A Bayesian Approach in the Non-Inferiority Setting

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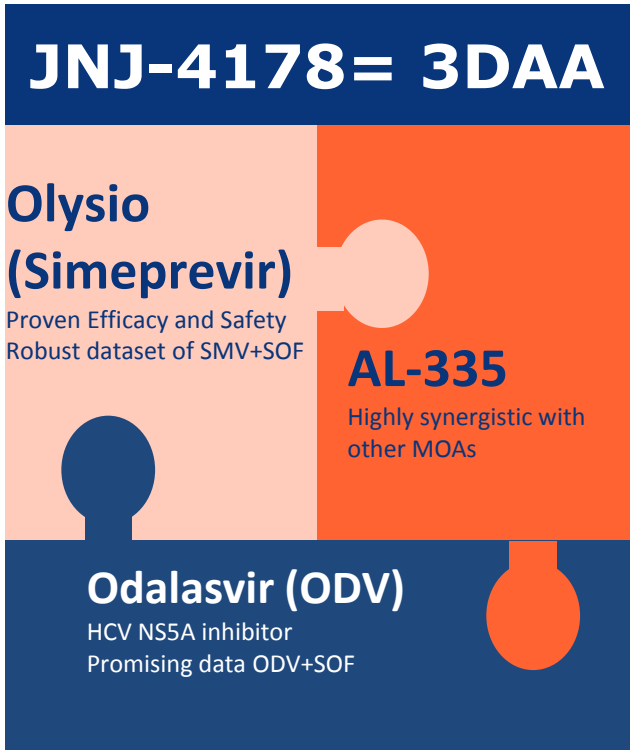
janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

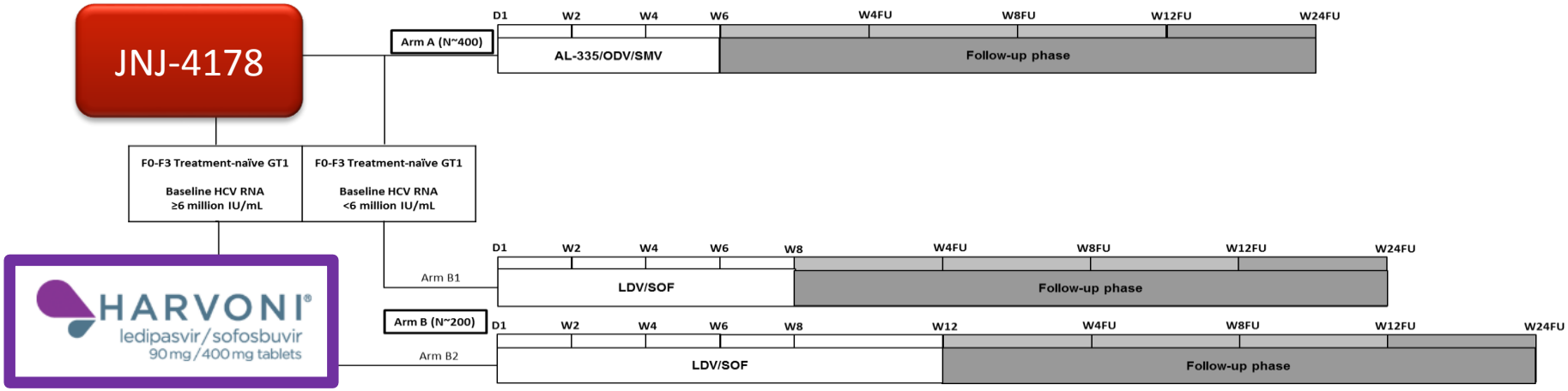
Hepatitis C



- 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

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?

