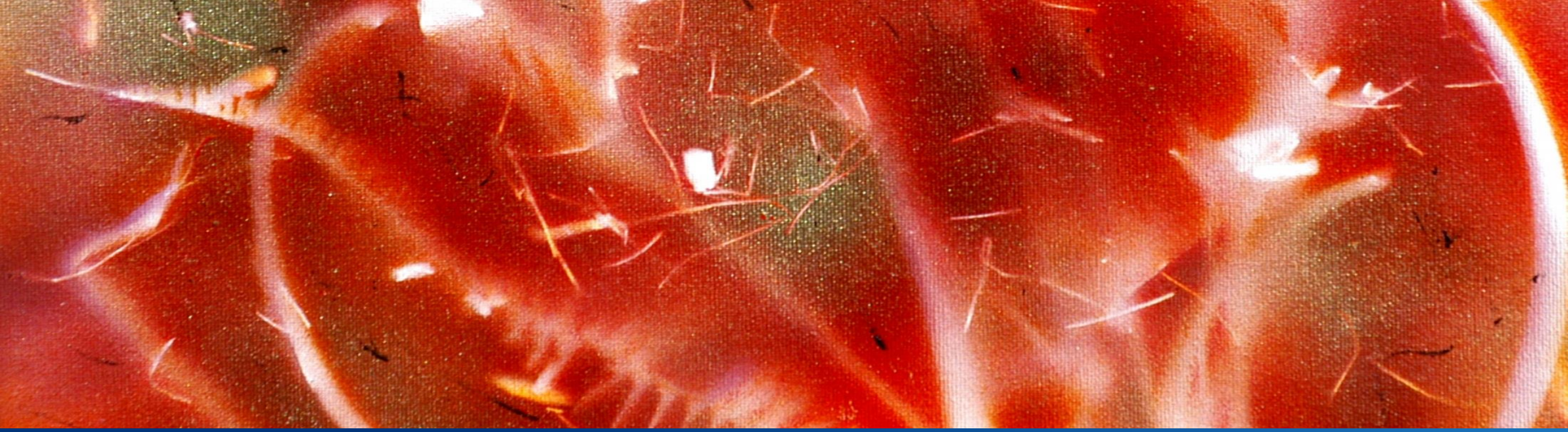


A Bayesian Approach to Augment Active Comparator Efficacy Information with Historic Randomized Clinical Trial Data in a Non-Inferiority Trial

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

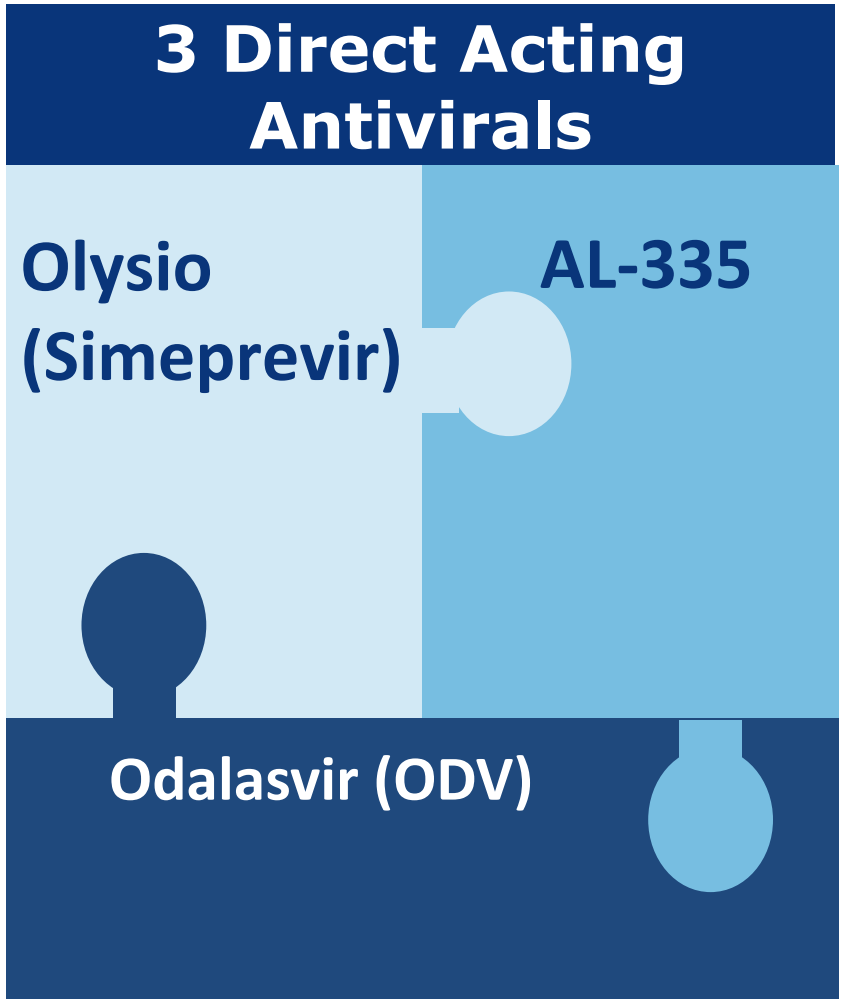
Wouter Willems
In collaboration with Cristiana Mayer, Kyle Wathen, and the project team

