



PAGE 2015, Crete



PKPD modelling of the relationship between testosterone and PSA in patients with prostate cancer during treatment with leuprorelin

What is the optimal testosterone level?

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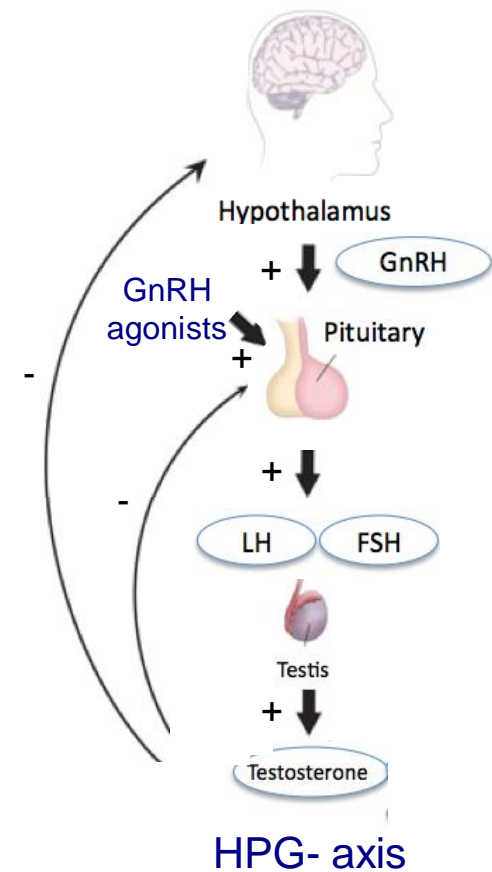
Introduction



- “ The main goal in the treatment of prostate cancer with gonadotropin-releasing hormone (GnRH) agonists is to achieve and maintain testosterone concentrations below castration level
 - “ Traditionally in Europe: 50 ng/dL
 - “ Proposed level: 20 ng/dL
- “ A relationship between testosterone and clinical outcome, i.e. survival is lacking
- “ Prostate Specific Antigen (PSA) serum concentrations are used as a surrogate marker for disease control in clinical practice
 - “ PSA serum levels above 4 ng/mL are considered an indication for prostate cancer

Leuprorelin

- “ Leuprorelin, a GnRH agonist, has been in clinical use for the treatment of prostate cancer for over 20 years in different long acting depot formulations
- “ GnRH agonist first stimulate the receptor (surge) and later down-regulate the receptor
- “ Due to receptor down regulation testosterone levels are reduced



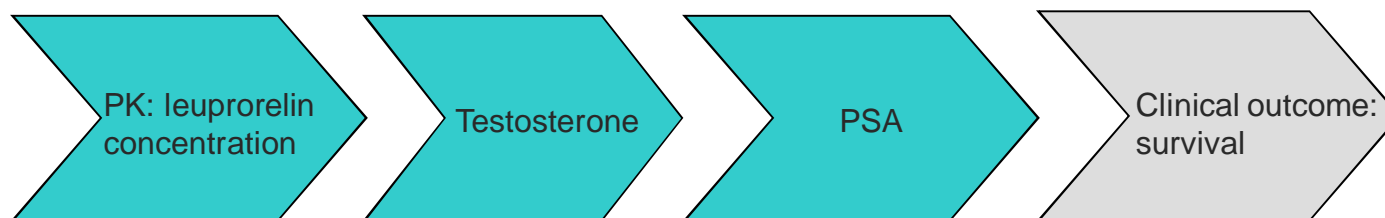
Objective and Approach

” Objective:

- ” Identification of a target testosterone concentration which optimizes the balance of the benefits of testosterone suppression whilst reducing the risks of futile over-suppression

