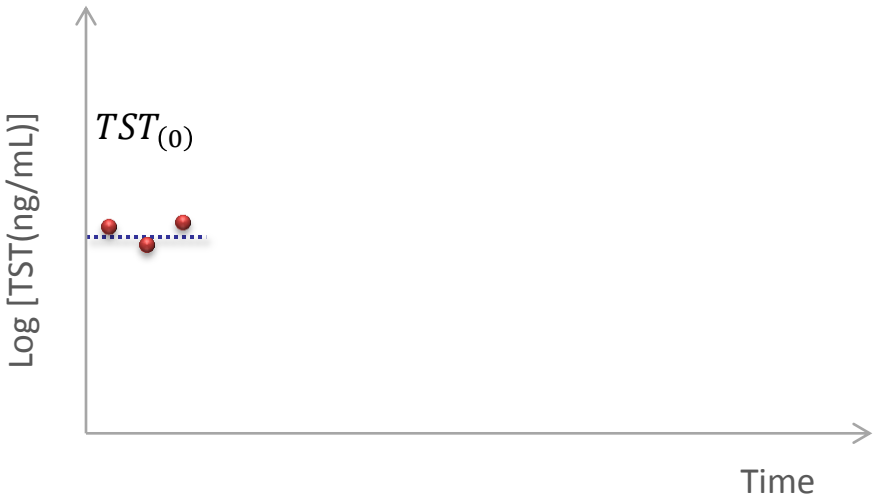
$C_{AGN}$ concentration of endogenous agonist

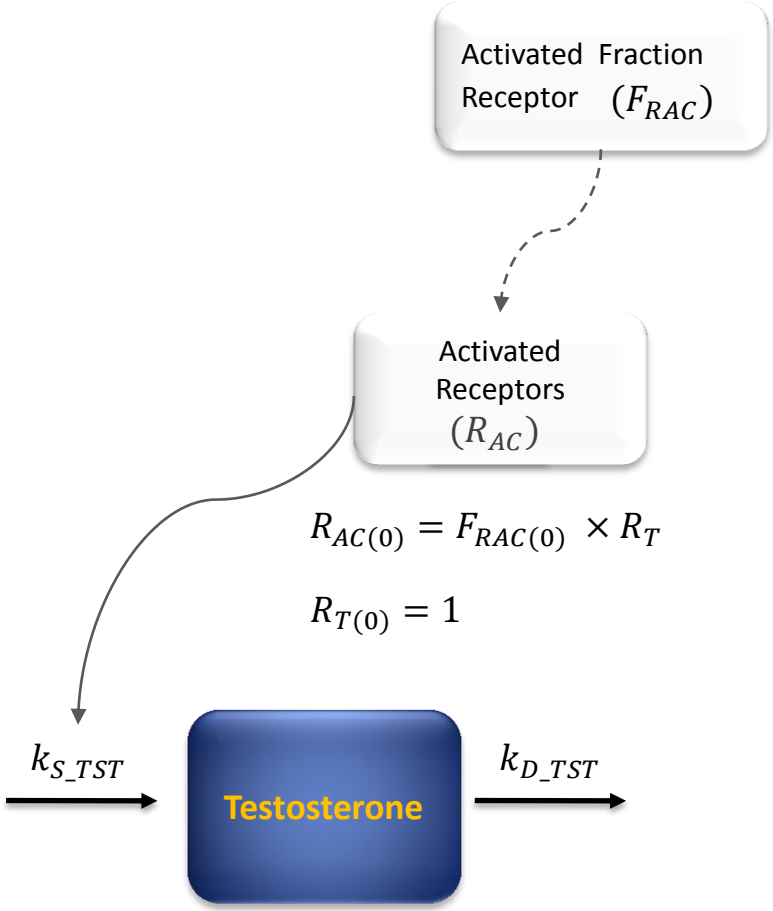
$K_{D\_AGN}$ agonist-receptor equilibrium dissociation constant

$$F_{RAC(0)} = \frac{\frac{C_{AGN}}{K_{D\_AGN}}}{1 + \frac{C_{AGN}}{K_{D\_AGN}}}$$

Assuming $C_{AGN}$ and $K_{D\_AGN}$ are constant over time

$$\boldsymbol{AGN} = \frac{C_{AGN}}{K_{D\_AGN}}$$



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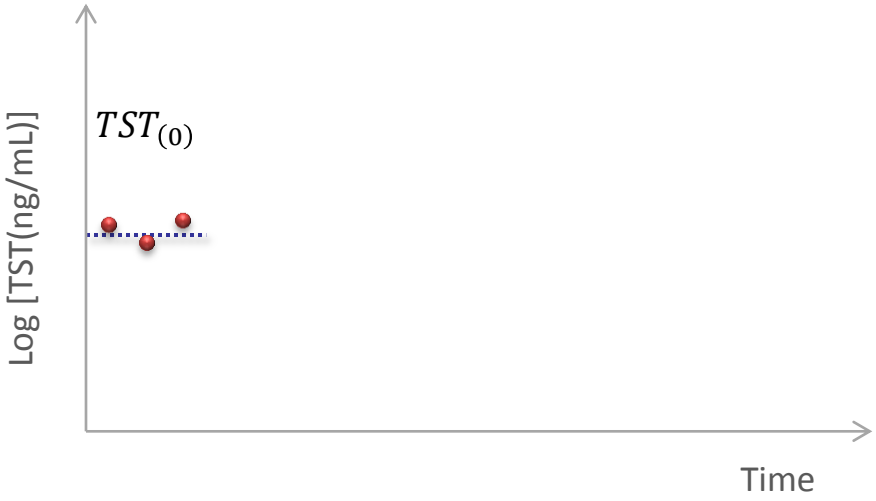



$$F_{RAC(0)} = \frac{AGN}{1+AGN}$$

Activated Fraction Receptor $(F_{RAC})$

Activated Receptors $(R_{AC})$

$$R_{AC(0)} = F_{RAC(0)} \times R_T$$

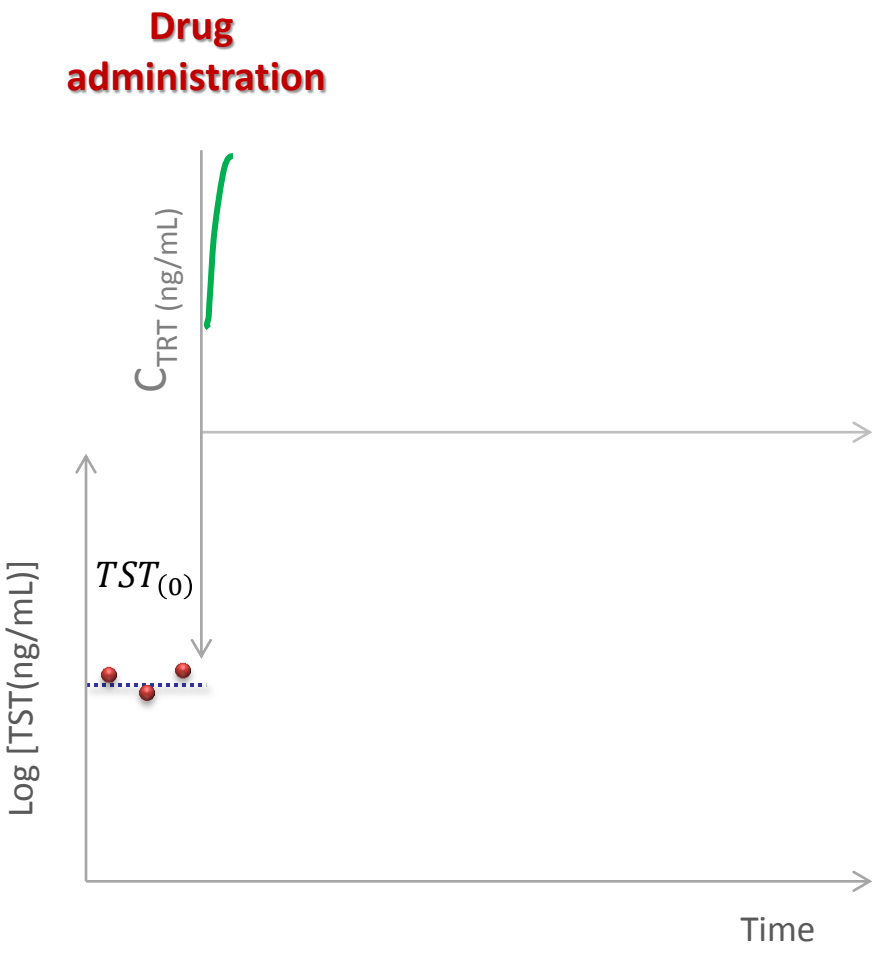
$$R_{T(0)} = 1$$

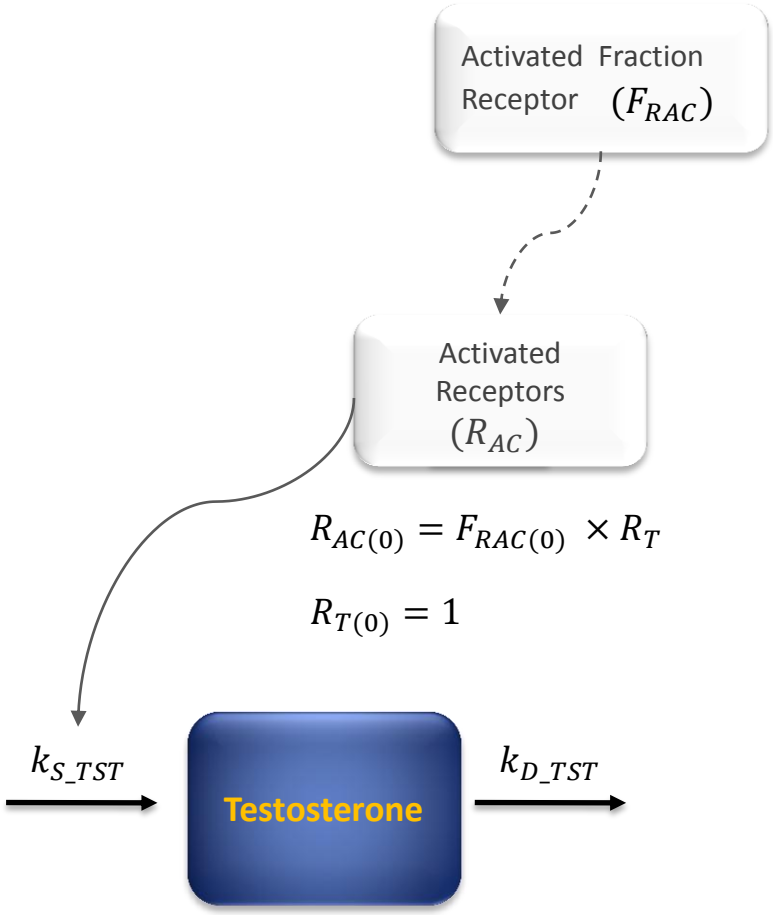
$k_{S\_TST}$ → Testosterone → $k_{D\_TST}$

