

Development of a drug-disease model describing individual IPSS trajectories in BPH patients:



Implications of disease progression and covariate factors on long term treatment response

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Background

Lower Urinary Tract Symptoms (LUTS) caused by Benign Prostatic Hyperplasia (BPH) are typically measured by the International Prostate Symptom Score (IPSS). Whilst changes in IPSS provides information on LUTS improvement as well as deterioration, little attention has been given to individual IPSS trajectories [1, 2]. Instead, current practice considers changes relative to baseline as a measure of BPH progression. The current investigation aimed to develop and validate a drug-disease model describing individual IPSS trajectories in moderate and severe LUTS/BPH patients receiving placebo, dutasteride, tamsulosin or combination treatment (FDC). Simulations were then performed to assess the impact of the underlying disease progression and covariate factors on the deterioration of symptoms, disentangling it from the drug effects.

Methods

DATA: A meta-analytical approach was used including pooled data from moderate and severe LUTS/BPH patients (N=10238) enrolled into six dutasteride clinical trials [3-6]. To ensure that patient and disease-specific fluctuations in trajectory were disentangled from treatment-specific changes, individuals treated only with placebo were used for model development.

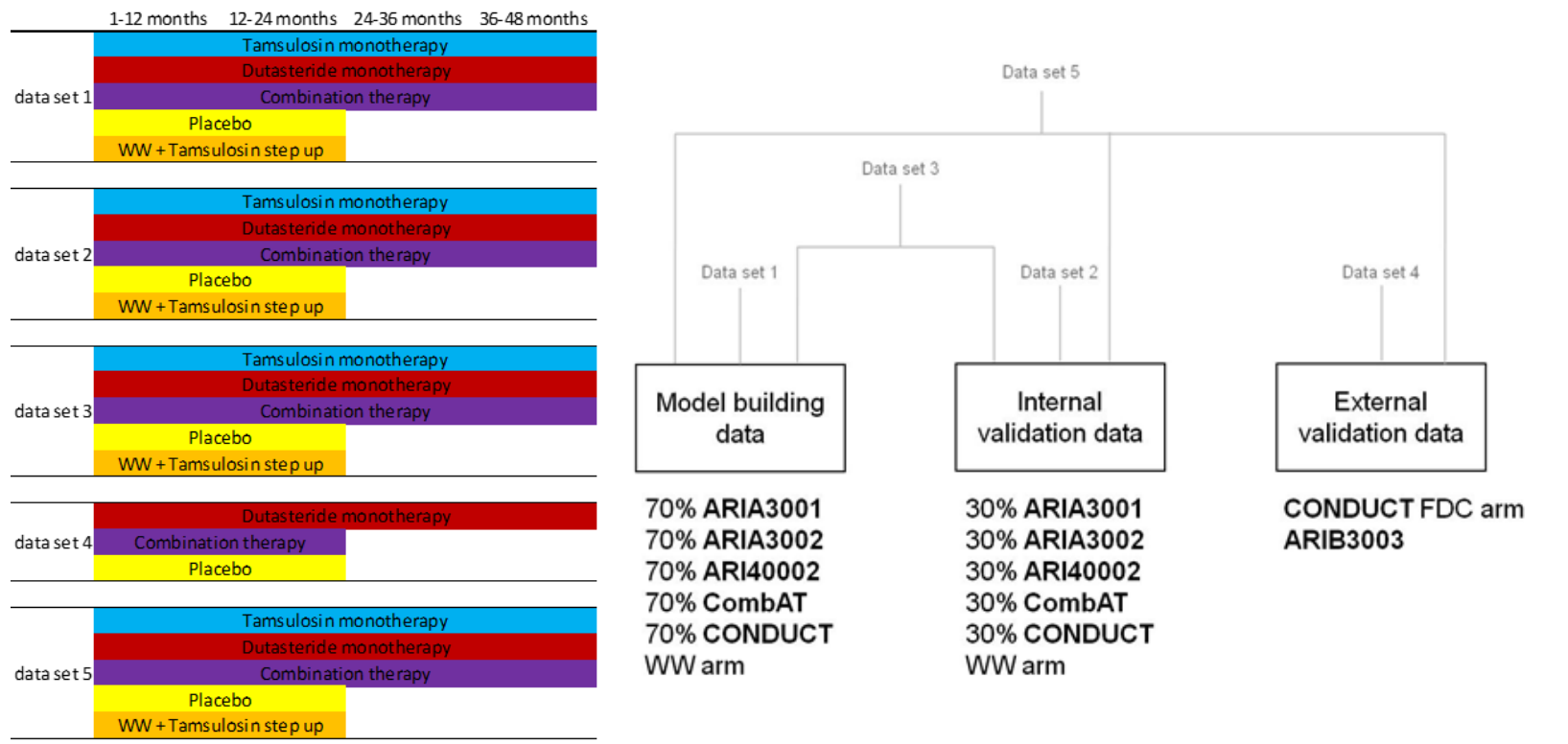


Figure 1. (Left) Diagram summarising the treatment duration and interventions associated with each data set included in the analysis. (Right) Data set 1: model building data set. Data set 2: internal validation data set. Data set 3: model building + internal validation data set. Data set 4: external validation data set. Data set 5: overall population data set from all six studies. WW = watchful waiting.

MODEL DEVELOPMENT AND VALIDATION: A nonlinear mixed effects model was developed, in which disease specific characteristics were parameterised independently from drug effects. Consequently, treatment response was evaluated as a covariate on the parameter describing the underlying disease progression, as defined by a Gompertz function. Standard graphical and statistical methods were used for model building, covariate selection and evaluation. Predictive performance was assessed using internal and external validation procedures. All modelling and simulation steps were implemented in NONMEM v7.2

