A Bayesian Approach to Augment Active Comparator Efficacy Information with Historic Randomized Clinical Trial Data in a Non-Inferiority Trial

Donna Williams, Cheerful
Donna Williams, an autistic artist, author and renowned autism advocate, was diagnosed with breast cancer in 2011.

Wouter Willems
In collaboration with Cristiana Mayer, Kyle Wathen, and the project team

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Amsterdam, 5 June 2018
Hepatitis C

JNJ-4178: 3DAA combination drug
- HCV leading cause of liver disease
- 2% of global population is infected
- Chronic infection, can lead to liver cirrhosis, hepatocellular carcinoma, liver transplantation or death
- Decreased life expectancy (-20 years)
- <5% treated in G5 countries

3 Direct Acting Antivirals

Olysio (Simeprevir)  AL-335

Odalasvir (ODV)
HPC3003 trial

• Pivotal, phase 3 head-to-head non-inferiority study
• Active control: Harvoni®, the current standard of care (SOC)
• Primary efficacy hypothesis: 6w with JNJ-4178 is non-inferior to 8 or 12 weeks of Harvoni®
• Primary efficacy endpoint: SVR12 (binary)
• Non-inferiority considered as sufficient as efficacy of Harvoni® close to 100%.
• Original design N=400 in JNJ-4178 and N=200 in Harvoni® arm

But there is already a lot of efficacy data on Harvoni®. Do we need to repeat the efficacy assessment of the comparator? Can we incorporate the available data?

• Scientific publications
• Label
WHY? - Borrowing Historic Control Data in NI Setting

- **Motivation**: Augment the efficacy data SOC with historic data in a comparable patient population to:
  - Increase probability of positive study to claim non-inferiority: **power**
  - Reduce resources allocated on Harvoni arm in HTH: **Harvoni ss**
  - Reduce total time to complete the study: **trial duration**

- **Method**: Use Bayesian approach to **statistically combine** Harvoni efficacy data from historic control with HTH trial data

- **Stats Recommendation**: Inquire about FDA/EMA openness to explore this alternative approach with a question in the briefing book
Factors Supporting Borrowing Historical Data

✓ Expected large treatment effect: yes, SVR12 >95%

✓ Consistency across historical control response rates: yes, consistent in SOC ph3 results

✓ Difficult to bias outcome assessment: yes, lab assessment

✓ Accurately ascertained outcome not alterable by other therapy or management choices

✓ Use of historic data from randomized clinical trials of similar design rather than KOL opinions or subjective sources: yes, SOC ph3 results

✓ Historic data not too far back in time (reduced time effect and other potential confounding factors in older clinical trials): SOC ph3 results published in 2014

✓ Large, broad-based historical datasets especially relative to total size of patient population and size of treatment arm: large ph3 dataset from SOC
How to Prove Non-Inferiority

**Bayesian approach:** synthesis of historic SOC data with the HTH results, calculate the posterior probability criterion to declare NI

**Posterior Probability** = $\Pr[ \text{JNJ-4178 SVR12 rate is no worse than SOC by more than 5% NI margin given the study results}]$

$\text{Posterior probability } P(r_{JNJ-4178} - r_{Harvoni} > -0.05|\text{data}) \geq \text{cutoff}$

$\Rightarrow$ Which cutoff to chose?

**Frequentist approach:** The conventional NI design which tests by using **95% Confidence Interval**

$H_0 : \ r_{JNJ-4178} - r_{SOC} \leq -NI \ margin$

$H_a : \ r_{JNJ-4178} - r_{SOC} > -NI \ margin$

*Lower Bound 95% CI > -NI margin*
## SOC Historic Ph3 Studies – A Simplification

<table>
<thead>
<tr>
<th>Study SOC</th>
<th>ION1 w/o cirrhosis</th>
<th>ION3 w/o cirrhosis</th>
<th>ION3 w/o cirrhosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 or 12 wks</td>
<td>177 12 wks</td>
<td>216 12 wks</td>
<td>215 8 wks</td>
<td>608</td>
</tr>
<tr>
<td>sample size</td>
<td>176</td>
<td>208</td>
<td>202</td>
<td>586</td>
</tr>
<tr>
<td>Successes</td>
<td>99.4%</td>
<td>96.3%</td>
<td>93.9%</td>
<td>96.4%</td>
</tr>
</tbody>
</table>

=> How much should we borrow?

