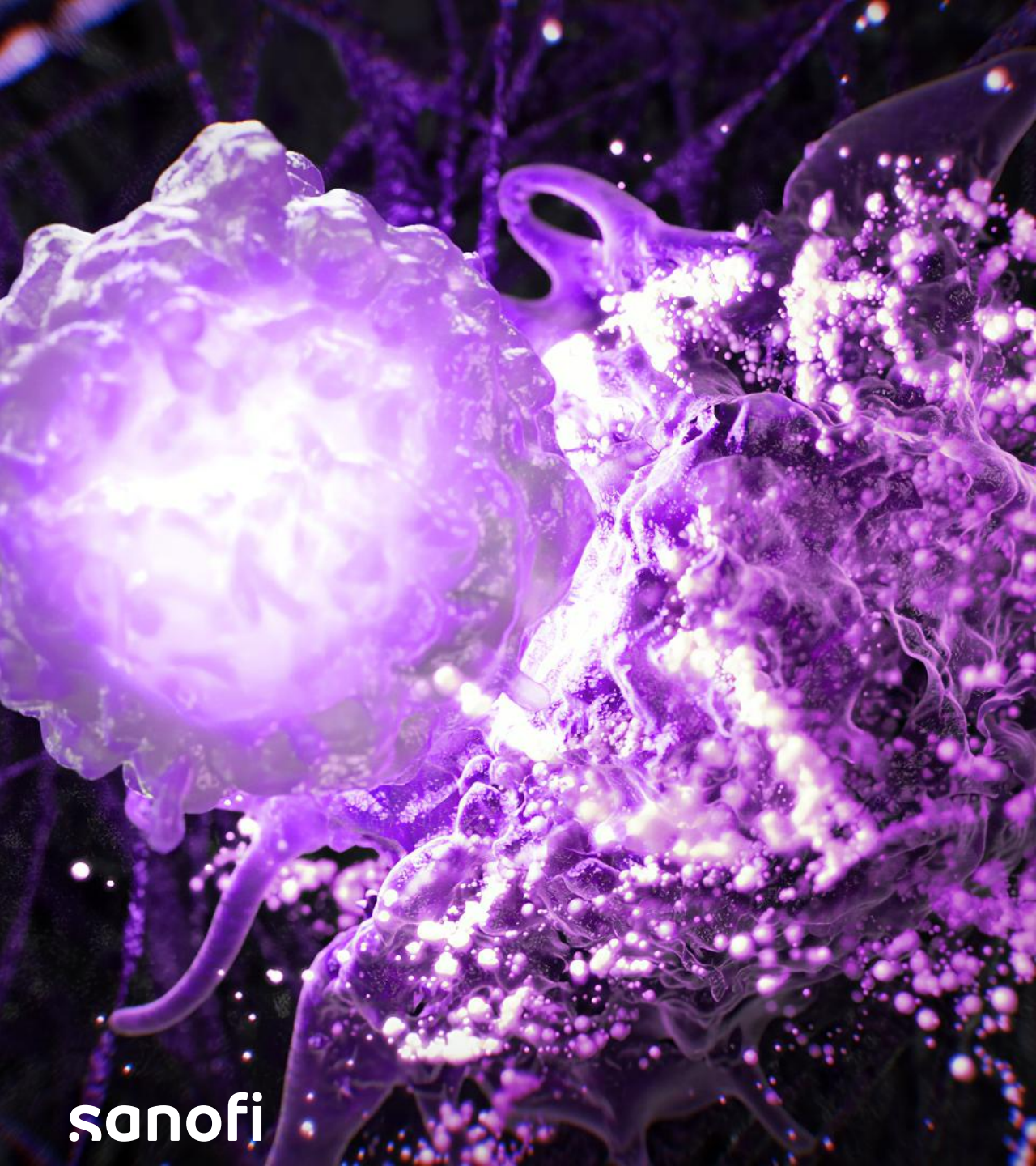


An abstract, artistic representation of a molecular or cellular structure, rendered in vibrant shades of purple, blue, and white. The image features a large, textured, cloud-like mass on the left, with numerous smaller, glowing particles and intricate, branching structures extending from it towards the right. The overall effect is one of dynamic, complex biological or chemical activity.

Bayesian vs. Frequentist Methods: Implications for Preclinical Vaccine Research

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Abstract: Bayesian vs. Frequentist Methods: Implications for Preclinical Vaccine Research

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Abstract:

Preclinical in vivo studies are guided by established principles of good practice. The implementation of robust statistical methodologies is essential for minimizing bias in these studies. Vaccine research utilizing animal models involves specific experimental designs, requirements, and readouts that necessitate the consideration of multiple endpoints and often require longitudinal analyses across multiple time points. Although the application of parametric approaches can be challenging, these methods offer significant advantages over non-parametric alternatives, particularly by enabling the estimation of effect sizes and their corresponding 95% confidence intervals.

Typically, the estimation of boost and adjuvant effects is performed using ANOVA (both one-way and two-way), and, when feasible, using repeated measures or mixed models that account for the animal as a random effect. Ensuring the validity of these models is essential, particularly by evaluating the normality of residuals, which can be problematic in the presence of small sample sizes and non-responders (i.e. value below the LOQ or first dilution).

Preclinical research is often constrained by a limited number of animals per group, in accordance with the 3Rs principle aimed at reducing animal use. This constraint poses challenges for maximizing the interpretability of results obtained from small sample sizes. To address this, we propose the use of Bayesian methods, which offer a probabilistic and more flexible framework for characterizing the distribution of parameters of interest, rather than relying solely on p-values.

In contrast to frequentist approaches, which typically emphasize hypothesis testing and yield binary conclusions based on p-value—potentially leading to the exclusion of relevant groups due to arbitrary or overly stringent significance thresholds—Bayesian methods enable a more nuanced interpretation of data and integration of prior knowledge. These approaches allow researchers to quantify the probability of a true vaccine effect given the observed data, thereby supporting more informed decision-making.

Our findings, based on the probability that the observed difference exceeds a predefined margin, demonstrate the advantages of this Bayesian approach, showing that parameter evaluation can yield meaningful probabilities. Overall, this method improves the interpretability of results in preclinical vaccine studies and enhances the use of in vivo data, enabling researchers to draw more informative conclusions.

Bayesian vs. Frequentist:
Which framework drives
smarter preclinical
decisions?

Context : In Vivo Vaccine Studies



Why Preclinical In Vivo Studies Matter

The Role of Animal Studies in Vaccine Research

- **In vivo studies** are **essential** for evaluating **vaccine safety** and **efficacy**
- **Robust statistical methods** are needed to reduce bias and support valuable decision making



Statistical Challenges in Vaccine Research

Complex Data, Small Samples

- Animal models involve **multiple endpoints** and **repeated measurements**
- Traditional methods like **ANOVA** and **Mixed Model** are commonly used but small sample sizes limit both their power and the reliability of their inference.



Ethical Constraints and Data Limitations

Working with Fewer Animals

- The **3Rs** principle (Reduce, Refine, Replace) limits animal use
- **Small sample** sizes make it harder to validate statistical models

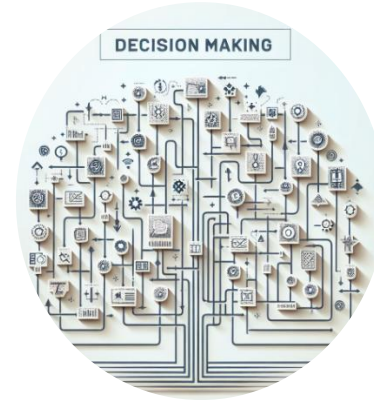


A Bayesian Alternative

Why Consider Bayesian Methods?

- Bayesian analysis offers a **probabilistic view** and provide a **more nuanced interpretations**
- It allows **integration of prior knowledge** and avoids over-reliance on p-values.

Context : Use case



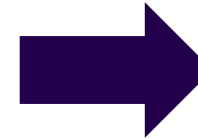
Situation: Health Authorities requested to show the non inferiority for some preclinical studies while non-inferiority margins are difficult to justify



Constraints : In Preclinical there is a need to minimize the animal use according to 3R principle



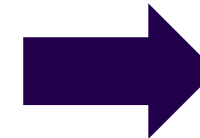
Challenge: Maximise the interpretation of the results considering the low number of animals per group which impact the actual power when a hypothesis testing driven sample size is used



Action : Reviewing the sample size/methodology, considering Bayesian approach



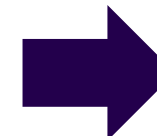
Proposal: Evaluate Bayesian approach in comparison with the Mixed Model classically used



As a result, it was possible to provide the $P[\text{Diff} \geq \text{NI Margin} \mid \text{Data}]$ in addition of the classical Yes/No frequentist approach

