Model-Based Drug Development
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Disclaimer and Acknowledgments

– Disclaimer

• Views presented herein are mine alone, and do not necessarily reflect those of Quintiles

• All examples presented have been modified (new endpoints, new indication, etc.) to protect client confidentiality

– Acknowledgments

• Also contributing to this work is Seth Berry, Lei Pang, Wei Xiao, and Bradley Ferguson
Talk Outline

– Examples of Model-Based Drug Development (MBDD)
  • Antiviral modeling
  • Disease progression modeling in rheumatoid arthritis (RA)
  • CNS
Antiviral Biomarker Modeling

- **Population:** Patients Infected with a Specific Type of Virus
- **Treatment:** New Molecular Entity (NME)
- **Problem:** Multiple Biomarkers Related to Efficacy of NME; Which Ones Predict Best?
  What’s the Dose-Response Curve Look Like?
  Should We Screen the Biomarkers to Enhance the Power of the Study, or is it Quicker to Include All-Comers?
- **Methodology:** Model Fitting to Find Biomarkers
  Dose-Response Modeling to Fit the Curves
  Trial Simulation (Clinical and Operational) to Answer Questions of Inclusion / Exclusion Criteria
Results

- Found 5 biomarkers predictive of patients most likely to respond to therapy.
- Response is function of number of biomarkers present.
- Dose-response curve was evident ($p<0.05$ for $F$-test of $H_0$: curve flag).
- Depending on recruitment rate, could use biomarkers to enhance the probability of success in trial design.
Antiviral Biomarker Modeling Impact

• Targeting concentration of 30 (have PK model as well)
• Power based on $F$-test as a function of treatment effect
• Inclusion
  • All Comers (N=82 for 80% power)
  • Best 2 inclusion groups (N = 22)
  • Best 1 inclusion group (N = 16)
• What is the preferred I/E criteria?
  • Will approach through simulation
  • Other variables could be included, including differential drop out rates, etc.
Antiviral Biomarker Modeling: Options for planned studies

Statistical distribution for last patient randomized for different I/E options
Disease Progression Modeling & Simulation for RA

- **Problem:** Need to Design Studies in Rheumatoid Arthritis (RA)
- **Constraints:** Rarely Enough Data to Support One-Off Modeling
  Preferred Endpoints Not Consistent Between US and EU
- **Methodology:** Construct Dose- and Time-Response Models in RA for Several Different Endpoints
  Model Constructed in Pharsight’s Trial Simulator for Quick Deployment to Design Trials
  Developing Models for etanercept, adalimumab, tocilizumab, anakinra, CZP, golimumab, infliximab, abatacept
  Development Used for Comparators in Simulations and Experience with Similar Compounds Applied to a Novel Compound
Disease Progression
Modeling & Simulation for RA

- Client Uses
  - Tocilizumab Example
    - Model for other compounds also
  - Model Incorporated into Several Trial Simulations
  - Plan Biosimilar Program
  - Utilize Adaptive Design
    - PK BE
    - Followed by Sample Size Re-estimation
  - Apply Design Changes When Changing Endpoints (ACR20 to DAS28)
Disease Progression Modeling & Simulation for RA

Drug/Dose Effects

ACR20 Response (percentage)

Time (week)

- Low Dose
- Medium Dose
- High Dose
Disease Progression Modeling & Simulation for RA: Impact

• Models used to design biosimilar trials
• Used as inputs into trial simulations
  • Design then optimized for length of trial, number of subjects, statistical analysis method, missing data handling, etc.
• Reduced proposed sample sizes
• Can improve imputation methodologies
Disease Progression Modeling & Simulation for RA: Predictability

• How useful are these models?
• Can they predict trial results?
Roche's RoACTEMRA monotherapy showed superior improvement in rheumatoid arthritis signs and symptoms versus adalimumab monotherapy

Statistically significant greater improvement in signs and symptoms, as measured by mean change in DAS28 (primary endpoint), DAS28 remission and low disease activity, ACR20, 50 and 70 (secondary endpoints)
Focus on just adalimumab and tocilizumab

Our model uses methotrexate as background versus monotherapy in the Roche study, but we still predicted the results.
Disease Progression Modeling & Simulation: Use with NME

- Can be used to predict behavior of new antibody-based therapeutic
- Have distribution of shapes and dose-responses that can be used as prior
- Trial data can be combined with prior to get estimate of curve faster than using data alone
Disease Progression Modeling & Simulation: Other diseases available

- Other disease progression models based on literature data are available, including
  - Alzheimer’s
  - Parkinson’s

- Many sponsoring organizations have other models as well
CNS Drug Development: Go/no-go Decision, Retrospective Review

– Problem: CNS drug was developed previously, and we wanted to see if using MBDD methods would improve decision making

– Methodology: Data from Phase I through III available

  Analyze the data by Phase, and using the models from that phase to design trials for the next phase

  Phase I model: PK (no PD endpoints)

  Analyzed Phase II data to develop PK/PD model, and using this model to develop plan for Phase III
CNS Drug Development

Loess curves for dose-response and exposure-response

Higher is worse scores

Colors represent sex of subjects
CNS Drug Development: Modeling

Linear models (95% CI) for dose-response and exposure-response

No dose-response. Hint of exposure-response, but it is wrong direction!
CNS Drug Development: Conclusion

Efficacy

Incidence of AE

$C_{\text{max}}$

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CNS Drug Development: Conclusion

• Tried other types of models as well (e.g., Hill model), but linear was best fit

• Recommendation
  • Discontinue development, or at most continue with Phase II development

• Actual results of Phase III: Active failed to show improvement vs placebo
Conclusion

• Models can predict clinical trial results
  o Need to spend effort to develop the models
  o Model becomes increasingly useful as it is being built
  o Modeling efforts can reduce costs by stopping programs early when needed
  o Optimizing trial design