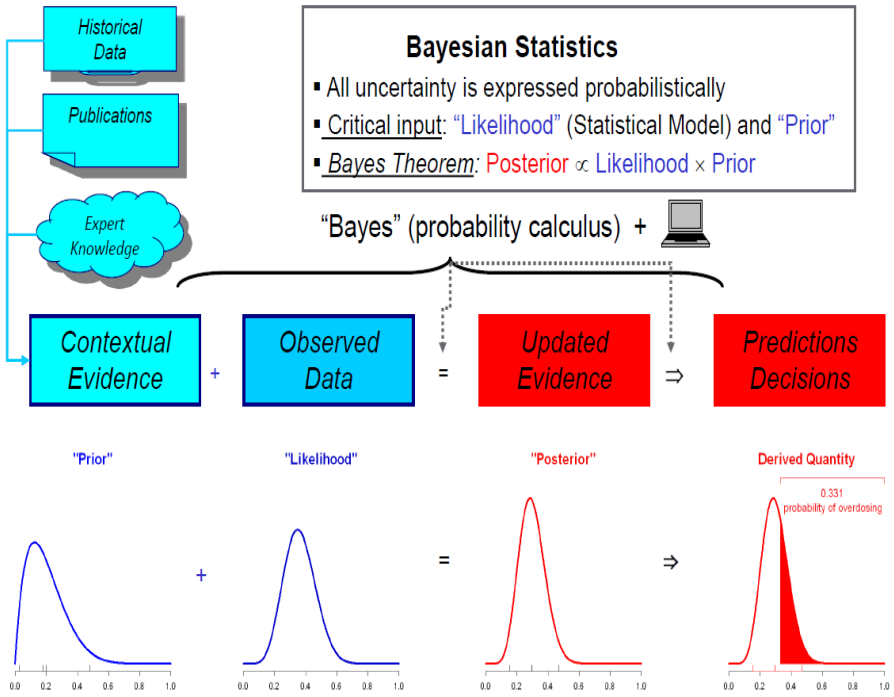
Leveraging SOC Historic Data in the Bayesian Framework

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



From D. Ohlssen (Novartis) April 2016 with permission

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

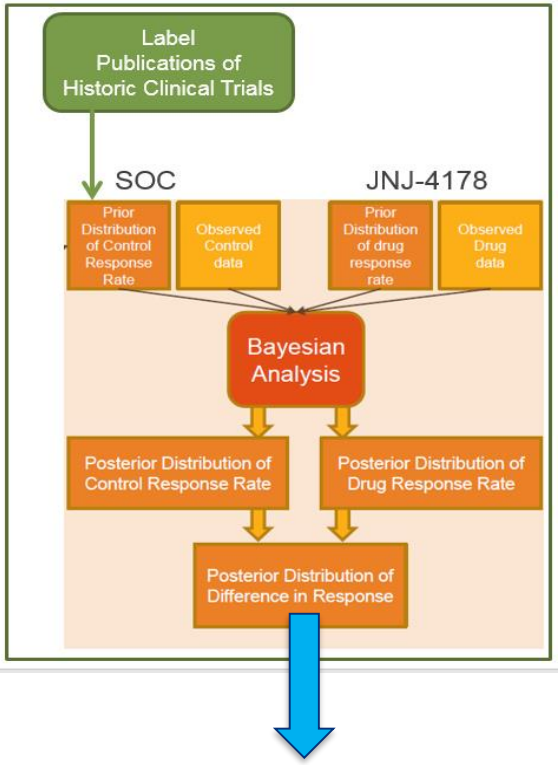
Factors Supporting The Approach in The Hep C Context

- ✓ 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



VS.

