



Non-inferiority Trial – Growing Significance:

Anubrata Kundu
Novartis

Disclaimer

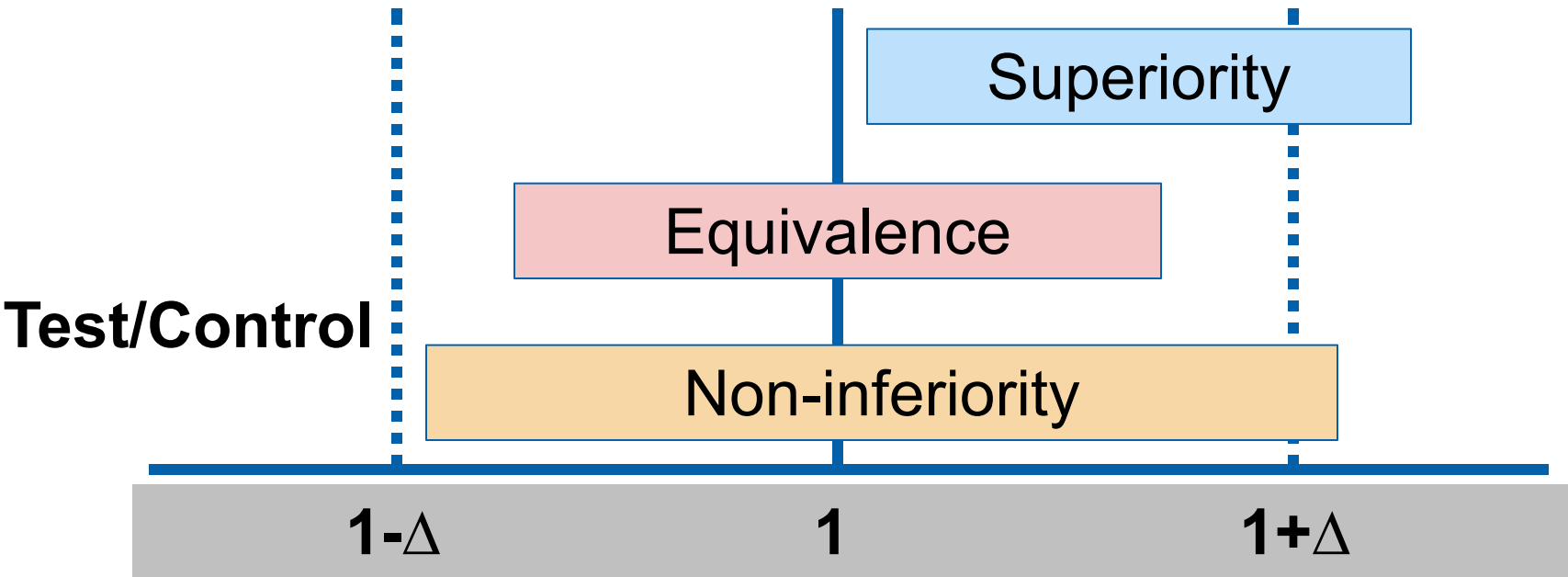
- The views presented are the views of the presenter, not necessarily those of Novartis
- These slides are intended for educational purposes only and for the personal use of the audience. These slides are not intended for wider distribution outside the intended purpose without presenter approval
- The content of this slide deck is accurate to the best of the presenter's knowledge at the time of production

Agenda

- Introduction
 - Different randomized clinical trials
 - Possible treatment comparisons
- Reasons for using NI trial
- NI design
 - Objective and hypothesis
 - NI Margin
 - Assay sensitivity
- Example
- Take away messages

Introduction

There are various types of testing strategies in randomized clinical trials



In pharma industry, **sometimes** we design non-inferiority trials.

*This is an attempt to describe the **non-inferiority (NI)** trial and its different properties are further illustrated with an example.*

3 Different Randomized Clinical Trials

Superiority
>

Intend to assess whether a new treatment is more efficacious than a current standard treatment.