# Details of the model developed

$$BGN = \frac{C_{TRT}}{K_D}$$

$$F_{RAC(0)} = \frac{AGN}{1+AGN}$$



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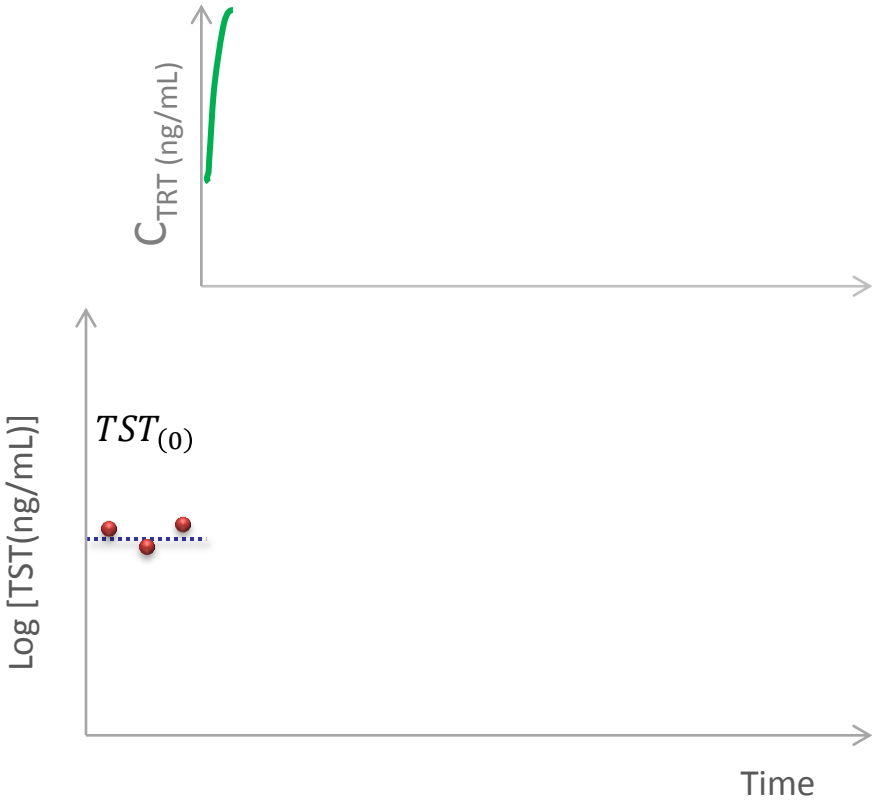


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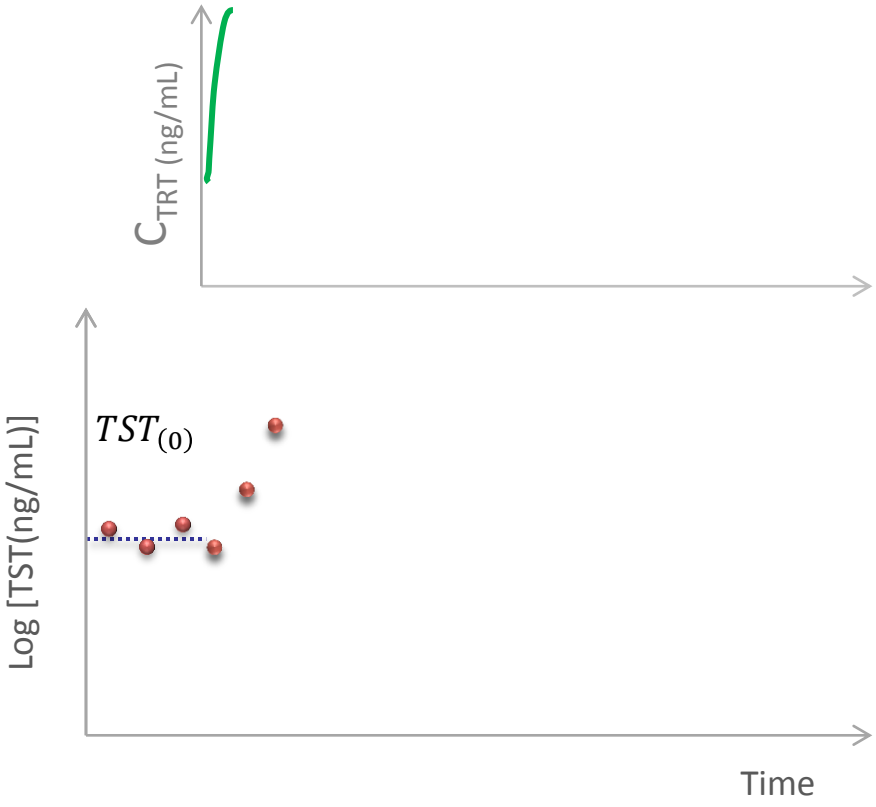