95% Confidence Interval approach

To test:

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

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

Lower Bound 95% CI > - NI margin

Posterior prob(r_JNJ4178–r_SOC > - 5% | data)> cutoff

SOC Historic Ph3 Studies – A Simplification

Study SOC 8 or 12 wks	ION1 w/o cirrhosis 12 wks	ION3 w/o cirrhosis 12 wks	ION3 w/o cirrhosis 8 wks	Total
sample size	177	216	215	608
Successes	176	208	202	586
SVR12 rate	0.994	0.963	0.939	**0.964**

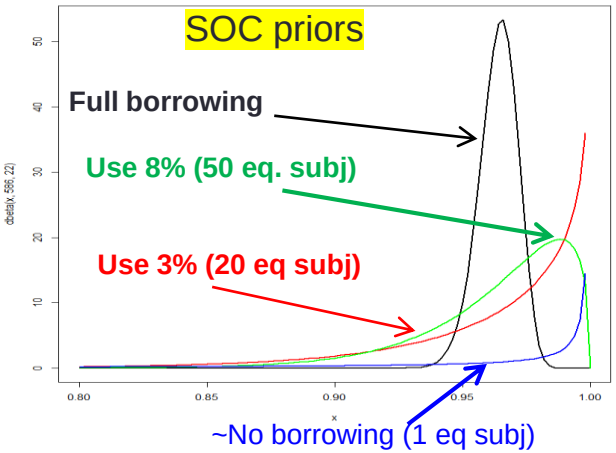
Source: SOC USPI Label Revised 2016: Tables 10; 11; 8

Note: Simplification for initial exploratory simulations= 8 wks and 12 wks regimens pooled; ION1: subset of non cirrhotic subjects

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

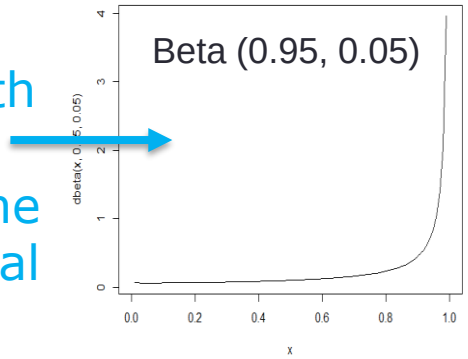
Beta(586* w, 22*w)