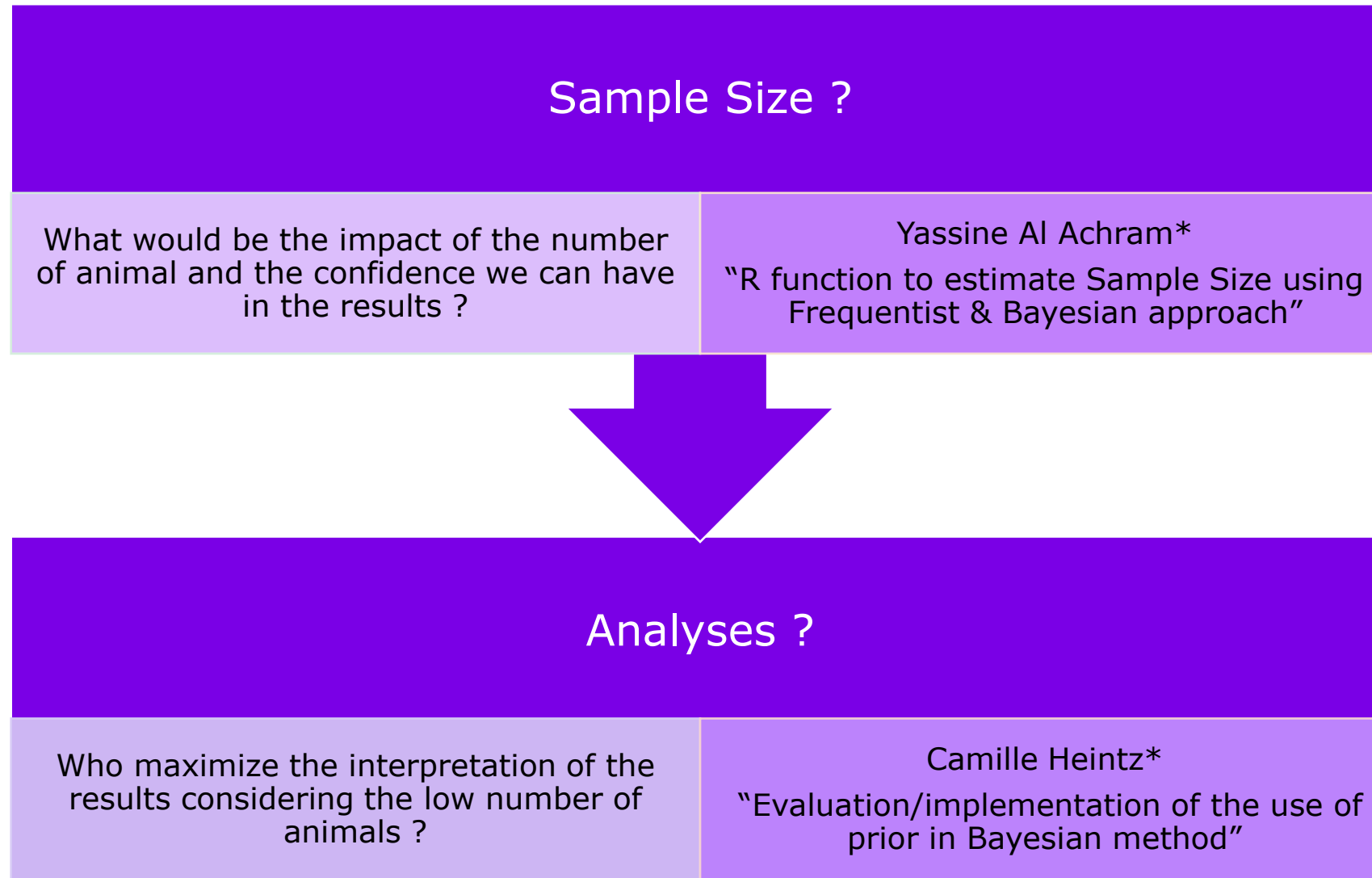
Move
from

Frequentist : how likely your observed data are likely to come from a given distribution (true parameter values)



Bayesian: Translate your observed data into a probability for the true parameters to be at least x (expected value)

Challenge : Improving In Vivo Vaccine Studies Through Bayesian Statistics – 2 pillars investigated



sanofi



Frequentist vs Bayesian Evaluation on the Sample Size And « Probability of Conclusive Trial »



Probability of conclusive trial : Conditional power vs Posterior Probability

For sample size planning, the Bayesian posterior probability of success plays a role analogous to frequentist power.

In the present setting, the two quantities will be considered side by side.

Conditional Power

The power of a test. defined as:

$$1 - \beta = P(\text{reject } H_0 \mid H_1 \text{ true}) \quad \begin{array}{l} \bullet \quad H_0: \delta \leq -\Delta \\ \bullet \quad H_1: \delta > -\Delta \end{array}$$

depends directly on the **sample size**.

For a **one-sided t-test** comparing two means with equal variances and equal sample size per group. the power can be approximated by:

$$\text{Power} \approx \Phi\left(\frac{\delta + \Delta}{\sigma} \sqrt{\frac{n}{2}} - z_{1-\alpha/2}\right)$$

where:

- $\delta = \mu_1 - \mu_2$: true difference between means
- Δ : non-inferiority margin ($\Delta > 0$)
- σ : common standard deviation
- n : sample size **per group**
- Φ : cumulative distribution function of the standard normal distribution
- $z_{1-\alpha/2}$: normal quantile corresponding to threshold α

Non-inferiority is concluded when :

the lower bound of the two-sided $100(1 - \alpha)\%$ confidence interval for δ is greater than $-\Delta$.

Posterior Probability

The posterior distribution : $p(\theta \mid D)$ represents the updated knowledge of the parameter after the observation of the data D . It results from the combination of prior information and the information provided by the data via the likelihood in accordance with Bayes' theorem:

$$p(\theta \mid D) = \frac{p(D \mid \theta) p(\theta)}{p(D)}$$

Where:

- $p(\theta)$ is the prior distribution of the parameter θ
- $p(D \mid \theta)$ is the likelihood function
- $p(D) = \int p(D \mid \theta) p(\theta) d\theta$ is the marginal likelihood (or evidence). which serves as a normalizing constant ensuring that the posterior distribution integrates to one

For a **non-inferiority test** with margin $\Delta > 0$. the decision is based on the **posterior probability**:

$$P(\delta > -\Delta \mid D) = \int_{-\Delta}^{\infty} p(\delta \mid D) d\delta$$

Non-inferiority is concluded if:

$P(\delta > -\Delta \mid D) \geq \gamma$, where γ is the prespecified posterior probability threshold (e.g. 0.95).

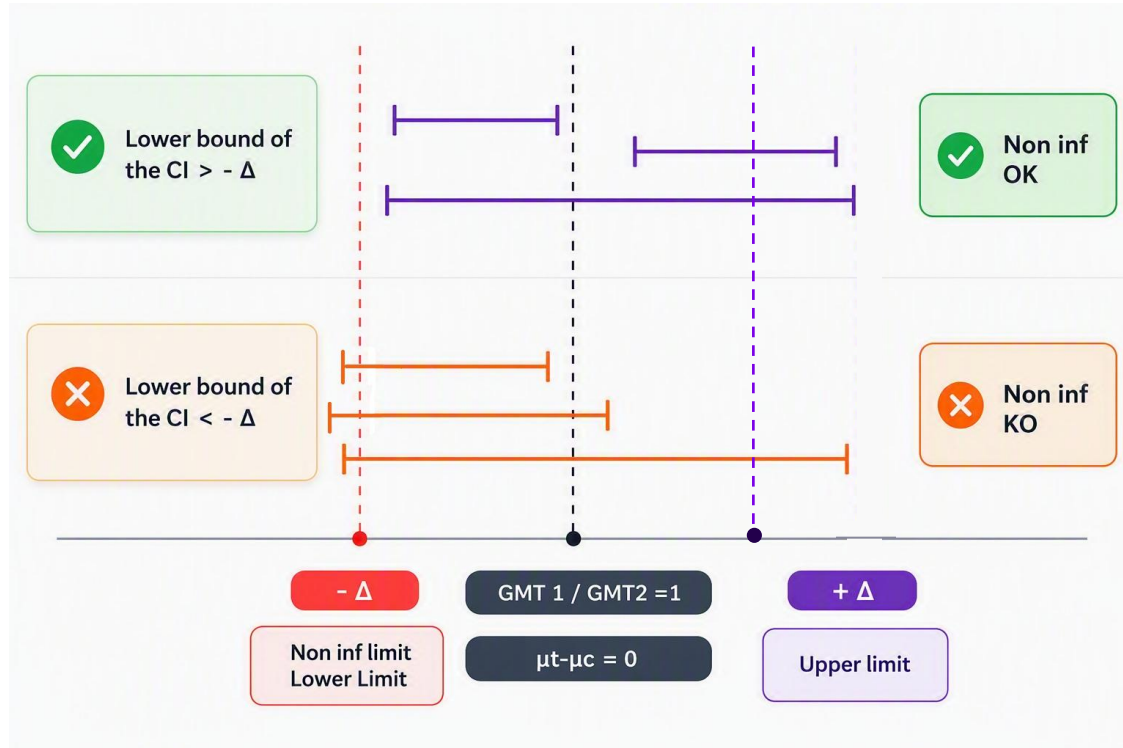
And so, if the lower bound of the $100(1 - \alpha)\%$ posterior credible interval exceeds $-\Delta$.

Frequentist vs Bayesian approach – Non inferiority

Example in comparison with 2 different vaccine formulations

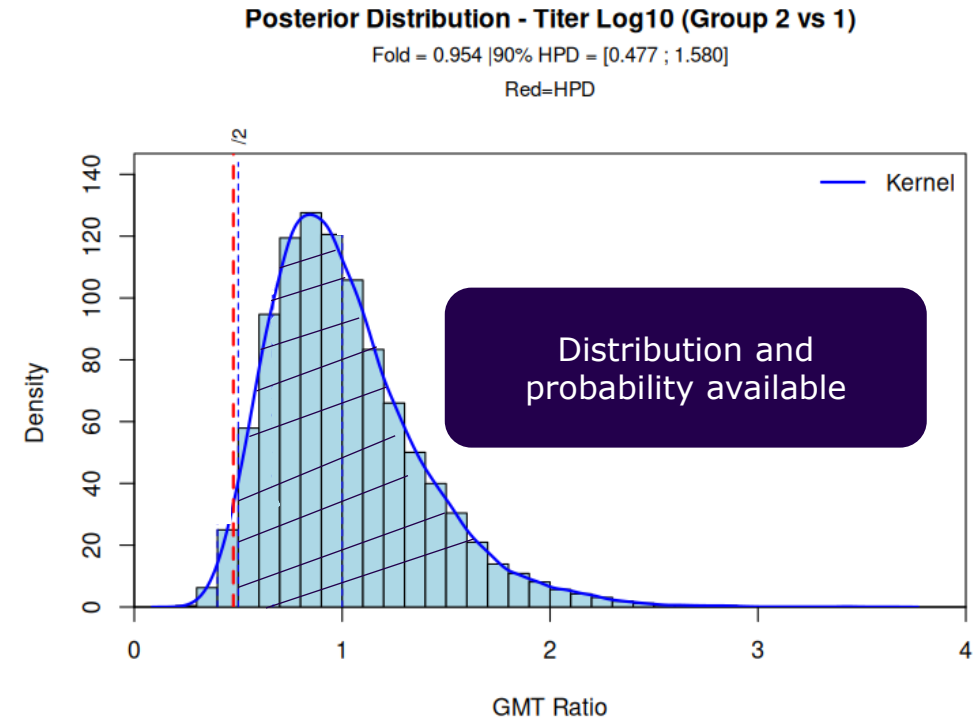
Frequentist approach

Estimate and CI



Bayesian approach

Posterior Distribution



Design

Design: Non inferiority study, comparison between 2 groups : New vaccine and a benchmark

Aim: To show that the experimental treatment is not unacceptably worse than the benchmark by more than a pre-specified non-inferiority margin (Δ).

Notation:

- μ_T : mean effect of the test vaccine
- μ_R : mean effect of the reference treatment
- Δ : non-inferiority margin ($\Delta > 0$)
- $\delta = \mu_T - \mu_R$: treatment difference

Hypotheses:

- H_0 : The new treatment is worse than the standard treatment by more than the non-inferiority margin Δ : $H_0: \delta \leq -\Delta$
- H_1 : The new treatment is not worse than the standard treatment by more than Δ : $H_1: \delta > -\Delta$

Interpretation:

- Rejecting H_0 provides evidence that the test treatment is **non-inferior** to the reference treatment.