$$\frac{d(IPSS)}{dt} = \left(DISP \cdot \left(1 - \frac{IPSS}{35} \right) \right) - ((PLACEBO + TREATMENT) \cdot IPSS)$$
$$PLACEBO = DELTA_{placebo} \cdot e^{-TIME \cdot \frac{\ln(2)}{T_{1/2}}}$$
$$TREATMENT = DELTA_{treatment}$$

The term d(IPSS)/dt represents the rate of change (i.e., derivative) in IPSS. DISP represents the coefficient describing the fluctuation and increase in IPSS (i.e., the disease progression rate). The DELTA term represents the relative drop from baseline and $T_{1/2}$ is the half-life of placebo, expressed as the time required to halve the effect by 50%. The effect of any intervention was parameterised in an additive manner to the underlying disease progression and placebo effect.

SIMULATION SCENARIOS: Simulations were performed using the final model to investigate how individual parameter estimates, treatment and covariate factors affect individual IPSS trajectories. Individual IPSS vs. time profiles were simulated for a virtual BPH population including baseline characteristics resampled from the original clinical studies. Mean profiles along with 95%-CI were used to illustrate the effect of combination therapy in patients with varying disease progression rates. For the purposes of our analysis, clinical response was defined as change in IPSS $\geq 25\%$ relative to baseline.

Results

Despite considerable noise in IPSS measurements, individual IPSS trajectories were accurately described by a Gompertz function. Interindividual variability was identified for the parameters describing the zero-order disease progression parameter as well as the magnitude and half-life of placebo effect. Covariate factors (namely, baseline IPSS, BMI, duration of symptoms and alcohol user status) were found to affect both the parameters describing the disease progression and placebo effect. Residual variability in IPSS was described by a proportional and additive error model. Model parameters and bootstraps estimates are shown in Table 1. Correlation matrix including clinical and demographic characteristics, observed and predicted individual trajectories, goodness-of-fit plots, visual predictive check and post-predictive check for the responder rate at 48 months are shown in figures 2 and 3, respectively.