- SOC (8 & 12 weeks) SVR12 rate from the label
- Assume a prior Beta(586,22)
- Too informative

\[
\text{Beta}(586* w, 22*w) \quad \text{w is the weight TBD based on false positive error control}
\]
Regulatory Interactions
1 Year Story: Design and Regulatory interactions

Stats/Team Activities
- Brainstorm/Propose
- Bayesian design to CT
- Run simulations

September 2016
- BB to the FDA
- Type C mtg
- BB to the CHMP
- Sc.Advice

Non-Inferiority Clinical Trials to Establish Effectiveness
Guidance for Industry

September 2016
- Non Inferiority Clinical Trials to Establish Effectiveness
- Guidance for Industry

September 2017
1 Year Story: HPC3003 Design Development

Stats/Team Activities

Brainstorm/Propose
Bayesian design to CT
Run simulations

September 2016

HA Interactions

BB to the FDA
Type C mtg

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Non-Inferiority Clinical Trials to Establish Effectiveness
Guidance for Industry

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Can prior information or other data (e.g., studies of related drugs, pharmacologic effects) be considered statistically in choosing the NI margins or in deciding whether the NI study has demonstrated its objective?

Bayesian methods that incorporate historical information from past active control studies through the use of prior distributions of model parameters provide an alternative approach to evaluating non-inferiority in the NI trial itself. Although discussed in the literature and used in other research settings, CDER and CBER have not had much experience to date in evaluating NI trials of new drugs or therapeutic biologics that make use of a Bayesian approach for design and analysis. If a sponsor is planning to conduct a Bayesian NI trial, early discussions with the Agency are advised.
1 Year Story: HVC3003 Design Development

Stats/Team Activities
Brainstorm/Propose Bayesian design to CT
Run simulations

September 2016

HA Interactions
BB to the FDA Type C mtg
BB to the CHMP Sc.Advice

h) Support the use of a Bayesian approach to augment the efficacy data from the SOC subjects in the head-to-head study with SOC historical clinical trial data for the non-inferiority assessment?

**FDA Response to Question 8h:** Please provide detailed information regarding the framework of the Bayesian approach and how the approach will be used either in the randomization and/or final analysis stage. Please provide the full simulation report along with the programs for review.
h) Support the use of a Bayesian approach to augment the efficacy data from the SOC subjects in the head-to-head study with SOC historical clinical trial data for the non-inferiority assessment? The Applicant is free to include such features in the SAP. However, the primary analysis should be of a standard, frequentist nature, as this is, in any case, the analytic approach that will be taken from a regulatory perspective.
1 Year Story: HPC3003 Design Development

Stats/Team Activities

Brainstorm/Propose Bayesian design to CT
Run simulations

(1) Make Bayesian NI as key secondary analysis
(2) Run simulations

Submit MSR to the FDA

September 2016

HA Interactions

BB to the FDA
Type C mtg

BB to the CHMP
Sc.Advice

Meeting with the FDA

Non-Inferiority Clinical Trials to Establish Effectiveness
Guidance for Industry

Response from CHMP

September 2017
Simulations
Assumptions and Simulations Scenarios

How much historical information to borrow?
Which cutoff for probability?
False positive error rate?
Power?

Simulation parameters
- **Historic studies**: pooled mean SVR=0.964
- **Non inferiority margin**: 0.05
- **SOC rates**: range between 0.96 and 0.99
- **JNJ-4178 rates**: range between 0.90 and 0.99
- **N for JNJ-4178** = 400
- **N combined for SOC** = 200 (including borrowed subjects)
False positive by Amount of Borrowing, Delta= -0.05

The larger the observed SOC rate (each panel), the larger the inflation of false positive rate.

