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ORIGINAL ARTICLE

Model-based meta-analysis of individual International Prostate Symptom Score trajectories in patients with benign prostatic hyperplasia with moderate or severe symptoms

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Aims: International Prostate Symptom Score (IPSS) is a marker of lower urinary tract symptoms (LUTS) deterioration or improvement in benign prostate hyperplasia (BPH). Whereas changes in IPSS relative to baseline have been used as endpoints in clinical trials, little attention has been given to the time course of symptoms. The current investigation aimed to develop a drug-disease model to describe individual IPSS trajectories in moderate and severe BPH patients.

Methods: A model-based meta-analytical approach was used including data from 10 238 patients enrolled into Phase III and IV studies receiving placebo, tamsulosin, dutasteride or combination therapy over a period of up to 4 years. Model predictive performance was assessed using statistical and graphical criteria. Subsequently, simulations were performed to illustrate the implications of treatment with drugs showing symptomatic and disease-modifying properties in patients with varying disease progression rates.

Results: Improvement and worsening of IPSS could be characterized by a model including a sigmoid function which disentangles drug effects from placebo and varying disease progression rates on IPSS. Mean estimate (95% confidence intervals) for the disease progression rate was 0.319 (0.271–0.411) month^{-1}. Treatment effect on IPSS (DELTA) was found to be 0.0605, 0.0139 and 0.0310 month^{-1} for placebo, tamsulosin and combination therapy, respectively. In addition, it appears that individual trajectories can be clustered together into different phenotypes describing the underlying disease progression rate (i.e. slow, moderate and fast progressors).

Conclusions: The availability of a drug-disease model enables the evaluation of inter-individual differences in disease progression rate, deterioration of symptoms and treatment effects on LUTS/BPH.

KEYWORDS
benign prostatic hyperplasia, disease modelling, disease progression, dutasteride, International Prostate Symptoms Score, lower urinary tract symptoms, tamsulosin

1 | INTRODUCTION

Benign prostatic hyperplasia (BPH) is characterized by growth of both epithelial and stromal tissues in the prostate. It is common among aging males with a reported prevalence of up to 50% and 80% in the fifth and eighth decades of life, respectively.[1,2] Lower urinary tract symptoms (LUTS)/BPH management is aimed at achieving two goals: (a) improving LUTS and (b) reducing the risk of disease progression (in terms of symptoms and/or complications such as acute urinary retention or surgery). Whilst it is recognized that increasing severity and progression of symptoms have a significant impact on the quality of life (QoL) of patients, it is difficult to predict the deterioration of LUTS in individuals.

Among the available treatment options, conservative management (ie, education, reassurance, lifestyle advice, periodic monitoring) or interventions with drugs are frequently used in clinical practice without assessing the likelihood of LUTS deterioration for a given patient. Conservative treatment is recommended by both the American Urological Association (AUA) and the European Association of Urology guidelines for patients with mild LUTS/BPH (International Prostate Symptom Score [IPSS] < 8), or moderate-to-severe symptoms with low QoL impairment.[3,4] However, this strategy is less appropriate for patients with moderate or severe LUTS/BPH, at risk of disease progression or with existing complications due to bladder outlet obstruction related to BPH (ie, benign prostatic obstruction). The use of combination therapy, including an α-blocker (**tamsulosin**) and a 5α-reductase inhibitor (**dutasteride**), has proven to be effective for the management of these patients. Currently, this drug treatment is also available as a once-daily fixed-dose combination. Evidence from clinical trials shows that combination therapy significantly reduces the risk of BPH disease progression compared with monotherapy in moderate-to-severe patients (CombAT study),[5] and in treatment-naïve patients with moderate symptoms compared with watchful waiting with protocol-defined initiation of tamsulosin monotherapy in patients whose symptoms did not improve (CONDUCT study).[6]

Traditionally, LUTS have been measured using the standardized and validated IPSS questionnaire, which captures and quantifies the severity of storage and voiding symptoms for a recall period of 4 weeks. The IPSS was developed as a screening tool combining seven symptom questions and one QoL question for fast symptom assessment to guide LUTS management in patients with LUTS/BPH.[7] The IPSS was designed to be easily and quickly self-administered by the patient and, consequently, it can be used in both urology clinics and primary care settings. In addition to its role in the assessment of LUTS and charting of disease progression, the IPSS is effective in helping to determine treatment options for patients. Moreover, the IPSS can be used to evaluate the progression and severity of LUTS over time. In fact, the primary efficacy endpoint in most clinical trials is defined in terms of change in IPSS relative to baseline.

On the other hand, mean IPSS values have been used as prognostic risk factors for disease progression regardless of ongoing or prior pharmacological treatment. This approach may not accurately predict an individual patient's treatment response because it is difficult to separate the placebo effect and the progressive nature of the disease from the actual pharmacological effect. Here we describe the methodology used to develop and evaluate a longitudinal model aimed at the characterization of the individual IPSS trajectories of patients affected by LUTS/BPH following treatment with placebo, tamsulosin, dutasteride or tamsulosin-dutasteride combination therapy. The goal of this analysis was to identify a mathematical function that reflects progression (improvement or deterioration) of LUTS over the course of treatment, taking into

What is already known about this subject

- Large interindividual variability is observed in lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH).
- Whereas treatment response (symptomatic improvement) can be assessed by a standardized questionnaire, the International Prostate Symptom Score (IPSS), there is limited understanding of individual phenotypes associated with the progression of disease (symptomatic deterioration).

What this study adds

- This model-based meta-analysis shows that individual IPSS trajectories are affected by both treatment-related effects and disease progression rate.
- In addition to the identification of baseline covariates affecting IPSS trajectories, our results provide insight into the factors that explain interindividual differences in the deterioration of symptoms, allowing for the distinction of different phenotypes.
- It can be anticipated that the use of a model-based algorithm may provide a basis for prediction of the disease progression rate and individual response to different interventions in patients with moderate or severe BPH symptoms.

account the potential effect of disease- or medication-related covariate factors and any placebo effect.

Analogously to epidemiological research on natural history and disease burden, the use of longitudinal models provides a parametric representation of time-varying disease characteristics. In fact, numerous longitudinal studies of the natural time course of disease were conducted in the 1970s,[8,9] a trend that has continued despite the challenges in obtaining information from untreated patients as new drugs have become available in numerous therapeutic indications. Consequently, the evaluation of drug effects on disease trajectory has represented an important advancement not only for clinical pharmacology, but also for drug development.[10,11]

It can be anticipated that the availability of a longitudinal model, including parameters describing inter- and intra-individual variability, may allow the assessment of the impact of different treatment scenarios on LUTS and consequently the course of clinical symptoms. Such a parameterization may also unravel correlations or interactions between treatment and baseline characteristics that could be considered predictors of individual IPSS trajectories. In addition, model parameter estimates obtained from this retrospective analysis of clinical trials with varying treatment durations may be used subsequently in conjunction with clinical trial simulations to evaluate the potential benefit of early versus delayed onset of treatment with combination therapy.

