Model-based Approaches for Improved Decision Making in R&D

Marc Pfister, MD, FCP, Chief Medical Officer
Quantitative Solutions, Bridgewater, NJ
High development cost, low development success, cost-disciplined healthcare policies, and intense competition demand an efficient drug development process. New compounds need to bring value to patients by being safe, efficacious and cost-effective compared to existing treatment options. Model-based approaches facilitate integration and utilization of summary level efficacy and safety data, providing a quantitative framework for efficacy/safety assessments of new drugs.
Models For Diseases, Drugs, and Trials

Disease Model
- Biology
  - Biomarkers/outcome relationship
  - Natural progression
- Placebo effect

Drug Model
- Pharmacology
  - Effectiveness
- Safety
- Preclinical/Healthy Patient
- Product Features

Trial Model
- Patient Population
- Drop-out
- Adherence

Source: Gobburu & Lesko, FDA, 2009
C-Path FDA Conference
• Population exposure-response models
• Mechanism-based models
• Disease progression models
• Model-based meta-analyses
• Model-based trial simulations
Goal is to Enhance Decision Making Throughout Drug R&D Continuum

Goal is to Accelerate Drug R&D by Iterative Knowledge Generation

- Summarize
- Analyze
- Interpret
- Experiment
- Observe
- Collect Data
- Model
- Simulate
- Predict

12/6/2011 C-Path FDA Conference
Goal is to Accelerate Drug R&D by Iterative Knowledge Generation & Integration

- Summarize
- Analyze
- Interpret

Publicly Available Data

- Experiment
- Observe
- Collect Data

Model
- Simulate
- Predict

12/6/2011

C-Path FDA Conference
… By Quantitatively Addressing Key Questions in R&D

Which candidates are most likely to succeed? What biomarkers should we capture? What dose range is needed to compete with the leader in this drug class?

What indications are most promising? What is the optimal dose? What is our drug’s product profile relative to competitors?

How do we differentiate our drug in the market place? How do we facilitate market access? What other indications is the drug likely to succeed?

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Phase I | Phase II | Phase III
--- | --- | ---
Target Identification | Lead Identification | Lead Optimization
Pharmacology | Toxicology | First in Man
Proof of Concept | EoP2 Meeting | Approval
Market Access

MBMA can integrate internal and external experimental data

MBMA can facilitate/enhance decision making in drug research and development

- **Go/no-go decisions** Quantitatively comparing new treatments/compounds with other emerging/existing treatment options to quantify the benefits for patients, reviewers, and payers

Dilemma: most trials in drug development are placebo controlled or vs. standard of care (SOC)
Compare Approved Biologic Agents (RA) With Model-based Meta-analysis

Source: Mandema, Salinger, Baumgartner, & Gibbs, *Clinical Pharmacology & Therapeutics*, 2011
Compare Dose Response For Metformin + DDP-IV Inhibitor Combination Therapies

HbA1c, baseline adjusted change from placebo

NewDP4

alogliptin

saxagliptin

sitagliptin

vildagliptin

Dashed line, sitagliptin

Dose (mg/day)

C-Path FDA Conference 12/6/2011
Compare Dose Response For Metformin + DDP-IV Inhibitor Combination Therapies

![Graphs showing HbA1c, baseline adjusted change from placebo vs. Dose (mg/day) for NewDP4, alogliptin, saxagliptin, sitagliptin, and vildagliptin.](image-url)
The meta analysis provided a comparison of dose response after adjusting for the impact of differences in baseline HbA1c and drug combinations across the trials.
Assess Trade-off between Efficacy and Safety for Decision Making

Dropouts due to AEs (%)
Seizure frequency (median % change)
0 5 10 15 20 25 30
-50 -45 -40 -35 -30 -25 ... 3000 mg
Oxcarbazepine 1200 mg
Pregabalin 450 mg
Tiagabine 32 mg
Topiramate 400 mg
Zonisamide 400 mg

NEW COMPOUND

12/6/2011 C-Path FDA Conference
Apply Trial Simulations to Optimize Phase 2 Dose Selection

Results from trial simulations for selected phase 2 doses of drug X

Source: Kerbusch, Wada, & Zandvliet, American Conference on Pharmacometrics, 2011
What is Required to Successfully Apply Model-based Approaches in R&D?