Equivalence
=

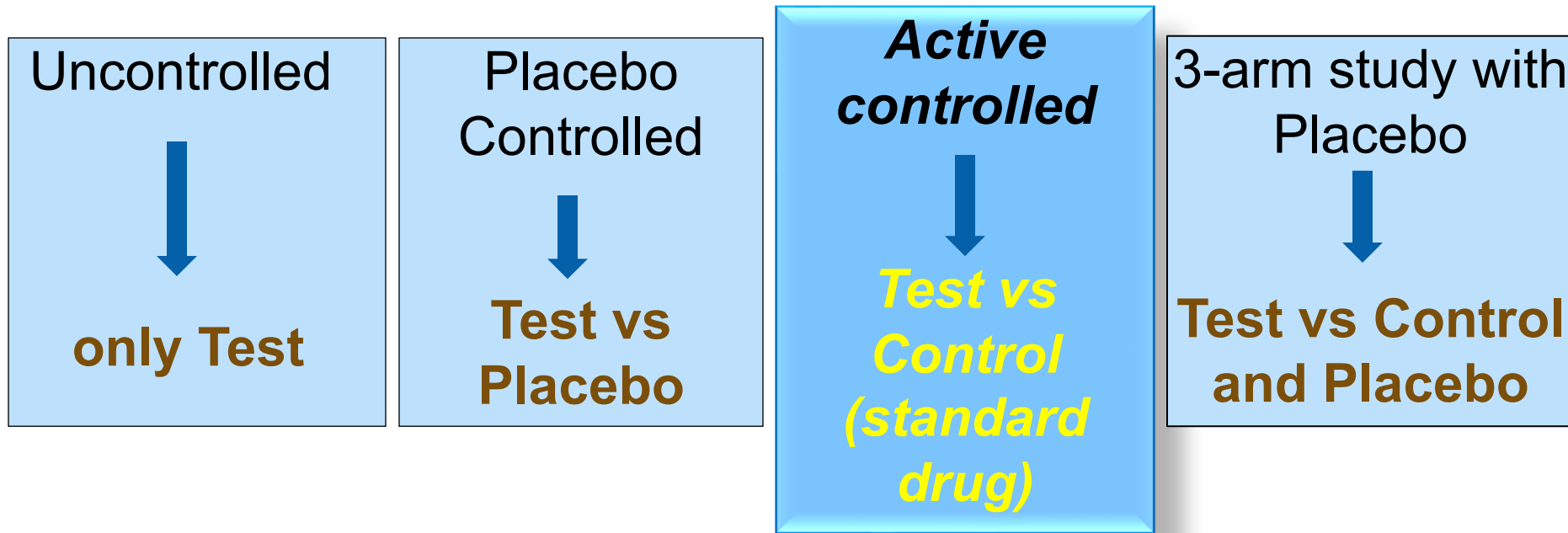
Aim to show that the two treatments are not too different in characteristics.

Non -
inferiority



Attempt to establish that the effect of a new experimental treatment is **not worse** than that of an active control treatment already in use without compromising its efficacy, when only superiority over placebo is not needed or not sufficient as the new treatment may offer important advantages over currently available standard treatments, in terms of improved safety and quality of life, better compliance.

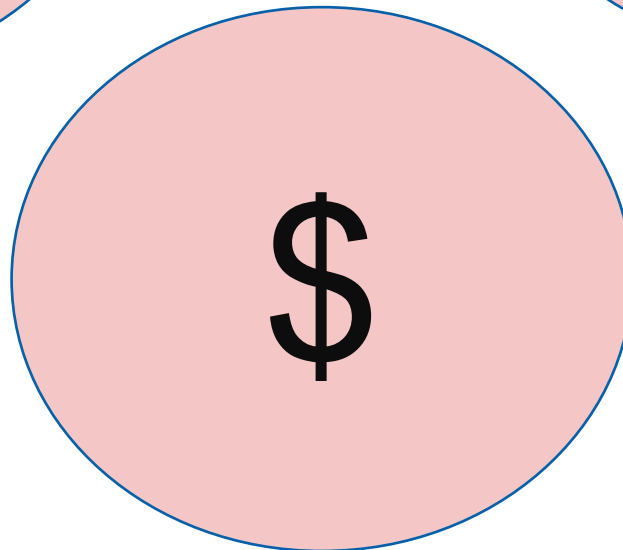
Possible treatment comparisons



NI problems usually appears in Active controlled or 3-arm study with Placebo.

Here, we will be discussing NI of an active controlled design.