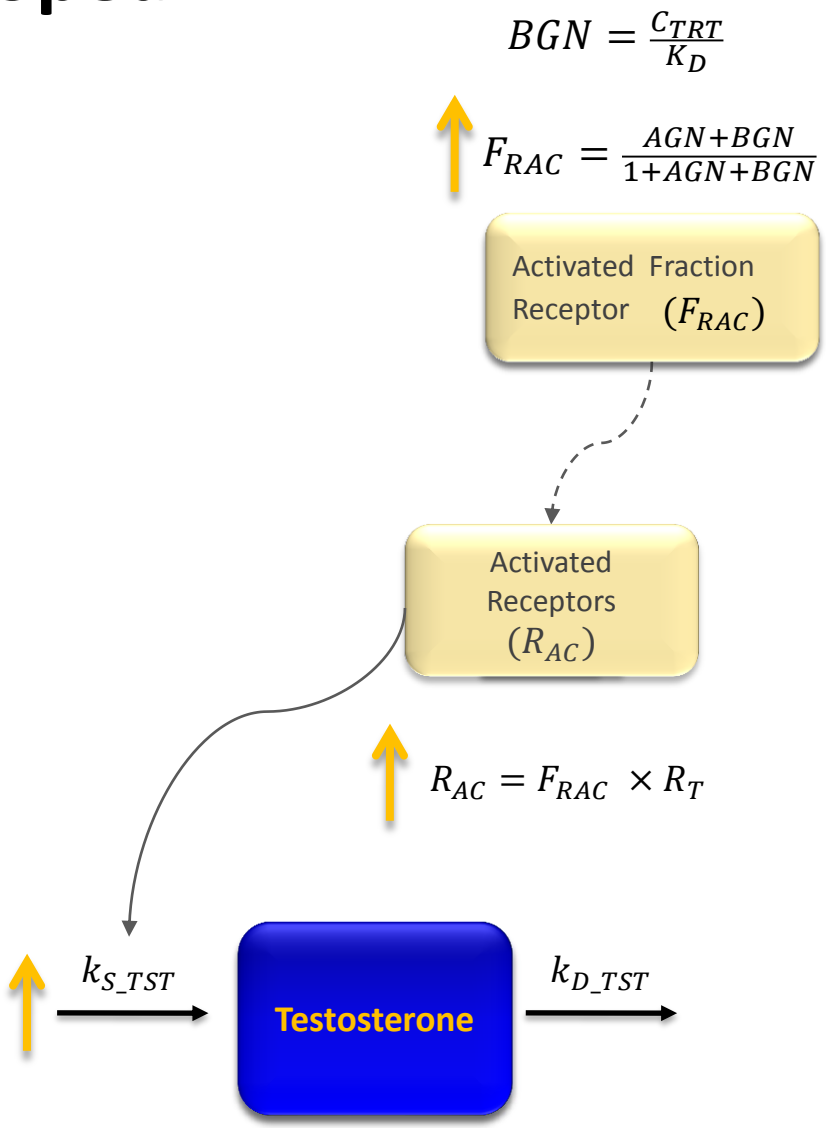

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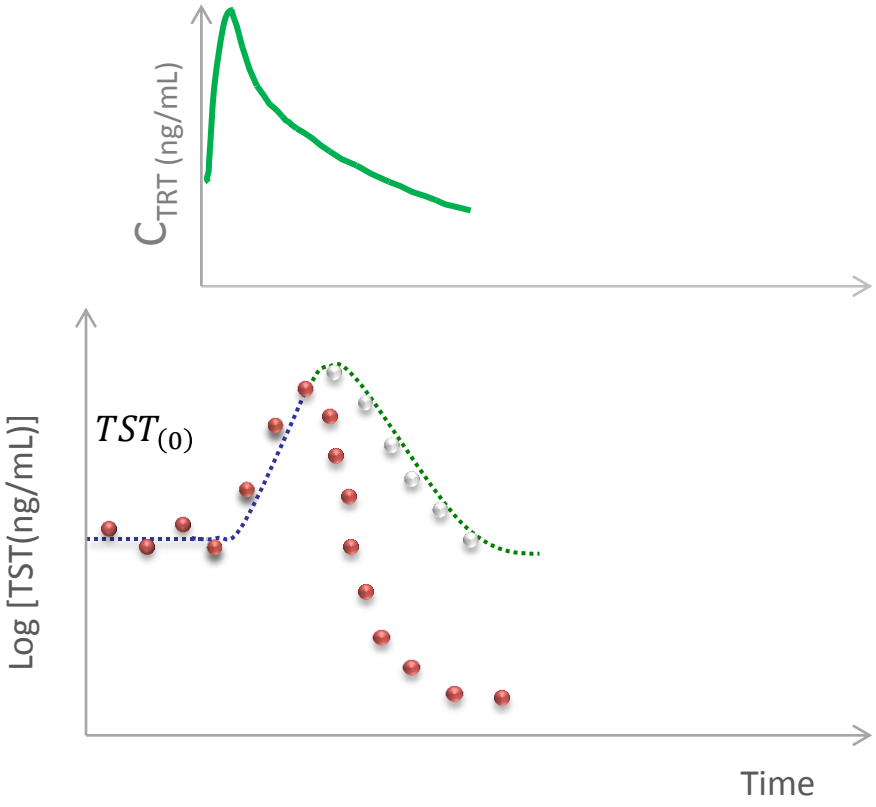
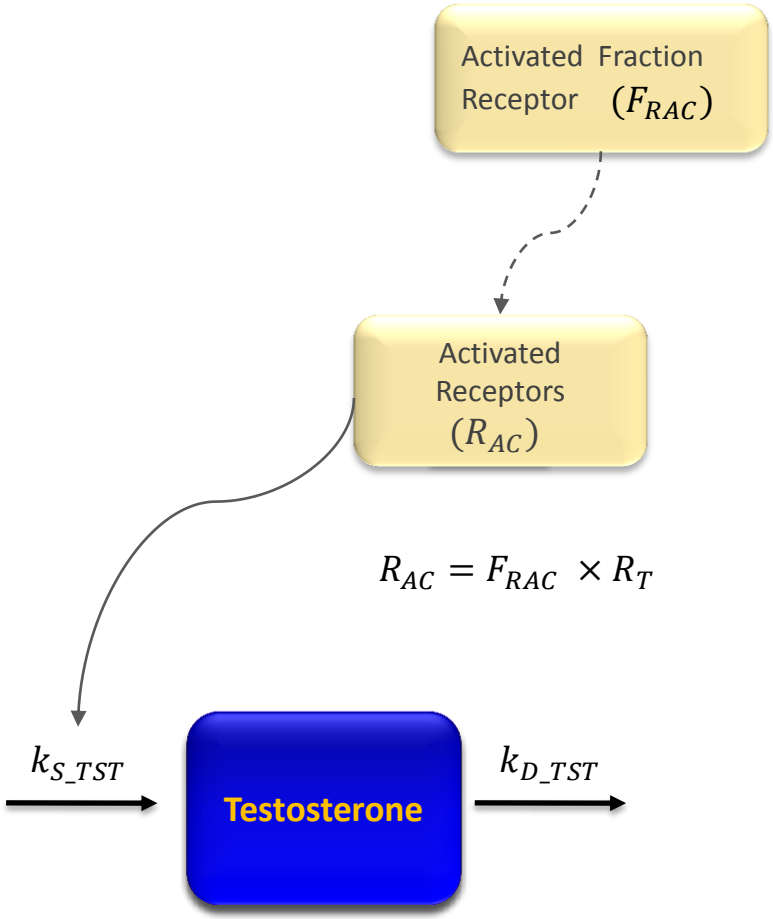


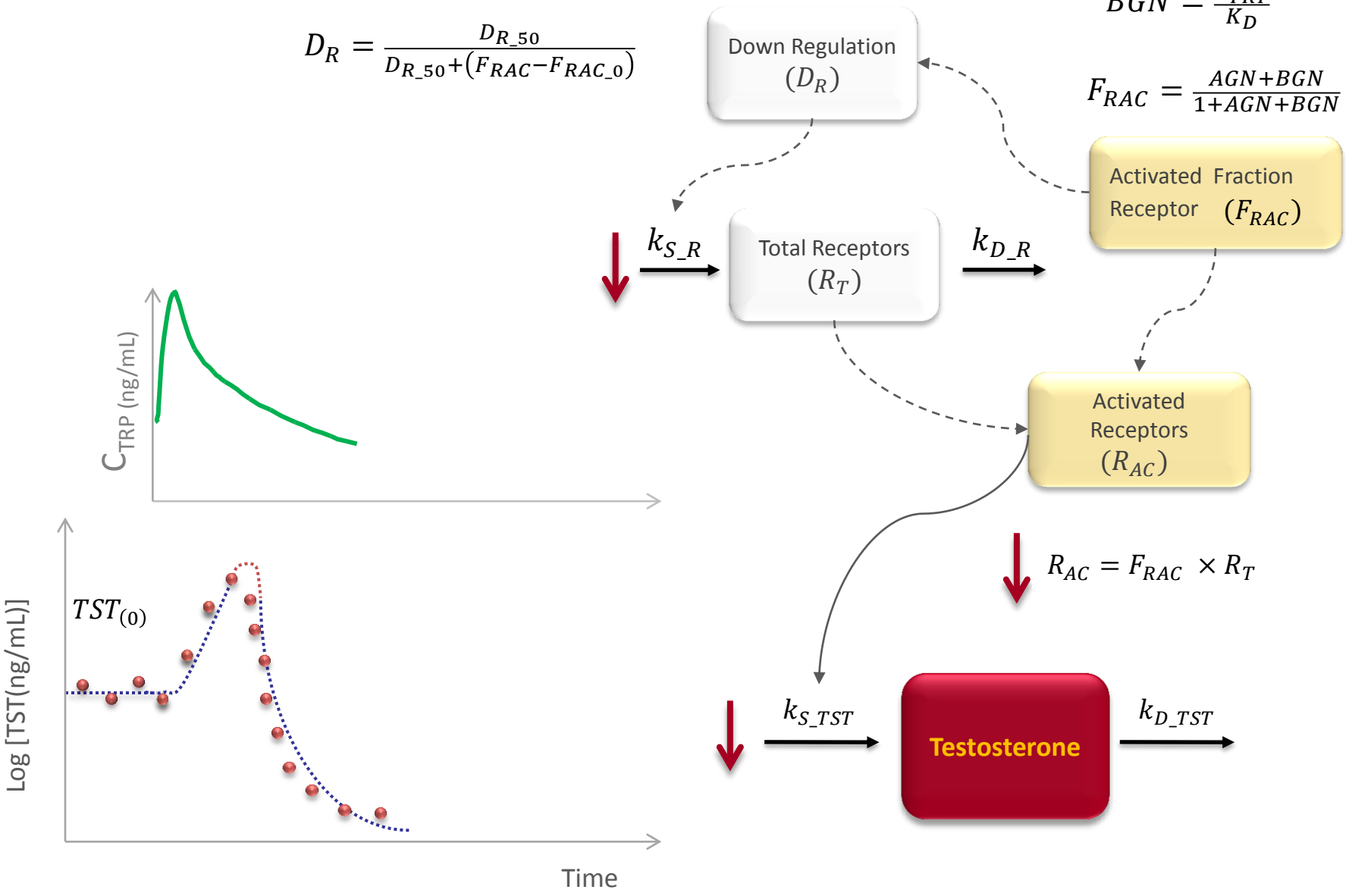



# Details of the model developed

$$D_R = \frac{D_{R\_50}}{D_{R\_50} + (F_{RAC} - F_{RAC\_0})}$$

$$BGN = \frac{C_{TRT}}{K_D}$$

$$F_{RAC} = \frac{AGN + BGN}{1 + AGN + BGN}$$



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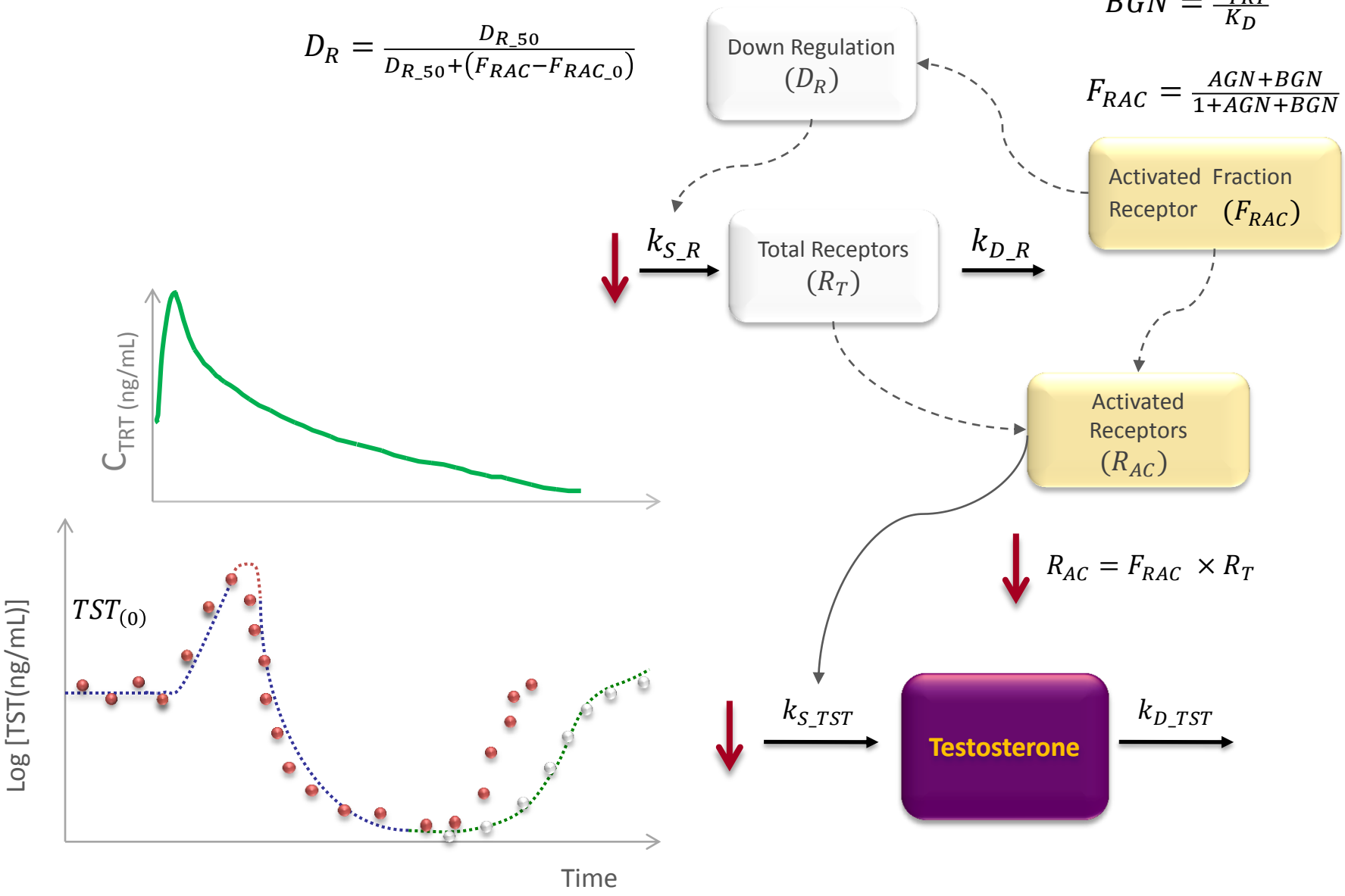