- Quantitative Model-based Approaches
  - Therapeutic Area expertise
  - Technical M&S (pharmacometric) expertise
  - Integrated disease databases
  - Clinical and regulatory experience
Model-based approaches for quantitative knowledge integration

• **Require cross-disciplinary collaboration**
• Provide quantitative rationale for next step in drug development
• Offer opportunity to test assumptions through “virtual” experiments
• Can improve success through quantitatively informing dose/design and go/no-go decisions
A Drug Development Tool for Trial Simulation in Cognitive Trials in Mild to Moderate Dementia of the Alzheimer’s Type

Jim Rogers, with

Brian Corrigan, Kaori Ito, Dan Polhamus, Ruolun Qiu, Klaus Romero, Bill Gillespie
The Pharmacometrics group within the Office of Clinical Pharmacology has been fostering disease-drug-trial models within the FDA to aid regulatory and drug development decisions. Several of the contributions are discussed here and references for others are provided. The following is our vision with respect to these models:

1. Given the limited resources, consortia on focused topics would be an effective approach to developing these models. The Predictive Safety Testing Consortium (PSTC) (http://www.c-path.org/Portals/0/PSTC%20Overview.pdf) is one example of such a consortium.

2. The main focus of our work at the FDA will continue to be in the area of semimechanistic disease-drug-trial models. We intend to launch a public website to share our model library. Our group will continue to publish its results in scientific journals.

3. The disease-drug-trial models, as they become available, will be employed to design pediatric trials using clinical trial simulations. Our target is to design 50% of all pediatric trials using clinical trial simulations by 2015 and 100% by 2020. Industry will need to play an important role in this initiative.

4. As adequate experience is gained with a particular disease-drug-trial suite, we intend to standardize the data and analysis submission specifications. Our goal is to develop standard templates for 15 therapeutic indications by 2020. These 15 therapeutic areas will be selected based on public health priority, prior experience, and richness of the pipeline.
The Model as a Drug Development Tool

Guidance for Industry
Qualification Process for Drug Development Tools

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5600 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Shaniece Gathers, 301-796-2600.

October, 2010

• Guidance predominantly for biomarkers and PROs
• Will be first Drug-Disease-Trial model to be submitted under the new Guidance
• Will set the precedent for the Profession
Comprehensive Use of Available Data

**Literature Meta-data**
- 73 Trials (1990 to Present)
- Interstudy variability
- Effects of marketed therapeutics (magnitude, onset, offset)

**CAMD Database**
- 9 trials, 3223 patients
- Interpatient Variability
- Patient Specific Factors
- Placebo Effect

**Sponsor Proprietary Data**
- Preclinical
- Related products
- Hypothesized effects of novel therapy

- Natural History
- Interpatient Variability
- Patient Specific Factors
- Imaging and CSF Biomarkers
Number of Patients By Region

Observed ADAS-cog Over Time by Baseline Severity* in CAMD

(lowess is in red)
Model Integration

Ito Literature (2009)

- The use of a Bateman-type function to describe the incremental placebo effect
- The use of Emax functions to describe the incremental effects of approved AChE inhibitors as a function of dose

Ito ADNI (2010)

- The placement of candidate covariate effects in the model. Specifically, the use of baseline severity as a covariate on the model intercept, and the use of baseline severity, ApoE genotype, and baseline age as covariates on rate of progression

Samtani ADNI (2011)

- The use of a generalized logistic function to describe the natural progression of the disease on a constrained scale

Faltaos (2011)

- A Bayesian implementation allowing for a probabilistically correct synthesis of literature meta-data with patient-level data.
- The generalized logistic function is used in conjunction with Beta-distributed residuals (i.e. “beta regression”), resulting in a predictive distribution that falls entirely within the allowable range of ADAS-cog scores (0–70) during simulation.
- The covariance structure is extended to include inter-study variation in intercepts and rates of progression
- The covariance structure is extended to include inter-study heterogeneity in variance components.

- The use of baseline age and baseline severity as covariates on the hazard of drop-out
Key Features of ADAS-cog Model

\[
\log \left( \frac{S(t)/70}{1 - S(t)/70} \right) = \mu + \alpha \cdot t + f_{pbo}(t) + f_{drug}(t) + \varepsilon
\]

- \(\mu\): baseline disease “state”
- \(S(t)\): expected “state” at a time “\(t\)”
- \(\alpha\): disease progression rate
- \(t\): time
- \(\varepsilon\): prediction variability
- \(f_{pbo}(t)\): placebo effect
- \(f_{drug}(t)\): symptomatic drug effects

Note: if the drug is disease modifying (DM) type, the effect is on the slope (\(\alpha\)):

\[
\log \left( \frac{S(t)/70}{1 - S(t)/70} \right) = \mu + \alpha \cdot f_{DM}(t) \cdot t + f_{pbo}(t) + \varepsilon
\]

..or combination with symptomatic effect
## Covariates on Rate of Progression

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<th>ApoE4</th>
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Modeling Drop-out