Use cases:

- the non-inferiority will be concluded if :
 - the **lower bound** of the two-sided 90% confidence interval for δ is greater than $-\Delta$
 - or similar the **lower bound** of the one-sided 95% confidence interval
- One margin is not prespecified, and several margins will be considered

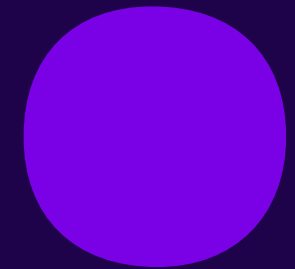
Simulation

The following simulation has been performed considering:

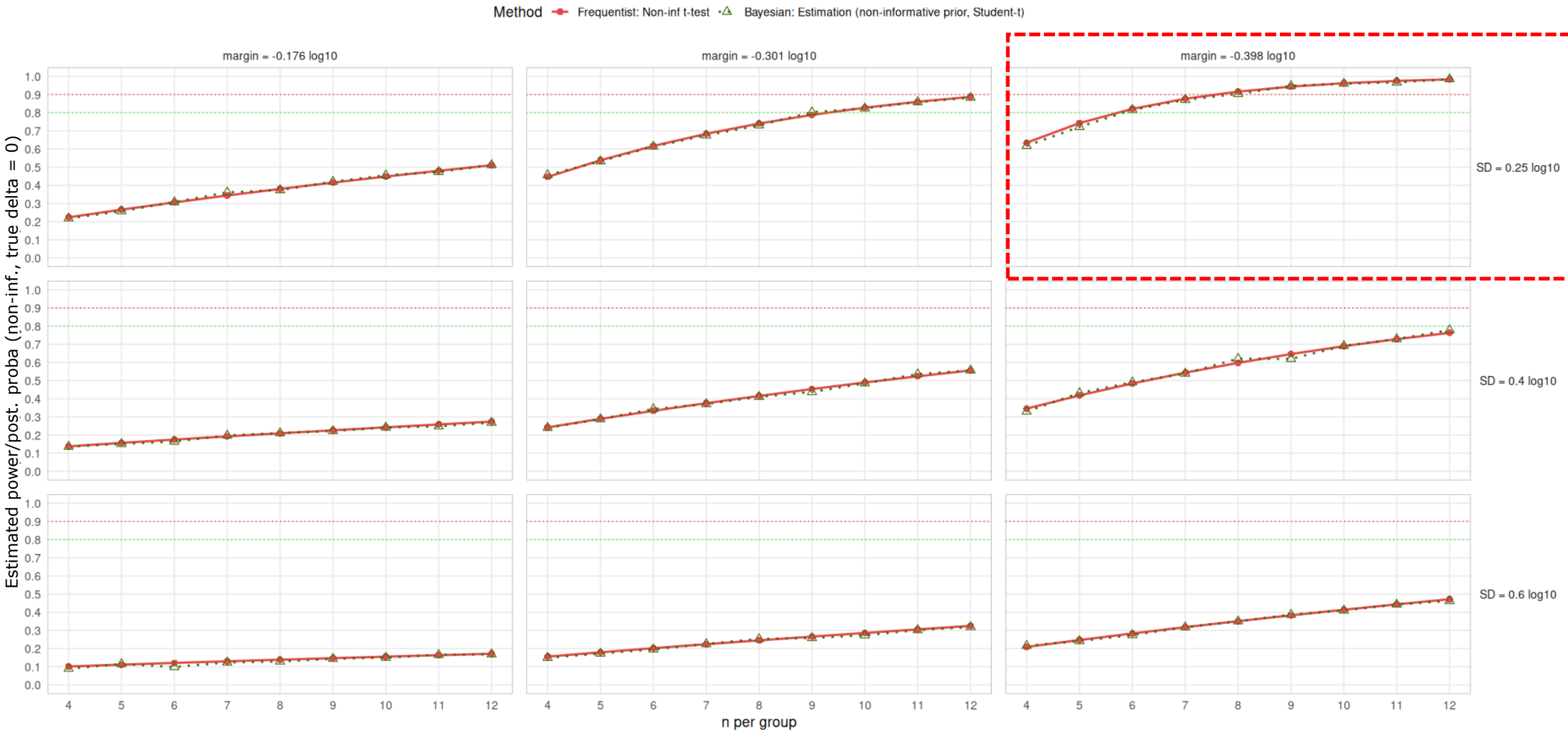
Simulation considering:			Frequentist	Bayesian With Non Informative Prior	Bayesian with Non informative prior for the new group and Informative Prior for the benchmark n per group= 4			Bayesian With Informative Prior (Mean Diff = 0) n per group= 4			Bayesian With Informative Prior (Mean Diff = 0) SD per group 0.40		
Lower Margin Log10 (fold)	SD of the group (Log10)	n per group			SD per group 0.25	SD per group 0.40	SD per group 0.60	SD per group 0.25	SD per group 0.40	SD per group 0.60	npg= 4	npg= 6	npg= 8
-0.176 (1/1.5)	0.25	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.40	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.60	4-12	X	X	X	X	X	X	X	X	X	X	X
-0.301 (1/2)	0.25	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.40	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.60	4-12	X	X	X	X	X	X	X	X	X	X	X
-0.398 (1/2.5)	0.25	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.40	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.60	4-12	X	X	X	X	X	X	X	X	X	X	X

SD: Standard Deviation; npg : number of animal per group
All simulations were performed using R (version 4.5.1.).

1 Impact of Non Informative Prior in Comparison to Frequentist Approach

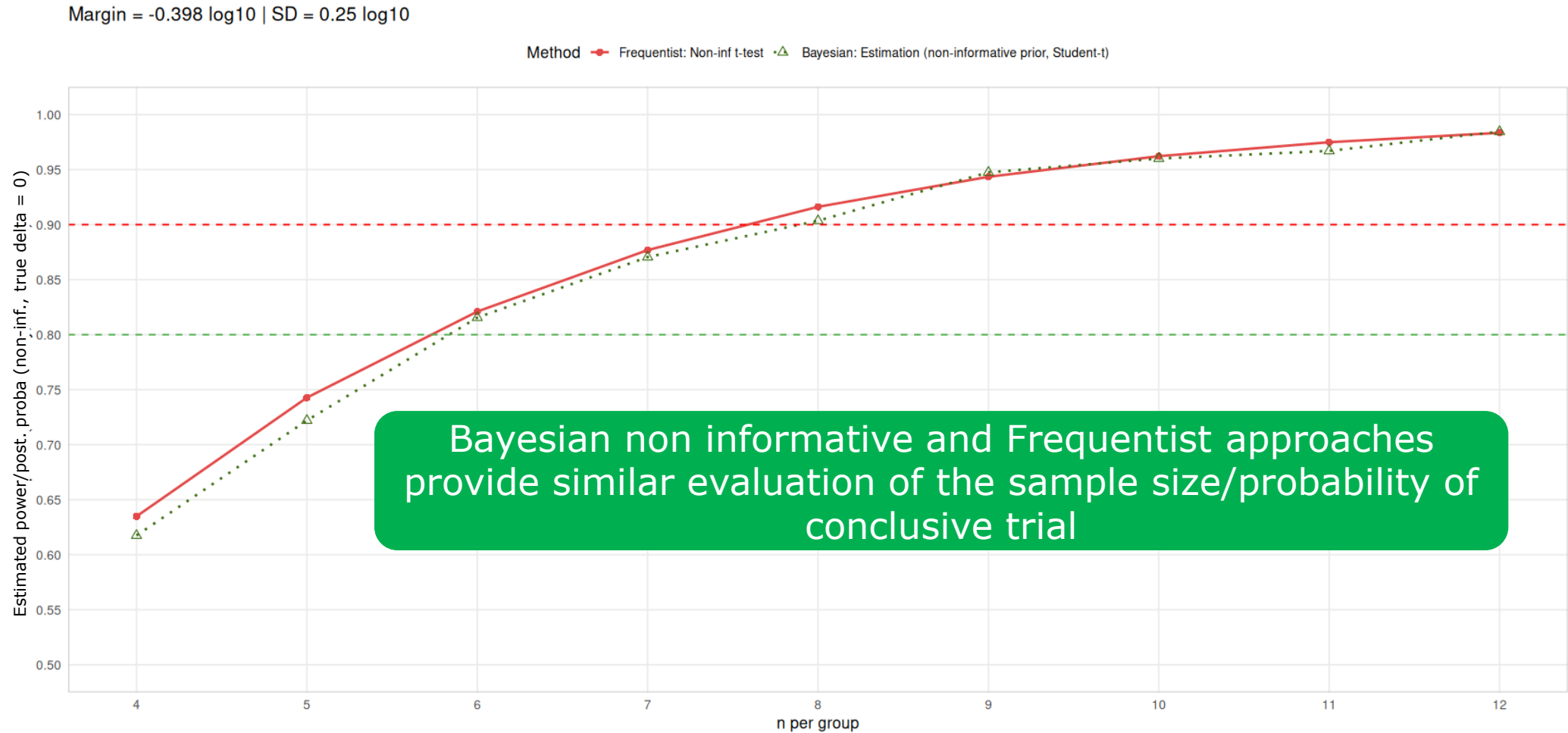


Impact of the Use of a Non Informative Prior vs Frequentist Approach



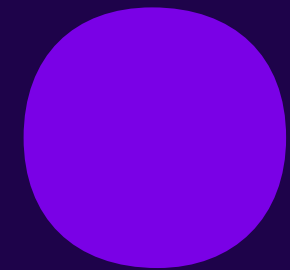
Parameters — margins: 0.176, 0.301, 0.398 log10 | SD: 0.25, 0.4, 0.6 log10 | n per group: 4-12 (step 1) | true delta: 0 | alpha: 0.1 (alpha_ni = 0.05) | Post Proba Threshold: 0.95 | n_sim: 2000
Informative priors: n=4, SD=0.25, mean=0.00 ; n=4, SD=0.40, mean=0.00 ; n=4, SD=0.60, mean=0.00

Impact of the Use of a Non Informative Prior vs Frequentist Approach



Parameters — margins: 0.176, 0.301, $0.398 \log_{10}$ | SD: 0.25, 0.4, $0.6 \log_{10}$ | n per group: 4-12 (step 1) | true delta: 0 | alpha: 0.1 (alpha_{ni} = 0.05) | Post Proba Threshold: 0.95 | n_{sim}: 2000
Informative priors: n=4, SD=0.25, mean=0.00 ; n=4, SD=0.40, mean=0.00 ; n=4, SD=0.60, mean=0.00