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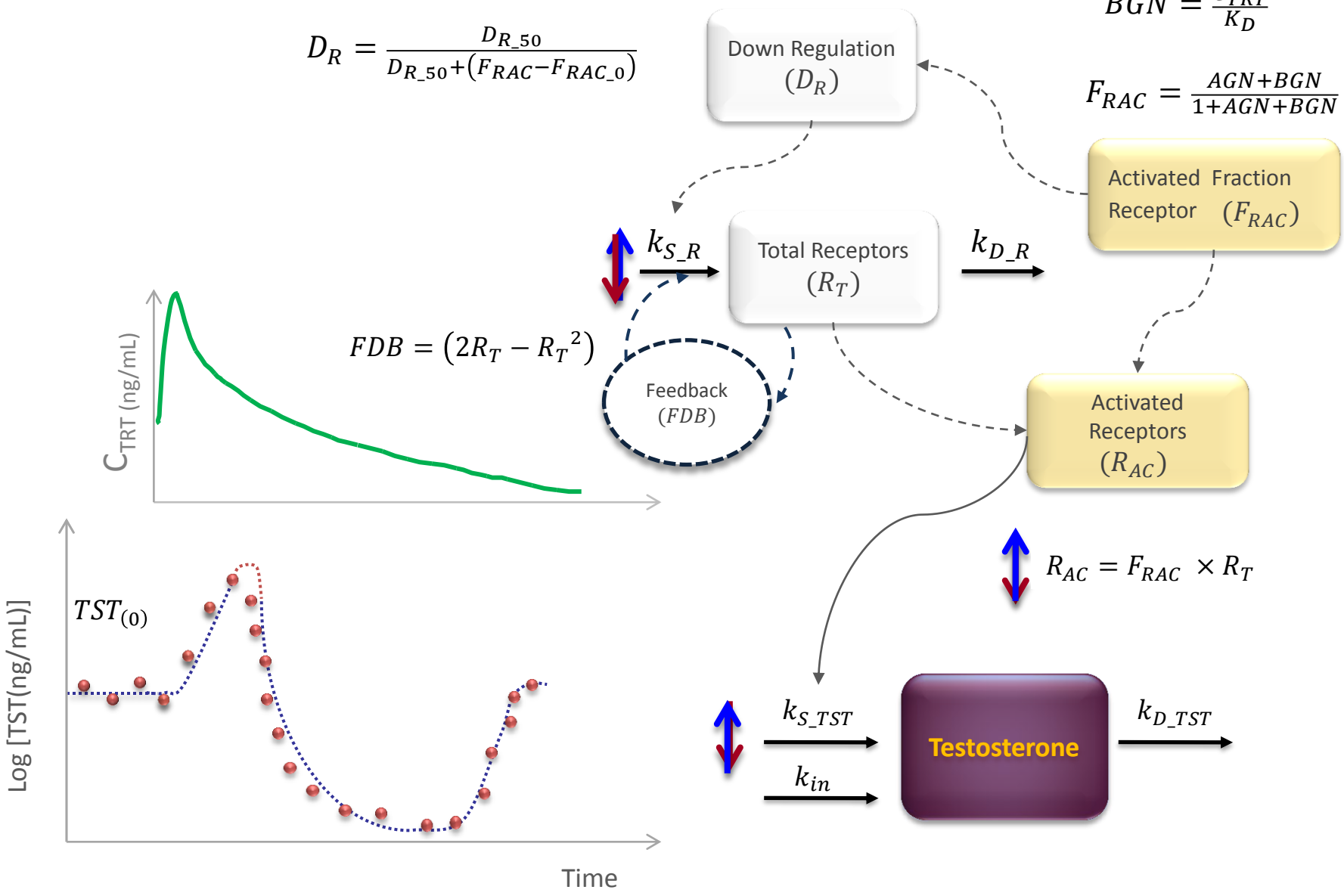