2 | MATERIALS AND METHODS

2.1 | Data source

The data used for this analysis were obtained from six clinical trials of dutasteride (ARIA3001, ARIA3002, ARI40002, CombAT, CONDUCT and ARIB3003) and include 140 733 clinical observations from 10 238 participants who were randomized to placebo, watchful waiting with protocol-defined initiation of tamsulosin 0.4 mg or dutasteride 0.5 mg once-daily monotherapy, or immediate oral tamsulosin-dutasteride combination therapy for up to 4 years. A total of 3790 patients received dutasteride over 2 or 4 years (ARIA3001, ARIA3002, CombAT, ARIB3003) and 2143 patients received tamsulosin-dutasteride combination therapy over 2–4 years (ARI40002, CombAT, CONDUCT). Placebo was received by 2158 participants for 2 years (ARIA3001, ARIA3002, ARIB3003). With the exception of CONDUCT, all study protocols included a placebo run-in phase. An overview of baseline demographic characteristics, along with the actual doses, regimens and eventual deviations is shown in Table 1, where the efficacy population is summarized along with the original treatment details in the clinical study protocols. See the Supporting Information for details on the analysis populations and preparation of the data sets used during model development and validation (Table S1 and Figure S1). A

TABLE 1 Demographics and baseline characteristics of the pooled patient population included in the meta-analysis

Baseline demographics	*N*	Mean	SD	Median	Minimum	Maximum
Age (y)	10 236	66.2	7.2	66	47	94
Body weight (kg)	10 206	83.2	13.6	82	37	179
Height (cm)	10 204	174.1	7.48	175	132	208
BMI (kg/m^2)	10 210	27.44	3.99	26.91	12.36	59.73
Baseline PSA (ng/mL)	10 206	3.98	2.1	3.4	0.6	23.2
Baseline prostate volume (cm^3)	9875	54.5	23	48.6	16.6	296.9
Baseline IPSS	10 228	16.48	6.1	16	1	35
Baseline maximum urinary flow (mL/s)	9163	10.5	3.6	10.2	2.2	36.2
Duration of BPH symptoms (y)	9881	5.17	4.77	4	0	54.8
Time from BPH diagnosis (y)	10 080	2.65	4.26	2.3	0.58	52
Alcohol use (Y/N)	6198/3992					
Sexually active (Y/N)	7244/2984					
Race (white/black/Hispanic/Asian)	9268/229/276/374					
Smoking status (Y/N)	1239/8998					

Treatment information	Placebo	WW	Tamsulosin	Dutasteride	Combination therapy
Total number of patients	2158	373	1611	3790	2143
Treatment duration:					
≤12 months	475	44	180	659	610
≤18 months	638	60	296	872	694
≤24 months	2158	373	381	1181	940
≤36 months	2158	373	536	1625	1125
≤48 months	2158	373	1611	3790	2143

Abbreviations: BMI, body mass index; BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; SD, standard deviation; WW, watchful waiting.

schematic diagram of different subsets of the aggregated data set is presented in Figure 1.

As the clinical trials included in this meta-analysis have been previously published and the current investigation remains within the scope of the consent given by participants, additional approval by an ethics committee was not required.

2.2 | Parameterization of IPSS trajectory, model evaluation and refinement

The longitudinal model describing individual IPSS trajectories and symptom deterioration and/or improvement over time was developed using a sigmoid function (Equation 1). Despite the discrete nature of the IPSS data, the analysis was implemented by treating IPSS as a continuous scale. Treatment effect was then parameterized in addition to the placebo intervention[12] as covariate effects on the disease progression rate (Equations 2 and 3).

$$\frac{d(IPSS)}{dt} = \left(DISP \cdot \left(1 - \frac{IPSS}{35}\right)\right) - ((PLACEBO + TREATMENT) \cdot IPSS), IPSS(0) = IPSS_b \quad (1)$$

$$PLACEBO = DELTA_{placebo} \cdot e^{-TIME \cdot \frac{\ln(2)}{T_{\frac{1}{2}}}} \quad (2)$$

$$TREATMENT = DELTA_{treatment} \quad (3)$$

The term *dIPSS/dt* in Equation 1 represents the rate of change (ie, derivative) in IPSS. IPSS(0) indicates the initial condition for the IPSS compartment. $IPSS_b$ represents the observed baseline disease state, whereas *DISP* represents the coefficient describing the rate of progression or degeneration of symptoms (ie, disease progression rate). The $DELTA_{placebo}$ term represents the maximum rate of reduction of symptoms due to placebo intervention and $T_{½}$ is the half-life of the effect of the placebo intervention. The term $DELTA_{treatment}$ accounts for the effect of any active intervention in an additive manner to the

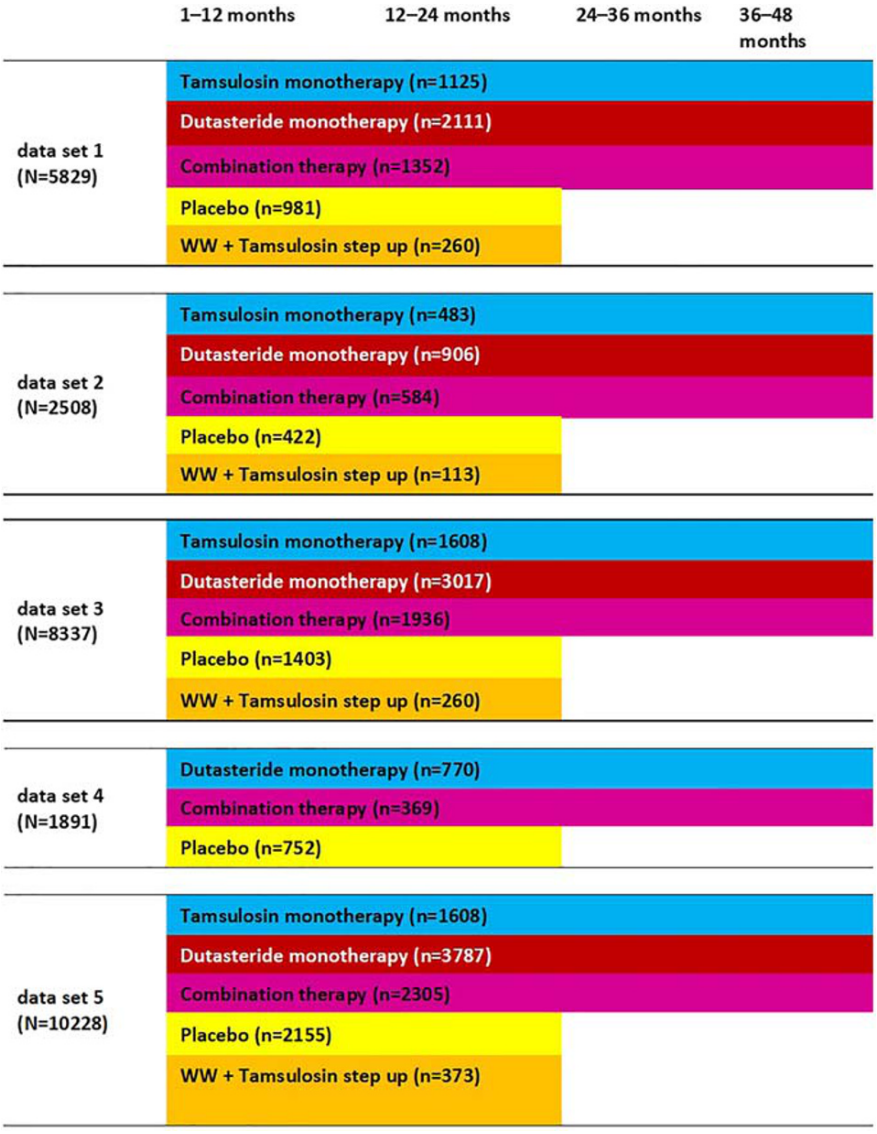

FIGURE 1 Diagram summarizing the treatment duration and interventions associated with each data set. Data set 1: Model-building data set. Data set 2: Internal-validation data set. Data set 3: Model-building + internal-validation data set. Data set 4: External-validation data set. Data set 5: Overall-population data set from all available studies. WW, watchful waiting

underlying disease progression rate and placebo effect. This model parameterization provides an easier interpretation of the effect of the intervention on disease progression (ie, on the individual IPSS trajectory) as compared to a turnover or indirect response (K_{in} – K_{out}) model. In fact, similar modelling approaches used a common parameterization to describe symptomatic and disease-modifying effects.[13,14]

For the sake of clarity, the term disease progression is used to describe the longitudinal variation in IPSS (ie, increase in severity or deterioration of symptoms). Whilst it should not be confounded with the clinical definition of disease progression, which considers other clinical parameters than IPSS, DISP does represent the rate of progression or degeneration of symptoms due to the underlying disease and as such encompasses the variation in the clinical features that determine IPSS itself.