2 Impact of Informative Prior



Simulation

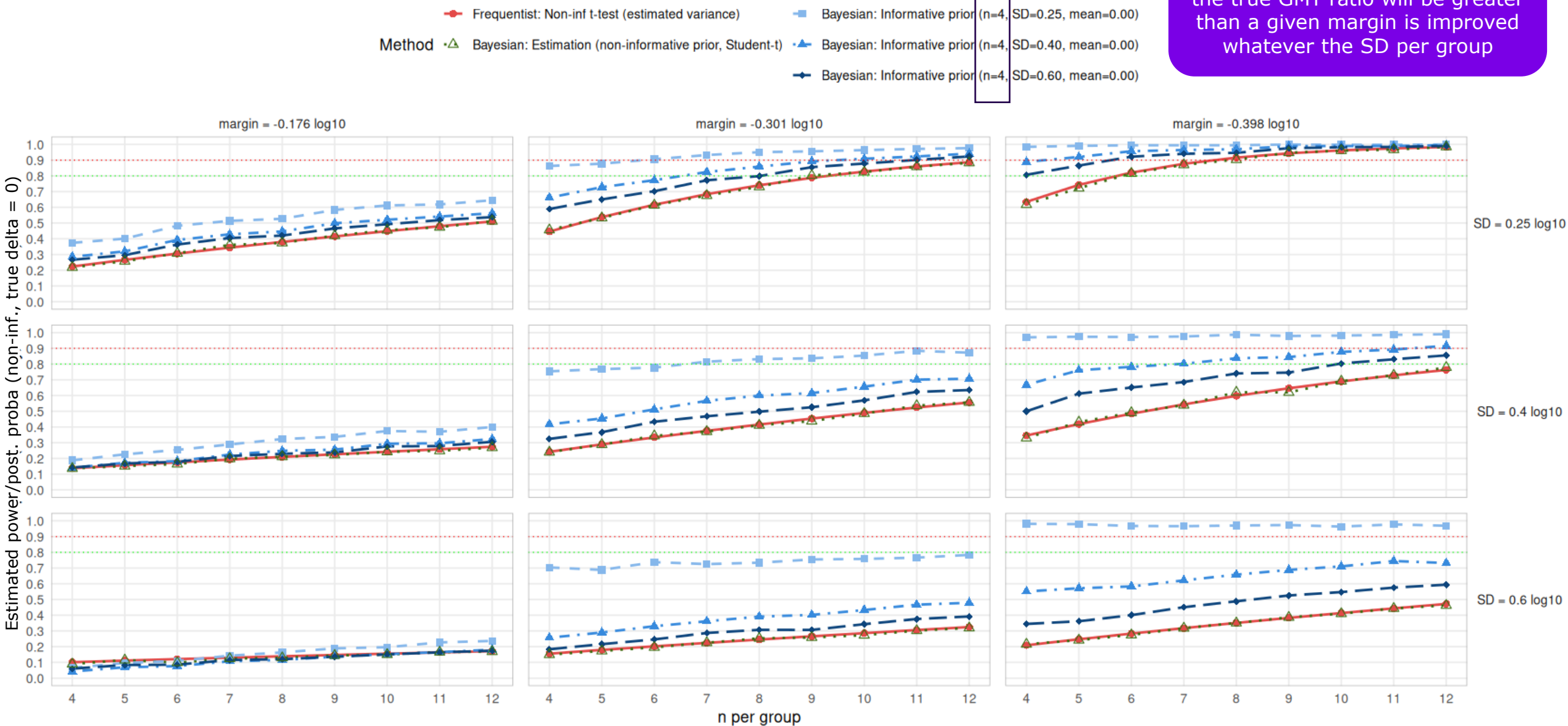
The following simulation has been performed considering:

Simulation considering:			Frequentist	Bayesian With Non Informative Prior	Bayesian with Non informative prior for the new group and Informative Prior for the benchmark n per group= 4			Bayesian With Informative Prior (Mean Diff = 0) n per group= 4			Bayesian With Informative Prior (Mean Diff = 0) SD per group 0.40		
Lower Margin Log10 (fold)	SD of the group (Log10)	n per group			SD per group 0.25	SD per group 0.40	SD per group 0.60	SD per group 0.25	SD per group 0.40	SD per group 0.60	npg= 4	npg= 6	npg= 8
-0.176 (1/1.5)	0.25	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.40	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.60	4-12	X	X	X	X	X	X	X	X	X	X	X
-0.301 (1/2)	0.25	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.40	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.60	4-12	X	X	X	X	X	X	X	X	X	X	X
-0.398 (1/2.5)	0.25	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.40	4-12	X	X	X	X	X	X	X	X	X	X	X
	0.60	4-12	X	X	X	X	X	X	X	X	X	X	X

SD: Standard Deviation; npg : number of animal per group
All simulations were performed using R (version 4.5.1.).

Impact of the Use of Informative Prior N = 4

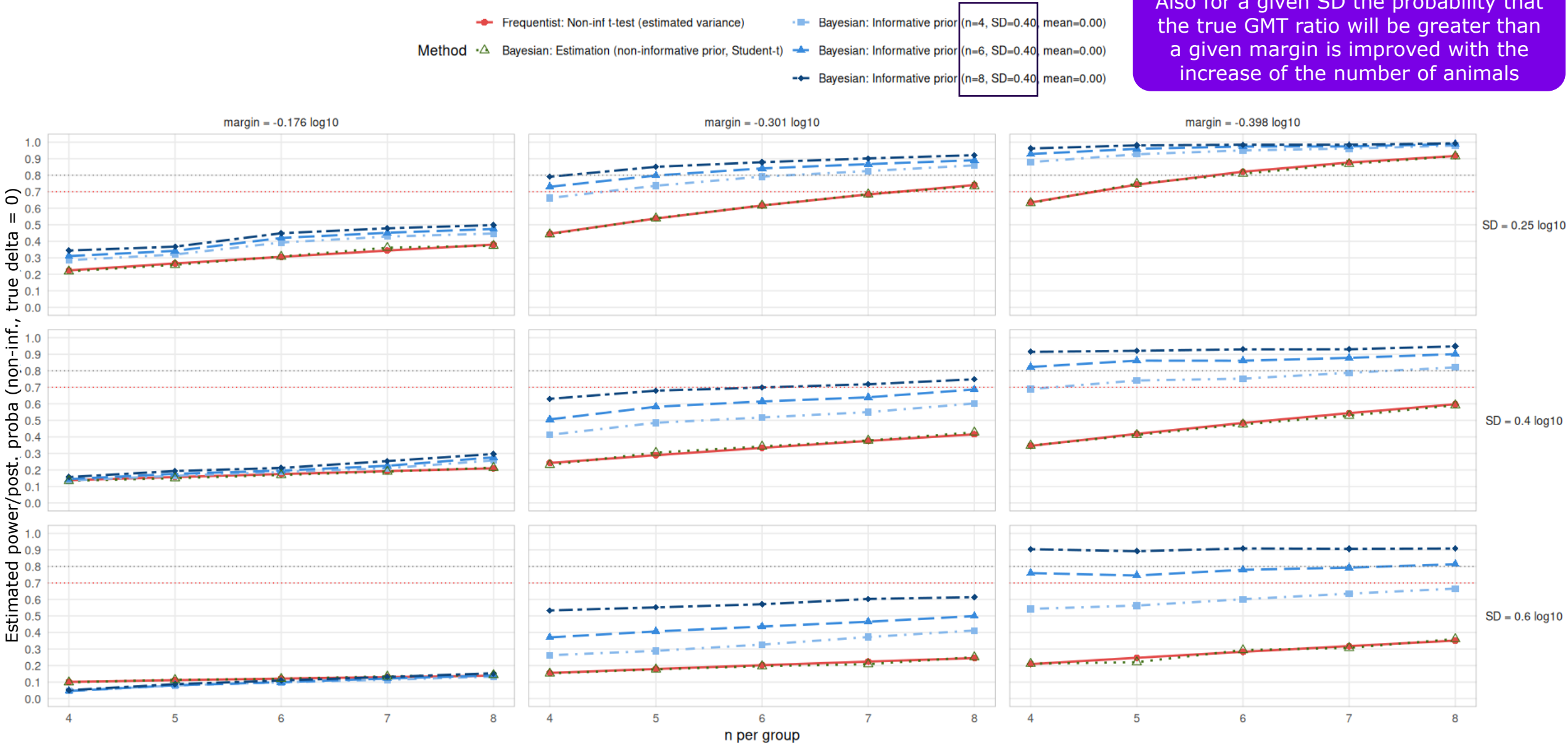
Even with a small informative prior (n=4) the probability that the true GMT ratio will be greater than a given margin is improved whatever the SD per group



Parameters — margins: 0.176, 0.301, 0.398 log10 | SD: 0.25, 0.4, 0.6 log10 | n per group: 4-12 (step 1) | true delta: 0 | alpha: 0.1 (alpha_{ni} = 0.05) | Post Proba Threshold: 0.95 | n_{sim}: 2000
Informative priors: n=4, SD=0.25, mean=0.00 ; n=4, SD=0.40, mean=0.00 ; n=4, SD=0.60, mean=0.00

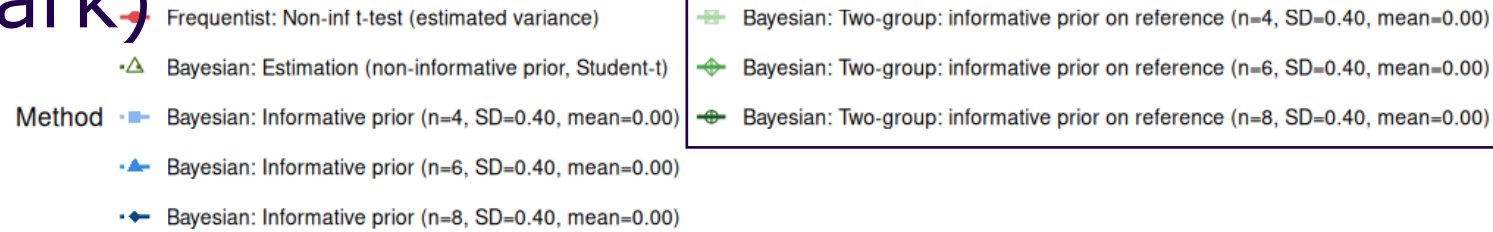
Impact of the Use of Informative Prior SD=0.40 & N = 4, 6, 8

Also for a given SD the probability that the true GMT ratio will be greater than a given margin is improved with the increase of the number of animals