2018 PSI Conference

Amsterdam, 5 June 2018

janssen Infectious Diseases
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

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

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

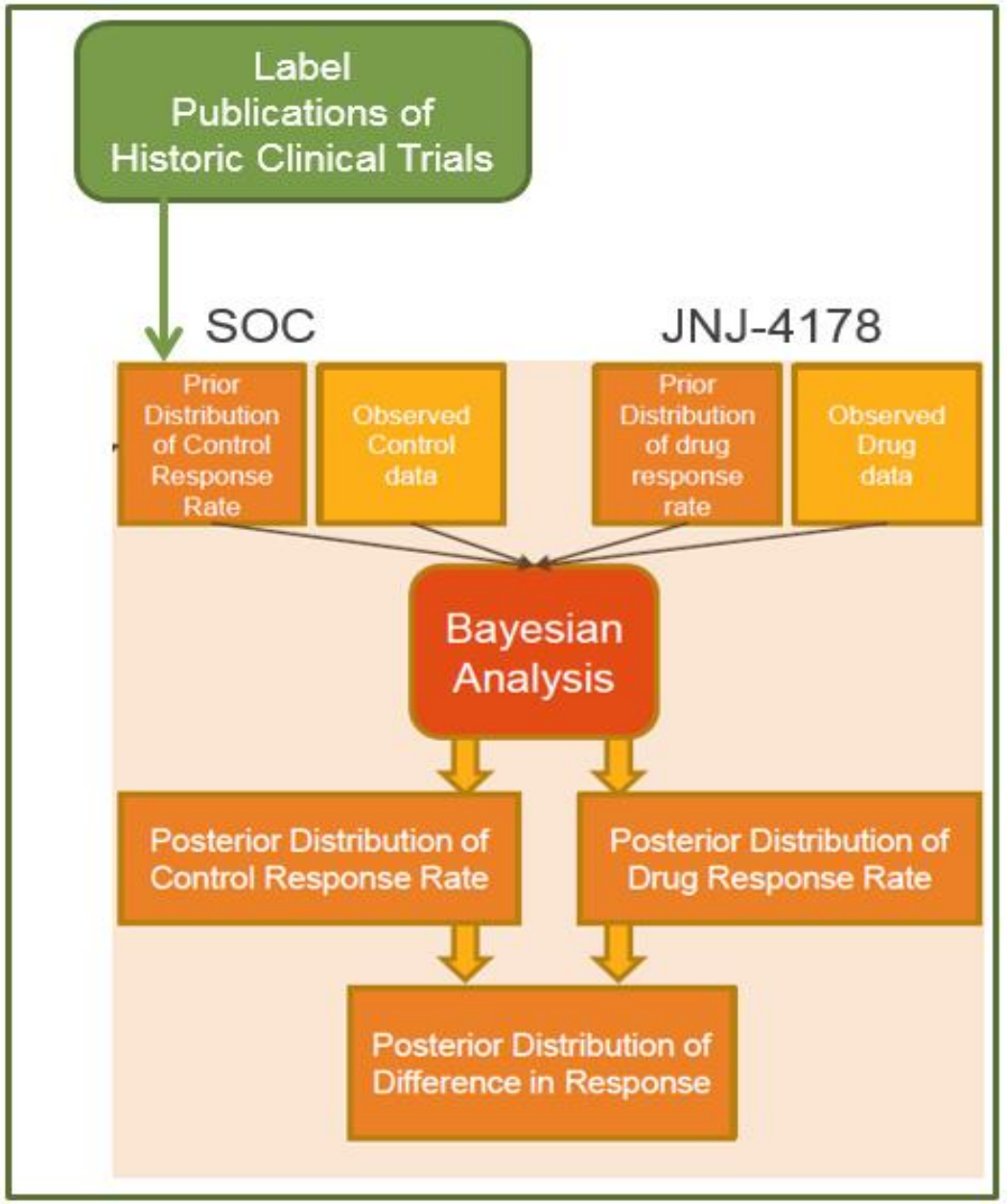
Posterior Probability= Pr[JNJ-4178 SVR12 rate is no worse than SOC by more than 5% NI margin given the study results]

Posterior probability P(r_JNJ-4178 – r_Harvoni >-0.05|data)≥cutoff

=> Which cutoff to chose?