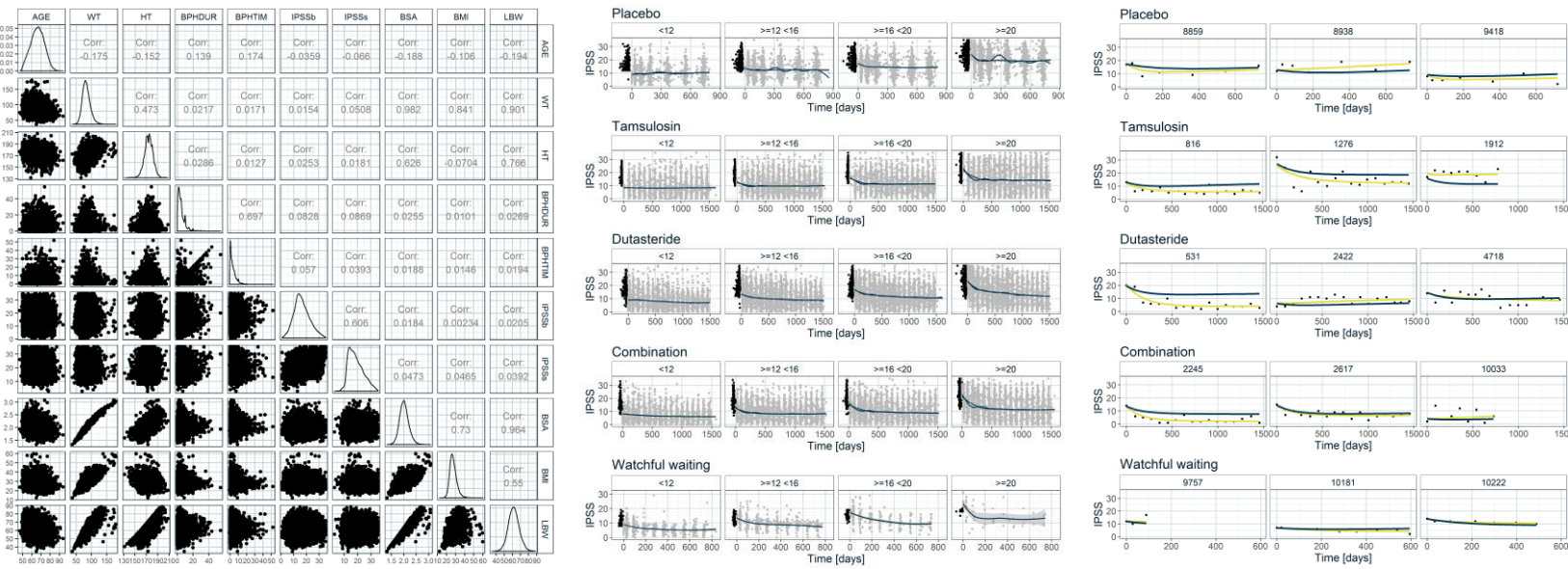


Figure 2. (Left) Correlation matrix between baseline clinical and demographic characteristics included in the covariate analysis. Diagonal items show the underlying data distribution. Figures in the off-diagonal elements indicate the degree of correlation or lack thereof. (Middle) Mean IPSS trajectory over time (solid line) and corresponding data distribution (dots) after treatment with placebo, tamsulosin, dutasteride, combination therapy and watchful waiting stratified by IPSS quartiles at baseline. (Right) Random selection of individual IPSS measurements along with model-predicted trajectories; blue and yellow lines represent population and individual predictions, respectively.