General model-building criteria were applied to ensure that the appropriate structural model was identified to capture the changes in IPPS following the placebo treatment (Figure S2). Next, the appropriate stochastic models describing between-subject variability were identified to expand the base model. Given the heterogeneity of the profiles, a log-normal distribution was found to best describe the variability of the model parameters.[15] Selected covariates were added to the base model according to a stepwise forward addition-backward elimination procedure. As shown in Table 1, the wide range of variation in baseline characteristics (eg, age, body weight [WT], prostate-specific antigen [PSA], prostate volume) allowed for a comprehensive evaluation of influential clinical and demographic covariates on key disease-model parameters. Given that only a single treatment level was available, the drug effect was treated as a discrete term and estimated after characterization of placebo effect on individual IPSS trajectories. All steps were implemented in NONMEM version 7.3 software (Icon Development Solutions, MD, USA) based on the FOCE-I estimation method. Additional details on model refinement and an example of the control stream file for the final model are presented in the Supporting Information.

2.3 | Simulation-based evaluation of the effect of disease progression and treatment on individual IPSS trajectories

Simulations were subsequently performed using the final model parameter estimates to assess the implications for treatment response when drugs with symptomatic and disease-modifying properties are used in individual patients with varying disease-progression rates. For comparison purposes, individual IPSS trajectories were generated along with the predicted profiles in the absence of any active treatment. Graphical summaries were created using the percentiles of the disease progression (DISP) parameter distribution to visualise and distinguish the contribution of different disease progression rates to the predicted IPSS response. Likewise, simulations were performed to illustrate the impact of disease state on IPSS trajectories, as defined by IPSS severity at baseline.

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Demographics and baseline characteristics

The age of the patients across all studies included in the current analysis ranged from 47 to 94 years (median 66 years). At screening, 61% and 39% of patients were categorized as having moderate and severe LUTS/BPH, respectively. These values were found to shift to 66% and 29% immediately prior to the start of treatment. A summary of demographics and clinical baseline characteristics, along with the studied covariates, is presented in Table 1.

3.2 | Exploratory data analysis

A detailed description of the exploratory analysis and model development steps, including covariate analysis and parameterization of disease and drug-specific properties, is presented in Figures S3–S5. No outlying IPSS values were identified. No correlations or interactions were found between demographics and baseline clinical characteristics and baseline/screening IPSS, other than those due to the known co-linearity between variables (Figure 2).

3.3 | Longitudinal model development and validation

3.3.1 | IPSS trajectory (disease progression) and placebo effect

A longitudinal model based on a sigmoid function described the individual IPSS trajectories, including deterioration and improvement of symptoms after onset of treatment. Such a model structure appears to explain the initial fast improvement followed by slowly progressive changes in IPSS in most patients. The treatment effect was parameterized in addition to the placebo intervention as covariate effect on the disease progression rate. Given that pharmacokinetic (PK) data were not available, and variability in pharmacokinetics may propagate into interindividual differences in pharmacodynamics, it was decided to assign random effects to the parameters describing the active treatment, while fixing the variability in the placebo effect as estimated in the previous model building step (ie, the disease progression and placebo effect model). Full details of the model building and validation are presented in Figures S6–S16.

For completeness, some important steps of the model development and validation procedures are highlighted in the following paragraphs. First, covariates that showed statistical significance were included in the model describing disease progression and placebo

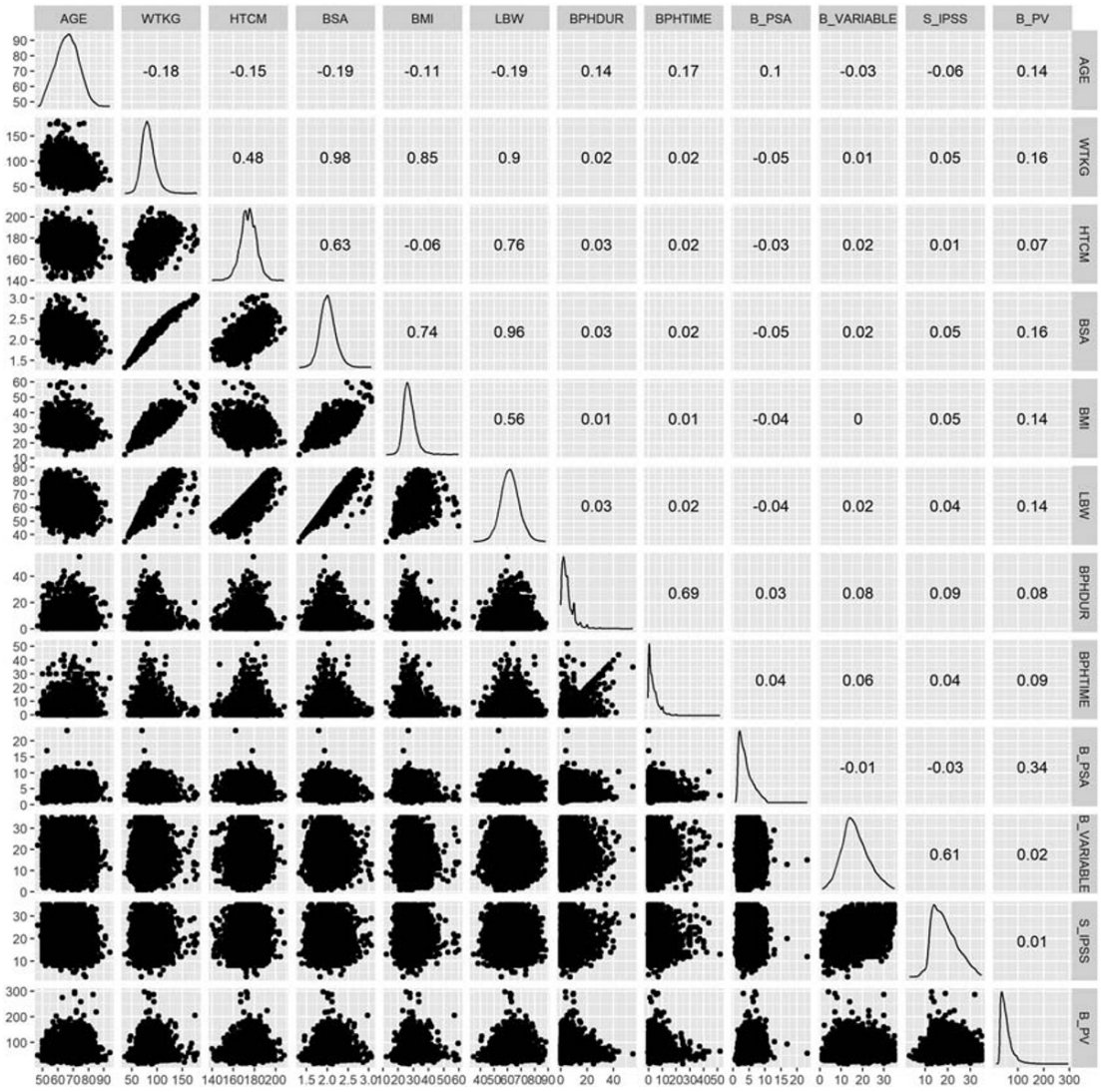

FIGURE 2 Pearson correlation matrix between the parameters: AGE, age (years); WTKG, body weight (kg); HTCM, height (cm); BSA, body surface area (m^2); BMI, body mass index (kg/m^2); LBW, lean body weight; BPHDUR, duration of BPH symptoms (years); BPHTIME, time since BPH diagnosis (years); B_PSA, serum PSA concentration at baseline (ng/mL); B_VARIABLE, IPSS at baseline; S_IPSS, IPSS at screening; B_PV, prostate volume at baseline (cm^3). Diagonal items show the underlying data distribution. Figures in the off-diagonal elements indicate the degree of correlation or lack thereof. BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen

effect. These covariates were baseline IPSS (correlated with disease progression rate), duration of symptoms (correlated with magnitude of placebo effect) and alcohol user status (correlated with half-life of the placebo effect). Despite a wide span between start and completion of treatment across the different studies, model parameterization allowed the characterization of individual and population IPSS profiles, as shown by the visual predictive checks (VPCs) stratified by treatment (Figures 3 and S6). Re-estimation of model parameters including all the available data showed that the magnitude of covariate effects may vary considerably, which reflects the differences in patient baseline characteristics across studies. Mirror plots for model diagnostics revealed no misspecification or correlations between parameters describing between- and within-subject variability (Figures S15 and S16). Validation procedures also showed that the placebo effect is a key component of the initial response and can last more than 6 months, as assessed by its half-life. Given the heterogeneity in IPSS trajectories, no clear baseline prognostic factors were identified that could be used as a single predictor of treatment response or time course of symptoms in individual patients.