w is the weight TBD based on false positive error control



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

JNJ-4178 prior

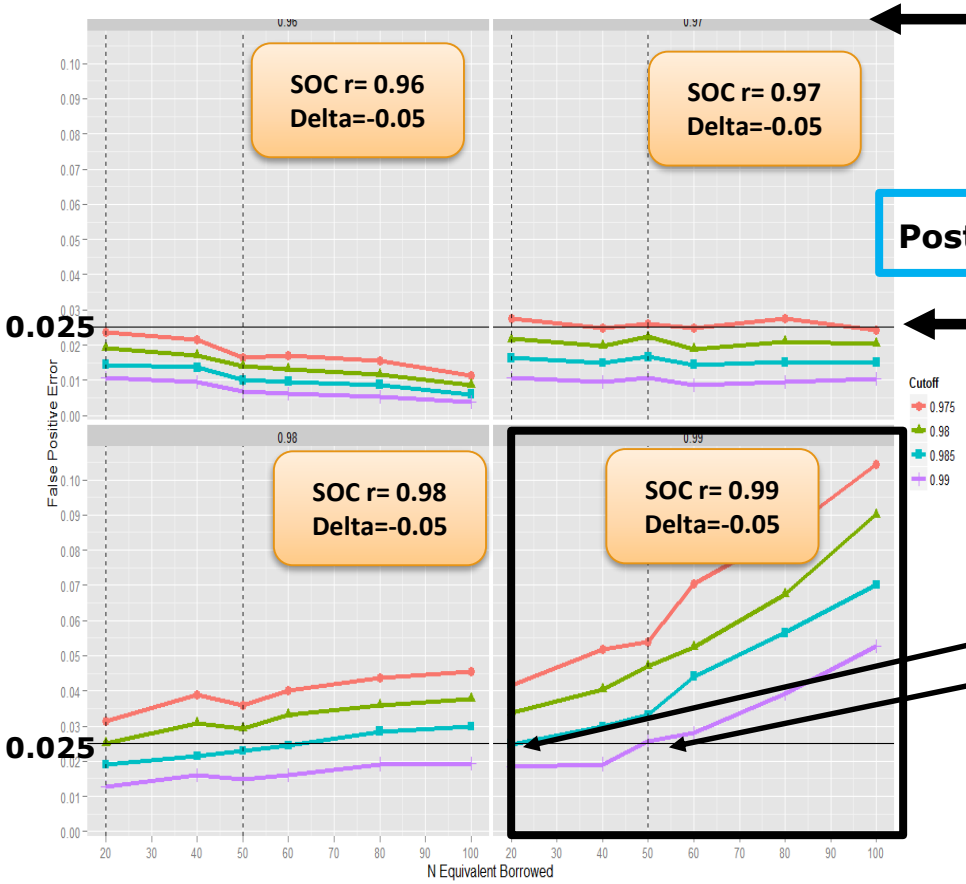


FDA Guidance: "We may recommend discounting of historical/prior information if the prior distribution is too informative relative to the current study. What constitutes "too informative" is also a case-by-case decision. "

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, Delta= -0.05



SOC Rate

Posterior prob(r_JNJ4178−r_SOC >- 5%|data)>cutoff

0.025 threshold

If SOC SVR12= 99% (bottom right panel)
cutoff of 0.985 (cyan line), borrow no more than 20 subj eq.;

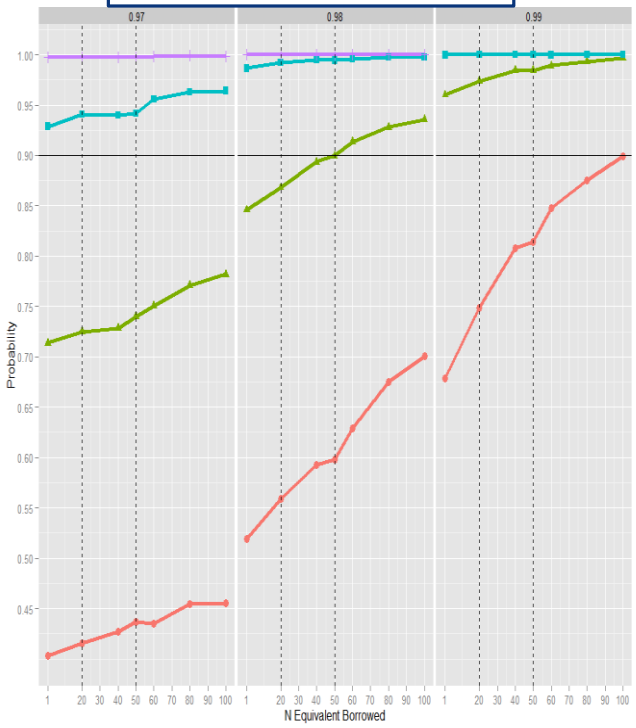
cutoff of 0.99 (purple line) borrow no more than 50 subj eq.

The larger the observed SOC rate (each panel from top to bottom left to right), the larger the inflation of false positive rate

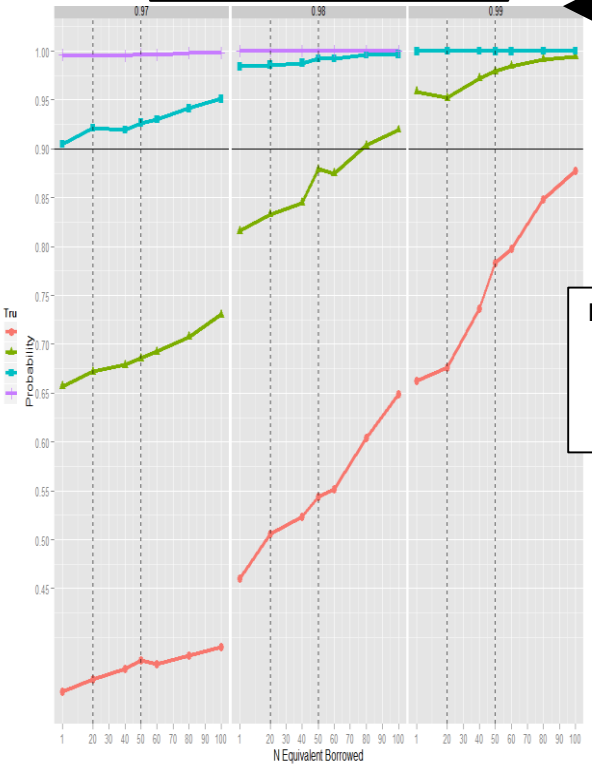
The smaller the cutoff for posterior prob. (red line vs. purple line), the larger the inflation of false positive rate, with increasing amounts of "borrowing" (x-axis)