The smaller the cutoff for posterior prob. (red line vs. purple line), the larger the inflation of false positive rate. With increasing amounts of “borrowing”

If SOC SVR12= 99%: cutoff of 0.985, borrow no more than 20 subj eq.; cutoff of 0.99 borrow no more than 50 subj eq.
Posterior Prob > 98.5% vs 99% Criterion

The more we borrow (x-axis), the higher prob. of declaring non-inferiority.

With less stringent cutoff (panel on the left), the prob. of success is higher.

Larger gains in prob. of success with more borrowing for negative delta’s, i.e. JNJ-4178 rate< SOC rate (red, green lines vs purple).
### SOC Sample Size in HTH Study

SOC rate 97% ; JNJ-4178 rate = 97%; Delta =0; JNJ-4178 n=400 ; 5% Margin

Posterior Probability \( (r_{JNJ4178} - r_{SOC}) > -5\% \mid \text{data, priors} \) ≥ cutoff

<table>
<thead>
<tr>
<th>N SOC in study</th>
<th>N borrowed (equivalent)</th>
<th>Weight on prior</th>
<th>Cut off</th>
<th>False positive (delta= -0.05)</th>
<th>Prob Success (%)</th>
<th>NI Conventional Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>20</td>
<td>3.3%</td>
<td>0.985</td>
<td>0.016</td>
<td>94.0%</td>
<td>91.3%</td>
</tr>
<tr>
<td>160</td>
<td>40</td>
<td>6.6%</td>
<td>0.985</td>
<td>0.015</td>
<td>94.1%</td>
<td>90.2%</td>
</tr>
<tr>
<td>150</td>
<td>50</td>
<td>8.2%</td>
<td>0.985</td>
<td>0.016</td>
<td>94.2%</td>
<td>89.5%</td>
</tr>
<tr>
<td>140</td>
<td>60</td>
<td>9.9%</td>
<td>0.985</td>
<td>0.014</td>
<td>96.0%</td>
<td>88.9%</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
<td>16.4%</td>
<td>0.985</td>
<td>0.015</td>
<td>96.4%</td>
<td>85.1%</td>
</tr>
</tbody>
</table>

More stringent cutoff 0.99 makes the Type 1 error control tighter.

Which cutoff?

Do we need to be so stringent?
## SOC Sample Size in HTH Study

SOC rate 97%, 98%, 99% ; JNJ-4178 rate = 97%; JNJ-4178 n=400 ; 5% Margin
Cut off = 0.985

<table>
<thead>
<tr>
<th>N SOC in study</th>
<th>N borrowed (equivalent)</th>
<th>SOC Rate</th>
<th>JNJ-4178 Rate</th>
<th>False positive (delta= -0.05)</th>
<th>Prob Success (%)</th>
<th>NI Conventional Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>20</td>
<td>0.97</td>
<td>0.97</td>
<td>0.016</td>
<td>94.0%</td>
<td>91.3%</td>
</tr>
<tr>
<td>160</td>
<td>40</td>
<td>0.97</td>
<td>0.97</td>
<td>0.015</td>
<td>94.1%</td>
<td>90.2%</td>
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<tr>
<td>150</td>
<td>50</td>
<td>0.97</td>
<td>0.97</td>
<td>0.016</td>
<td>94.2%</td>
<td>89.5%</td>
</tr>
<tr>
<td>140</td>
<td>60</td>
<td>0.97</td>
<td>0.97</td>
<td>0.014</td>
<td>96.0%</td>
<td>88.9%</td>
</tr>
<tr>
<td>180</td>
<td>20</td>
<td>0.98</td>
<td>0.97</td>
<td>0.019</td>
<td>86.8%</td>
<td>83.2%</td>
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<tr>
<td>160</td>
<td>40</td>
<td>0.98</td>
<td>0.97</td>
<td>0.021</td>
<td>89.3%</td>
<td>82.0%</td>
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<tr>
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<td>0.97</td>
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<td>90.0%</td>
<td>81.4%</td>
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<tr>
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<tr>
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<td>0.97</td>
<td>0.0249</td>
<td>74.9%</td>
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<tr>
<td>160</td>
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<td>0.99</td>
<td>0.97</td>
<td>0.030</td>
<td>80.8%</td>
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<tr>
<td>150</td>
<td>50</td>
<td>0.99</td>
<td>0.97</td>
<td>0.033</td>
<td>81.4%</td>
<td>67.6%</td>
</tr>
<tr>
<td>140</td>
<td>60</td>
<td>0.99</td>
<td>0.97</td>
<td>0.044</td>
<td>84.8%</td>
<td>67.1%</td>
</tr>
</tbody>
</table>