3.3.2 | Watchful waiting, tamsulosin and dutasteride monotherapy

Validation procedures revealed that patients assigned to watchful waiting who respond to the intervention show an immediate improvement of the same order of magnitude as individual patients responding to tamsulosin. These changes are independent of the underlying placebo effect. Visual inspection of diagnostic measures indicated that patients with very high baseline IPSS, who do not

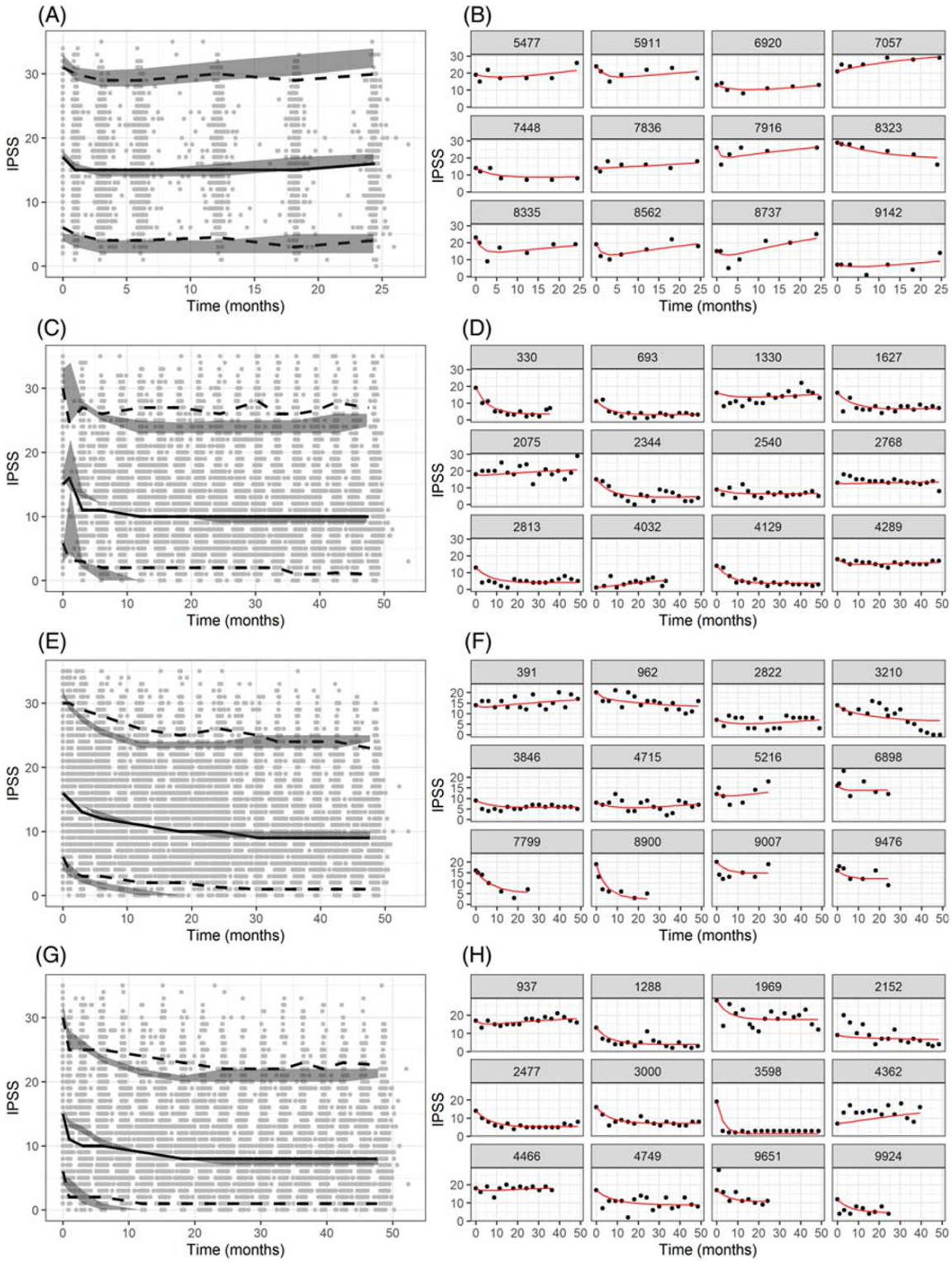

FIGURE 3 Visual predictive checks showing predicted and observed IPSS profiles (left panels) and examples of individual IPSS trajectories (right panels) after placebo treatment (A, B), tamsulosin (C, D), dutasteride (E, F) or tamsulosin-dutasteride combination therapy (G,H) in patients randomly selected from the analysis population (n = 12 per treatment group). The proposed model parameterization allowed the description of different patterns of response. Observed data for VPCs include random sampling for patients enrolled in CombAT, ARIA3001, ARIA3002, ARIB3003, ARI40002 and CONDUCT. Red lines show model-predicted individual profiles over a period of up to 2 years for placebo or 4 years for the other interventions. Dots are actual observations in the pooled data set. IPSS, International Prostate Symptom Score

appear to respond to any intervention, show IPSS trajectories that are less well-described than patients who show improvement during treatment. As this potential model misspecification is limited to the upper 2.5th percentile of the population, discrepancies between model predictions and observed data were deemed to have no further implications for the characterization of the individual trajectories, the impact of treatment on the deterioration of symptoms and underlying disease progression for most patients.

3.3.3 | Tamsulosin-dutasteride combination therapy

Given the objective of the current analysis in identifying a model parameterization, which enables the distinction between drug- and disease-specific properties, it was essential to demonstrate adequate model performance in describing symptomatic effects following initial treatment with tamsulosin as well as symptomatic and disease-modifying effects after dutasteride or combination therapy. In fact, model performance was deemed adequate for the internal and external validation data sets. Re-estimation of model parameters using all data sets yielded robust parameter estimates with relative differences between data sets substantially <30%.

In addition to the standard model-evaluation procedures, posterior predictive checks were also performed to assess model performance on secondary response parameters, such as responder rate according to the different definitions of clinical response outlined in the statistical methods. Figure 4 shows the predicted percentage of responders at 48 months after start of treatment with tamsulosin or combination therapy, along with the observed results for the corresponding study arms. The plots show very good predictions for tamsulosin and combination therapy, indicating no model bias or misspecification for the evaluation of early versus delayed onset of treatment with combination therapy. The observed response rate for dutasteride monotherapy was found to be slightly higher than mean model predictions, but within the 95% prediction intervals. This discrepancy for dutasteride monotherapy was not deemed to be a model misspecification, so it should have no impact on the objectives of the current analysis.

3.3.4 | Final model

The final model parameter estimates and bootstrap results for the longitudinal model describing the effect on individual IPSS trajectories (disease progression) of placebo, tamsulosin, dutasteride and tamsulosin-dutasteride combination therapy are shown in Tables 2 and 3. Model parameters describing LUTS deterioration and disease progression reveal that individual IPSS trajectories are influenced not only by the interaction between different baseline covariates, but also by a strong initial placebo effect, which is characterized by large inter-individual variability, in terms of both its magnitude and duration. It is the magnitude of the parameters describing progression (*DISP*) and amplitude (*delta*) of the symptomatic effect that ultimately determine the trajectory. While a fully mechanistic interpretation of parameters may not be possible, estimates of the effect of the combination therapy on progression of IPSS are twice the effect of tamsulosin alone (0.015 *vs* 0.032 months^{-1}). Our results also show that for a typical patient with moderate LUTS/BPH symptoms (baseline IPSS = 17.5), interventions with symptomatic and disease-modifying properties (eg, tamsulosin-dutasteride combination therapy) contribute to a sustained reduction in disease progression rate and overall rate of change in IPSS with estimates that are 40% higher than the placebo effect at the start of treatment. By contrast, symptomatic interventions (eg, tamsulosin, watchful waiting) result in overall rate of change IPSS with estimates that are approximately 20% higher than the placebo effect at the start of treatment. Such an effect wanes over time together with the placebo effect. For completeness, an example of the predicted individual IPSS trajectories in patients with varying rates of disease progression after incorporation of residual variability is shown in Figure S17.