Posterior Prob > 98.5% vs 99% Criterion

Cutoff= 98.5%



Cutoff= 99%



SOC Rate

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

Delta JNJ4178-SOC
- **+0.01**
- **0**
- **-0.01**
- **-0.02**

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%; **Delta =0;** JNJ-4178 **n=400 ;** 5% Margin

Posterior Probability (r_JNJ4178 – r_SOC > - 5% | data, priors) ≥ cutoff

N SOC in study	N borrowed (equivalent)	Weight on prior	Cut off	False positive (delta= -0.05)	Prob Success (%)	NI Conventional Power (%)
180	20	3.3%	0.985	0.016	94.0%	91.3%
160	40	6.6%	0.985	0.015	94.1%	90.2%
150	50	8.2%	0.985	0.016	94.2%	89.5%
140	60	9.9%	0.985	0.014	96.0%	88.9%
100	100	16.4%	0.985	0.015	96.4%	85.1%
180	20	3.3%	0.99	0.011	92.1%	91.3%
160	40	6.6%	0.99	0.010	92.0%	90.2%
150	50	8.2%	0.99	0.011	92.7%	89.5%
140	60	9.9%	0.99	0.009	93.0%	88.9%
100	100	16.4%	0.99	0.010	95.1%	85.1%

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

N SOC in study	N borrowed (equivalent)	SOC Rate	JNJ-4178 Rate	False positive (delta= -0.05)	Prob Success (%)	NI Conventional Power (%)
180	20	**0.97**	**0.97**	0.016	94.0%	91.3%
160	40	**0.97**	**0.97**	0.015	94.1%	90.2%
150	50	**0.97**	**0.97**	0.016	94.2%	89.5%
140	60	**0.97**	**0.97**	0.014	96.0%	88.9%
180	20	**0.98**	**0.97**	0.019	86.8%	83.2%
160	40	**0.98**	**0.97**	0.021	89.3%	82.0%
150	50	**0.98**	**0.97**	0.023	90.0%	81.4%
140	60	**0.98**	**0.97**	0.025	91.4%	80.7%
180	20	**0.99**	**0.97**	0.0249	74.9%	68.6%
160	40	**0.99**	**0.97**	0.030	80.8%	67.9%
150	50	**0.99**	**0.97**	0.033	81.4%	67.6%
140	60	**0.99**	**0.97**	0.044	84.8%	67.1%

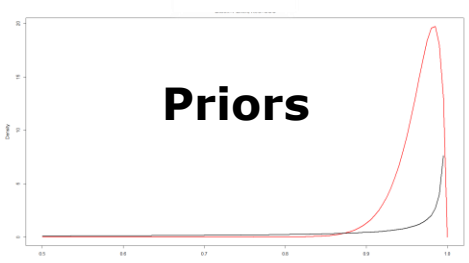
Team Proposal To Start Thorough Simulations