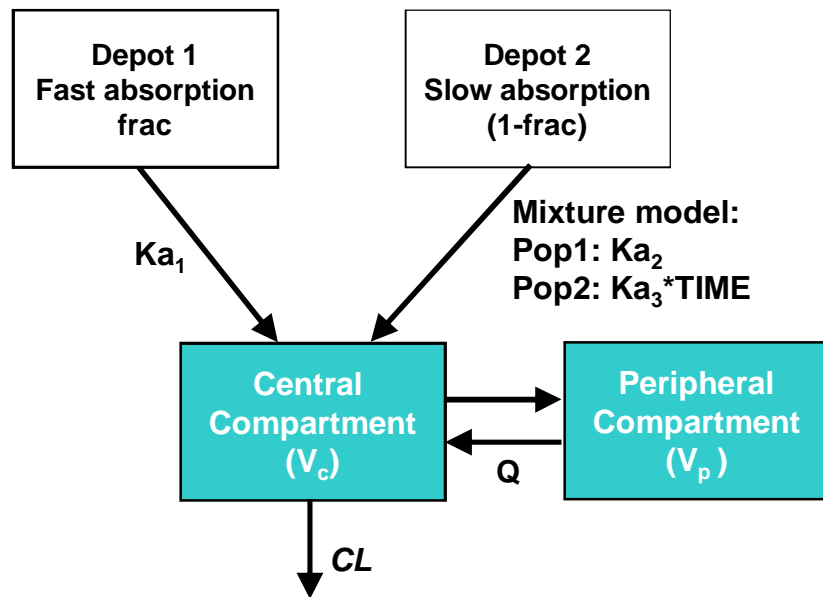
” Approach:

- ” Characterization of the relationship between leuprorelin, testosterone and PSA concentrations over time in a quantitative manner



Pharmacokinetics

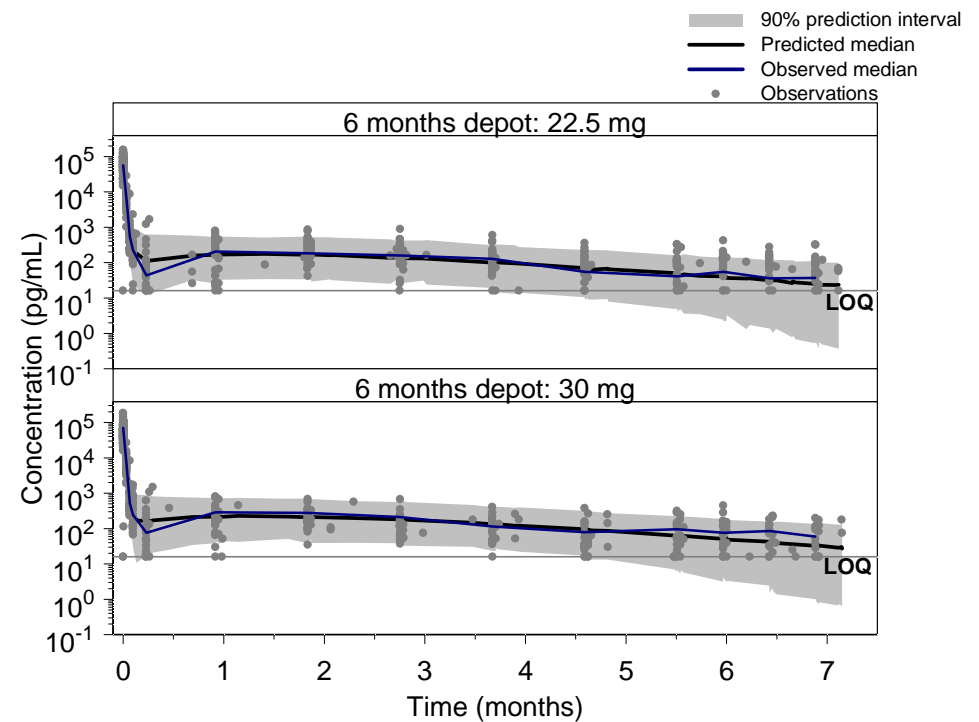
Population PK model



Stochastic model:

- “ IIV: CL , Ka_2 and Ka_3 , frac and relative bioavailability
- “ Proportional residual error