3.3.5 | Impact of disease progression rate and baseline symptom severity on individual IPSS trajectories

An overview of the potential effect of varying disease-progression rates and baseline IPSS symptom severity on individual IPSS trajectories when patients are treated with combination therapy, ie, with drugs that show both symptomatic and disease-modifying properties, is presented in Figures 5–7. Summary statistics of the simulated trajectories (ie, median and 90% confidence intervals) are provided in the Supporting Information (Tables S2–S5).

4 | DISCUSSION

Whereas the management of LUTS/BPH has changed significantly over the last two decades in response to the availability of new treatment options,[3,16,17] the use of IPSS to assess LUTS/BPH and define treatment initiation as well as type still varies significantly across countries, often mirroring local clinical practice preferences and drug availability. This seems to overlook the findings from a range of epidemiologic and clinical studies that highlight the implications of disease progression in a significant proportion of BPH patients.[18,19] It also reflects the lack of a clear marker or predictor of treatment response in individual patients.

Our analysis focused primarily on evidence arising from controlled clinical trials, in which different interventions were used to improve LUTS, as assessed by the IPSS questionnaire. Despite numerous clinical features, its use as primary endpoint in randomized clinical trials has been limited to the assessment of mean population changes from baseline. In contrast, the current analysis shows the feasibility of a parametric approach to describe individual IPSS trajectories in patients with moderate or severe LUTS/BPH. The availability of a longitudinal model for IPSS provides the basis for evaluation of a range

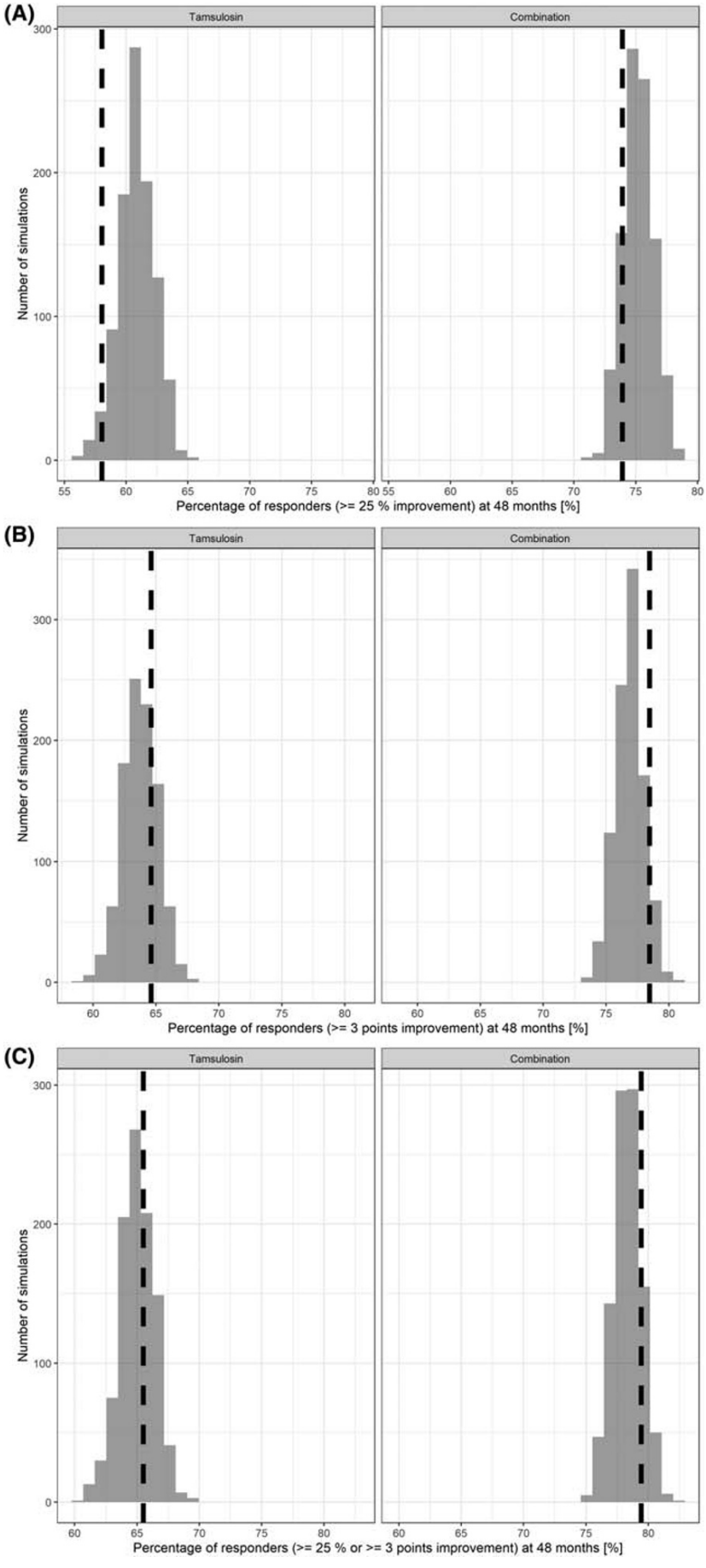

FIGURE 4 Histograms showing the percentage of responders based on different definitions of clinical response, namely change in IPSS ≥ 25% relative to baseline (A), change in IPSS ≥ 3 units relative to baseline (B) and change in IPSS ≥25% or 3 units relative to baseline (C). The histograms display the number of simulations in each percentag prediction (N_{tot} = 1000). The vertical line shows the observed responder rate in the ComBAT study using the same definition applied to the simulated data. IPSS, International Prostate Symptom Score

TABLE 2 Final model parameter estimates and bootstrap results (N = 1000) for the longitudinal model describing the individual IPSS trajectories, disease progression and placebo effect

	Population estimate	Bootstrap mean (95%CI)
DISP, disease progression rate (months^{-1})	0.347	0.342 (0.266–0.419)
$DELTA_{placebo}$, placebo effect (months^{-1})	0.061	0.061 (0.054–0.068)
$T_{1/2}$, placebo $t_{1/2}$ (months)	7.263	7.148 (5.394–8.813)
BPHDUR on magnitude of placebo effect (duration of symptoms) (–)	–0.025	–0.024 (–0.03 – –0.018)
$IPSS_b$ on disease progression rate (–)	0.027	0.025 (0.009–0.037)
Alcohol user status at baseline on placebo $t_{1/2}$ (–)	–0.135	–0.123 (–0.229 – –0.011)
IIV on disease progression rate	0.997	1.01 (0.819–1.233)
IIV on placebo effect	2.822	2.865 (2.308–3.507)
IIV on placebo $t_{1/2}$	2.758	2.795 (2.366–3.327)
Additive RUV	3.224	3.223 (3.131–3.307)

Abbreviations: BMI, body mass index; BMI_0, BMI at baseline; BPHDUR, duration of BPH symptoms; IIV, interindividual variability (expressed as variance); IPSS, International Prostate Symptom Score; $IPSS_b$, IPSS at baseline; RUV, residual unexplained variability (expressed as standard deviation); $t_{1/2}$, half-life. Units are shown between parentheses; dimensionless parameters are shown as (–).