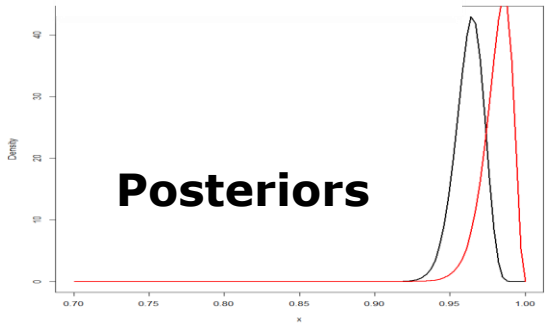
N SOC in study	N borrowed (equivalent) ~ 8.2% of historic data	SOC Rate	JNJ-4178 Rate	False positive (delta= -0.05)	Prob Success (%)	NI Conventional Power (%)
150	50	0.97	0.97	**0.016**	94.2%	89.5%
150	50	0.98	0.97	**0.023**	90.0%	81.4%
150	50	0.99	0.97	**0.033**	81.4%	67.6%

Savings ~7MM=

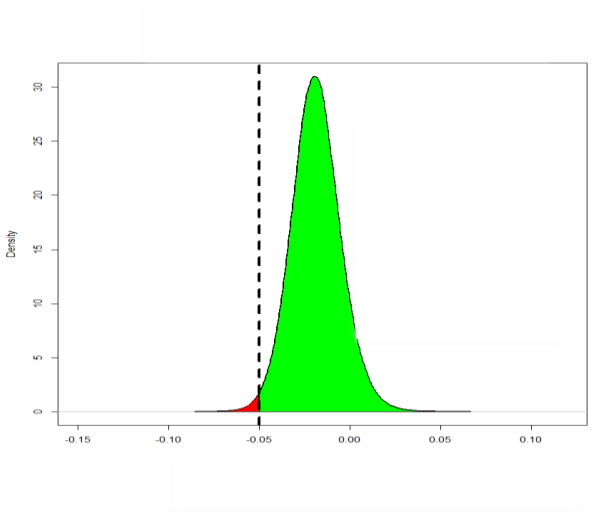
- Δ^- Cost SOC treatment +
- Δ^- Total time recruitment +
- Δ^- Time to complete study +
- Δ^- Cost of visits & procedures/patient

Show Team One Concrete Example





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



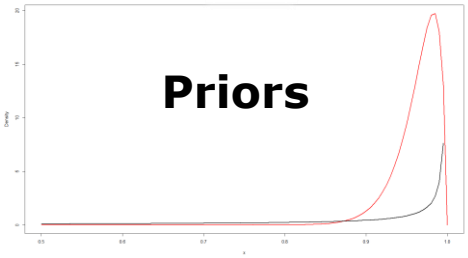
Results:
Bayesian approach**: Prob[JN4178>SOC-0.05| study data]= 99.1%**

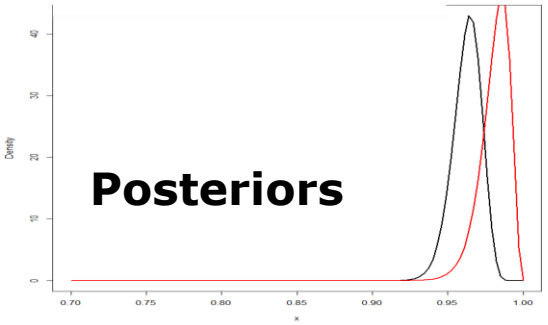
Conventional NI design : **95% CI: [-0.0505; 0.012]**

Conclude NI?

