A Bayesian Approach in the Non-Inferiority Setting

Cristiana Mayer
Janssen R&D, Johnson & Johnson
In collaboration with Wouter Willems and the project team

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Hepatitis C

- 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

JNJ-4178 = 3DAA

Olysio (Simeprevir)
Proven Efficacy and Safety
Robust dataset of SMV+SOF

AL-335
Highly synergistic with other MOAs

Odalasvir (ODV)
HCV NSSA inhibitor
Promising data ODV+SOF
HPC3003 Phase 3 Trial

- Required pivotal phase 3 head-to-head non-inferiority study
- The current standard of care (SOC) is the active control (Harvoni® by Gilead)
- Primary efficacy endpoint: SVR12 (binary) endpoint
- Primary efficacy hypothesis: JNJ-4178 is non-inferior to 8 or 12 weeks of SOC
- Non-inferiority because efficacy of SOC >95%
- Conventional NI design powered with N=400 in JNJ-4178 and N=200 in SOC
How to Include Innovation in the NI Study Design?

There is a wealth of SOC efficacy data in the public domain. Why repeat the SOC efficacy assessment?

How can we use the external SOC data to make our study more EFFICIENT?
What the Bayesian Approach is NOT
- Matched-pairs design
- Extracting patient-level data from SOC historic trials
- Weighted average of historic SVR12 with the observed SVR12 in the study

What the Bayesian Approach IS
- Method to *synthesize* data by combining probability distributions with the observed data
Why?

**Motivation**: Augment the efficacy data of subjects randomized to SOC in the HTH study with historic SOC randomized historic control data in a *comparable* patient population to:

- Increase probability of positive study to claim non inferiority: **Power**

- Reduce resources allocated on SOC arm in HTH: **N**

- Reduce time to complete the study: **Trial duration**

**Method**: Use Bayesian approach to statistically combine SOC efficacy data from historic control with HTH trial data
Factors Supporting The Approach in The Hep C Context

✓ Expected **large treatment effect** (SVR12 >95% )

✓ **Consistency** across historical control response rates (Low variability)

✓ **Difficult to bias & accurately ascertained outcome** (lab assessment)

✓ Use of historic data from randomized **clinical trials** of similar design rather than KOL opinions or subjective sources

✓ Historic data **not too far back** in time (reduced time effect and other potential confounding factors in older clinical trials)

✓ **Large, broad-based historical datasets** especially relative to total size of patient population and size of treatment arm

✓ **Same similar key baseline characteristics** in historic and HTH trial

Concepts borrowed from M. Walton (Janssen); December 2012 Short Course at CDER FDA; with permission
Statistical Approaches to Be Compared

**Bayesian Posterior Probability**

- **To test:**
  - $H_0: r_{JNJ-4178} - r_{SOC} \leq -\text{NI margin}$
  - $H_a: r_{JNJ-4178} - r_{SOC} > -\text{NI margin}$

- **Lower Bound 95% CI > -\text{NI margin}**

**95% Confidence Interval approach**

- **To test:**
  - $H_0: r_{JNJ-4178} - r_{SOC} \leq -\text{NI margin}$
  - $H_a: r_{JNJ-4178} - r_{SOC} > -\text{NI margin}$

- **Posterior prob( r_{JNJ4178}-r_{SOC} > -5\% \mid \text{data} ) > \text{cutoff}**
SOC Historic Ph3 Studies – A Simplification

<table>
<thead>
<tr>
<th>Study</th>
<th>ION1</th>
<th>ION3</th>
<th>ION3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC 8 or 12 wks</td>
<td>w/o cirrhosis</td>
<td>w/o cirrhosis</td>
<td>w/o cirrhosis</td>
<td></td>
</tr>
<tr>
<td>12 wks</td>
<td>177</td>
<td>216</td>
<td>215</td>
<td>608</td>
</tr>
</tbody>
</table>

| Successes      | 176           | 208           | 202           |       |
| SVR12 rate     | 0.994         | 0.963         | 0.939         | 0.964 |

Source: SOC USPI Label Revised 2016: Tables 10; 11; 8
Note: Simplification for initial exploratory simulations= 8 wks and 12 wks regimens pooled; ION1: subset of non cirrhotic subjects

Run also a sensitivity analysis with different priors for the experimental treatment

JNJ-4178 prior

Beta (0.95, 0.05)

- SOC (8 & 12 weeks) SVR12 rate from the label
- Assume a prior Beta( 586,22)
- Too informative
- How much should we borrow?