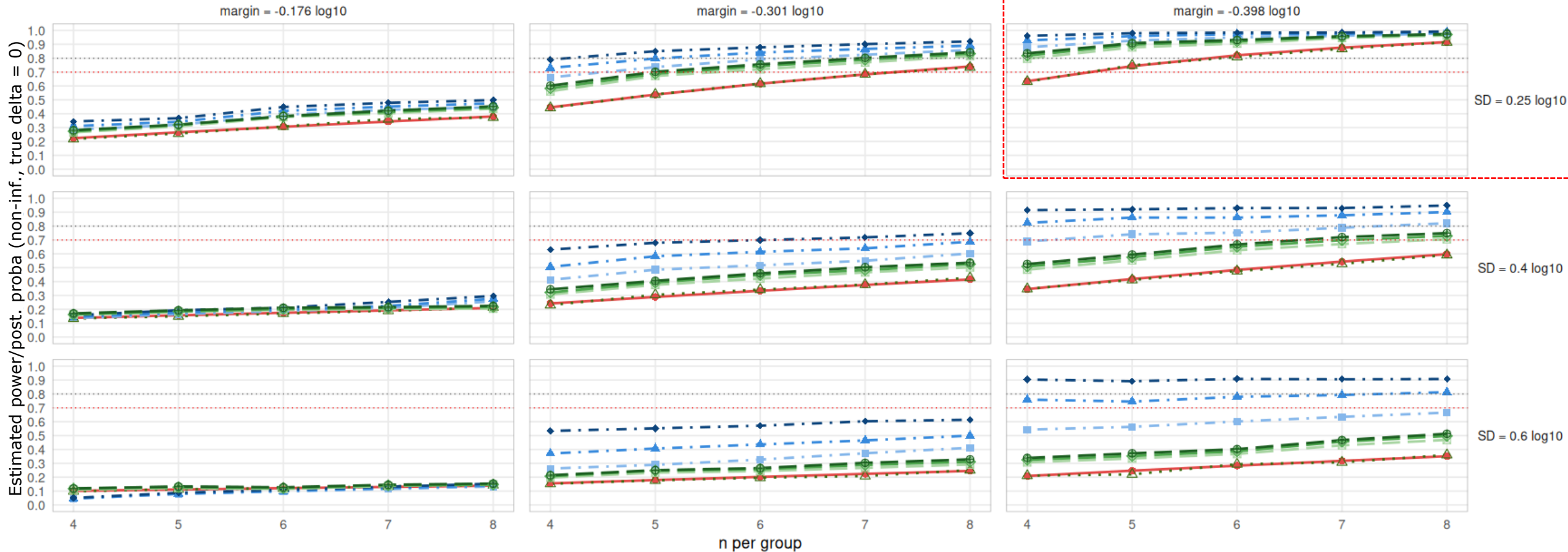


Parameters — margins: 0.176, 0.301, 0.398 log10 | SD pg: 0.25, 0.4, 0.6 log10 | n per group: 4-8 (step 1) | true delta: 0 | alpha: 0.1 (alpha_ni = 0.05) | Post Proba Threshold: 0.95 | n_sim: 2000
Informative priors: npg=4, SD pg=0.40, Diff mean=0.00 ; npg=6, SD pg=0.40, Diff mean=0.00 ; npg=8, SD pg=0.40, Diff mean=0.00

With Prior Non Informative (New) and Informative (Benchmark)



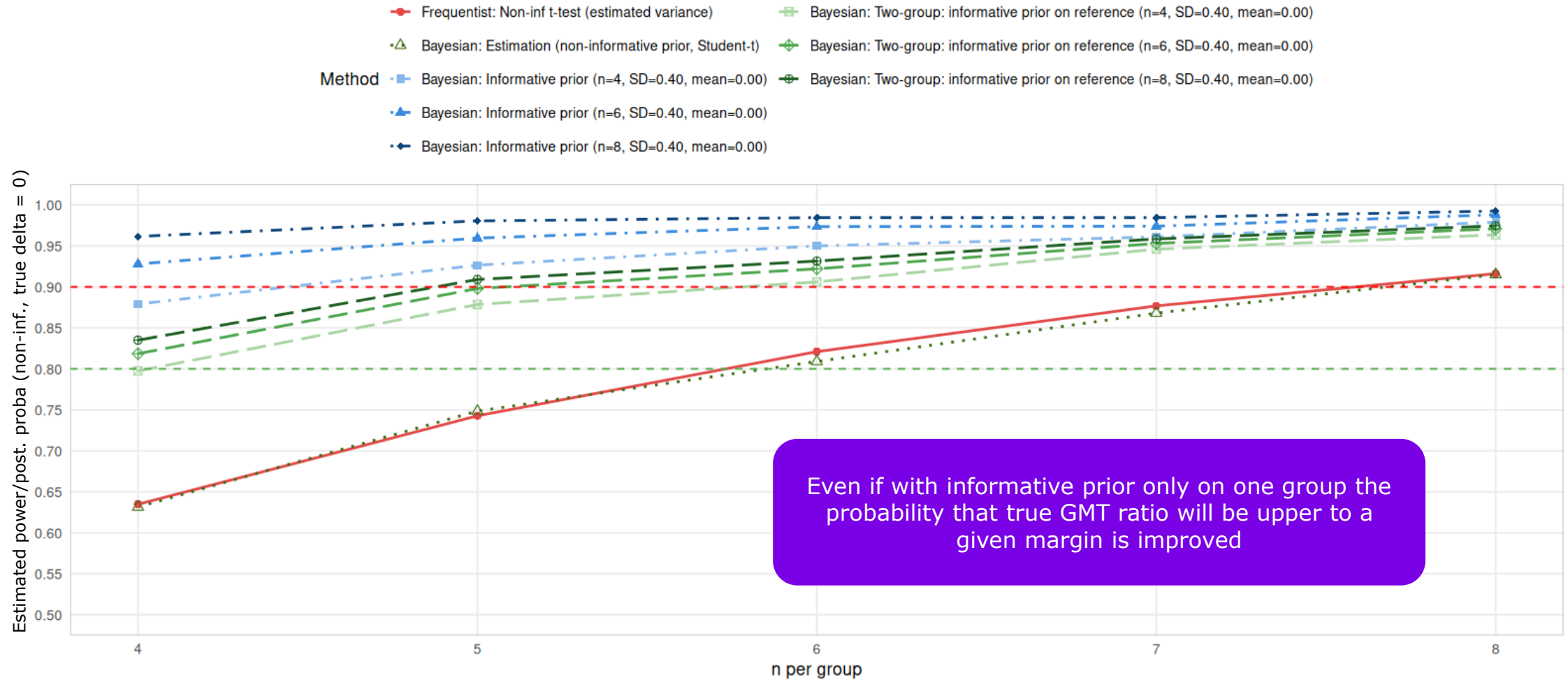
Intermediate results obtained



Parameters — margins: 0.176, 0.301, 0.398 log10 | SD: 0.25, 0.4, 0.6 log10 | n per group: 4-8 (step 1) | true delta: 0 | alpha: 0.1 (alpha_{ni} = 0.05) | Post Proba Threshold: 0.95 | n_{sim}: 2000
Informative priors: n=4, SD=0.40, mean=0.00 ; n=6, SD=0.40, mean=0.00 ; n=8, SD=0.40, mean=0.00

With Prior Non Informative (New) and Informative (Benchmark)

Margin = $-0.398 \log_{10}$ | SD = $0.25 \log_{10}$



Parameters — margins: 0.176, 0.301, $0.398 \log_{10}$ | SD: 0.25, 0.4, $0.6 \log_{10}$ | n per group: 4-8 (step 1) | true delta: 0 | alpha: 0.1 (alpha_{ni} = 0.05) | Post Proba Threshold: 0.95 | n_{sim}: 2000
Informative priors: n=4, SD=0.40, mean=0.00 ; n=6, SD=0.40, mean=0.00 ; n=8, SD=0.40, mean=0.00

Conclusion for the Impact of the Power/Posterior Probability

Lower margin	sd	npg	Frequentist: Non-inf-t-test	Bayesian: Estimation non-informative prior	Bayesian: Informative prior n=4.		
				Student-t	SD=0.60	SD=0.40	SD=0.25
0.301	0.6	4	0.156	0.150	0.184	0.257	0.704
		5	0.179	0.172	0.216	0.290	0.688
		6	0.202	0.196	0.246	0.330	0.738
		7	0.224	0.225	0.287	0.362	0.725
		8	0.245	0.253	0.307	0.391	0.734
		9	0.266	0.258	0.306	0.402	0.754
		10	0.286	0.273	0.343	0.433	0.758
		11	0.306	0.302	0.376	0.467	0.766
		12	0.325	0.319	0.392	0.479	0.783
	0.4	4	0.242	0.240	0.324	0.417	0.754
		5	0.289	0.288	0.367	0.454	0.768
		6	0.334	0.344	0.434	0.512	0.777
		7	0.376	0.371	0.468	0.567	0.816
		8	0.416	0.411	0.498	0.600	0.832
		9	0.454	0.438	0.525	0.616	0.837
		10	0.490	0.486	0.570	0.656	0.854
		11	0.524	0.535	0.623	0.701	0.884
		12	0.556	0.556	0.635	0.707	0.873
	0.25	4	0.446	0.456	0.590	0.661	0.863
		5	0.538	0.532	0.650	0.729	0.877
		6	0.617	0.614	0.703	0.772	0.906
		7	0.684	0.675	0.772	0.825	0.932
		8	0.740	0.731	0.798	0.859	0.951
		9	0.788	0.802	0.856	0.892	0.956
		10	0.827	0.824	0.878	0.909	0.964
		11	0.860	0.859	0.901	0.923	0.972
		12	0.887	0.883	0.923	0.942	0.977

Lower margin	sd	npg	Frequentist: Non-inf-t-test	Bayesian: Estimation non-informative prior	Bayesian: Informative prior n=4.		
				Student-t	SD=0.60	SD=0.40	SD=0.25
0.398	0.6	4	0.209	0.216	0.344	0.551	0.981
		5	0.247	0.242	0.362	0.572	0.979
		6	0.283	0.274	0.400	0.583	0.968
		7	0.318	0.318	0.451	0.622	0.966
		8	0.351	0.350	0.488	0.658	0.971
		9	0.383	0.386	0.525	0.688	0.974
		10	0.414	0.410	0.547	0.711	0.964
		11	0.444	0.443	0.576	0.745	0.978
		12	0.472	0.462	0.594	0.732	0.969
	0.4	4	0.346	0.330	0.500	0.668	0.970
		5	0.419	0.432	0.612	0.761	0.974
		6	0.484	0.491	0.651	0.782	0.972
		7	0.544	0.539	0.686	0.802	0.976
		8	0.598	0.621	0.741	0.837	0.987
		9	0.646	0.620	0.746	0.845	0.979
		10	0.690	0.692	0.804	0.877	0.982
		11	0.729	0.729	0.831	0.892	0.986
		12	0.763	0.778	0.856	0.916	0.990
	0.25	4	0.635	0.618	0.807	0.889	0.985
		5	0.743	0.722	0.866	0.920	0.991
		6	0.821	0.816	0.922	0.957	0.995
		7	0.877	0.871	0.941	0.965	0.995
		8	0.916	0.903	0.947	0.970	0.995
		9	0.943	0.948	0.976	0.989	1.000
		10	0.962	0.960	0.982	0.990	0.998
		11	0.975	0.967	0.985	0.990	0.998
		12	0.983	0.985	0.991	0.996	1.000