Why Non-Inferiority



Regulatory guidance

ICH E10:

“In cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control”

FDA Guidance:

“It would not be ethical to use a placebo, or a no treatment control, or a very low dose of an active drug, if there is an effective treatment that provides an important benefit (e.g., life-saving or preventing irreversible injury)”

Notations

- T = Test treatment
- C = Active control treatment
- P = Placebo
- ORR = Overall response rate (Primary endpoint: higher the rate better the result)
- R_T = ORR of T
- R_C = ORR of C
- R_P = ORR of P
- M = NI Margin

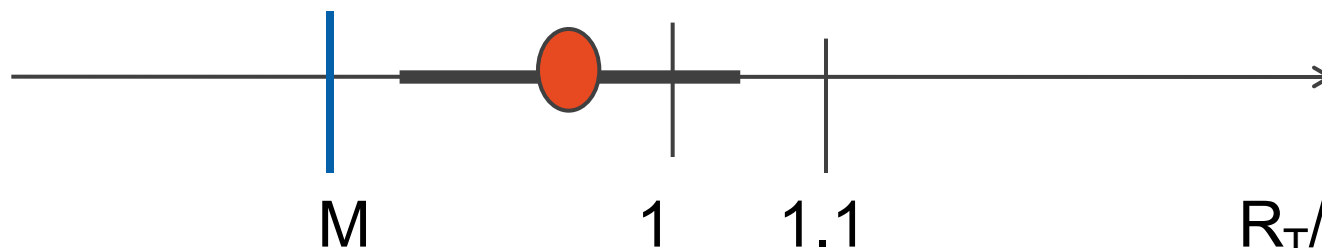
NI design: general considerations

Objective: To show that T is **non-inferior** to C (standard drug available) to an unacceptable extent, as measured by a **NI margin**.

Hypothesis: $H_0: \theta_1 \leq M$ vs $H_1: \theta_1 > M$
Where $\theta_1 = R_T/R_C$

- **Non-inferior:** This means T is not much worse than C. T, which demonstrate non-inferiority is effective, not that it is as effective as the active comparator.
- The degree of non-inferiority is measured by **NI margin (M)**

Confidence intervals are used to analyze NI studies.



Calculation of NI Margin

NI Margin M will be based on:

- M1 = the entire effect of the active control assumed to be present in the NI study
- M2 = the largest clinically acceptable difference (degree of inferiority) of the test drug compared to the active control

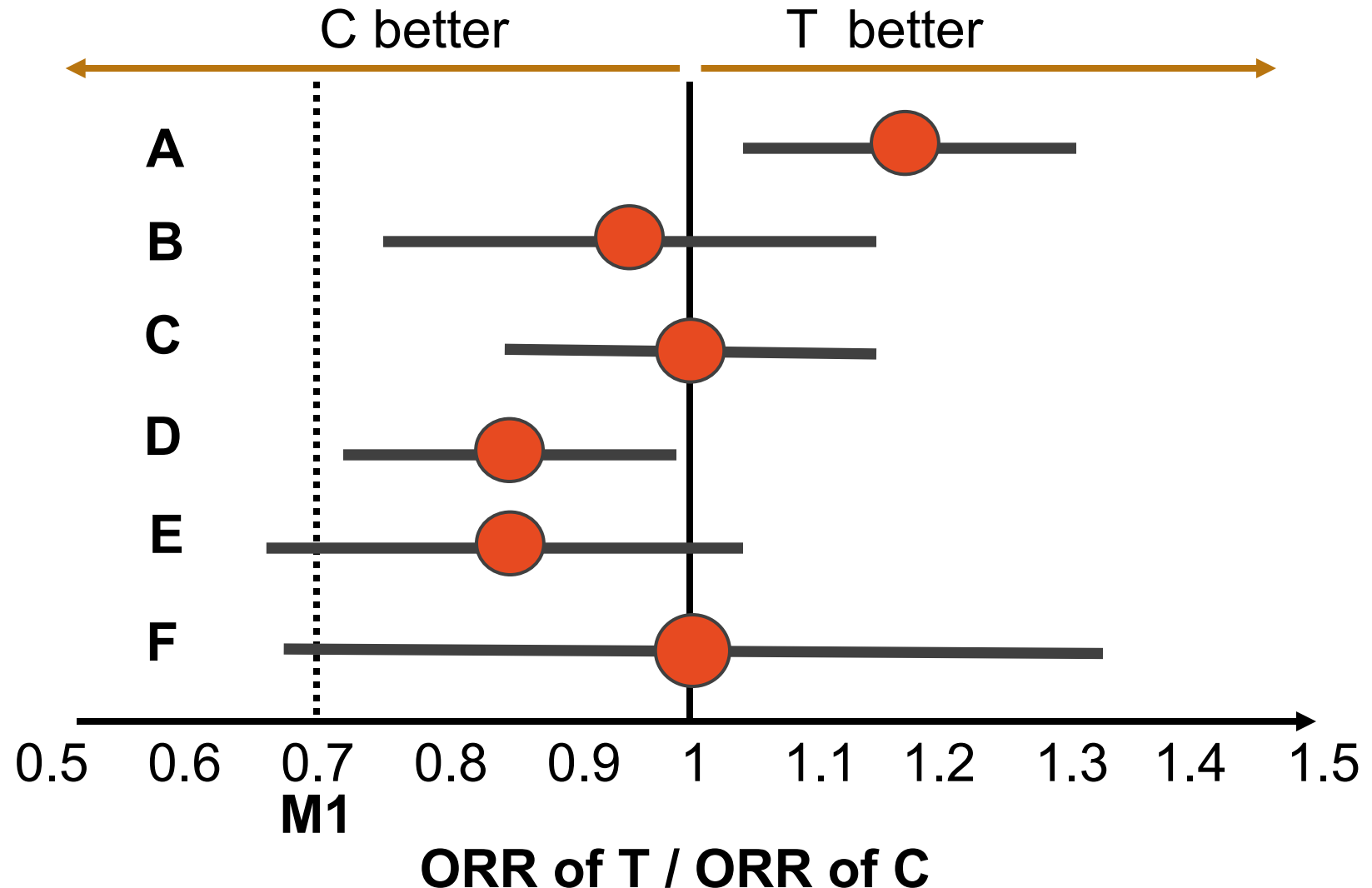
M1 must be determined based on the past performance of the active control