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

H_0 : $r_{JNJ\text{-}4178} - r_{SOC} \leq$ - NI margin
H_a : $r_{JNJ\text{-}4178} - r_{SOC} >$ - NI margin
Lower Bound 95% CI > - NI margin

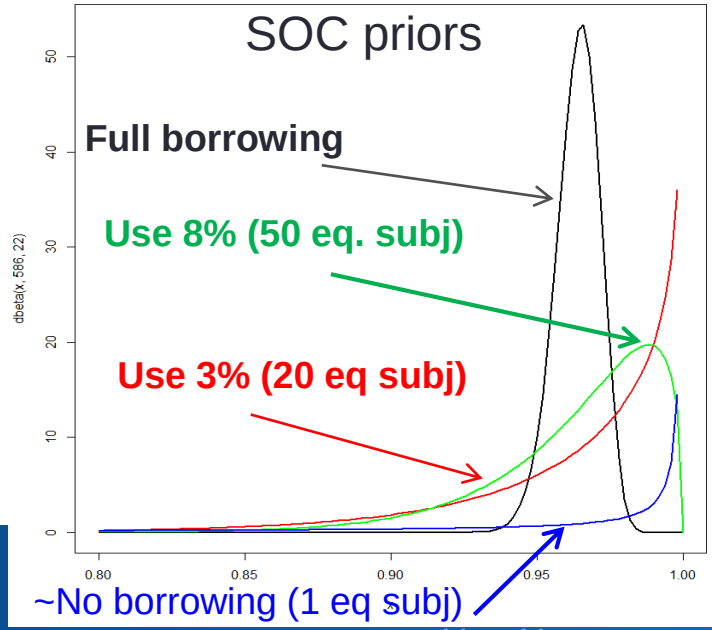


SOC Historic Ph3 Studies – A Simplification

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	99.4%	96.3%	93.9%	**96.4%**

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

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



=> How much should we borrow?

Regulatory Interactions

1 Year Story: Design and Regulatory interactions

Stats/Team Activities

Brainstorm/Propose Bayesian design to CT Run simulations

September 2016

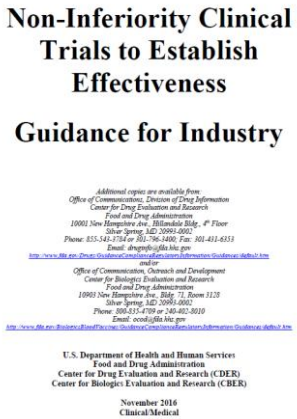
September 2017

Sept 2016 | Oct | Nov | Dec 2016 | Jan 2017 | Feb | Mar 2017 | Apr | May | June 2017 | July | Aug | Sept 2017

HA Interactions

BB to the FDA Type C mtg

BB to the CHMP Sc.Advice



Non-Inferiority Clinical Trials to Establish Effectiveness

Guidance for Industry

Additional copies are available from
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2016
Clinical/Medical

1 Year Story: HPC3003 Design Development

Stats/Team Activities

Brainstorm/Propose Bayesian design to CT
Run simulations

September 2016

Sept 2016 | Oct | Nov | Dec 2016 | Jan 2017 | Feb | Ma 201

HA Interactions

BB to the FDA Type C mtg

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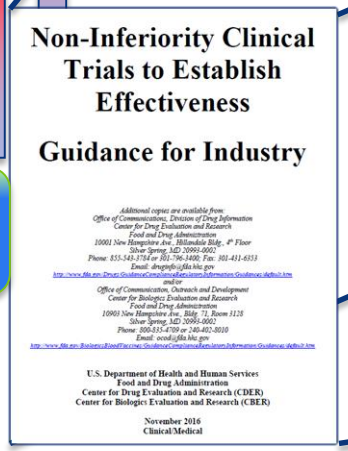


Non-Inferiority Clinical Trials to Establish Effectiveness

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2016
Clinical/Medical

Page 33:

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 Run simulations

September 2016

Sept 2016

Oct

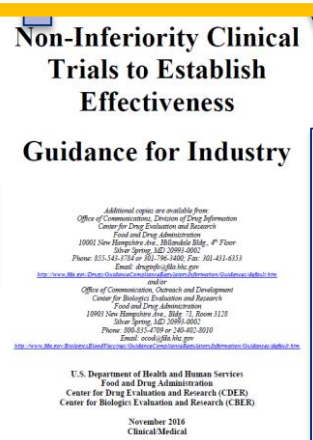
HA Interactions

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



Non-Inferiority Clinical Trials to Establish Effectiveness

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2016
Clinical/Medical

Meeting with the FDA

Response from CHMP

1 Year Story: HVC3003 Design Development

Stats/Team Activities

Brainstorm/Propose Bayesian design to CT
Run simulations

September 2016

September 2017

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HA Interactions

BB to the FDA Type C mtg

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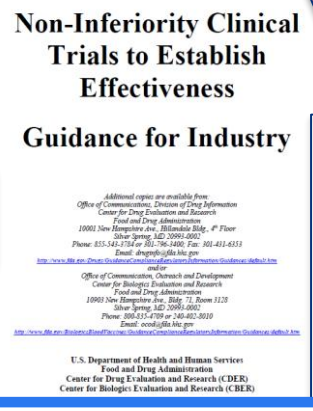
Non-Inferiority Clinical Trials to Establish Effectiveness