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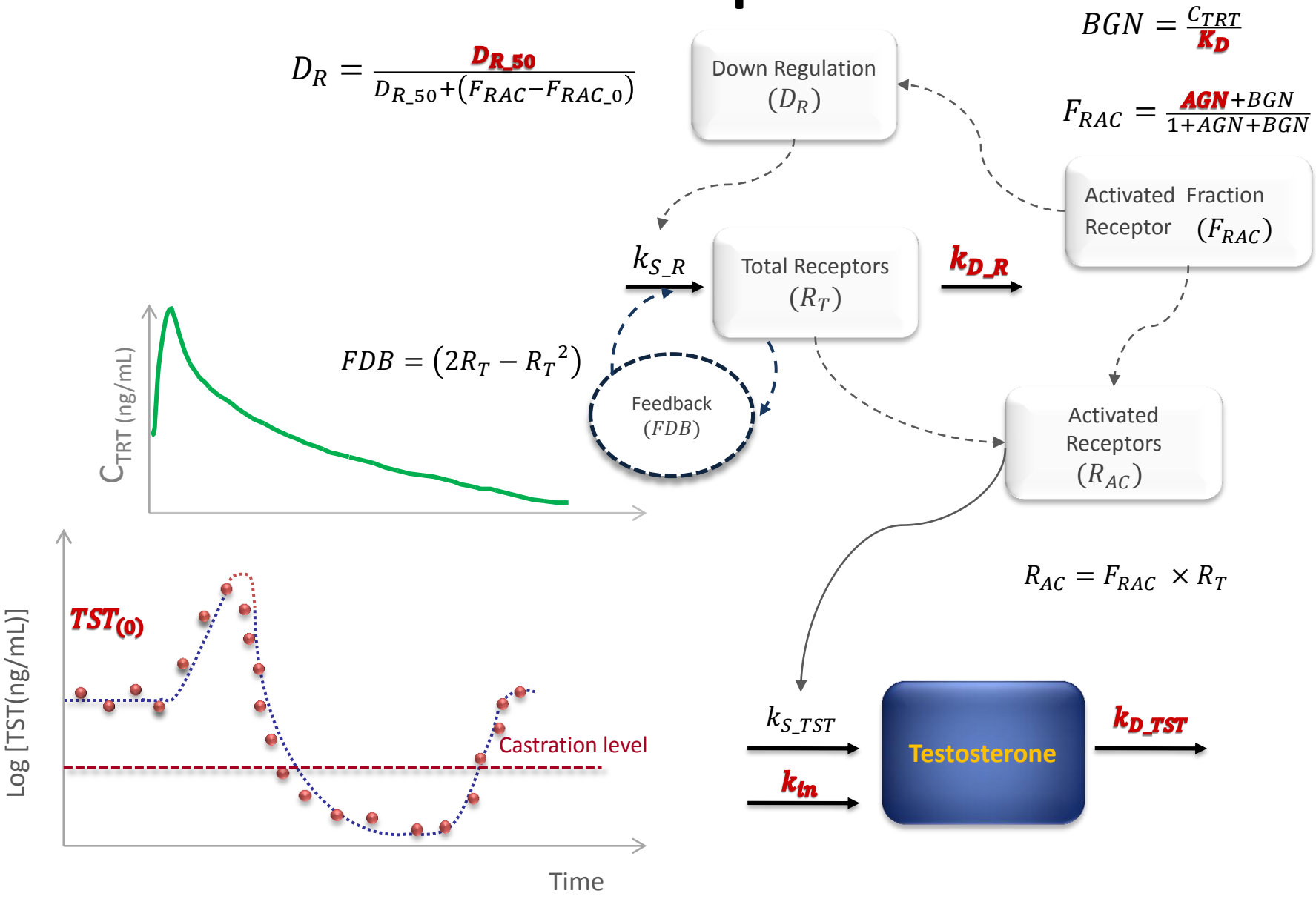
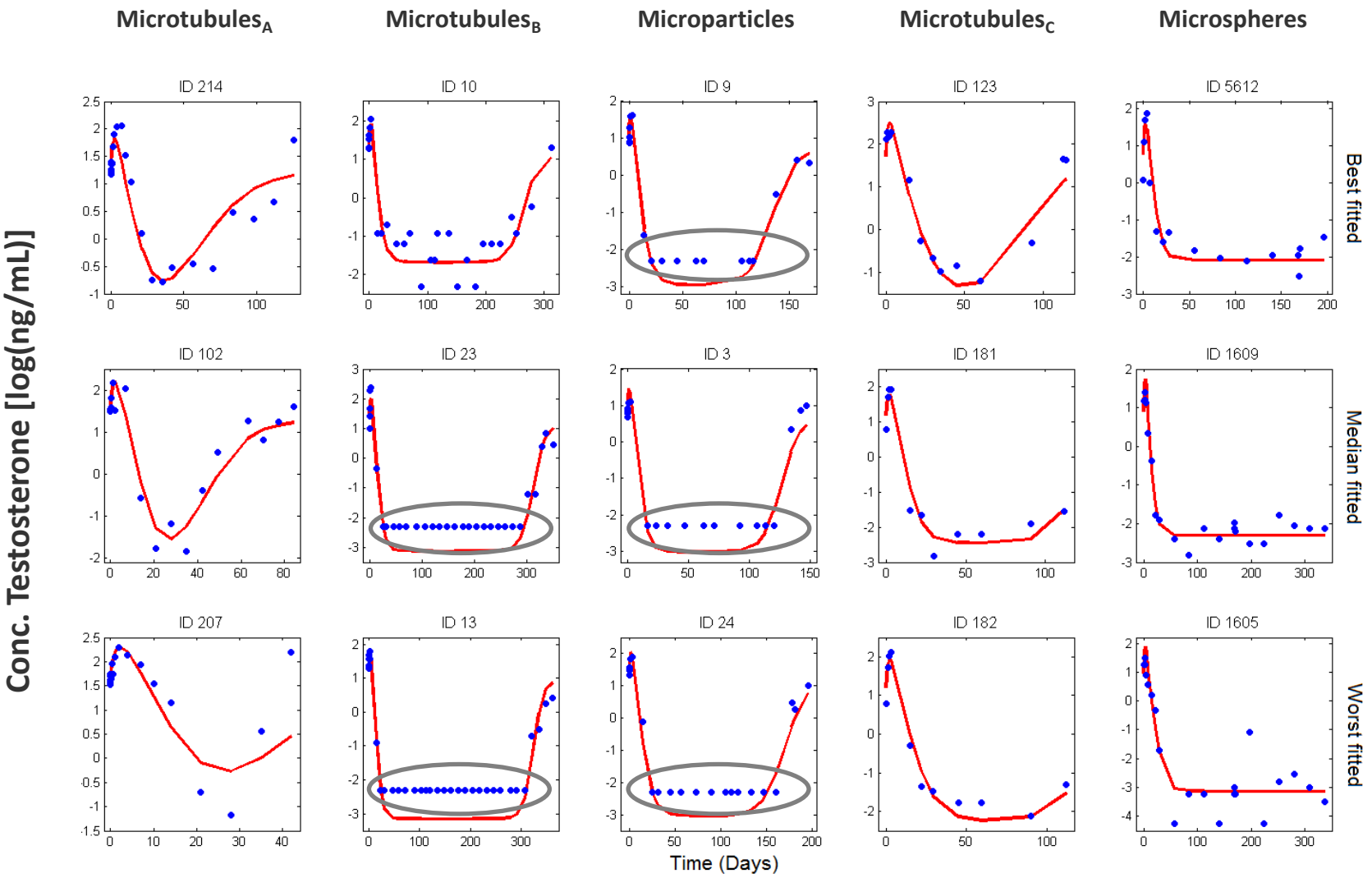
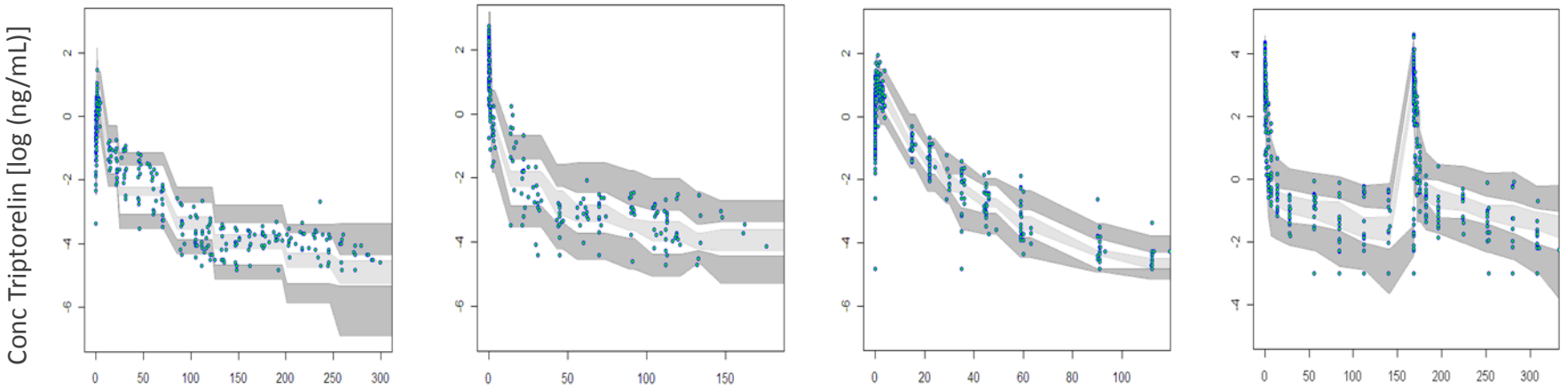


# Individual model performance



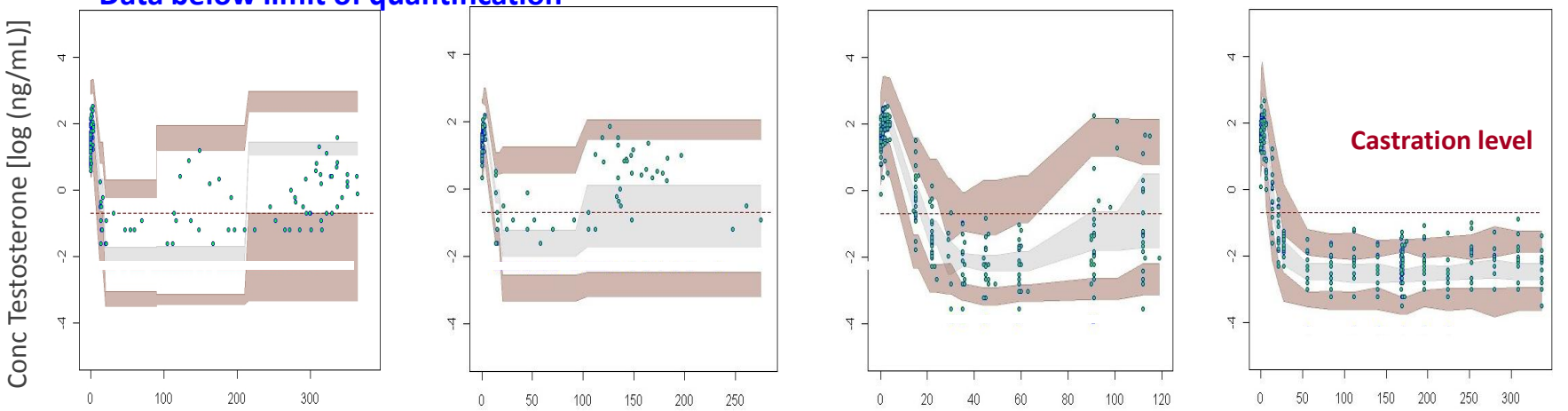
# VPC evaluation

## Triptorelin pharmacokinetics




## Testosterone PK/PD

Data below limit of quantification

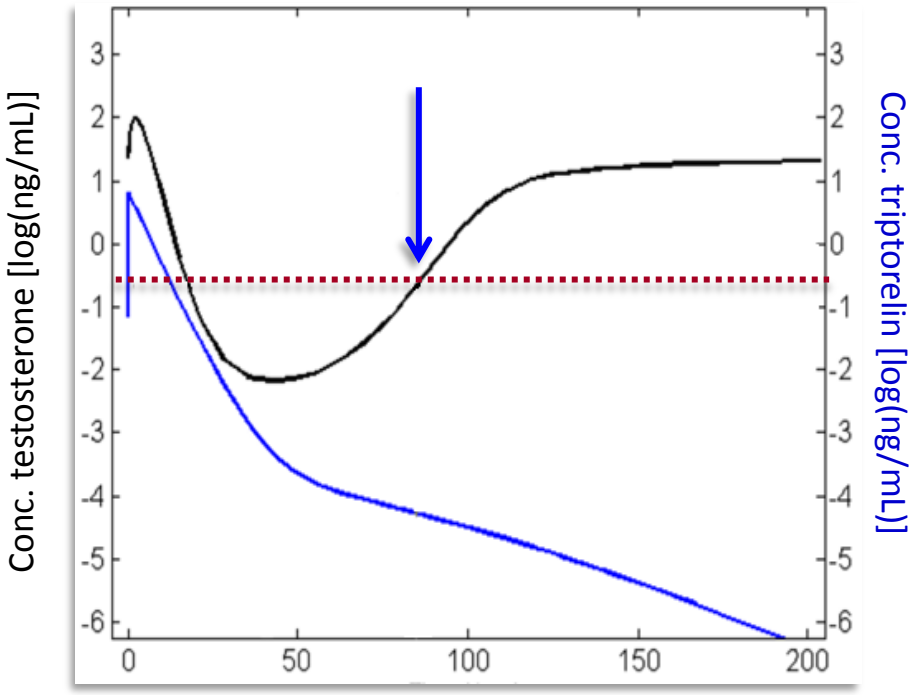



Time (days)

- Model was applied to obtain relevant clinical descriptors
- Those aiding to develop optimal delivery systems
  - Minimum plasma concentration of triptorelin required to keep patients under castration level ($C_{TRT\_min}$)

Conceptually $C_{TRT\_min}$ is independent on the type of formulation administered (independent of PK profiles)