Beta( 586* w, 22*w)
w is the weight TBD based on false positive error control

Full borrowing
- Use 8% (50 eq. subj)
- Use 3% (20 eq subj)

~No borrowing (1 eq subj)

FDA Guidance: “We may recommend discounting of historical/prior information if the prior distribution is too informative relative to the current study. What constitutes “too informative” is also a case-by-case decision.”
Assumptions and Initial Scenarios

- **Historic studies**: ION1 and ION3, subgroup GT=1, non cirrhotic patients (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
- **Prior Distribution**: Beta family for SOC and JNJ-4178
- **N for JNJ-4178**: 400
- **Amount of borrowing**: N-equivalent= 1, 10, 20, 40, 50, 60, 80 and 100
- **N for SOC**: 199, 190, 180, 160, 150, 140, 120 and 100
- **N-eq. borrowed + N SOC in study = 200 fixed**
- **10,000** simulations per scenario
False Positive by Amount of Borrowing, and Rate in SOC, \( \text{Delta} = -0.05 \)

The larger the observed SOC rate (each panel from top to bottom left to right), 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" (x-axis).

If SOC SVR12 = 99% (bottom right panel) cutoff of 0.985 (cyan line), borrow no more than 20 subj eq.; cutoff of 0.99 (purple line) borrow no more than 50 subj eq.
Posterior Prob > 98.5% vs 99% Criterion

**Cutoff = 98.5%**

**Cutoff = 99%**

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

With less stringent cutoff (panel on the right, cutoff = 98.5%), 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 or green lines).
SOC Sample Size in HTH Study
SOC rate 97%; JNJ-4178 rate = 97%; Δ = 0; JNJ-4178 n = 400; 5% Margin

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

<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 the cutoff 0.9, the tighter the Type 1 error control

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*

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<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>
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<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>
</tr>
<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>
</tr>
<tr>
<td><strong>150</strong></td>
<td><strong>50</strong></td>
<td><strong>0.98</strong></td>
<td><strong>0.97</strong></td>
<td><strong>0.023</strong></td>
<td><strong>90.0%</strong></td>
<td><strong>81.4%</strong></td>
</tr>
<tr>
<td>140</td>
<td>60</td>
<td>0.98</td>
<td>0.97</td>
<td><strong>0.025</strong></td>
<td>91.4%</td>
<td>80.7%</td>
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<tr>
<td>180</td>
<td>20</td>
<td>0.99</td>
<td>0.97</td>
<td>0.0249</td>
<td>74.9%</td>
<td>68.6%</td>
</tr>
<tr>
<td>160</td>
<td>40</td>
<td><strong>0.99</strong></td>
<td>0.97</td>
<td><strong>0.030</strong></td>
<td>80.8%</td>
<td>67.9%</td>
</tr>
<tr>
<td>150</td>
<td>50</td>
<td><strong>0.99</strong></td>
<td>0.97</td>
<td><strong>0.033</strong></td>
<td>81.4%</td>
<td>67.6%</td>
</tr>
<tr>
<td><strong>140</strong></td>
<td><strong>60</strong></td>
<td><strong>0.99</strong></td>
<td><strong>0.97</strong></td>
<td><strong>0.044</strong></td>
<td><strong>84.8%</strong></td>
<td><strong>67.1%</strong></td>
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**Team Proposal To Start Thorough Simulations**

<table>
<thead>
<tr>
<th>N SOC in study</th>
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<th>SOC Rate</th>
<th>JNJ-41 78 Rate</th>
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<td>0.97</td>
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<td>81.4%</td>
<td>67.6%</td>
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**Savings ~7MM=**

- $\Delta^{-}$ Cost SOC treatment +
- $\Delta^{-}$ Total time recruitment +
- $\Delta^{-}$ Time to complete study +
- $\Delta^{-}$ Cost of visits & procedures/patient
Results:
Bayesian approach: \( \text{Prob}[\text{JNJ4178}>\text{SOC}-0.05 \mid \text{study data}] = 99.1\% \)

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

Conclude NI?
- Bayesian YES because 99.1% > 98.5%
- Conventional CI NO because -0.0505 < -0.050
Results:
Bayesian approach: \( \text{Prob}[\text{JN4178} > \text{SOC}-0.05 \mid \text{study data}] = 99.55\% \)
Conventional NI design: 95% CI: \([-0.0453; 0.0219]\)

Conclude NI?
- Bayesian YES because 99.1% > 99.55%
- Conventional CI YES because -0.0453 > -0.050
Possible Study Outcomes

Green area: SOC>97.7% JNJ4178 > 95%
Bayes declares NI or both methods

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

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

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

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

CI declares NI, not Bayes
One-Year Story and Regulatory Interactions

Modeling and Simulation Report

We understand the attractiveness of the Bayesian approach in the setting where there is previous information on the highly efficacious active control, and we encourage exploration of the approach. We have the following comments:
Conclusions

- **Bayesian designs** can bring innovation into drug development

- Statisticians to work with the team in “education” on new approaches and in thinking “out of the box”

- **Discuss** Bayesian designs early with the Regulatory Agencies

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

- More experience discussing the **Simulation Report** with the FDA is needed

- **Plan early** with the team and **simulate, simulate and simulate**