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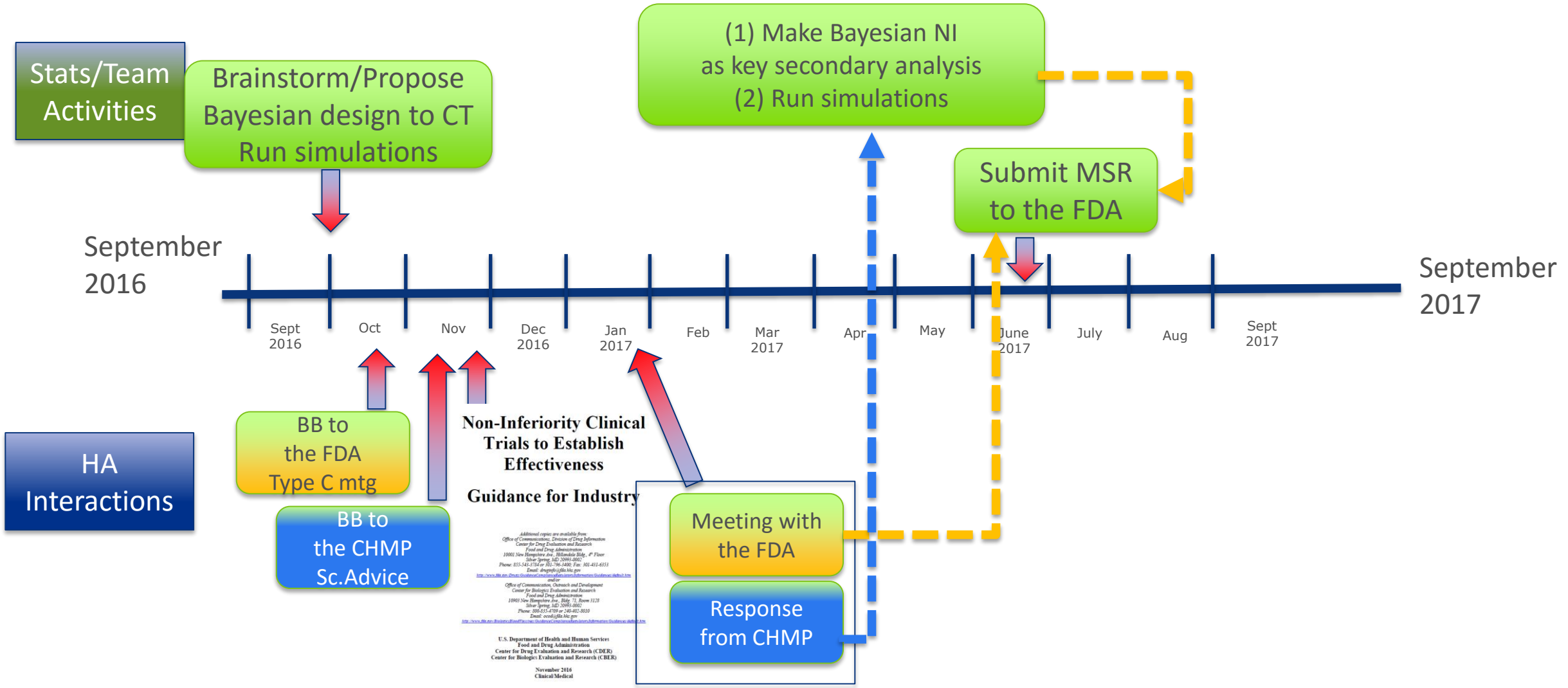
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