TABLE 3 Final model parameter estimates and bootstrap results (N = 1000) for the longitudinal model describing the effect of tamsulosin, dutasteride watchful waiting and combination therapy on the individual IPSS trajectories and disease progression

Tamsulosin monotherapy	**Population estimate**	**Bootstrap mean (95%CI)**
$DELTA_{tamsulosin}$, effect of tamsulosin (months^{-1})	0.015	0.015 (0.013–0.017)
IIV on the effect of tamsulosin	1.923	1.909 (1.652–2.167)
Additive RUV	3.613	3.614 (3.508–3.717)
Dutasteride monotherapy	**Population estimate**	**Bootstrap mean (95%CI)**
$DELTA_{dutasteride}$, effect of dutasteride (months^{-1})	0.016	0.015 (0.014–0.017)
IIV on the effect of dutasteride	1.734	1.722 (1.551–1.895)
Additive RUV	3.506	3.508 (3.439–3.577)
Watchful waiting	**Population estimate**	**Bootstrap mean (95%CI)**
$DELTA_{WW}$, effect of watchful waiting (months^{-1})	0.018	0.018 (0.014–0.024)
IIV on the effect of watchful waiting	1.812	1.785 (1.257–2.408)
Additive RUV	2.778	2.775 (2.566–2.988)
Combination therapy	**Population estimate**	**Bootstrap mean (95%CI)**
$DELTA_{FDC}$, effect of combination therapy (months^{-1})	0.032	0.032 (0.03–0.034)
IIV on the effect of combination therapy	1.449	1.447 (1.295–1.608)
Additive RUV	3.141	3.144 (3.058–3.227)

Abbreviations: IIV, interindividual variability (expressed as variance); IPSS, International Prostate Symptom Score; RUV, residual unexplained variability (expressed as SD).

of clinical questions regarding the effect of different interventions on LUTS/BPH progression. It also represents an efficient approach for knowledge integration, allowing for study protocol optimization and improved patient and treatment selection.

Furthermore, our analysis shows that no single baseline characteristic can be considered as the primary predictor of an individual IPSS trajectory. The interaction between different baseline characteristics only explains part of the interindividual differences in the underlying disease progression rate and placebo effect. It is the magnitude of the parameters describing progression (*DISP*) and amplitude (*delta*) of the symptomatic effect that ultimately determines the trajectory. In fact, the lack of clear correlation between baseline characteristics and IPSS at screening/baseline suggests that repeated measurements over time are required to characterize the different clinical phenotypes associated with the individual IPSS trajectory.

While this analysis appears to be the very first application of longitudinal modelling in the field of urology, similar approaches have been applied in other therapeutic areas to address similar clinical and regulatory questions.[20–23] Irrespective of differences in the methodology, the characterization of individual IPSS trajectories can be compared with previous attempts to assess the impact of treatments with disease-modifying properties on disease progression.[24] As such, this work offered a unique opportunity to assess the impact of different interventions on the improvement/deterioration of symptoms.

From a clinical perspective, the approach proposed here contrasts with traditional pivotal clinical trials in which a predefined hypothesis is tested. In conjunction with simulation scenarios, longitudinal models become inferential tools, which in turn can be used to explore a range of interventions that have either not been tested experimentally or cannot be implemented without confounding from factors that cannot be controlled in an experimental protocol.[25] Justifying the claim that a treatment shows disease-modifying rather than symptomatic properties requires the ability to identify both types of effects, including when they occur at the same time. Whilst there is a strong pharmacological basis for the differences in the effects induced by 5α-reductase inhibitors and α-blockers, the analysis of longitudinal data from standard study designs suggest that the distinction between symptomatic and disease-modifying effects may be ambiguous and not easily disentangled from each other.[26–28] This problem highlights the

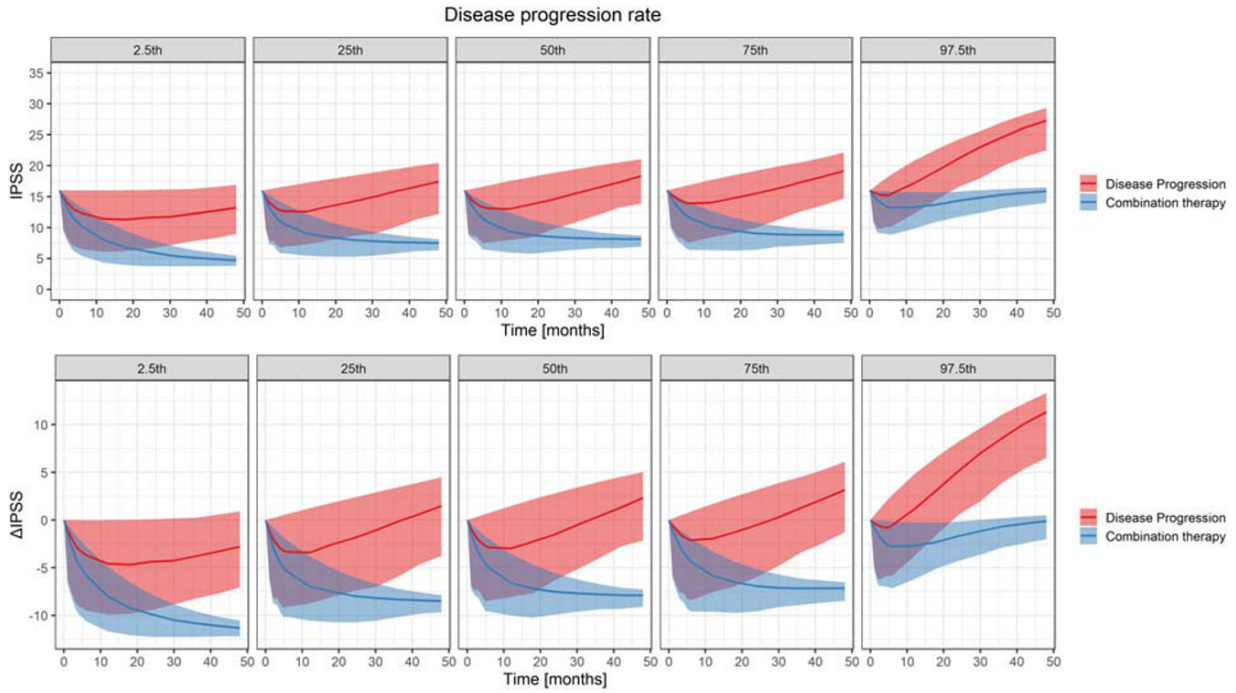

FIGURE 5 Impact of the disease-modifying properties of tamsulosin-dutasteride combination therapy on the IPSS response in individual patients with varying rates of disease progression. Each panel depicts the IPSS trajectories (upper panels) and the Δ*IPSS* (lower panels) over 48 months for patients across a range of disease progression rates (2.5th, 25th, 50th, 75th and 97.5th percentiles). Red areas represent predicted profiles in the absence of any active treatment; blue areas show the effect of combination therapy for patients across different percentiles of disease progression rate distribution; solid lines are the median predicted IPSS; shaded areas represent the 95% prediction interval (n = 200 simulations). The predicted trajectories describing disease progression are depicted assuming a hypothetical scenario in which patients remain untreated despite deterioration of symptoms. Clinical trial simulations show predicted IPSS without residual errors. Numerical summaries of the simulated profiles are shown in Table S2

challenges one may face when addressing common clinical questions, such as the long-term implications of starting treatment with symptomatic versus disease-modifying therapies.

4.1 | Development and validation of a disease-progression model describing IPSS trajectory

First, it should be noted that we have attempted to describe IPSS profiles from the different clinical studies, with different interventions and treatment durations and protocol designs. This has created opportunities and challenges for the identification of suitable parameterization. A few key points became clear during model development and covariate analysis, in that baseline characteristics were identified as covariate factors, corroborating evidence from clinical practice (eg, effect of baseline IPSS on IPSS trajectory) and shedding light on new factors (eg, effect of alcohol use on placebo half-life).[29] Even though different approaches have been proposed for the characterization of baseline for pharmacodynamic endpoints, observed baseline IPSS was used, taking into account the prospective application of the model for new patients. Another important feature of this analysis was the possibility to describe the magnitude and duration of the placebo effect, which coexists with underlying disease progression, as assessed by IPSS. This finding indicates that trials of longer than 2 years may be required to discriminate placebo effects from drug-specific effects on the progression of IPSS.[30] Despite the high variability in the parameters governing the placebo effect, there is no reason to assume that such variation is caused by protocol procedures or other extrinsic factors. They reflect the heterogeneity in the population. In addition, it is worth mentioning that such a variation in symptoms occurs within a timescale during which prostate volume is unlikely to vary significantly. For clarity, observations at screening were excluded under the assumption that the variation in IPSS prior to baseline visit reflects regression to the mean, rather than a placebo effect.