Plot of $1 - P(\text{dropout})$ Over Time by Baseline MMSE (left Panels) and Age Right Panels
Visual Predictive Check: CAMD and ADNI

![Graph showing visual predictive check for CAMD and ADNI datasets. The graph displays data points and trends over time for different patient IDs. The x-axis represents weeks, and the y-axis represents ADAS-cog scores.]
Simulation of Delayed Start Designs

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<th>Effect</th>
<th>Design</th>
<th>P(reject $H_0^1$)</th>
<th>P(reject $H_0^1$ &amp; $H_0^2$)</th>
<th>$H_0^3$ 5% LB*</th>
<th>$H_0^3$ 95% UB*</th>
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<td>5 %</td>
<td>91 week delayed start, n=600/arm</td>
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<td>10 %</td>
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<td>20 %</td>
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<td>0.280</td>
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<td>0.610</td>
<td>-0.777</td>
<td>0.609</td>
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<td>50 %</td>
<td>78 week parallel, n=600/arm</td>
<td>0.89</td>
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<td>50 %</td>
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<td>0.88</td>
<td>0.720</td>
<td>-0.794</td>
<td>0.596</td>
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* Typical (median) lower and upper bounds for the (treatment-placebo) difference in mean change during the last 6 months of the trial.
From Hypothetical Schematics to Quantitative Inferences

Figure: Hypothetical progression of pathological and clinical events that lead to Alzheimer’s disease, as detected by use of different imaging techniques, functional measures, or biomarkers. Increases in the extent of pathological abnormality are shown for each imaging measure and biomarker. ADL=activities of daily living, EMCI=early MCI, FDG-PET=FD-fluorodeoxyglucose PET, LMCI=late MCI.
Disease Progression Analysis for ADNI MCI Subjects Utilizing ADAS-cog/11 Scores

Mahesh N. Samtani, Ph.D.
Principal Scientist
Clinical Pharmacology
Janssen Research & Development
Factors Influencing Baseline Disease Score

1) Years Since AD Onset
2) Baseline Hippocampal Volume
3) Baseline Ventricular Volume

Factors Influencing Disease Progression Rate

1) Baseline Age in years
2) APOE Carrier Status
3) Baseline Serum Cholesterol
4) Current ADAS-cog Score
5) Baseline Trail Making Test Part B

\[
\frac{d\text{ADAScog}}{dt} = r \cdot \text{ADAScog}^\alpha \left[ 1 - \frac{\text{ADAScog}}{\text{ADAScog}_{\text{max}}} \right]; \quad \text{ADAScog}(0) = \text{ADAScog}_0
\]
MCI subjects have cognitive impairments beyond that expected for their age and education.

Cognitive impairments in MCI do not interfere significantly with their daily activities.

MCI is a boundary or transitional stage between normal aging & Alzheimer’s disease.

When memory loss is the predominant symptom it is termed amnestic MCI.

Studies suggest that MCI subjects progress to AD at a rate of 10-15%/yr (vs. base rate 1-2%).

There is no proven treatment for MCI i.e. all MCI phase III trials have failed.

MCI trial failures have been attributed to:

- Very heterogeneous nature of the MCI population
- Inappropriate scale for measuring disease severity and/or tracking disease
- Inappropriate endpoint (Conversion vs. Continuous scale) as the primary efficacy variable

Unmet need for trial optimization to ensure higher probability of technical & regulatory success.

Petersen, 1999; Grundman, 2004; Tabert 2006; Petersen, 2010.
Objectives of the MCI Model Based Analysis

• Model the longitudinal change in ADAS-cog
  – Assess the ability of ADAS-cog to track progression during MCI

• Assess the applicability of the AD model and its covariate relationships to the MCI population

• Identify a subset of MCI subjects that carry the underlying AD pathology
  – Identify subjects who are at a higher risk of disease progression
  – Use these subset of subjects for MCI trial enrichment
The Variability Parameters were Higher in MCI vs. AD Subjects i.e. More Heterogeneity

Comparison of Covariate Free Base Models in Both Populations

\[ \theta_{\text{ADAScog0}} = 10.6 \]

\[ \text{SD } \eta_{\text{ADAS-cog0}} = 0.395 \]

\[ \theta_r = 0.032 \]

\[ \text{SD of } \eta_r = 0.037 \]

\[ \text{SD of } \epsilon = 0.26 \]

\[ \theta_{\text{ADAScog0}} = 17.6 \]

\[ \text{SD } \eta_{\text{ADAS-cog0}} = 0.308 \]

\[ \theta_r = 0.032 \]

\[ \text{SD of } \eta_r = 0.021 \]

\[ \text{SD of } \epsilon = 0.17 \]
Mixture Model for ADAS-cog in MCI

Fast-Progressers (71%)