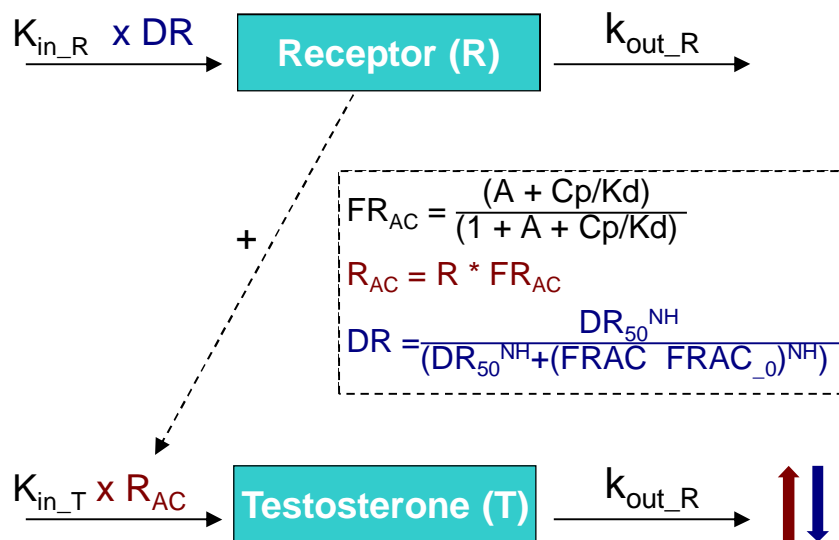
Adequate description of the data



Data from single dose study in patients with prostatic cancer
 6-month depot formulation: 22.5 and 30 mg

Testosterone

Population testosterone model

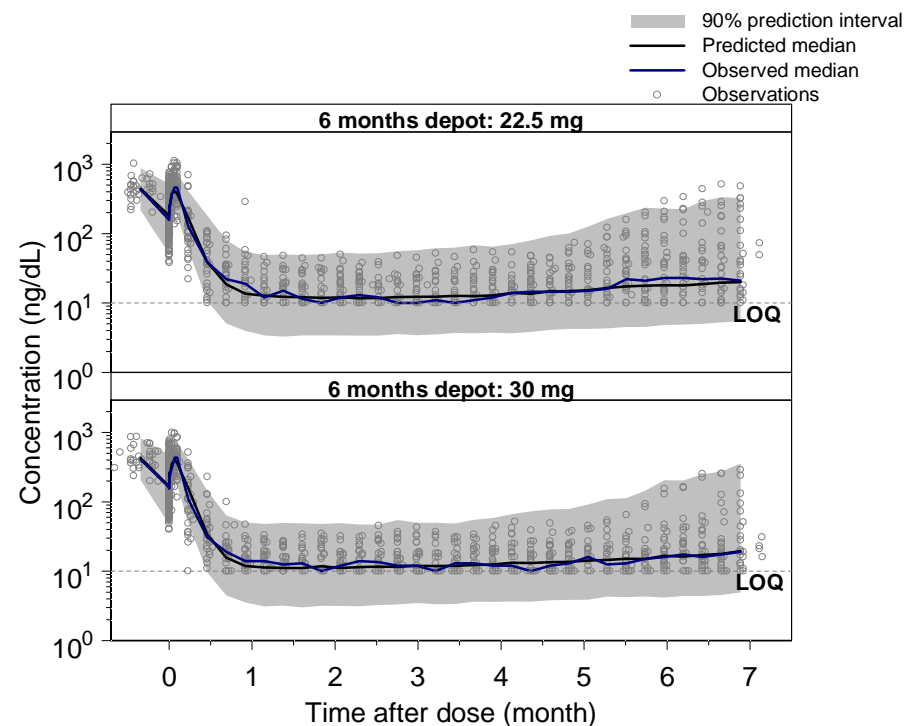


Cp: leuprorelin concentration; Kd: dissociation constant
A: endogenous GnRH concentration over Kd

Stochastic model:

- ~ IIV: DR_{50} , Kd , K_{out_R} , BSL_T , NH , CPA
- ~ Proportional residual error