Time to achieve $C_{TRT\_min}$ will be dependent on the formulation



# Determination of $C_{TRT\_min}$

***Model based simulation***

***Model based system analyses***

# Determination of $C_{TRT\_min}$

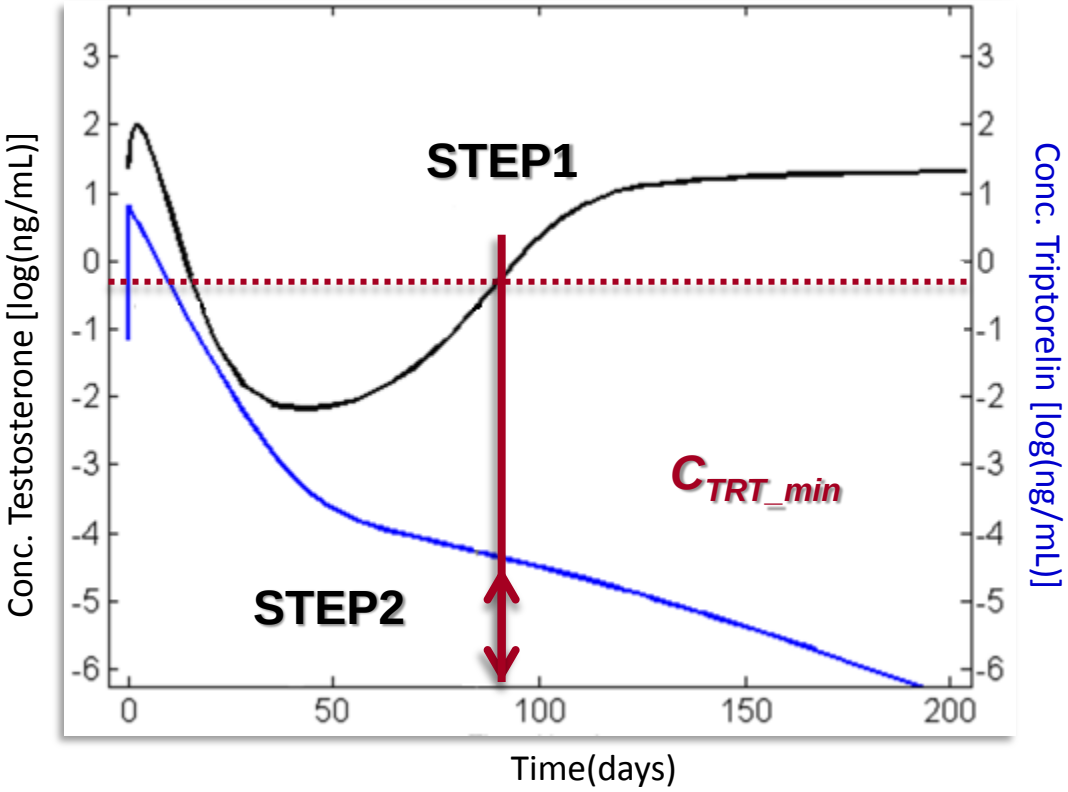
***Model based simulation***

For each type of formulation 1000 subjects were simulated

**STEP1.**Determination of the time once testosterone plasmatic concentrations is crossing the castration level*

**STEP2.**Identification of triptorelin plasma concentration at that time

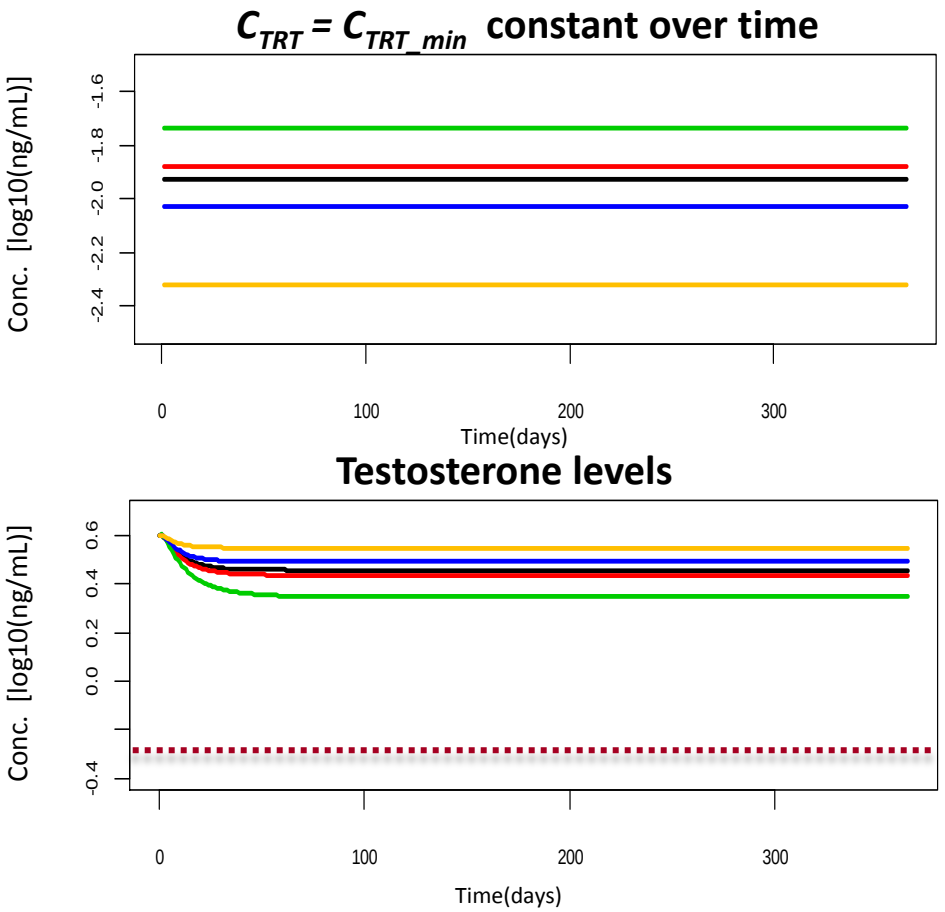
***, limitation , only subjects that reached castration level were considered to calculate $C_{TRT\_min}$***



# Determination of $C_{TRT\_min}$

| Formulation | Percentiles | $C_{TRT\_min}$ |
|---|---|---|
| | 5th | 0.0042 |
| Microtubules$_A$ | 50th | **0.0119** |
| | 95th | 0.0264 |
| | 5th | 0.0063 |
| Microtubules$_B$ | 50th | **0.0133** |
| | 95th | 0.0273 |
| | 5th | 0.0106 |
| Microparticles | 50th | **0.0185** |
| | 95th | 0.0338 |
| | 5th | 0.0064 |
| Microtubules$_C$ | 50th | **0.0094** |
| | 95th | 0.0175 |
| | 5th | 0.0024 |
| Microspheres | 50th | **0.0048** |
| | 95th | 0.0106 |

***$C_{TRT\_min}$ differs among formulations !!***




***In any case castration limit is not achieved!!***

# Determination of $C_{TRT\_min}$

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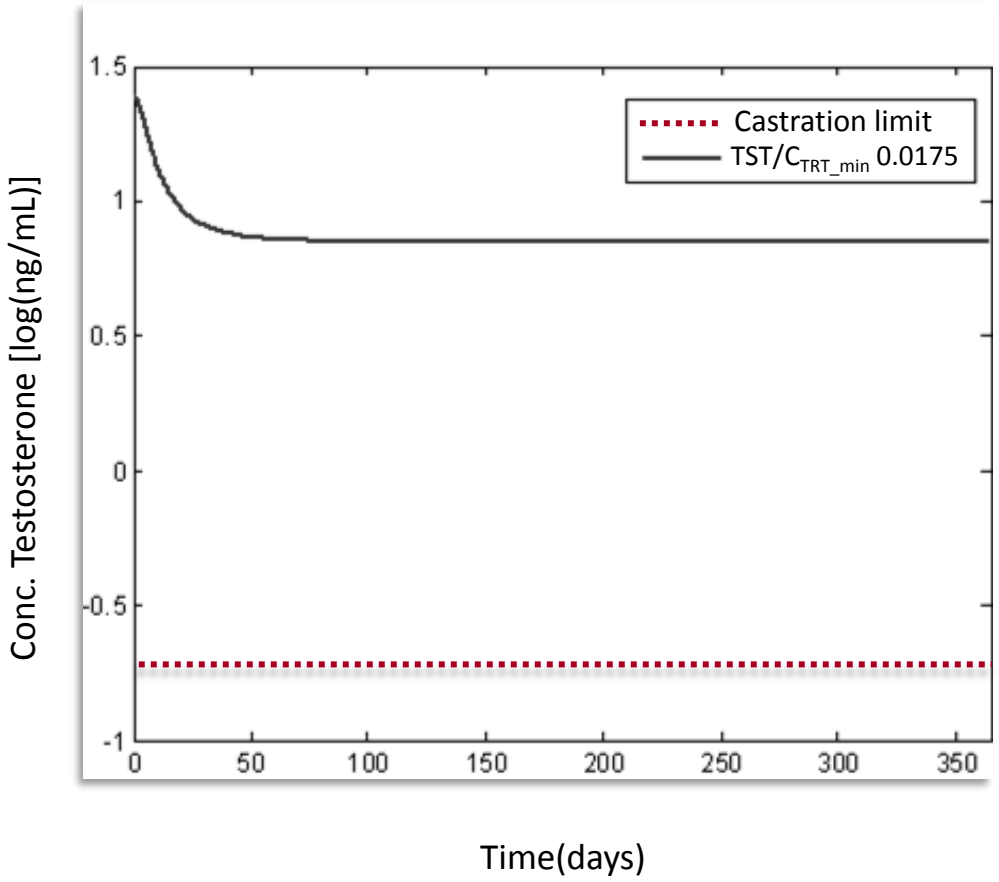
| | 95th | 0.0175 |
| | 5th | 0.0024 |
| **Microspheres** | 50th | **0.0048** |
| | 95th | 0.0106 |
| | 5th | 0.0078 |
| **Median** | 50th | **0.0175** |
| | 95th | 0.0379 |