How much borrowing?
### Team Proposal

<table>
<thead>
<tr>
<th>N SOC in study</th>
<th>N borrowed (equivalent)</th>
<th>SOC Rate</th>
<th>JNJ-41 78 Rate</th>
<th>False positive (delta=-0.05)</th>
<th>Prob Success (%)</th>
<th>NI Convention al Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>50</td>
<td>0.97</td>
<td>0.97</td>
<td>0.016</td>
<td>94.2%</td>
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<td>50</td>
<td>0.98</td>
<td>0.97</td>
<td>0.023</td>
<td>90.0%</td>
<td>81.4%</td>
</tr>
<tr>
<td>150</td>
<td>50</td>
<td>0.99</td>
<td>0.97</td>
<td>0.033</td>
<td>81.4%</td>
<td>67.6%</td>
</tr>
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</table>

**Savings ~7MM=**

- $\Delta^-$ Cost SOC treatment +
- $\Delta^-$ Total time recruitment +
- $\Delta^-$ Time to complete study +
- $\Delta^-$ Cost of visits & procedures/patient
EXAMPLE
Borrow N Equivalent = 50; JNJ-4178 N=400; SOC N=150

Results:
Bayesian approach:
Prob[JN4178>SOC-0.05 | study data] = 99.1%
Conclude NI?
- Bayesian YES because 99.1% > 98.5%
- Conventional CI NO because -0.0505 < -0.050

Conventional NI design:
95% CI: [-0.0505; 0.012]

Observed SVR12 (delta=-2.5%)
JNJ-4178 96.2% = 385/400
SOC 98.7% = 148/150

EXAMPLE
Borrow N Equivalent = 50; JNJ-4178 N=400; SOC N=150

Conclude NI?
Results:
Bayesian approach:  
Prob[JN4178>SOC-0.05 | study data] = 99.55%

Conventional NI design:  
95% CI: CI:[-0.0453; 0.0219]

Conclude NI?
- Bayesian  YES because 99.1% > 99.55%
- Conventional CI  YES because -0.0453 > -0.050
Bayesian versus frequentist

SOC = 148/150 = 98.7%
JNJ4178 = 385/400 = 96.2%

SOC = 147/150 = 98.0%
JNJ4178 = 385/400 = 96.2%

Green area: SOC > 97.7% JNJ-4178 > 95%
Bayes NI or the same

Orange area:
SOC < 96.7% and JNJ4178 ≤ 95%
CI NI or the same

If JNJ4178 SVR12 ≤ 95%, it is not commercially viable;
If JNJ4178 SVR12 > 95%, Bayesian offers either the same conclusions as CI or a few more successes

CI declares NI, not Bayes
Conclusions

Bayesian approach allowed incorporating historical data in a statistical and regulatory acceptable way

PDUFA VI and FDA Pilot Program on Complex Innovative Design likely to stimulate a more frequent use of such designs

Advice from our experience:
• Start preparing and discussing early (internally and with Agencies)
• Choice and justification historical data are important
• Simulations needed for parameter choice
thank you