NI studies require additional choice of a greater margin that reflects largest loss of effect that would be clinically acceptable because in many cases M1 will not be sufficient to ensure that the drug had a clinically meaningful effect.

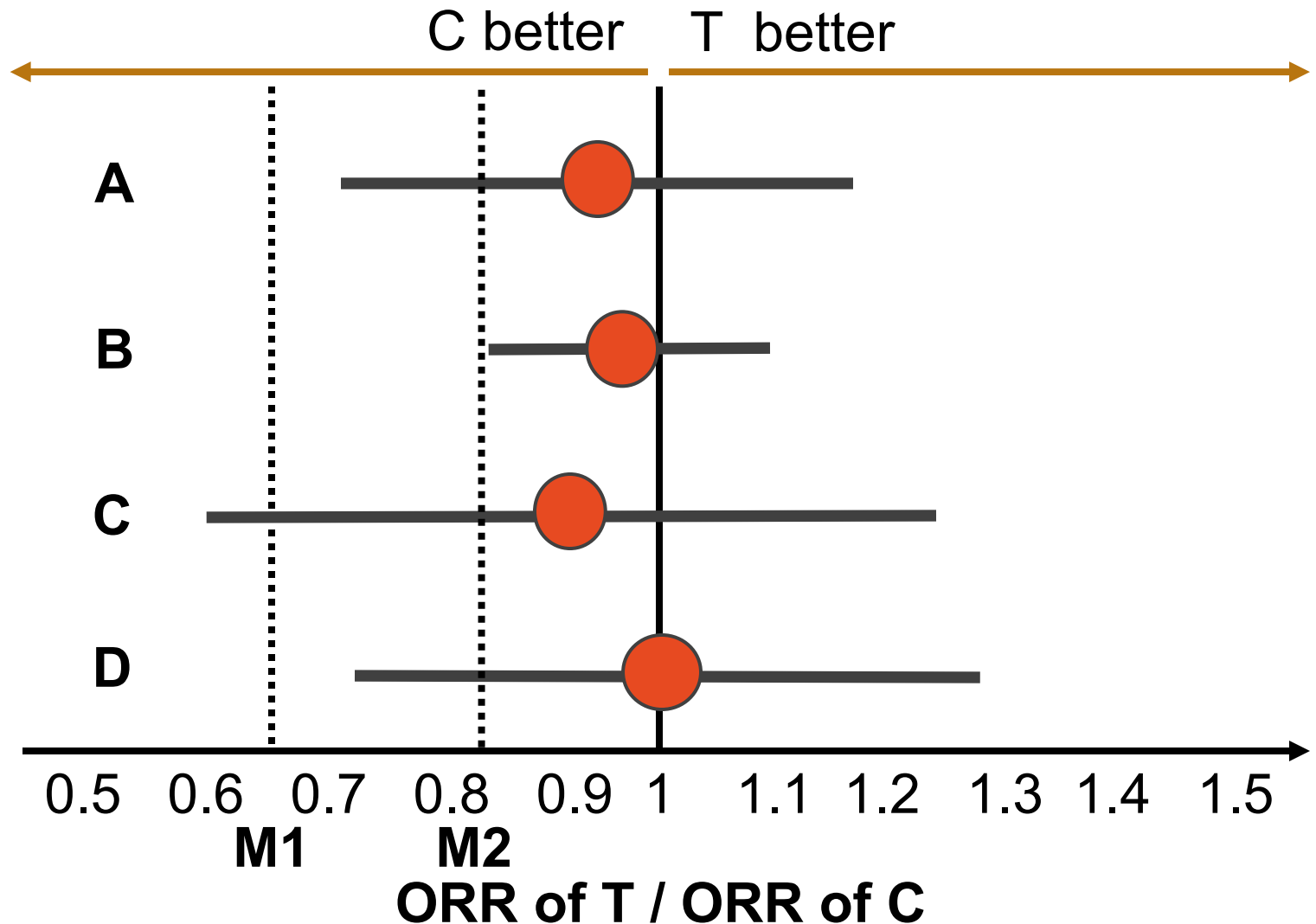


M2

Possible results of an NI study showing ratio of ORRs (T/C): (Point estimate and CI)



Possible results of an NI study showing ratio of ORRs (T/C): (Point estimate and CI)



Assay sensitivity

The choice of M1 and the conclusion that a trial has assay sensitivity is based on 3 considerations:

Historical
evidence of
sensitivity to
drug effects

The similarity of
the new NI trial to
the historical trials
(the constancy
assumption)

The quality of the
new trial (ruling out
defects that would
tend to minimize
differences
between
treatments)

An illustrative example

An illustrative example

Rationale and Objective

- | | |
|--|---|
| <ul style="list-style-type: none">• There are two important identified risks for the approved dosing regimen (say, 500mg).• We will be exploring whether a reduced dose (say, 300mg) may decrease the risk of these AEs without compromising the efficacy of the standard drug. | <ul style="list-style-type: none">• To evaluate the identified risks in the experimental drug• To evaluate each arm <i>w.r.t</i> safety and tolerability• To evaluate other RECIST endpoints such as PFS, CBR, TTR, DOR |
|--|---|

To determine whether the overall response rate (ORR) in the experimental arm (T) is **non-inferior** to the control arm(C) based on local tumor assessments (RECIST version 1.1) for all patients that have been treated for at least 6 months or have discontinued the study treatment.