Given the relative heterogeneity in the cohorts of patients, it also became evident that there is no single covariate factor at the onset of treatment that can be used as a proxy or predictive marker of individual treatment response. Therefore, it is not possible to anticipate which patients will cease to respond over time (ie, deterioration of IPSS) even if one takes into account prognostic factors of the progression of the disease. In fact, our analysis reveals that several factors or baseline characteristics shown in clinical trials to be associated with risk of progression of disease, such as prostate volume and serum PSA concentration,[31,32] are not predictive of individual treatment response. These findings are consistent with the view that many prognostic factors are not necessarily good predictors of individual treatment response (ie, have poor predictive value).[33–35] Therefore, before including biomarkers or clinical characteristics in guidelines to select

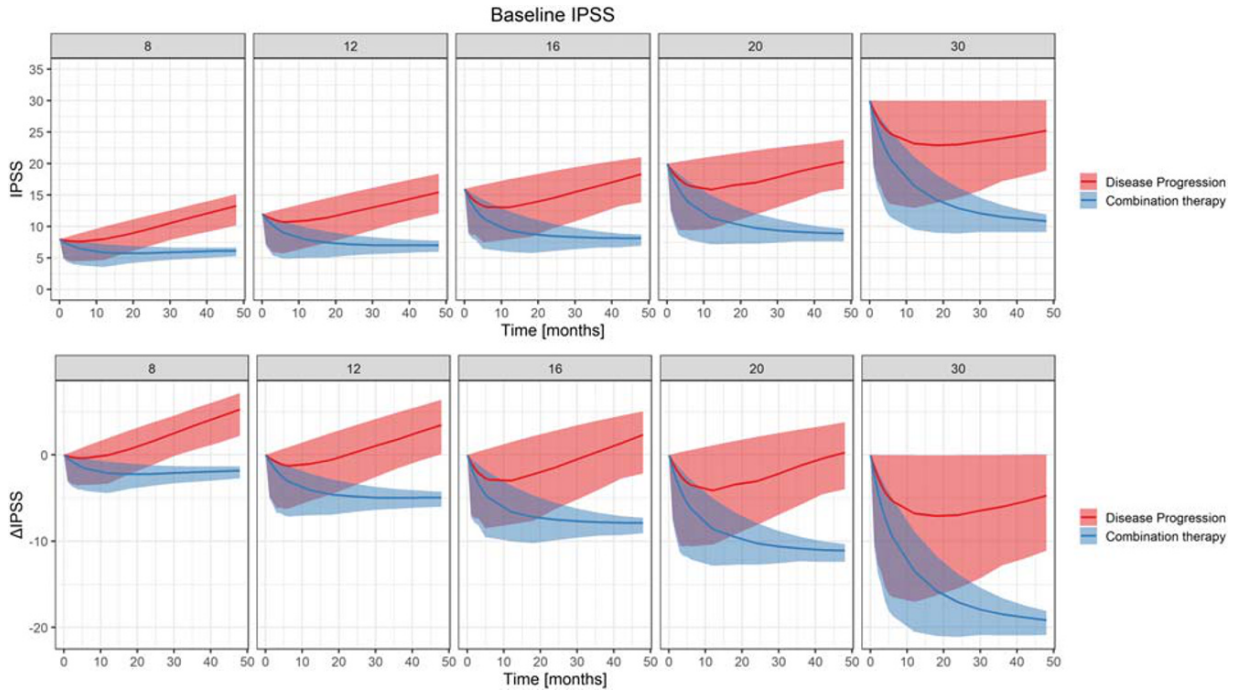

FIGURE 6 Impact of baseline symptom severity on individual IPSS trajectories and disease-modifying properties of tamsulosin-dutasteride combination therapy in individual patients with comparable rates of disease progression. IPSS trajectories (upper panels) and Δ*IPSS* (lower panels) over 48 months are depicted for patients with different baseline IPSS (8, 12, 16, 20 and 30). Red areas represent the predicted profiles in the absence of any active treatment; blue areas show the effect of combination therapy for patients with different baseline IPSS symptom severity; solid lines are the median predicted IPSS; shaded areas represent the 95% prediction intervals (*n* = 200 simulations). The predicted trajectories describing disease progression are depicted assuming a hypothetical scenario in which patients remain untreated despite deterioration of symptoms. Clinical trial simulations show predicted IPSS without residual errors. Numerical summaries of the simulated profiles are shown in Table S3

patients for specific treatments, it is important that clinically relevant endpoints are evaluated and the prognostic effects of these factors are distinguished from their ability to predict a differential clinical benefit from the specific treatment.[34]

IFrom a methodological viewpoint, population mean response and 90% prediction intervals revealed acceptable predictive performance in the target patient population (ie, patients with moderate or severe LUTS/BPH who show improvement during the course of treatment). Furthermore, despite large intra-individual variability, simulated profiles mirror clinical observations across the different studies for the vast majority of patients, indicating a well-defined variance–covariance structure. In addition, this meta-analysis has shed light on the magnitude of intra-individual variability in IPSS trajectories, which is often overlooked when comparisons are made based on change from baseline at the end of a study or treatment period. Even though residual variability was found to contribute to intra-individual variation in IPSS scores with a standard deviation of 3.2 units, interindividual differences could be identified in disease-specific parameters; namely, the underlying disease progression rate, the placebo effect and half-life of the placebo effect.

There are limitations to the model, which are not unexpected. First, given the absence of pharmacokinetic data and the very long elimination half-life of dutasteride (3–5 weeks), interindividual variability in exposure has been assumed to have negligible effect on disease-specific parameters. In turn, this has made the application of the model easier and allowed a more straightforward interpretation of differences in parameter estimates. We also acknowledge that the selection of a log-normal distribution to describe interindividual variability is empirical. Exploratory data analysis did not show supporting evidence for multimodal distributions (ie, mixture model). In addition, as interoccasion variability could not be identified, residual variability estimates were considerably high, but this appears to be an intrinsic feature of IPSS, which shows high intrasubject variability. Lastly, a balance had to be found between goodness of fit and over-parameterization. Some discrepancy has been identified between observed data and mean predictions at the start of treatment and in patients around the 97.5th percentile. While a formal evaluation of the sensitivity and specificity of the model has not been performed yet, we aim to establish the positive or negative predictive performance of the model with regard to each patient's trajectory and final response at the end of treatment in a subsequent simulation study. Such an analysis will provide further insight into the implications of potential model misspecification.