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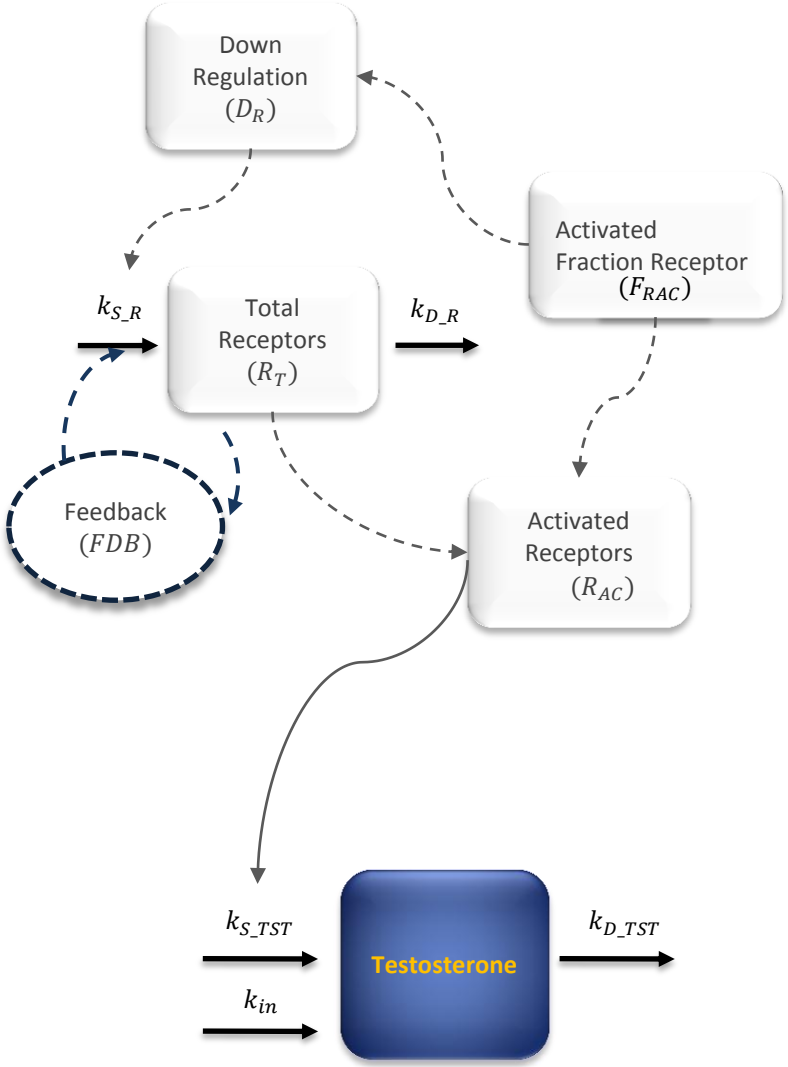
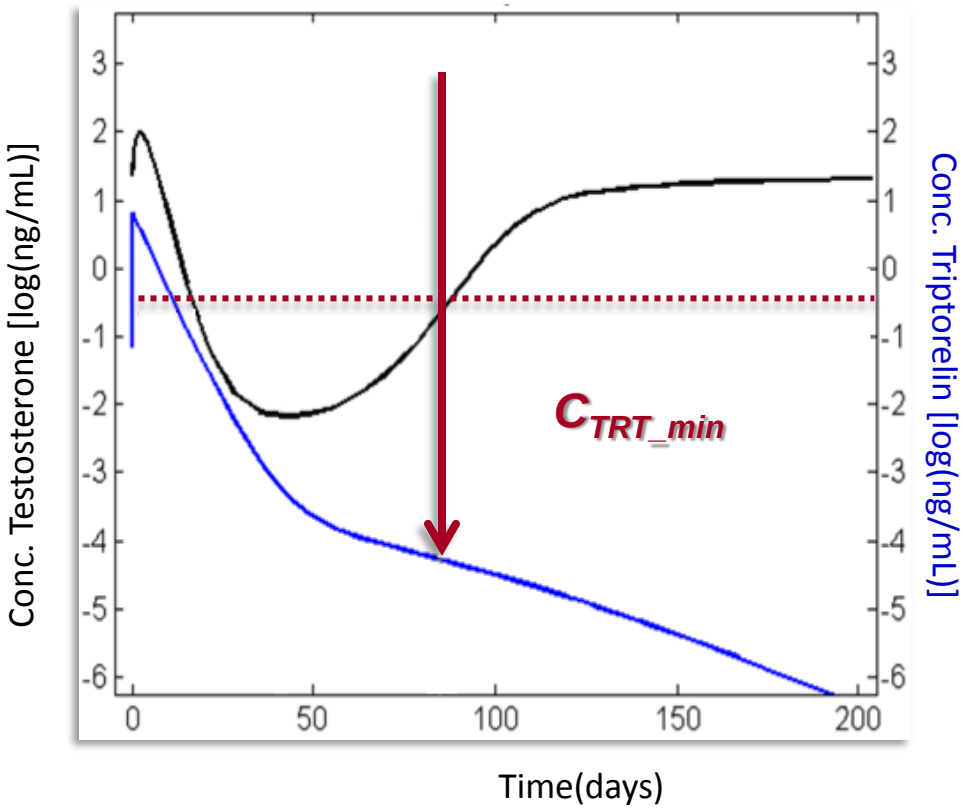


# Determination of $C_{TRT\_min}$

***Model based system analyses***

Determination of $C_{TRT\_min}$ value could be calculated solving the system of nonlinear equations

***TRT plasma concentration that makes TST to reach the castration level at steady state***

$$\frac{dR_T}{dt} = k_{S\_R} \times \frac{D_{R\_50}}{D_{R\_50} + \frac{AGN + \frac{C_{TRT}}{K_D}}{1 + AGN + \frac{C_{TRT}}{K_D}} - \frac{AGN}{1 + AGN}} \times \left(2R_T - {R_T}^2\right) - R_T \times k_{D\_R}$$

$$\frac{dTST}{dt} = k_{S\_TST} \times R_T \times \frac{AGN + \frac{C_{TRT}}{K_D}}{1 + AGN + \frac{C_{TRT}}{K_D}} + k_{in} - TST \times k_{D\_TST}$$

# Determination of $C_{TRT\_min}$

Determination of $C_{TRT\_min}$ value could be calculated solving the system of nonlinear equations

***To find what values fulfill a condition stated in the form of the equation***

$$k_{S\_R} \times \frac{D_{R\_50}}{D_{R\_50} + \frac{AGN + \frac{C_{TRT}}{K_D}}{1 + AGN + \frac{C_{TRT}}{K_D}} - \frac{AGN}{1 + AGN}} \times \left(2R_T - {R_T}^2\right) - R_T \times k_{D\_R} = \mathbf{0}$$

$$k_{S\_TST} \times R_T \times \frac{AGN + \frac{C_{TRT}}{K_D}}{1 + AGN + \frac{C_{TRT}}{K_D}} + k_{in} - TST \times k_{D_{TST}} = \mathbf{0}$$

***Testosterone concentration=castration level(0.5 ng/mL)***

# Determination of $C_{TRT\_min}$

Determination of $C_{TRT\_min}$ value could be calculate solving the system of nonlinear equations

***Replacement of typical values on equations***

$$0.185 \times \frac{0.024}{0.024 + \frac{0.31 + \frac{C_{TRT}}{0.931}}{1 + 0.31 + \frac{C_{TRT}}{0.931}} - \frac{0.31}{1 + 0.31}} \times \left(2R_T - {R_T}^2\right) - R_T \times 0.185 = 0$$

$$9.07 \times R_T \times \frac{0.31 + \frac{C_{TRT}}{0.931}}{1 + 0.31 + \frac{C_{TRT}}{0.931}} + 0.041 - 0.5 \times 0.55 = 0$$

***In order to solve a system where parameters are associate with subjects variability…***

# Determination of $C_{TRT\_min}$

By a computational methods to solve systems of nonlinear equations

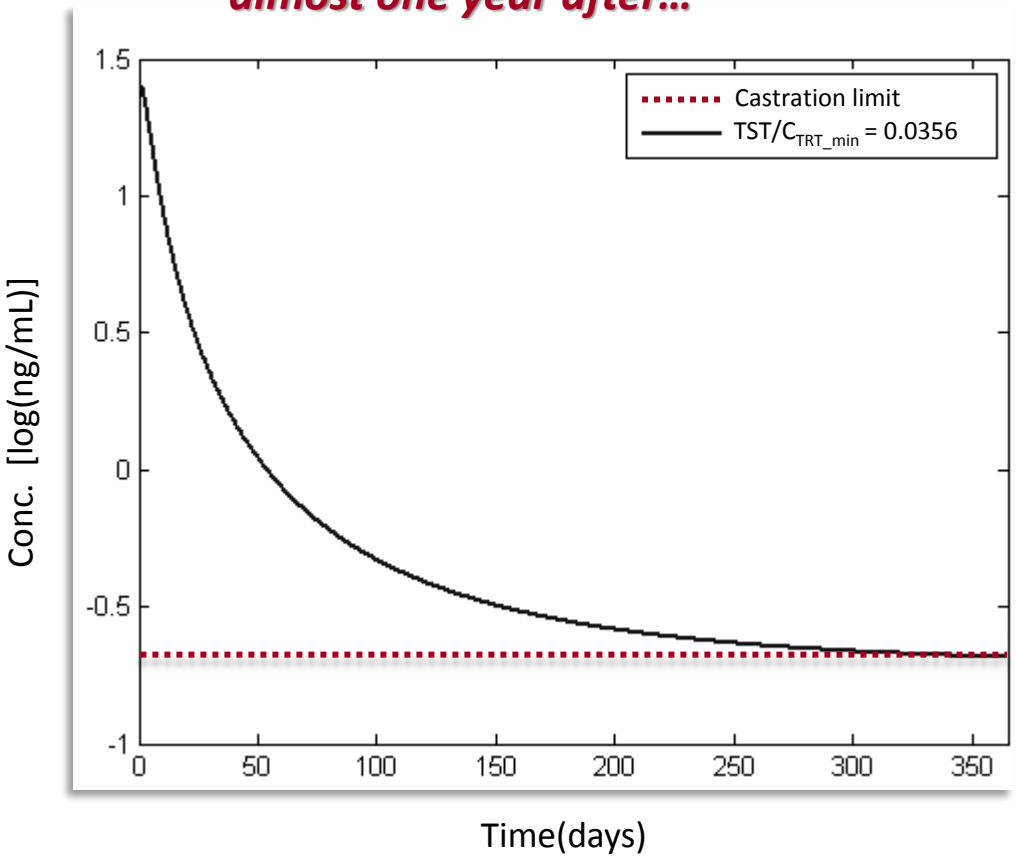
```
for i=1:numSimulations
    %Parameters
    eta_TST=random('norm',0,sqrt(0.1229));
    TST0=3.98*exp(eta_TST);

    eta_DR50=random('norm',0,sqrt(0.09834));
    DR50=0.024*exp(eta_DR50);

    eta_KDR=random('norm',0,sqrt(0.1029));
    KDR=0.185*exp(eta_KDR);

    eta_KIN=random('norm',0,sqrt(0.1279));
    KIN=0.041*exp(eta_KIN);

    KD=0.931;
    KDTST=0.55;
    AGN=0.31;

   [CP,RT]=Solve(system,parameters)

end
```

