When statistics and pharmacometrics join forces for advanced quantitative drug development: A case study

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Outline

1. Introduction:
   Design of clinical trials

2. Ophthalmology example:
   Sustained delivery device in nAMD

3. Neuroscience example:
   Alzheimer disease (AD) prevention program

4. Conclusion:
   Quantitative drug development
   from pharmacology to decision making
In novel drug development settings:

• Relevant information is scarce:
  – need better synthesis and additional assumptions

• Modeling, statistics & simulation as an intermediary to
  – synthesize available information
  – Assess design options by simulation to check impact of assumptions

• Two real case studies illustrate the impact of such an approach
  When statistics and pharmacometrics join forces for advanced quantitative drug development
Neovascular age-related macular degeneration (nAMD)

If Untreated Severe Degradation of Vision within ~1-2y

- Prevalent in elderly patients
- Treatment with intravitreal (IVT) injections of anti-VEGF inhibitor
- Standard clinical endpoint is best corrected visual acuity (BCVA) measured as letters read from ETDRS chart
- Usually assessed as change from baseline BCVA \( \Delta \)
Sustained delivery device in nAMD
Addresses an unmet medical need

• A less frequent need for retreatment: reducing the treatment burden and IVT-related undesired effects
• Valuable from a minimum refill interval of 4 months
Sustained delivery device in nAMD
Phase 2 design

- Primary objective: one high dose device arm is superior to low dose device arm
- Key secondary objective: one device arm is non-inferior to monthly IVT
- Lack of information for trial design assumptions for:
  - Primary endpoint: time to refill, Key secondary endpoint: BCVA change from baseline to month 9
  - Refill criteria
  - Dose response assessment
  - Pre-treatment and population selection
  - Sample size, duration and power
- Wealth of information on disease progression & IVT treatment effect on BCVA
Sustained delivery device in nAMD
PK/PD and trial modeling and simulation approach

In Vitro Device Release Profile

Pharmacokinetics
Drug PK in Vitreous

Pharmacodynamics
Drug effect and disease progression

E_{\text{max}}
EC_{50}
VA_{\text{prod}}
VA_{\text{deg}}

Predicted KM curves for time to first refill events

Simulated individual BCVA following initial implantation

Log-rank test and power calculation

Statistics & pharmacometrics for quantitative drug development - E Zuber - WCoP2016 Brisbane
Sustained delivery device in nAMD

Key trial design features informed by simulations

• Exploring impact on power of design features & device performance
  – 500 simulated trials, 60 simulated patients in each arm receiving implantation

• Sample size

<table>
<thead>
<tr>
<th>one-sided significant level $\alpha$</th>
<th>Sample size (# of patients per implant arm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=50</td>
</tr>
<tr>
<td>$\alpha = 0.1$</td>
<td>0.67</td>
</tr>
<tr>
<td>$\alpha = 0.15$</td>
<td>0.752</td>
</tr>
<tr>
<td>$\alpha = 0.2$</td>
<td>0.82</td>
</tr>
</tbody>
</table>

• Refill criteria

• Selection of IVT loadings responders to receive implantation
  – power decreases by ~6% with “all inclusive” design vs. responders only

• Number of monthly IVT loading doses prior to implantation
  – Small impact on power (<3%) with 6 vs. 3 loading doses

• Duration of study
  – 12 months follow-up time after implantation increases study power by ~4% vs. 9 months

• Variability in device performance
  – Decrease in release rate slightly increases power
Alzheimer’s disease (AD)

AD is a key unmet medical need, one of the most prevalent neurological disorders among older people worldwide.

- Aβ-based trials in dementia phase of AD have failed
- Idea: Early intervention may increase likelihood of success
- Challenges:
  - Definition and identification of preclinical population
  - Traditional cognitive endpoints for mild cognitive impairment (MCI) or dementia stages not adequate for preclinical AD
AD prevention program
Population and Endpoint

• Population enrichment strategy
  – APOE ε4 homozygotes (HM), cognitively unimpaired, 60-75 years
  – HM have high risk to be amyloid positive and to develop AD dementia