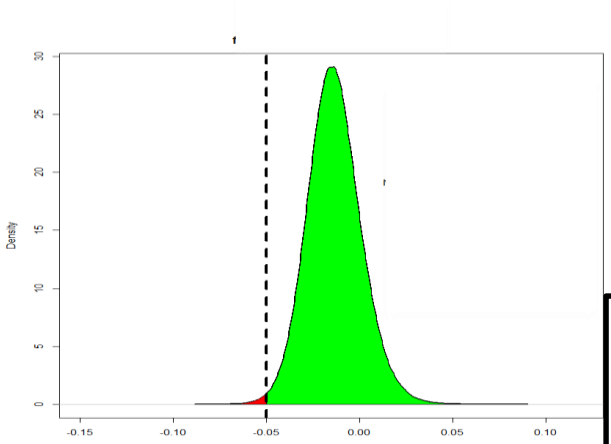
- **Bayesian** **YES because 99.1% > 98.5%**
- **Conventional CI** **NO because -0.0505 < -0.050**

Show Team Another Concrete Example





Observed SVR12 (delta=-2.5%)
JNJ-4178 96.2% = 385/400
SOC 98% = 147/150

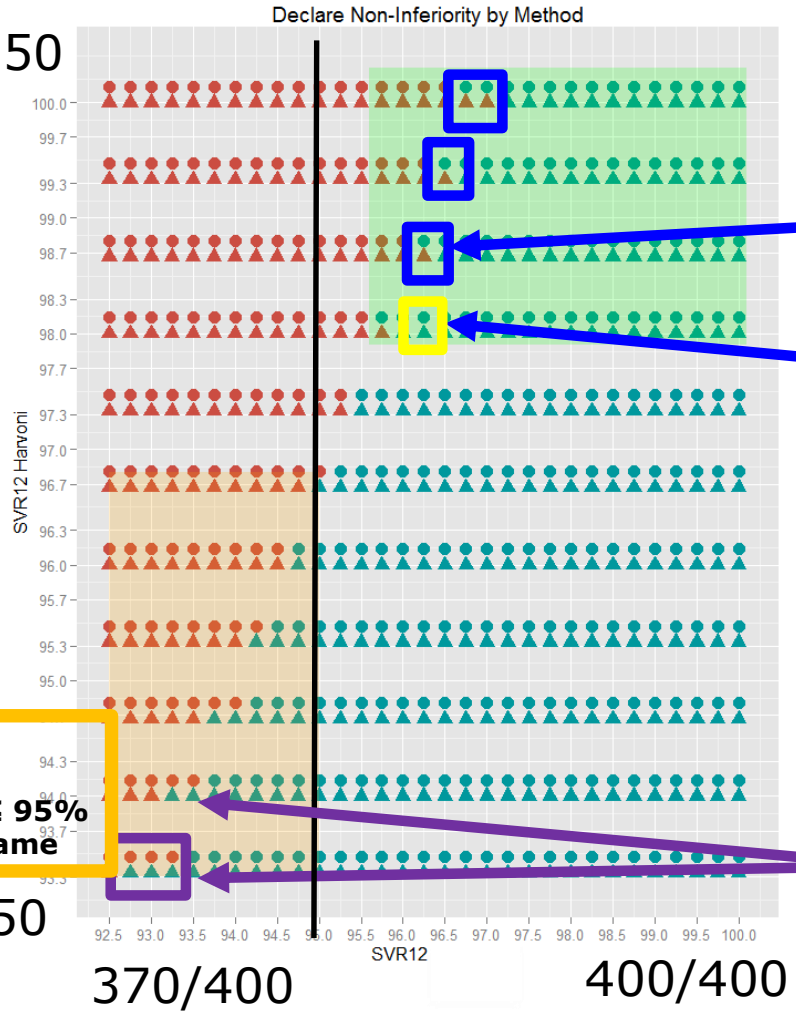


Results:
Bayesian approach: **Prob[JN4178>SOC-0.05| study data]= 99.55%**
Conventional NI design : **95% CI: [-0.0453; 0.0219]**

Conclude NI?