Meeting with the FDA

Response from CHMP

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



Simulations

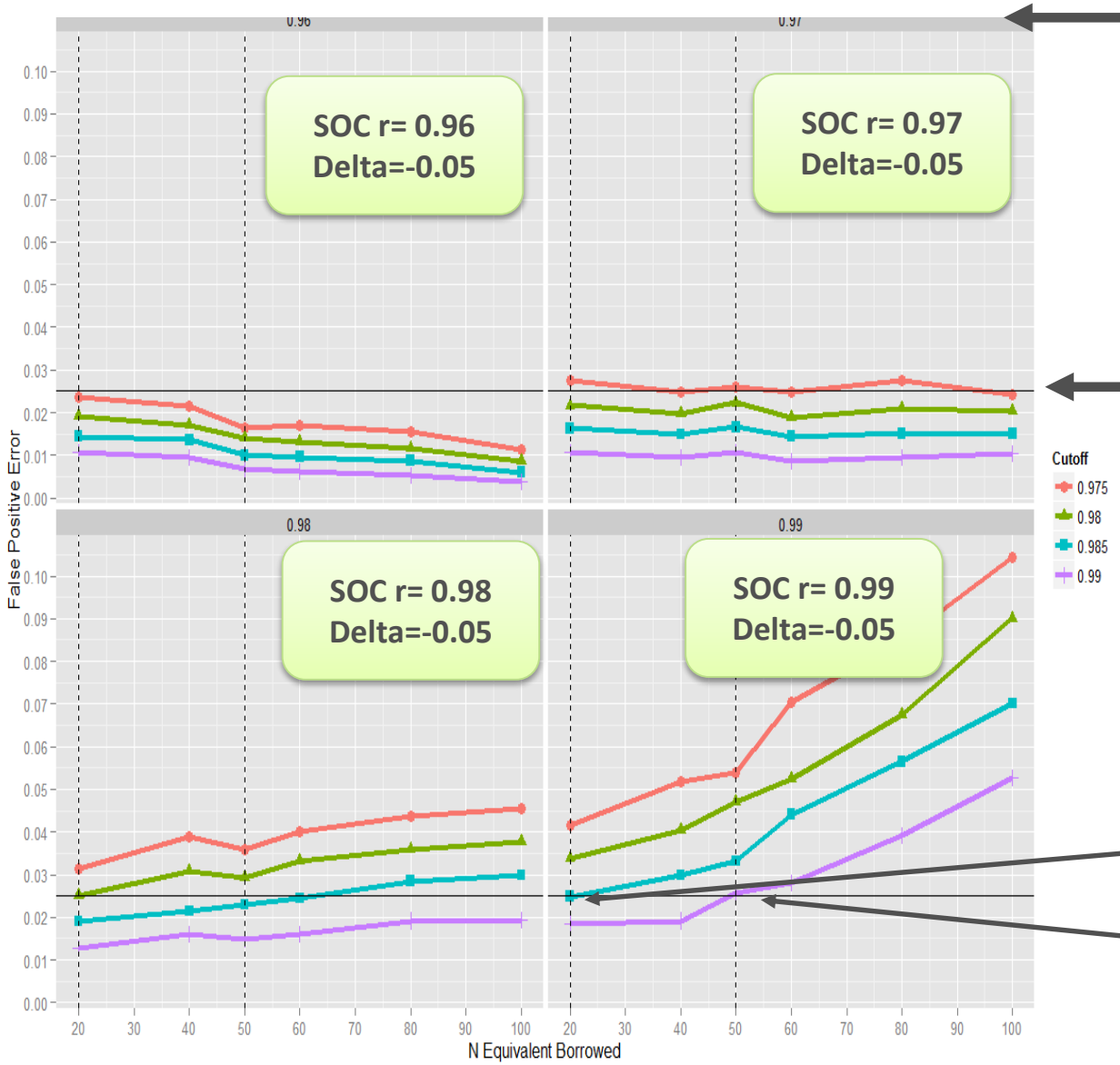
Assumptions and Simulations Scenarios

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



SOC Rate

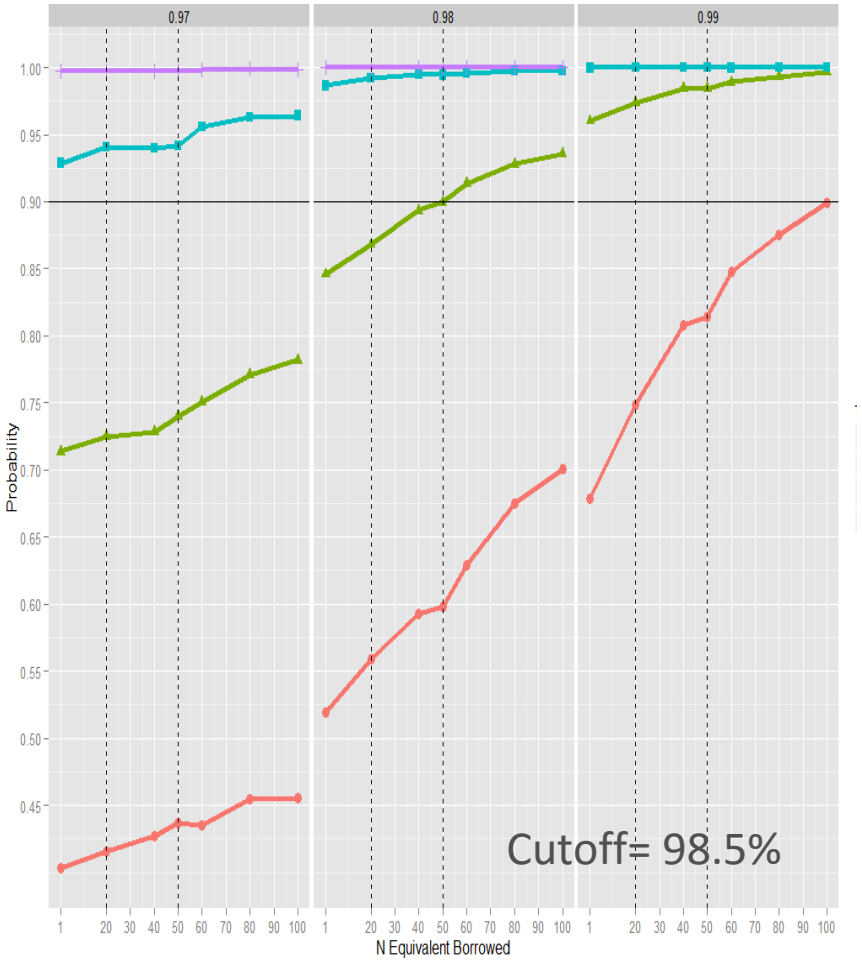
The larger the observed SOC rate (each panel), the larger the inflation of false positive rate