• Dual primary endpoint approach
  – Time to event (TTE):
    Postponing the diagnosis of MCI/dementia: important clinical outcome with high face validity
  – APCC (API* Composite Cognitive scale)
    – developed as a combination of well-established test scores to evaluate treatments in prevention trials in preclinical AD
    – expected to detect cognitive decline in individuals who subsequently progress to clinical stages of AD
  – Success determined by a positive result in at least one endpoint

* Alzheimer Prevention Initiative.
AD prevention program
Quantitative approach to inform trial design

• Exploration of endpoints in available cohort data
  – Rush, NACC, ADNI
  – Scarce relevant data
  – Not sufficient to inform trial design

• Fit TTE model based on important baseline characteristics

• Fit model for the APCC depending on the time of diagnosis

• Simulate trial data based on models
  – To investigate the performance of endpoints in the target population
  – To optimize enrichment strategy
  – To investigate other design features
AD prevention program
Exploration of endpoints in available cohort data
• APCC in Rush cohort data
AD prevention program
Exploration of endpoints in available cohort data

• TTE in NACC cohort data

After 5 years:
AD: 17%
AD/MCI: 42%
N = 177
AD prevention program

Exploration of endpoints in available cohort data

• TTE in Rush cohort data

- Increasing trend for progression in APOE4 HM
AD prevention program
Simulation of trial data based on models

• To optimize enrichment strategy: Investigate ratio of age groups [60,65] : [65,70] : [70,75] of 1:2:2 versus expected ratio of 3:2:1

• Simulate TTE data
  – More elderly population, shorter median TTE, more events => higher power for a given HR and follow up time


**AD prevention program**

Simulation of trial data based on models

- Simulate APCC profiles
  - More elderly population, steeper decline, greater difference at year 5 => higher power for a given HR
**Conclusion:**
Model informed drug development: quantitative scientific approaches to inform decision making

- Fundamental design features based on best available knowledge in both programs
  - modeling & simulation framework: combine pharmacometrics and biostatistics skills
  - Project team discussions guided by transparent review of available knowledge, explicit assumptions and identified uncertainties

- Collaboration illustrates good analytical practices & principles:

**Decisions** are informed by relevant results, with a known level of statistical confidence, from available data and background knowledge, using the best analytical approaches.
Conclusion:
Quantitative drug development: from pharmacology to decision making

- Beyond prejudices: twin disciplines
  - We are all modelers, discriminating signal vs. noise
  - We may think we have different dialects...

\[ y_{ij}^{PK} = f(x_{ij}, \psi_i^{PK}) \cdot (1 + \varepsilon_{ij}^{\text{prop,PK}}) + \varepsilon_{ij}^{\text{add,PK}} \]

Non-linear structural model

Error model

\[ \varepsilon_{ij}^{\text{prop,PK}} \sim N(0, \omega^{2,\text{prop,PK}}) \]
\[ \varepsilon_{ij}^{\text{add,PK}} \sim N(0, \omega^{2,\text{add,PK}}) \]

“What pharmacometricians dream about”

“What statisticians worry about”
Conclusion
Quantitative drug development:
from pharmacology to decision making

• Develop bilingual pharmacometricians and statisticians
  ➢ A broader perspective on drug development:
    From biology and pharmacology, to decision making and confirmatory statistics
  ➢ Learning and confirming in a closer dialogue, serving the same purpose

• A development opportunity for all
  ➢ Statisticians going back to the biological meaning of their work
  ➢ Pharmacometricians integrating the confirmatory purpose of their work

• A challenge for organizations to
  ➢ Provide a visionary, nurturing environment for multidisciplinary teams
  ➢ Educate stakeholders as much as collaboration partners
  ➢ ...e.g., through one integrated quantitative sciences department
**Conclusion:**
Learning from each other to facilitate better drug development

“Pharmacology and statistics are the two threads that run right through drug development. I hope that our two communities can increase our collaboration in the future, learn from each other, and help spread to others in drug development what we have learned.”

Pharmaceutical statistics

“pragmatic in purpose, empirical in method, and skeptical and pessimistic in attitude. Its approach to modelling is biologically innocent and its view of causality is 'voluntary'.”

Pharmacometrics

“explanatory in purpose, theory based, and optimistic in attitude. Its approach to modelling is biologically knowledgeable and its view of causality is mechanistic”.

Senn (2010)
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