***10000 simulations of individual parameters were generated***

# Determination of $C_{TRT\_min}$

| Percentiles | $C_{TRT\_min}$ |
|---|---|
| 5th | 0.0204 |
| 50th | **0.0356** |
| 95th | 0.0609 |

***As an infusion of triptoreline castration level is achieved almost one year after…***



# Potential application of $C_{TRT\_min}$

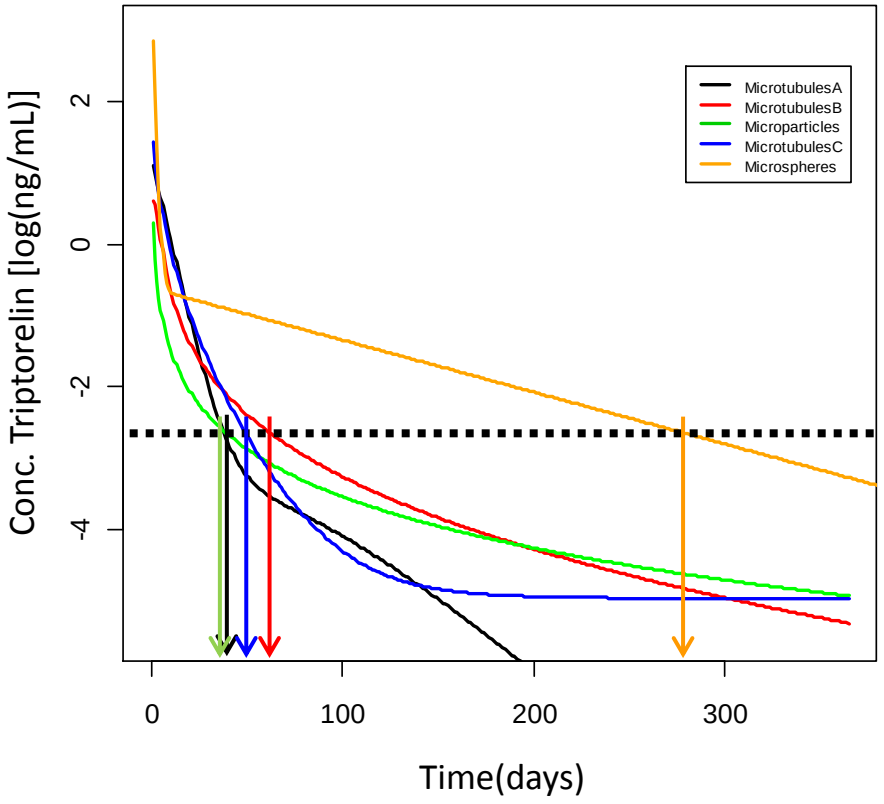
**Merging $C_{TRT\_min}$ with PK profiles to optimize time for a 2nd administration**

***To be certain that 95% of subject will be under castration levels***

| Percentiles | $C_{TRT\_min}$ |
|---|---|
| 5th | 0.0204 |
| 50th | 0.0356 |
| 95th | **0.0609** |

- Identification of the times required to achieve $C_{TRT\_min}$ values ($T_{TRT\_min}$)

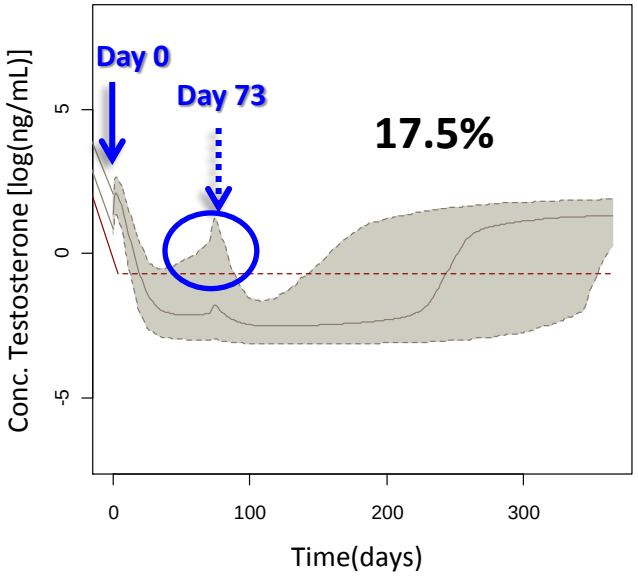
**Pharmacokinetic profiles**



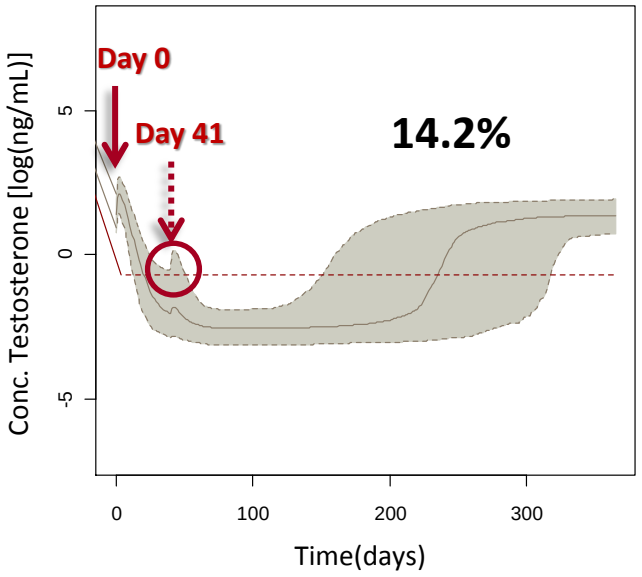
# Comparison of $C_{TRT\_min}$ formal vs. simulated approach

| Formulation | $T_{TRT\_min}$ | |
|---|---|---|
| | Simulated | Formal |
| $Microtubules_A$ | 73 | 41 |
| $Microtubules_B$ | 126 | 69 |
| Microparticles | 86 | 47 |
| $Microtubules_C$ | 88 | 53 |
| Microspheres | 535 | 294 |

**Simulated approach**




**Formal approach**



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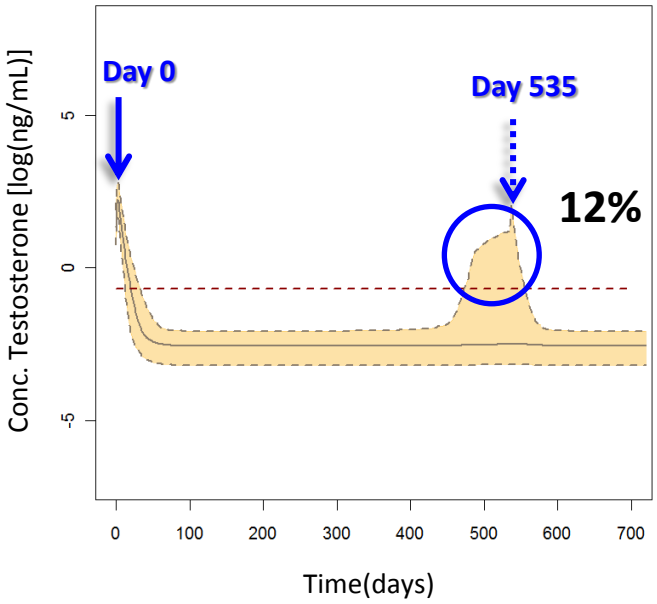
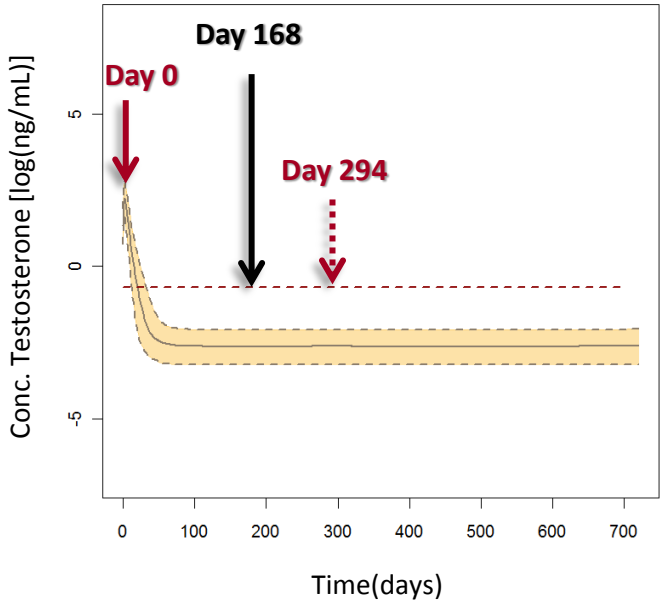



**Formal approach**



# Conclusions

- A semi-mechanistic model was implemented to describe the time-response of testosterone following treatment with triptorelin

- Model based system analyses is a tool that allows to explore complex models in order to extract relevant clinical information

# Acknowledgments

Thanks for their invaluable constructive critic

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Oscar Della Pasqua

Benjamin Ribba

Universidad de Navarra

CONACYT

National Council in Science and Technology, México

IPSEN Innovation for patient care

Ipsen Pharma/ Barcelona, Spain

University of Guadalajara, México