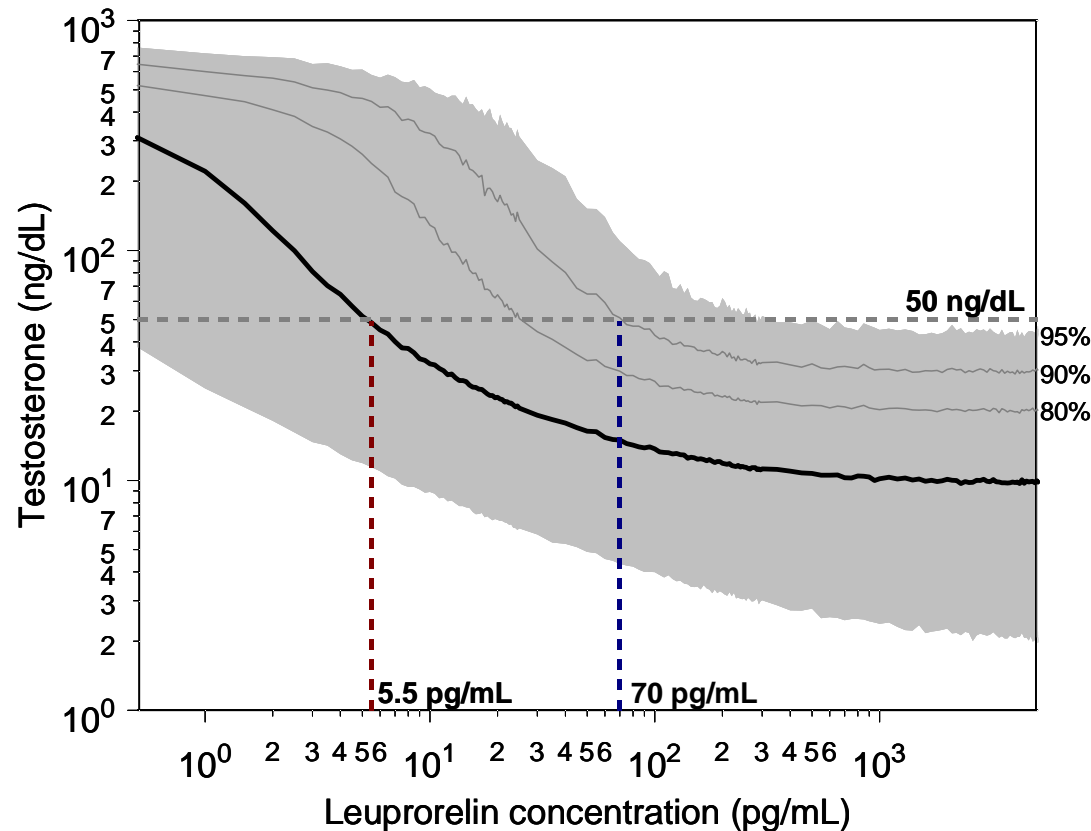
Adequate description of the data



Cyproterone effect: initial decrease
Agonistic effect: testosterone surge
Receptor down regulation: testosterone suppression

Testosterone

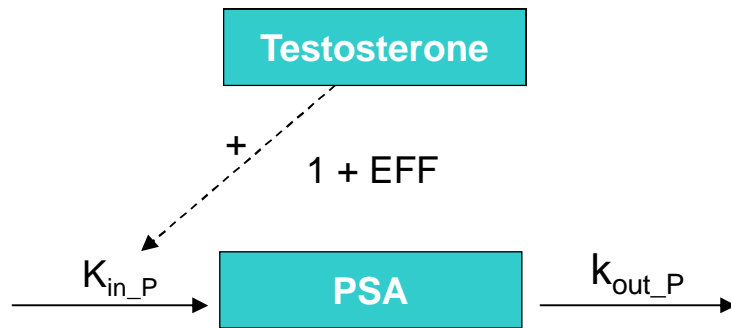
Steady-state concentration-effect relationship



- “ Testosterone concentrations <50 ng/dL in 50% of the subjects are reached for leuporelin concentrations > **5.5 pg/mL**
- “ Testosterone concentrations <50 ng/dL in 90% of the subjects are reached for leuporelin concentrations > **70 pg/mL**