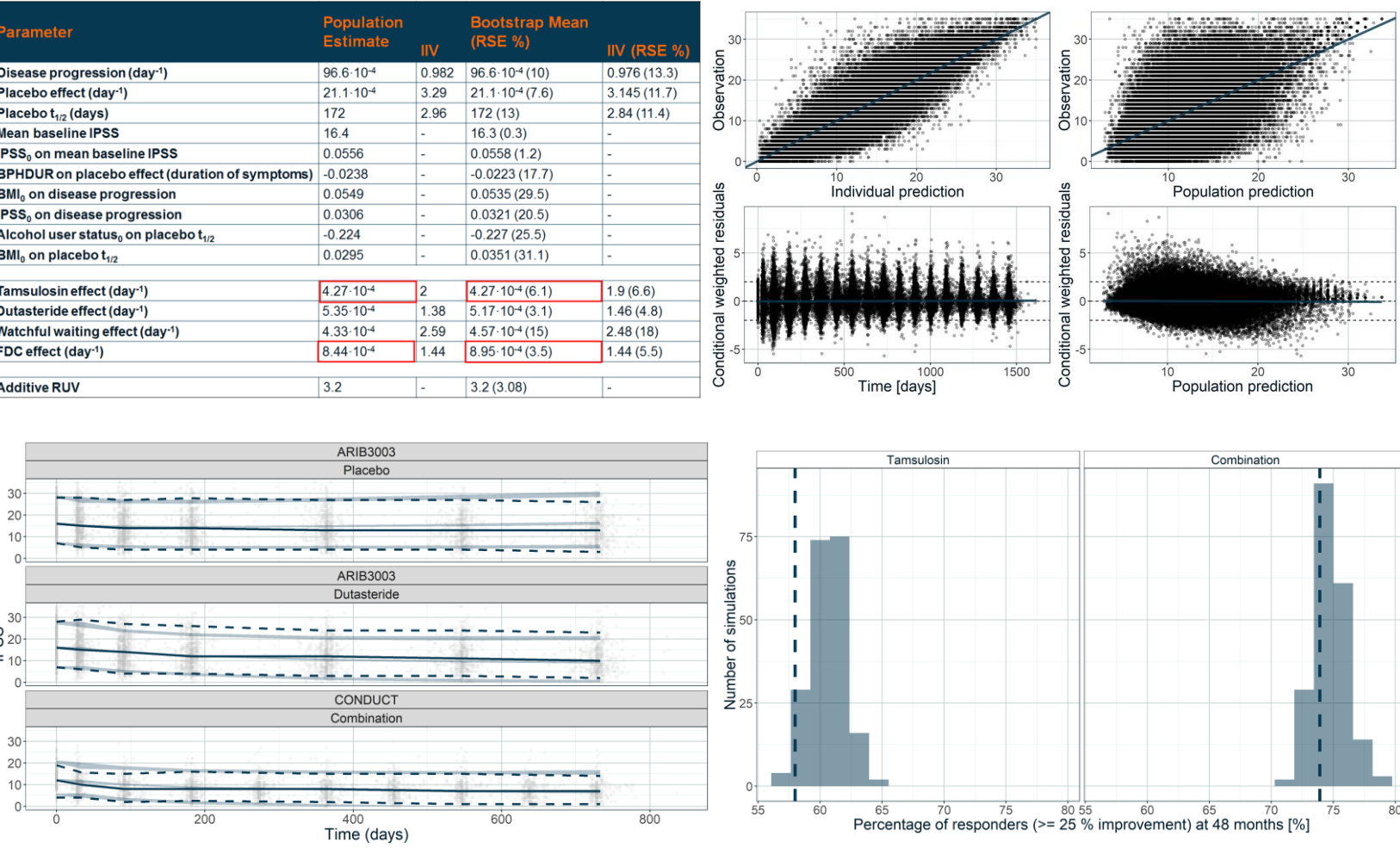


Figure 3. (Top left) Table 1. Model parameters and bootstrap estimates. (Top right) Goodness-of-fit plots for the final model. (Bottom left) Predicted vs. observed trajectories in arms included in the external validation. (Bottom right) Posterior predictive checks of treatment response for the CombAT.

Simulations showed that treatment response, as assessed by changes in IPSS relative to baseline, is determined predominantly by the interaction between the underlying disease progression rate, placebo and treatment effects, with baseline IPSS as a covariate factor. Consequently, it is not possible to distinguish the individual contribution of each factor when describing response based on changes relative to baseline (Figure 4). Our results also indicate that individual IPSS trajectories may be clustered according to the underlying rate of progression (i.e., fast, moderate, slow progressing phenotypes). No other independent prognostic baseline factor could be identified as a predictor of the individual trajectories or response to treatment.