Slow-Progressers (29%)

ADAS-cog₀

Baseline ADAS-cog

Progressers
n=141

Non-Progressers
n=57

Slope Parameter

Progressers
n=141

Non-Progressers
n=57
Correlation between sub-Population Assignment from ADAS-cog Mixture Model & Cut-off for log of $p$-tau$_{181p}$/Aß$_{1-42}$ Ratio

Log Ratio was chosen for further analysis
- Gave Highest %Correct Classification (CC) Statistic
- Incorporates Tau and Plaque Pathology
- Consistent with Literature and Generalizable

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<td>129</td>
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<tr>
<td>Ratio</td>
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<td>0.11</td>
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<td>Low LogRatio</td>
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<tr>
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<td>0.71</td>
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</table>

Chi^2 = 28.2562 d.f. = 1 (p=1.1e-007)
Fisher's exact test p-value < 0.0001
ADAS-cog Profiles Split by log $\text{p-tau}_{181p}/\text{A}\beta_{1-42}$ Ratio Threshold of -1.86

Other Statistically Significant Covariates in MCI

Log Ratio ≤ -1.86

Log Ratio > -1.86

Log Ratio > -1.86
Results from the Final Model

Non-Progressers

Log Ratio ≤ -1.86
35% of MCI Population
MCI NOT due to AD

Progressers

Log Ratio > -1.86
65% of MCI Population
MCI due to AD

- Baseline CSF biomarkers (Aβ & p-tau) carry information about disease pathology
- Progressers vs. Non-Progressers can be distinguished using biomarkers thresholds
- ADAS-cog can track progression in MCI once the right population is selected
APOE4 and CSF Biomarkers are Correlated
In absence of CSF biomarkers APOE4 may serve as a substitute

**All MCI Subjects**

- **APOE4 non-carrier**
- **APOE4 carrier**

![Graphs showing the difference in Mean ADAS-cog Score ± SE between APOE4 non-carrier and APOE4 carrier over time (year).](attachment:image.png)

**MCI Progressers (MCI due to AD)**

- **Log Ratio > -1.86**

- **MCI Non-Progressers (MCI NOT due to AD)**

- **Log Ratio ≤ -1.86**

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**APOE4 Log.CSF.Ratio.Threshold**

<table>
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<th>Non</th>
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<th>92</th>
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<td>20%</td>
<td>46%</td>
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<td><strong>89</strong></td>
<td><strong>106</strong></td>
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<td></td>
<td><strong>8.6%</strong></td>
<td><strong>45%</strong></td>
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<tr>
<td></td>
<td><strong>35%</strong></td>
<td><strong>65%</strong></td>
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- **84% (89/106) of APOE4 carriers had Log Ratio > -1.86**
- **Overall MCI population clearly exhibits APOE4 Effect**
- **Once MCI population is segregated APOE4 is not significant**

---

Test for independence of factors

\[ \text{Chi}^2 = 35.55 \text{ d.f.} = 1 \text{ (p=2.5e-009)} \]
Next Steps
Explore other suitable endpoints such as CDR-SB in MCI

- CDR Sum of Boxes includes cognitive and functional subscores
  - 18 point scale with 6 domains for cognition and function
- The subscores and total score are sensitive to CSF biomarker status
- CDR-SB may represent a more sensitive & less variable scale for MCI
Creating Consensus Science
New Tools and Tactics for Next-Gen Drug Development

SESSION IV: QUANTITIVE DISEASE PROGRESSION MODELS AS TOOLS

November 30th, 2011

JF Marier, PhD, FCP
VP & Lead Scientist
Pharsight - A Certara™ Company
jf.marier@certara.com
QUANTITIVE DISEASE PROGRESSION MODELS AS TOOLS

1. A Drug-Disease Modeling Framework to Predict Efficacy and Support Oncology Drug Development
   - Model made publicly available by FDA
   - Well adopted

2. How can Modeling and Simulation Support the Advancement of Additional Drug Development Tools such as Biomarkers
   - Polycystic Kidney Disease Consortium
   - TKV: Imaging Biomarker of disease progression
     - Disease Model
     - Drug Model + Trial Model
A Drug-Disease Modeling Framework to Predict Efficacy and Support Oncology Drug Development

Dose Reduction -> Dose

Dose -> Systemic Exposure

Systemic Exposure -> Tumor Growth Inhibition (TGI)

TGI -> Survival

Survival -> Change in Tumor Size (CTS)

CTS -> Progression-Free Survival (PFS)

PFS -> Objective Response Rate (ORR)

ORR -> Time to Progression

Sources of variability: PK/resistance, covariates, prognostic factors, gene expression, protein profile

A Drug-Disease Modeling Framework to Predict Survival and Support Oncology Drug Development

Phase Ib-II

Dose → Systemic Exposure → Tumor Growth Inhibition (TGI)

Phase III (prior knowledge)

Tumor Growth Inhibition (TGI) → Survival


Slide 4
How can Modeling and Simulation Support the Advancement of Additional Drug Development Tools such as Biomarkers?