PSA

Population PSA model

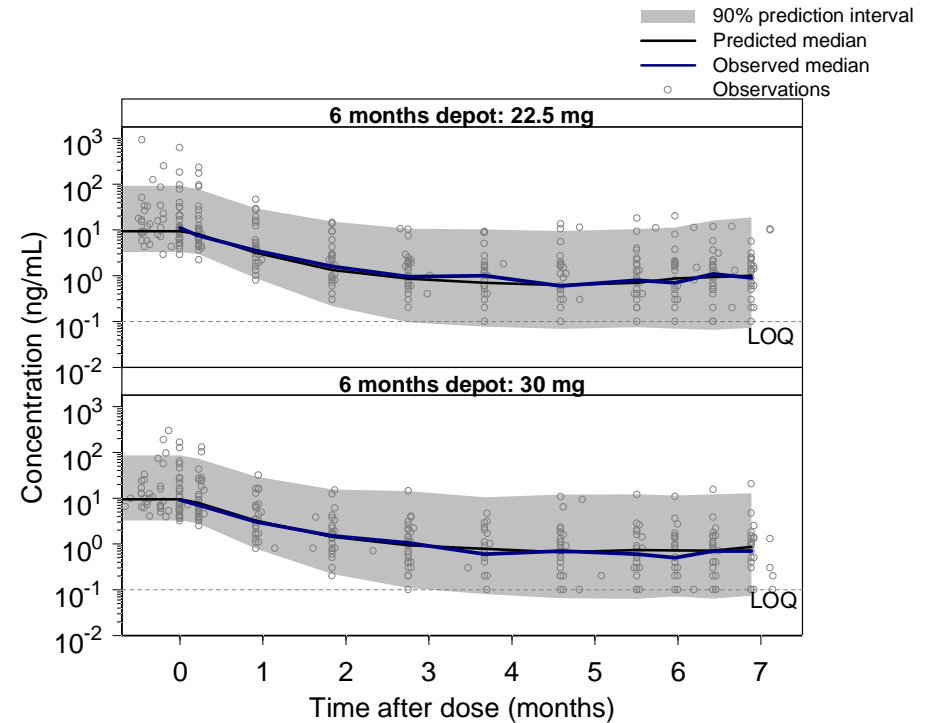


EFF: Sigmoid E_{max} model

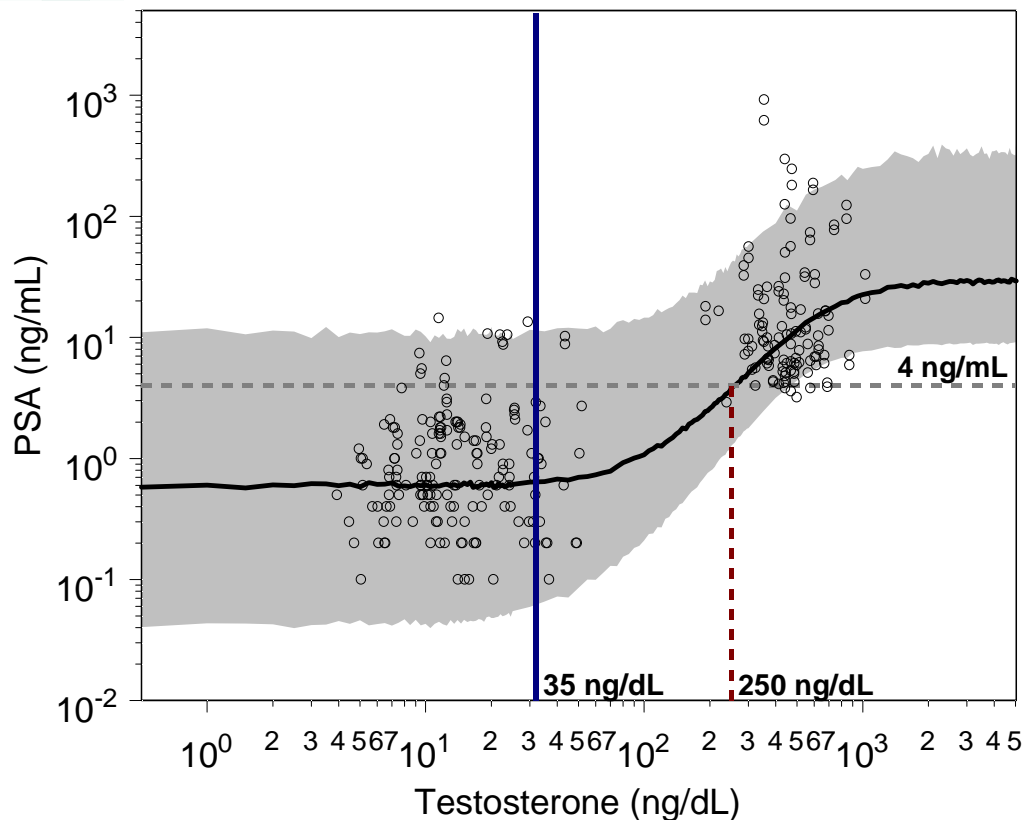
Stochastic model:

- ~ IIV: E_{max} , EC_{50} , NH , K_{out_P} , BSL_P
- ~ Proportional residual error

Adequate description of the data



Predicted steady-state PSA levels *versus* testosterone



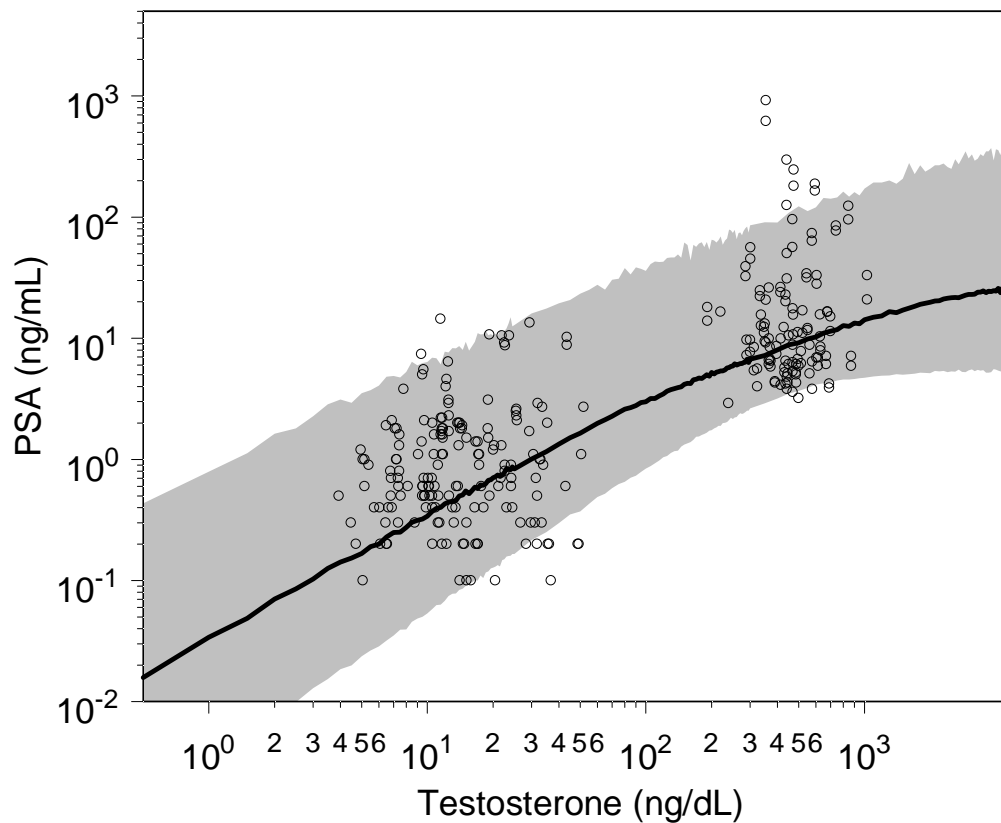
Reducing testosterone concentrations below **35 ng/dL** does not result in a further reduction of PSA levels (>95% of the minimal PSA level)

To reach PSA levels below **4 ng/mL** at steady state:

- “ in 50% of the subjects, testosterone concentrations should be lower than **250 ng/dL** at steady state
- “ in 80% of the subjects, testosterone concentrations should be lower than **130 ng/dL** at steady state (not shown)
- “ in 90% of the subjects: not reached. Subjects with a high baseline show a large decrease in PSA, but do not reach PSA < 4 ng/mL