Bayesian approach could really help to show non inferiority
at a lower margin with a small sample size

sanofi

Analyses

Frequentist vs Bayesian

Design: 2 different vaccines on 3 different doses

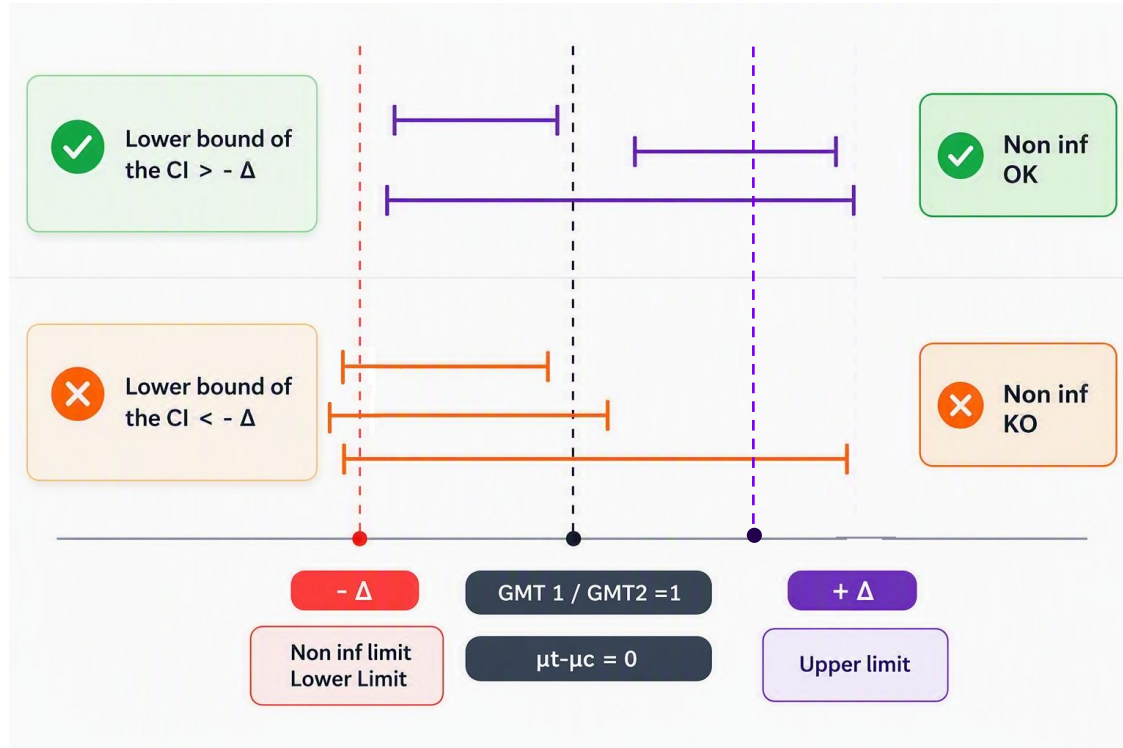
Aim: To show that the new vaccine is non inferior to the benchmark considering a non-inferiority margin (Δ)

Frequentist vs Bayesian approach – Non inferiority

Example in comparison with 2 different vaccine formulations

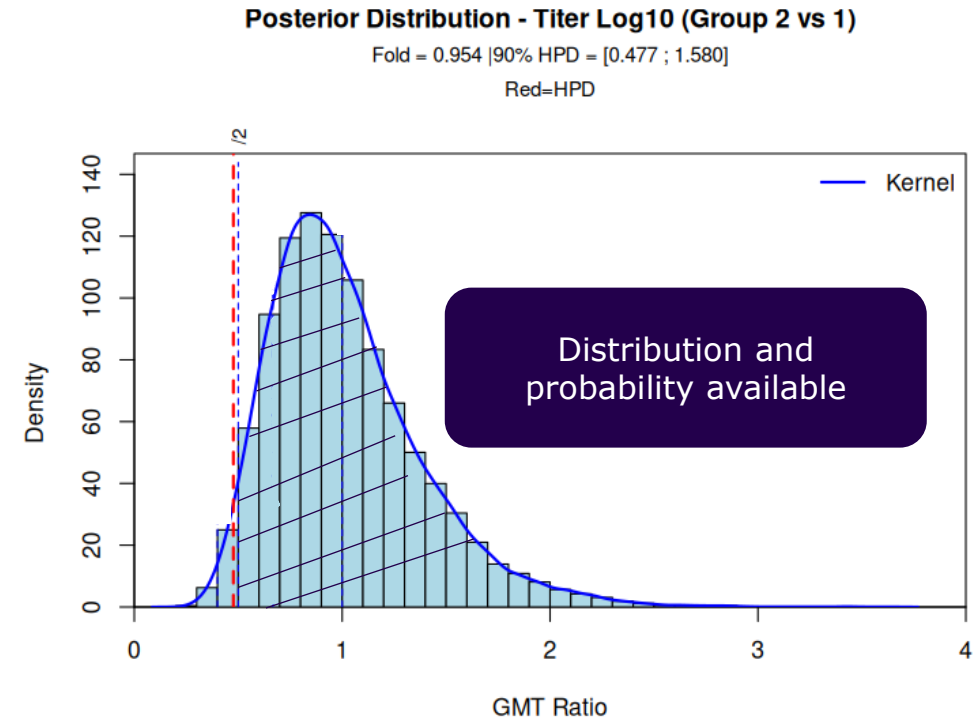
Frequentist approach

Estimate and CI



Bayesian approach

Posterior Distribution



Impact of the Use of Bayesian with Non Informative Prior vs Frequentist

Example of results with a frequentist approach

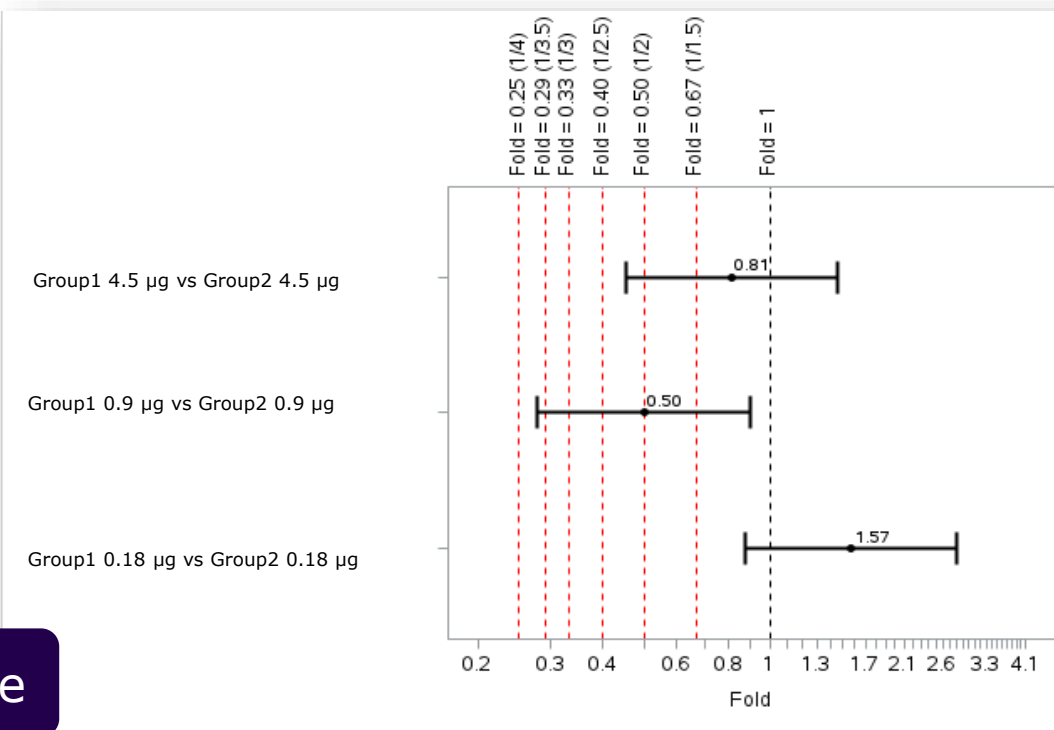
Comparison at the same doses			Fold and 90%CI				Example of Interpretation:					
							Non inferiority Margin =					
Time	Group	vs Group	Fold x/	Fold value	LCI	UCI	0.25 fold -0.602 log10 (1/4)	0.29 fold -0.544 log10 (1/3.5)	0.33 fold -0.477 log10 (1/3)	0.40 fold -0.398 log10 (1/2.5)	0.50 fold -0.301 log10 (1/2)	0.67 fold -0.176 log10 (1/1.5)
D35	Group 1 - 4.50 µg	Group 2 - 4.50 µg	/1.23	0.81	0.45	1.46	Yes	Yes	Yes	Yes	No	No
	Group 1 - 0.90 µg	Group 2 - 0.90 µg	/2.00	0.50	0.28	0.90	Yes	No	No	No	No	No
	Group 1 - 0.18 µg	Group 2 - 0.18 µg	x1.57	1.57	0.87	2.82	Yes	Yes	Yes	Yes	Yes	Yes

ANOVA model with the group and time as fixed factors

LCI: Lower confidence interval. UCI: Upper confidence interval

Fold = 10^{estimate}

- With that frequentist approach that could be very difficult to conclude. the intermediate dose provides inconsistent results certainly due to variability of the animals
- With such results we could conclude that the non inferiority of Group 1 vs Group 2 could be concluded:
 - For dose 4.5µg. at /2.5 (0.40 fold).
 - For dose 0.9µg. /4 (0.25 fold).
 - For dose 0.18 µg whatever the lower bound.