Polycystic Kidney Disease Consortium
1. ADPKD is a debilitating genetic disease affecting more than 12 million people worldwide for which there is currently no known cure or effective treatment.

2. Goals of Collaboration
   - Qualify Total Kidney Volume (TKV) as a biomarker that can be used as a measure of the progression of ADPKD
   - Develop a tool that can improve the efficiency and predictive accuracy of clinical trials that investigate ADPKD.

3. The PKD Consortium is a successful collaboration of the following:
   - C-Path
   - The PKD Foundation
   - Clinical Data Interchange Standards Consortium (CDISC)
   - Various Academic Centers
     - Tufts University
     - University of Colorado
     - Emory University
     - Mayo Clinic
   - Pharmacometrics Consulting Organization (Pharsight)
Changing The Paradigm for Measuring Disease Progression of PKD

![Graph showing kidney function (%) vs. age (years)].

- **Desired Endpoint**
  - Hematuria
  - Infections
  - Hypertension
  - ESRD
  - Mortality

- **Present Endpoint**

*Courtesy V. Torres*

Slide 7
Changing The Paradigm: TKV is the Disease

Exponential Growth of TKV (First-Order)

![Graph showing exponential growth of TKV](image)

Schematic Representation of Model

TKV Growth Rate (First-Order)

Sources of Variability
- Demographics (e.g., Age, Sex, Body Weight, Height, Race, Ethnicity)
- Kidney-specific (e.g., baseline TKV value, number of cysts, or cysts volume, if available)
- Genetic information (i.e., mutations on PKD1 or PKD2 genes)

Grantham et al., 2006 NEJM.
1. Biomarker-Disease Model

For example, the following parametric survival model may be used:

$$\log(T_{ESRD}) = \alpha_0 + [(\alpha_1 \times TKV_{t_{\text{timemax}}})] + (\alpha_2 \times PROG) + \varepsilon$$
Biomarker-Disease Model and Application to Drug Development

1. Biomarker-Disease Model

   TKV Expansion → Disease Outcomes

   Regulatory Qualification of TKV as Imaging Biomarker

2. Drug-Biomarker Model

   Dose → Systemic Exposure → Inhibition of TKV Expansion → Improved Disease Outcomes
Drug Effect Inhibits Growth Rate

Inhibits Proliferation
Slows Growth
“Static Effect”
(e.g., Vasopressin-2-receptor, antagonist, EGFR inhibitors)
Disease Progression Model for TKV and Drug Effect

Growth Rate

Total Kidney Volume

Drug Effect Stimulate

Cysts Fluid Loss (accumulation of cAMP in cyst)

“Shrinkage”

Log TKV vs Time

Drugs On and Off

“Shrinkage”
Disease Progression Model for TKV and Drug Effect

**Drug Effect Inhibit Growth Rate**

- **Total Kidney Volume**
  - **Drug Effect Stimulate**
  - **Cysts Fluid Loss** (accumulation of cAMP in cyst)

"Static + shrinkage"
For example, the following parametric survival model, including DRUG effect maybe used:

\[
\log(T_{ESRD}) = \alpha_0 + [(\alpha_1 \times TKV_{\text{timemax}}) \times DRUG] + (\alpha_2 \times PROG) + \varepsilon
\]

where \(T_{ESRD}\) is the time to ESRD, \(\alpha_0\) is the intercept, \(\alpha_1\) is the slope of effect of TKV, \(TKV_{\text{timemax}}\) is the TKV at a specific timepoint that maximizes the probability of ESRD, DRUG is the drug effect explained using an appropriate Emax model (Dose / Dose + ED\(_{50}\)), \(\alpha_2\) is the slope of a potential prognostic factor, PROG is a potential prognostic factor and \(\varepsilon\) is the residual variability following a normal distribution with a mean of zero and variance of \(\sigma\).

Based on the above “Drug-TKV-Disease” model, results from a Phase IIa study (“Drug-TKV” model) may be used to predict the probability of disease outcome.
Thank You