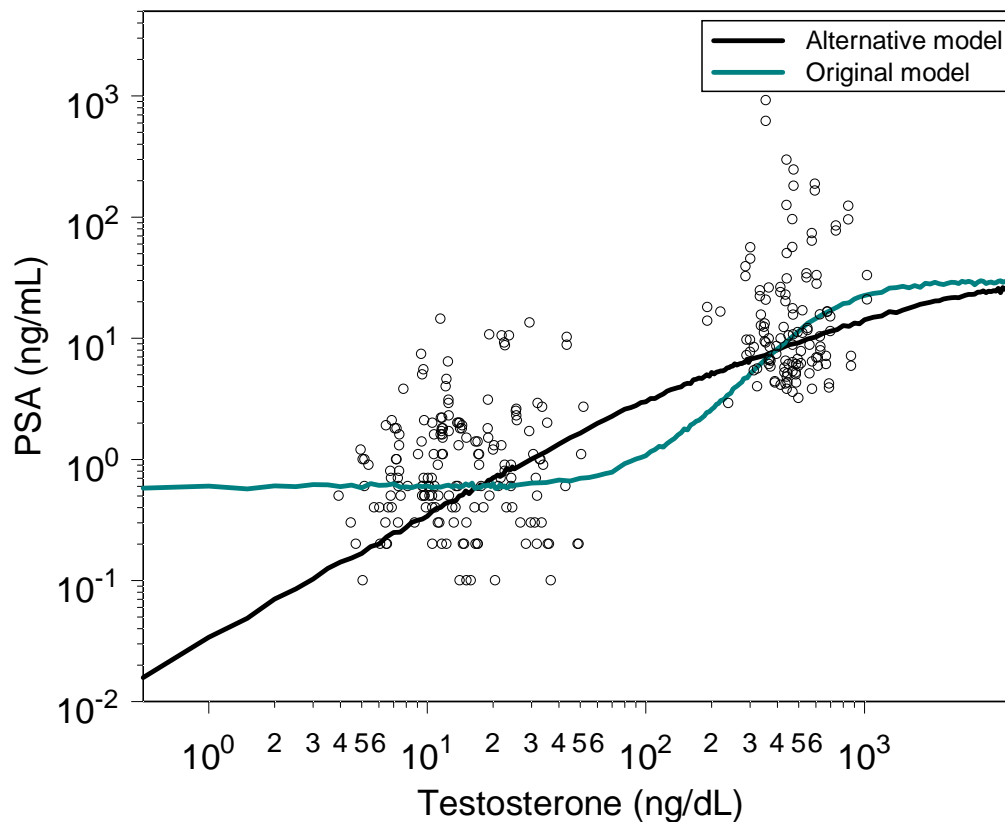
Alternative model results in a different prediction of the relationship between testosterone and PSA

PSA goes to zero when testosterone goes to zero



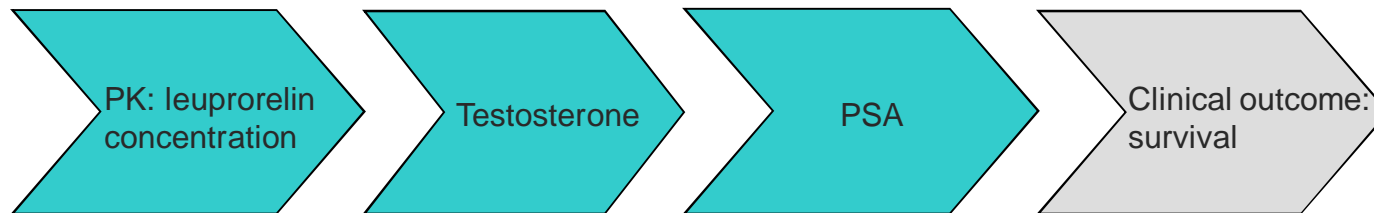
“ There are more observations above the predicted median than below

Steady-state and dynamic PSA data better described by the original model



- “ The original model predicts the steady-state observations better
- “ More data is required to further support this relationship in the lower testosterone and PSA range
- “ Testosterone is produced by the testes and adrenal glands.
 - “ Testosterone suppression via the HPG-axis will only inhibit the testosterone production by the testes

Conclusions and Future Perspectives



- “ The model-based analysis suggests that reducing testosterone concentrations below **35 ng/dl** does not result in a further decrease in PSA levels
 - “ Lower testosterone levels could be related to certain side effects
- “ Future research: quantification of the relationship between PSA levels and survival