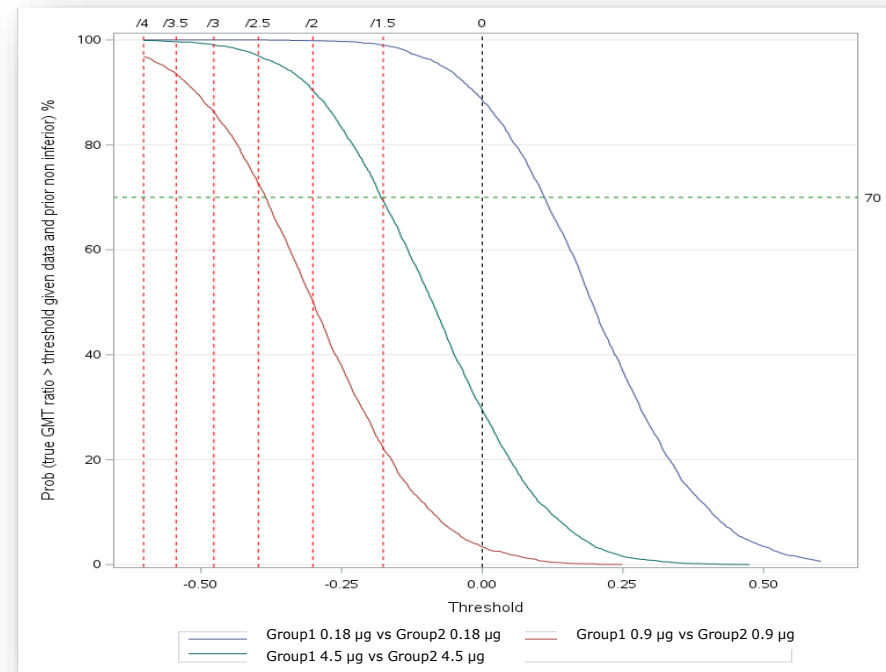
Impact of the Use of Bayesian with Non Informative Prior vs Frequentist

Example of results with the Bayesian approach

				Example of Interpretation:					
				Non inferiority Margin =					
Posterior probability	Estimate and 90% Credible interval in log10			0.25 fold -0.602 log10 (1/4)	0.29 fold -0.544 log10 (1/3.5)	0.33 fold -0.477 log10 (1/3)	0.40 fold -0.398 log10 (1/2.5)	0.50 fold -0.301 log10 (1/2)	0.67 fold -0.176 log10 (1/1.5)
Comparison at the same doses									
Label on Graph	Estimate	Credible interval		P(Diff> margin) %	P(Diff> margin) %	P(Diff> margin) %	P(Diff> margin) %	P(Diff> margin) %	P(Diff> margin) %
D35 Group 1 vs Group 2 - 4.5 µg	-0.09	-0.339	0.192	99.95	99.65	99.05	96.97	90.35	69.35
D35 Group 1 vs Group 2 - 0.9 µg	-0.30	-0.567	-0.036	96.85	93.55	86.30	72.60	50.20	22.17
D35 Group 1 vs Group 2 - 0.18 µg	0.197	-0.079	0.454	100.00	100.00	100.00	100.00	99.85	98.97

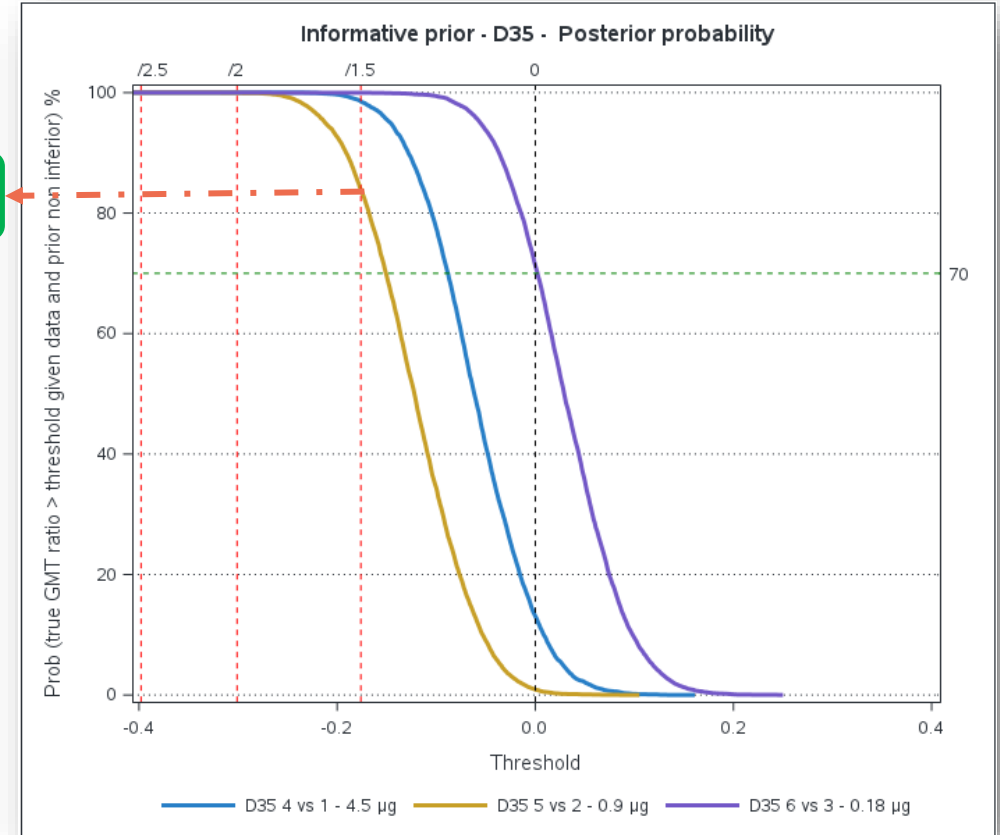
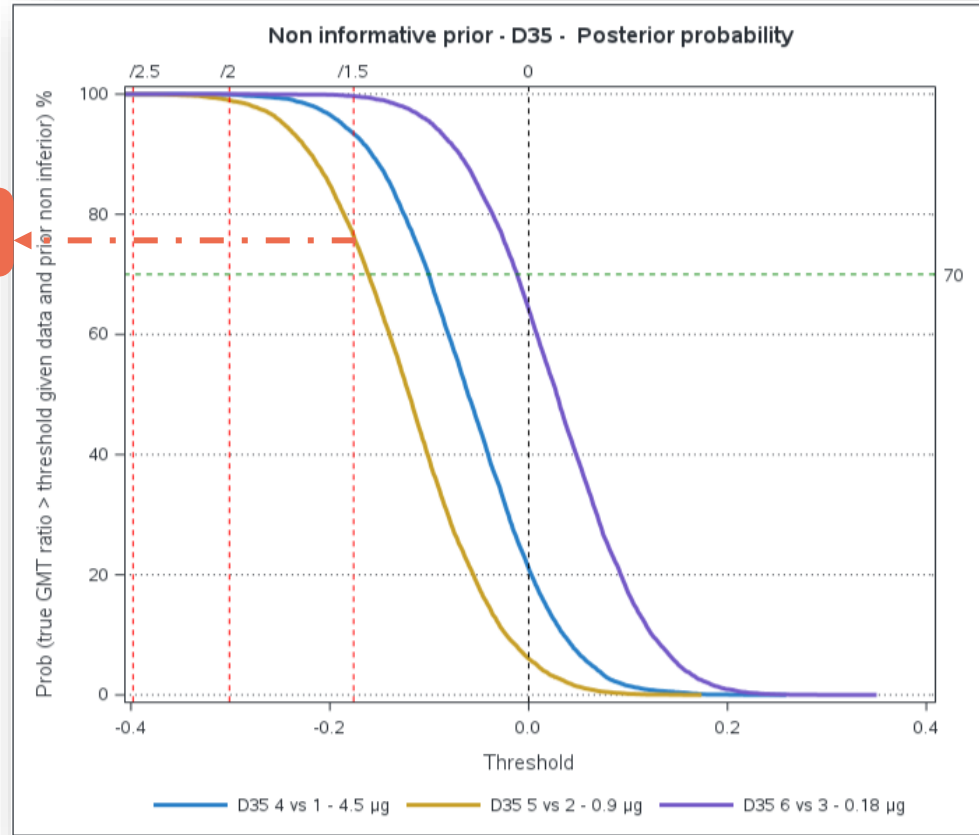
- Moving to the Bayesian approach we could conclude that :
- At D35, given data and a non-informative prior, the posterior probability of Group 1 vs Group 2 indicates that the probability that the true ratio is greater than 1/2.5 (-0.398 log10)
 - For dose 4.5µg: 96.97%
 - For dose 0.9µg: 72.60%
 - For dose 0.18 µg is 100%

That really helps us conclude ! 😊



Impact of the Use of Bayesian with Informative Prior vs Non Informative

The use of non informative prior vs informative prior



Example of Interpretation: Non inferiority with a lower bound =

				Frequentist approach			Non informative prior			Informative prior		
Comparison at the same doses	Estimate and 90%CI in log10			0.40 fold -0.398 log10 (1/2.5)	0.50 fold -0.301 log10 (1/2)	0.67 fold -0.176 log10 (1/1.5)	0.40 fold -0.398 log10 (1/2.5)	0.50 fold -0.301 log10 (1/2)	0.67 fold -0.176 log10 (1/1.5)	0.40 fold -0.398 log10 (1/2.5)	0.50 fold -0.301 log10 (1/2)	0.67 fold -0.176 log10 (1/1.5)
Label	Estimate	LCI	UCI				P(Diff> margin) %	P(Diff> margin) %	P(Diff> margin) %	P(Diff> margin) %	P(Diff> margin) %	P(Diff> margin) %
D35_4_vs_1	-0.061	-0.191	0.058	Yes	Yes	No	100	99.93	93.4	100	100	98.52
D35_5_vs_2	-0.121	-0.250	0.003	Yes	Yes	No	100	98.95	76.39	100	99.96	83.86
D35_6_vs_3	0.028	-0.097	0.150	Yes	Yes	Yes	100	100	99.66	100	100	99.99

Key messages

01

Question

Frequentist and Bayesian approaches answer different questions

02

Simulate

Posterior probabilities are easier for scientists to interpret because they directly address the question of interest

03

Evaluate

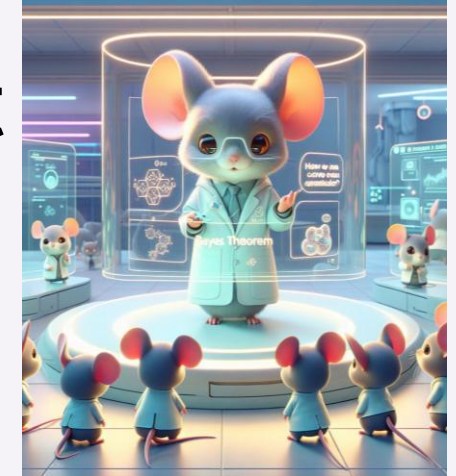
Model assumptions and prior information must be discussed and evaluated

04

Optimize

Rather than competing frameworks, frequentist and Bayesian methods should be viewed as complementary: the former focuses on long-run error control, while the latter provides a probabilistic assessment of the treatment effect and supports decision making.