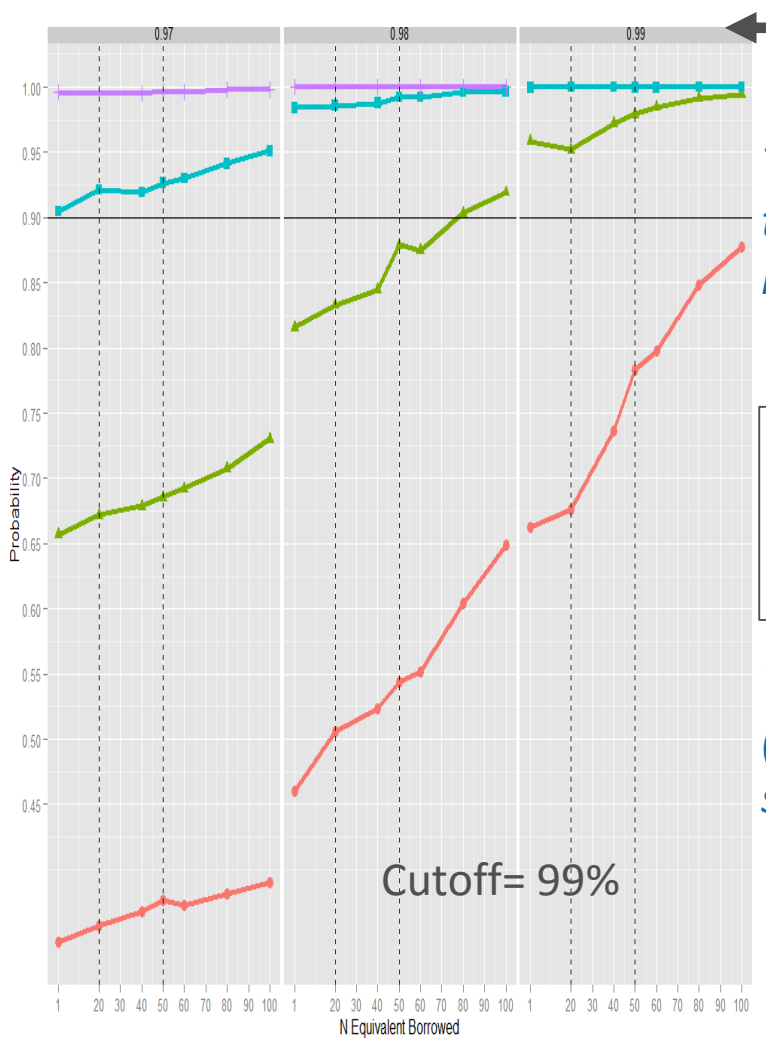
0.025 threshold

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% | 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 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

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%

How much borrowing?

Team Proposal

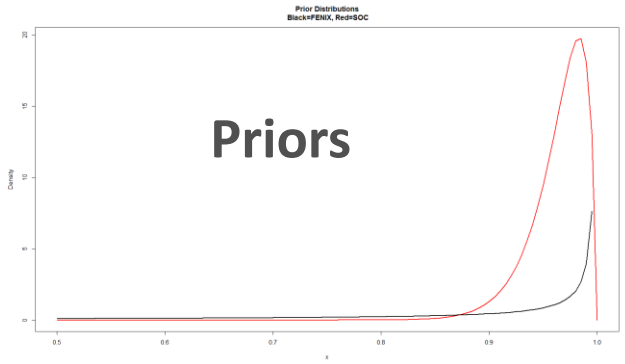
N SOC in study	N borrowed (equivalent) ~= 8.2% of historic data	SOC Rate	JNJ-4178 Rate	False positive (delta=-0.05)	Prob Success (%)	NI Conventional Power (%)
150	50	0.97	0.97	0.016	94.2%	89.5%
150	50	0.98	0.97	0.023	90.0%	81.4%
150	50	0.99	0.97	0.033	81.4%	67.6%