4.2 | Impact of disease progression rate and baseline symptom severity on individual IPSS trajectories

Initially, simulations were performed to illustrate the effect of varying disease-progression rates on individual IPSS trajectories when

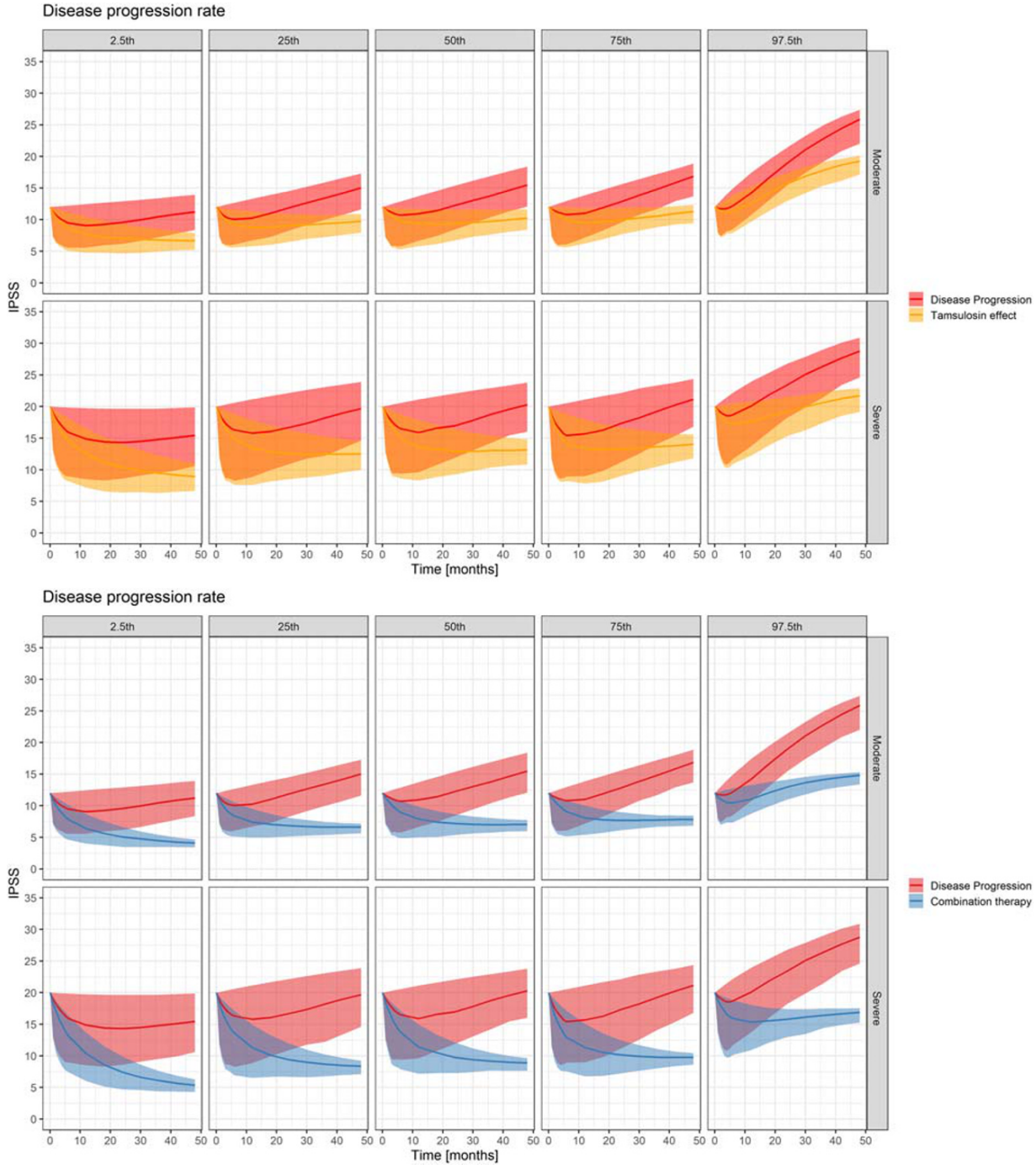

FIGURE 7 Impact of symptomatic (tamsulosin monotherapy, upper panel) and symptomatic and disease-modifying properties (tamsulosin-dutasteride combination therapy, lower panel) on individual IPSS trajectories in patients with varying rates of disease progression and varying IPSS at baseline. Panels are stratified by symptom severity, as defined by IPSS values at baseline. Red areas represent the predicted profiles in the absence of any active treatment; blue and orange areas show, respectively, the effect of tamsulosin monotherapy (upper panel) and combination therapy (lower panel) for patients across different percentiles of the disease progression rate distribution; solid lines are the median predicted IPSS; shaded areas represent the 95% prediction intervals (n = 200 simulations). The predicted trajectories describing disease progression (red) are depicted assuming a hypothetical scenario in which patients remain untreated despite deterioration of symptoms. Clinical trial simulations show predicted IPSSwithout residual errors. Numerical summaries of the simulated profiles are shown in Tables S4 and S5

patients are treated with drugs that show both symptomatic and disease-modifying properties (Figure 5). The predicted profiles for the different percentiles of the disease progression (*DISP*) parameter distribution clearly indicate that the resulting treatment response depends on the underlying progression rate. The interaction between disease progression rate, placebo and drug effects can be further characterized by the net change from baseline (Δ*IPSS*) over time. In addition, the impact of disease state, as

defined by IPSS severity at baseline on individual IPSS trajectories, was simulated in the absence of treatment and after administration of combination therapy with tamsulosin and dutasteride (Figure 6). These profiles demonstrate that baseline IPSS and disease-progression rates interact with treatment effect, making it difficult to disentangle the contribution of each factor to response, which in a typical clinical trial is often defined in terms of relative change from baseline. For completeness, a comparison of the effect of symptomatic (tamsulosin monotherapy) and symptomatic as well as disease-modifying properties (tamsulosin-dutasteride combination therapy, lower panel) on individual IPSS trajectories in patients with varying rates of disease progression and varying symptom severity at baseline is shown in Figure 7. Lastly, it should be noted that in a typical clinical trial setting, appraisal of the disease progression rate and its impact on the overall treatment response is confounded by residual variability in IPSS. The relevance of model-based characterization of individual IPSS trajectories is emphasized in Figure S17, where measurement noise is included in the simulated profiles. These results may also explain why no predefined set of baseline characteristics has been identified as a sufficiently sensitive marker of the deterioration of symptoms or treatment response. In fact, in a recent data-mining exercise including men with LUTS secondary to BPH, it was shown that baseline IPSS severity achieved sensitivity and specificity of 70% and ~50%, respectively, as predictors of individual response to placebo or tadalafil.[4] However, these values are below the sensitivity and specificity threshold of 80% that enables reliable allocation of an individual patient to either the responder or nonresponder group.[4] Hence, clinicians may not be able to accurately predict whether a patient will respond to symptomatic and disease-modifying interventions at the start of treatment.

IIn conclusion, a longitudinal drug-disease model was developed using pooled data from clinical trials, which allows for the characterization of individual IPSS trajectories. In contrast to traditional clinical trials, where efficacy is defined in terms of relative changes from baseline at completion of treatment, our approach allowed the identification of factors, and possible placebo effect, that contribute to the progression of symptoms. Most importantly, the model yielded individual response profiles, which are exchangeable with observed patient data. Our analysis also unravelled interactions between placebo treatment and baseline characteristics that had not been identified in previous studies. These covariates affect individual IPSS trajectories and contribute to differences in response to treatment.

It can be anticipated that the availability of this model, including parameters describing inter- and intra-individual variability, will provide insight into the impact of different treatment conditions on the progression of clinical symptoms.

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COMPETING INTERESTS

S.D. none to declare. M.O. has been a speaker, consultant and/or trial participant for Apogepha, Astellas, Duchesnay, Ferring, GSK, Lilly, Pierre Fabre and Pfizer, and received research grants from Astellas and Pfizer. C.R. was previously employed as a consultant to GSK. T.W. holds stocks/shares in GSK. O.D.P., B.A., M.M., J.M.P.M. and C.C. are GSK employees and hold stocks/shares in GSK.

CONTRIBUTORS

S.D. was involved in the conception/design of the study, analysis and interpretation of study data, drafting and critical revision of the manuscript, and approved its submission. T.W. was involved in the conception/design of the study, acquisition and interpretation of study data, drafting and critical revision of the manuscript, and approved its submission. B.A. was involved in the interpretation of study data, drafting and critical revision of the manuscript, and approved its submission. M.M. was involved in the conception of the study and interpretation of study data, drafting and critical revision of the manuscript, and approved its submission. J.M.P.M. was involved in the conception of the study and interpretation of study data, drafting and critical revision of the manuscript, and approved its submission. C.C. was involved in the interpretation of study data, drafting and critical revision of the manuscript, and approved its submission. M.O. was involved in the interpretation of study data, drafting and critical revision of the manuscript, and approved its submission. C.R. was involved in the interpretation of study data, drafting and critical revision of the manuscript, and approved its submission. O.D.P. was involved in the conception/design and interpretation of study data, drafting and critical revision of the manuscript, and approved its submission.

DATA AVAILABILITY STATEMENT

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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