Take Home Message for preclinical context



Better Insights, Smarter Decisions



Reduction of animal use

Bayesian methods **could support the reduction** of animal use



Posterior probability interpretation

Bayesian methods **could improve data interpretation**, even with limited samples



Enhancing Preclinical Research

Bayesian methods could support **more informed and transparent decision-making** in preclinical vaccine development



Thank you



sanofi

EMA and FDA Guidances for Non-Inferiority & Equivalence

- ◆ EMA Draft Guideline – Non-Inferiority & Equivalence Comparisons in Clinical Trials → recommends 95% CI 📄 [EMA Draft Guideline](#)

The EMA 95% CI applies to broader clinical equivalence/non-inferiority settings with clinical endpoints, reflecting a more conservative stance (one-sided $\alpha = 0.025$) to reduce the risk of falsely claiming equivalence.

- ◆ FDA Guidance (May 2026) – Statistical Approaches to Establishing Bioequivalence → recommends 90% CI 📄 [FDA Guidance](#)

The FDA 90% CI is tailored for PK bioequivalence studies (AUC, C_{max}) — well-characterized parameters with established acceptance ranges (80–125%), where a one-sided $\alpha = 0.05$ per boundary is considered sufficient.

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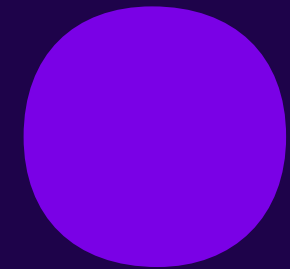
Backup slides



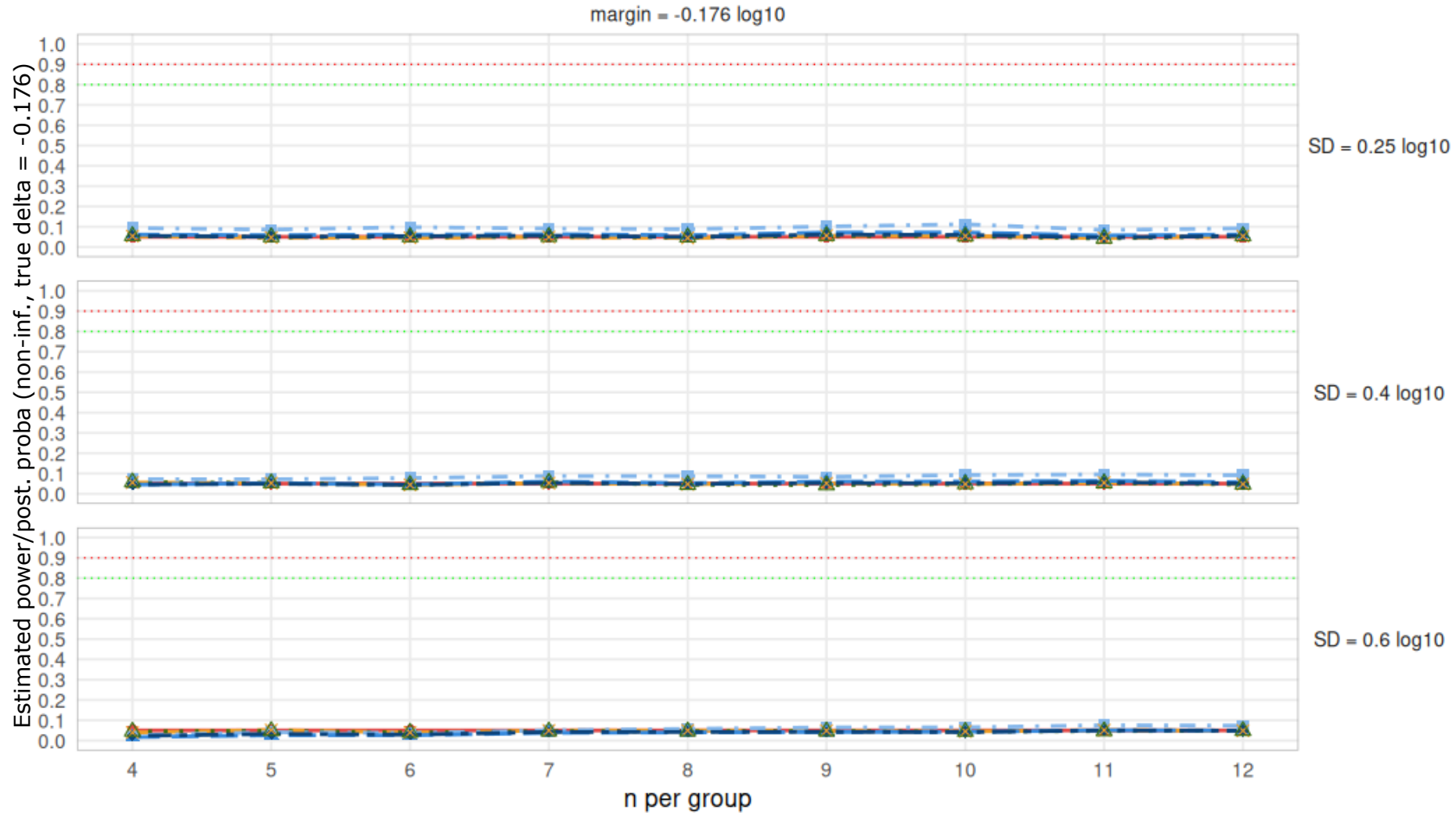
Alpha Inflation

BACK UP SLIDE

$$\textit{true delta} = -0.176 \log_{10}$$

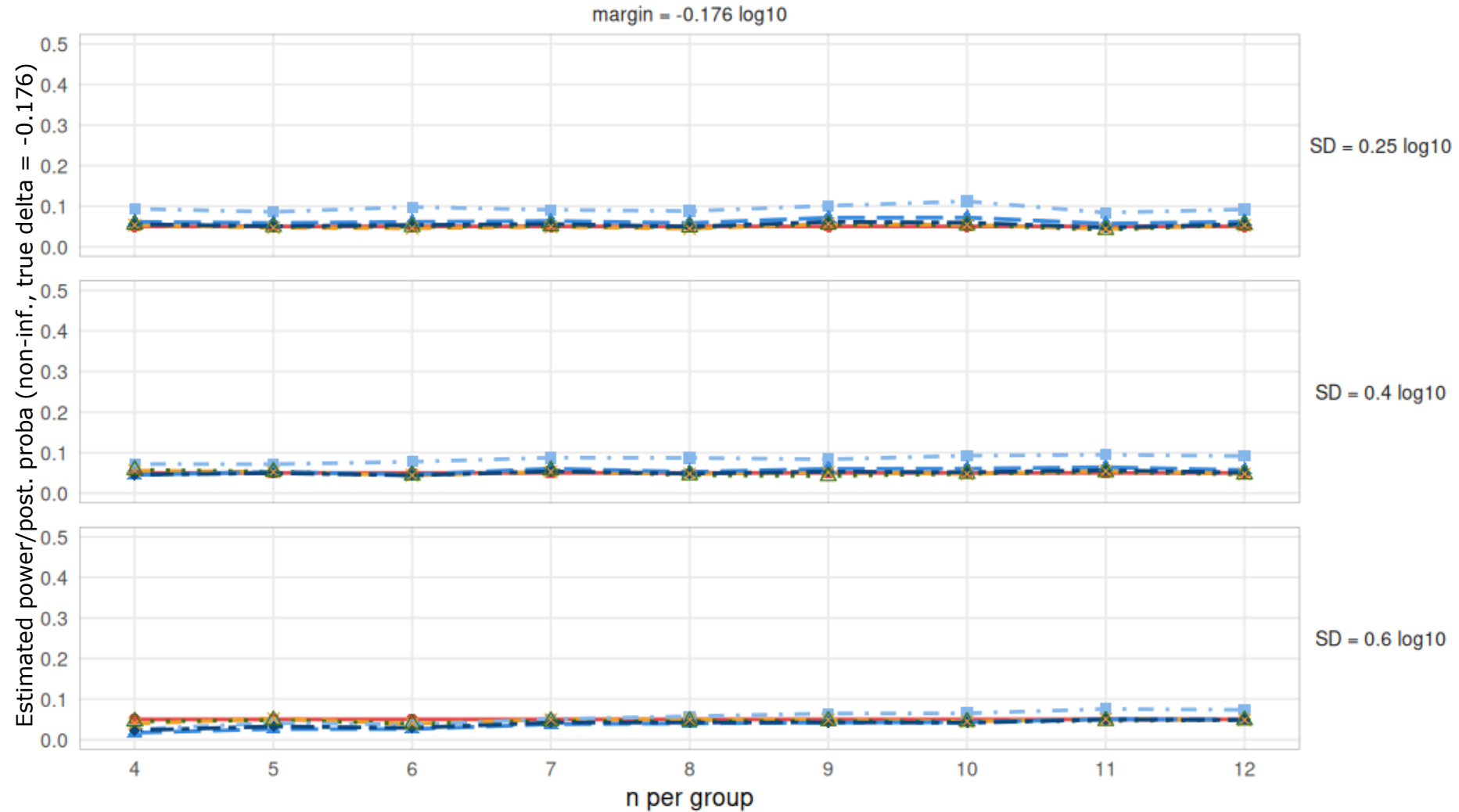


- Method
- Frequentist: Non-inf t-test (estimated variance)
 - Bayesian: Informative prior (n=4, SD=0.25, mean=0.00)
 - Bayesian: Estimation (non-informative prior, Normal: SD=Inf)
 - Bayesian: Informative prior (n=4, SD=0.40, mean=0.00)
 - Bayesian: Estimation (non-informative prior, Student-t)
 - Bayesian: Informative prior (n=4, SD=0.60, mean=0.00)



Parameters — margins: 0.176 log10 | SD: 0.25, 0.4, 0.6 log10 | n per group: 4-12 (step 1) | true delta: -0.176 | alpha: 0.1 (alpha_ni = 0.05) | Post Proba Threshold: 0.95 | n_sim: 2000
 Informative priors: n=4, SD=0.25, mean=0.00 ; n=4, SD=0.40, mean=0.00 ; n=4, SD=0.60, mean=0.00

- Method
- Frequentist: Non-inf t-test (estimated variance)
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Parameters — margins: 0.176 log10 | SD: 0.25, 0.4, 0.6 log10 | n per group: 4-12 (step 1) | true delta: -0.176 | alpha: 0.1 (alpha_ni = 0.05) | Post Proba Threshold: 0.95 | n_sim: 2000
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