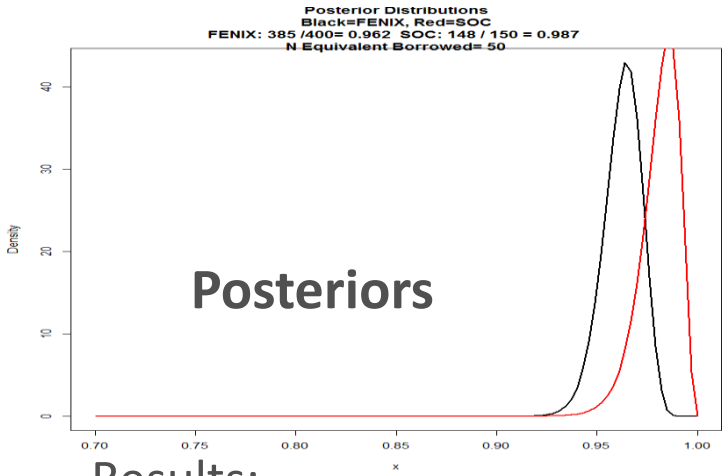
Savings ~7MM=

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

EXAMPLE

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

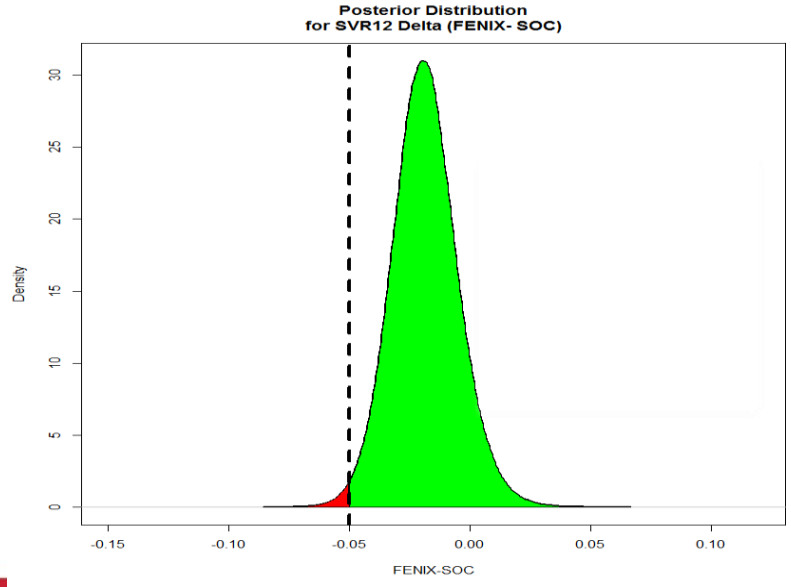




Observed SVR12 (delta=-2.5%)

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 :

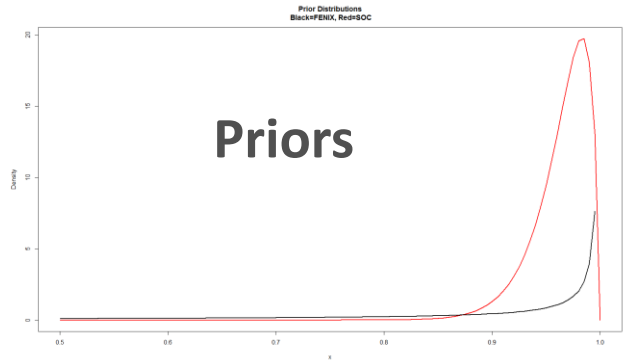
95% CI: CI:[-0.0505; 0.012]

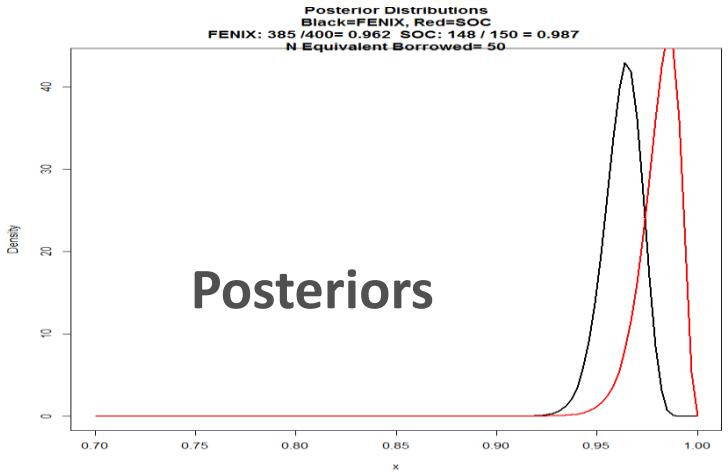
Conclude NI?

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

EXAMPLE

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

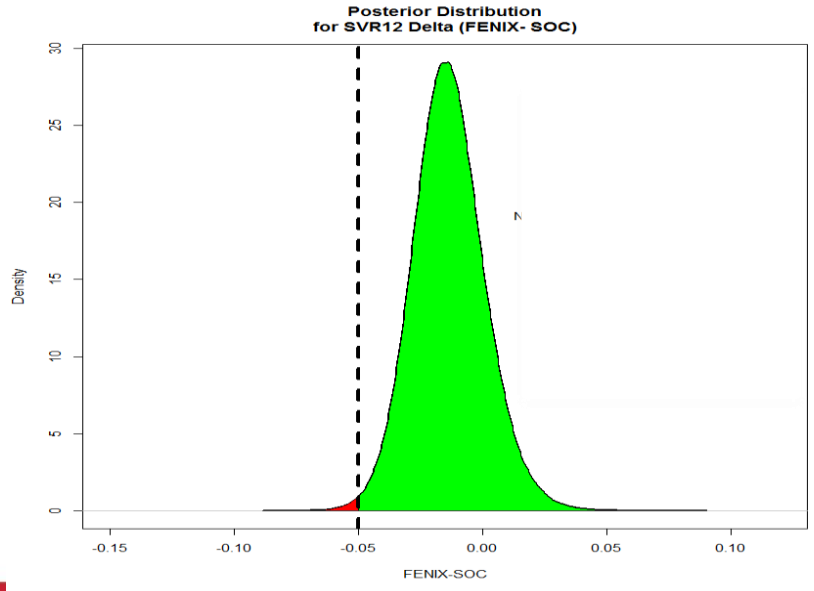




Observed SVR12 (delta=-2.5%)