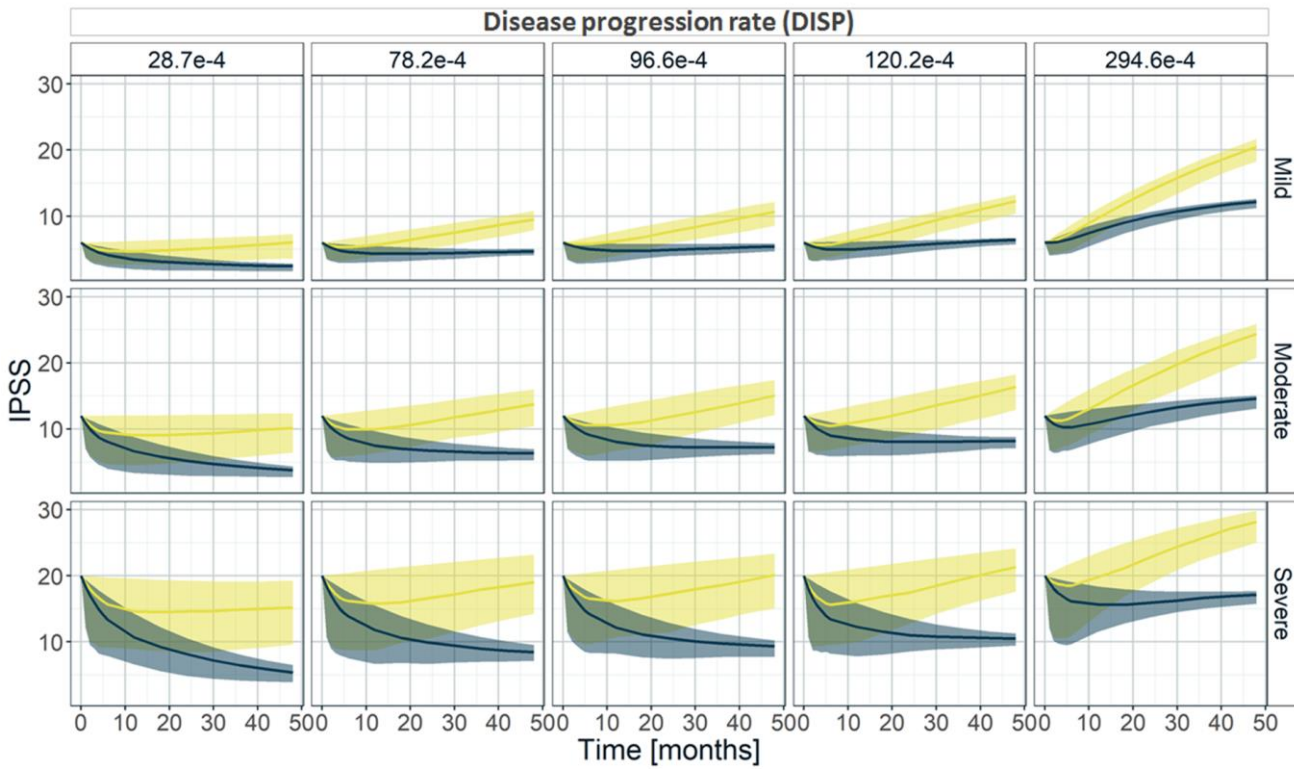


Figure 4. Impact of symptomatic and disease modifying properties of the combination therapy on the individual IPSS trajectories in patients with varying disease progression rates. DISP values from left to right represent, respectively the 2.5th, 25th, 50th, 75th and 97.5th percentiles of the parameter distribution. Panels are stratified by symptom severity, as defined by IPSS values at baseline. Solid lines are mean predicted trajectories; shaded areas represent the 95% prediction interval (n=200 simulations). In yellow are the predicted trajectories under the assumption of a hypothetical scenario in which patients remain untreated despite deterioration of symptoms, whereas in blue are the predicted trajectories following combination therapy.

Conclusion

Individual IPSS trajectories can be characterised by a longitudinal model, disentangling the contribution of the underlying disease progression from both placebo and treatment effects. In addition, it appears that the magnitude of the effect of the combination therapy on the parameters describing the initial improvement and slowly progressive changes in IPSS is twice that of tamsulosin alone (Table 1). Furthermore, our simulations also shed light into the factors that explain interindividual differences in the rate of disease progression and consequently in the deterioration of symptoms in patients with moderate and severe LUTS/BPH.

References

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Conflict of interest

This investigation was sponsored by GlaxoSmithKline. All authors are employees of GSK and own stock/stock options in the company. There are no other conflicts of interest. S. D'Agate is affiliated with UCL and has performed consultancy work for GSK.