- **Bayesian** **YES because 99.1% > 99.55%**
- **Conventional CI** **YES because -0.0453 > -0.050**

Possible Study Outcomes



150/150

140/150

370/400

400/400

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%

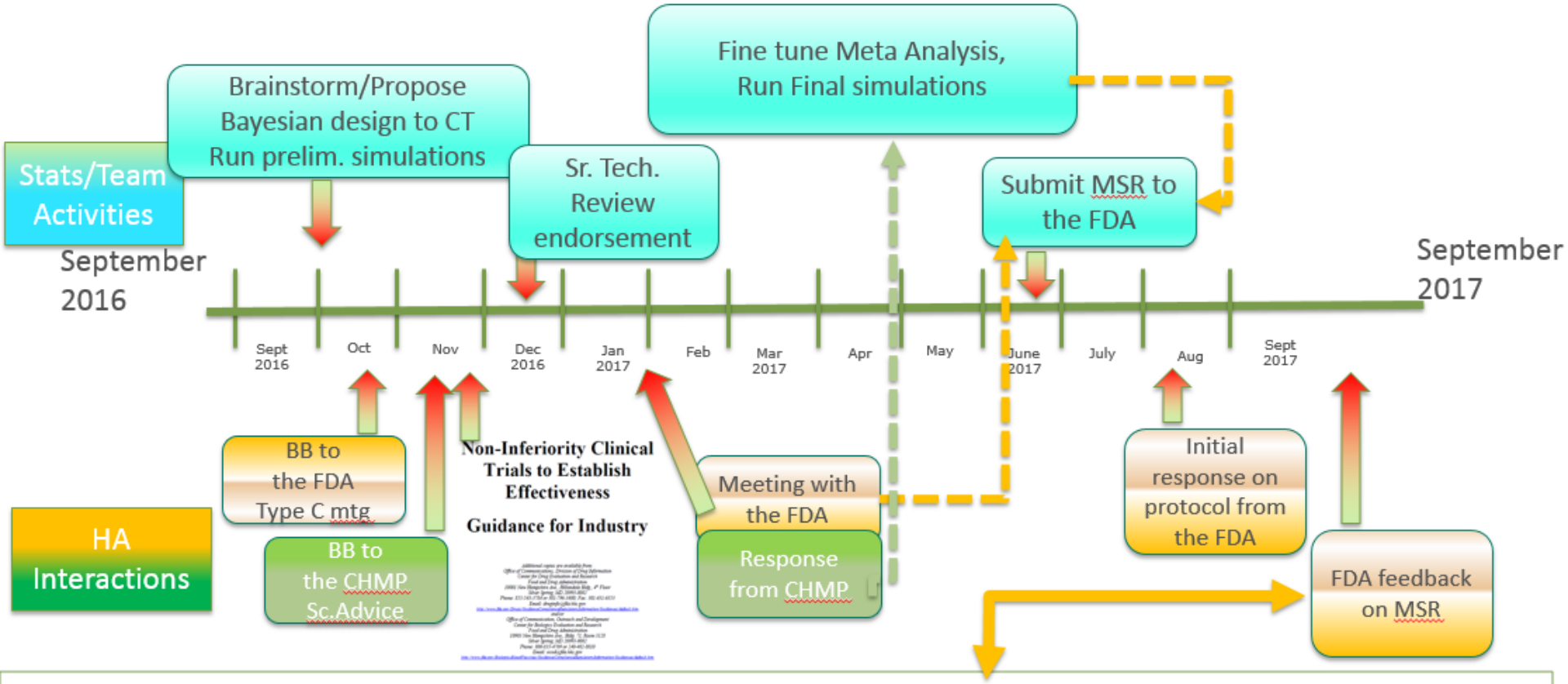
Orange area:
SOC <96.7%
and JNJ4178≤ 95%
CI NI or the same

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

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……


thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
dziękuję
bedankt
obrigado
sukriya
kop khun krap
go raibh maith agat
merci
dakujem
arigatō
grazie
terima kasih
감사합니다
ευχαριστώ
спасибо
рахмат
Баярлалаа
mauruuru
hvala
sagolun
dank je
tapadh leat
mochchakkeram
dhanyavadagalu
мерси


Q&A