JNJ-4178 96.2% = 385/400

SOC 98% = 147/150



Results:

Bayesian approach:

Prob[JN4178>SOC-0.05| study data]= 99.55%

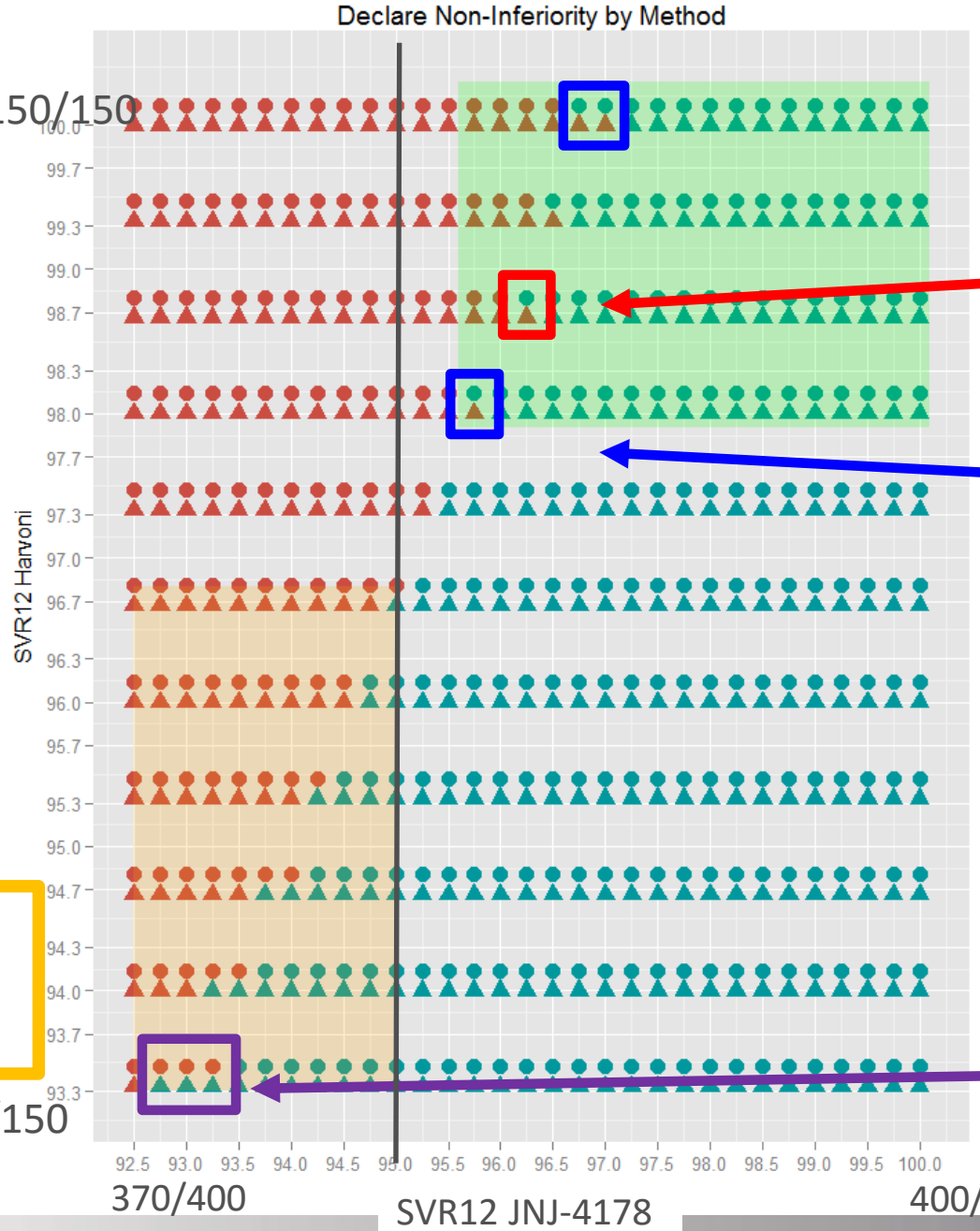
Conventional NI design :

95% CI: 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



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

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

CI declares NI, not Bayes

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

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
danke
謝謝
рахмат
ngiyabonga
teşekkür ederim
Баярлалаа
спасибо
faafetai lava
kiitos
dankie
dhanyavad
nanni
nandri
vinaka
спасибі
mersi
kia ora
barka
welalin
tack
spas
blagodaram
dank je
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matondo
paldies
grazzi
mahalo
tapadh leat
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asante
manana
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mochchakkeram
дякую
akun
dankon
aciu
kiszönöm
mauruuru
hvala
gràcie
bayarlalaa
enkosi
bedankt
dziękuję
dēkuji
sobodi
obrigado
mèsi
didi madloba
sagolun
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sulpáy
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go raibh maith agat
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ありがとう
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terima kasih
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rahmat
তোমাকে ধন্যবাদ
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diolch
dhanyavadagalu
shukriya
merçi
мерси
merci