Study design

- Women with advanced breast cancer
- No prior therapy for advanced breast cancer
- Measurable disease

N=350*

R

1:1

Test - 300mg (T)
N=175

Active control -
500mg (C)
N=175

*The sample size calculation are proposed such as to meet the non-inferiority margin of **0.824** with 80% power and one-sided 5% level of significance

Hypothesis

$$H_0: \theta_1 \leq 0.824 \text{ vs } H_1: \theta_1 > 0.824$$

where θ_1 is the ratio of ORR in T to ORR in C. The non-inferiority of T to C will be established if the lower 90% CI limit of θ_1 is greater than the pre-specified **NI margin 0.824**.

- ORR will be based on Per protocol set.
- As a sensitivity analysis, the primary analysis for ORR will be repeated in the Full analysis set.
- As a supportive analysis, the primary analysis will be repeated using Blinded Independent Review Committee (BIRC) assessment.

Non-inferiority margin calculation

The ORR improvement from historical evidence expressing as a ratio:

6-month ORR

Control drug (C)	Placebo (P)
45.9%	31.2%

$$M1 = 31.2\%/45.9\%=0.6797$$

The NI margin is calculated based on **50% retention** on the log-scale of the ratio of 45.9% to 31.2%, which leads to the NI margin of 0.824 (FDA 2016).

$$M2 = \text{NI Margin} = \text{Exp}[(\text{Log}(0.6797)) * (1 - 0.5)] = 0.824$$

This means that the lower 90% CI of the ORR Ratio of T vs C needs to be greater than 0.824 to conclude non-inferiority

Result

Overall Response Rate (ORR) assessment between treatment arms based on local investigator/radiology review Per Protocol Set

	T 300mg N = 174 n (%)	C 500mg N = 177 n (%)	90% CI
Overall Response Rate (ORR)	81 (46.5)	89 (50.3)	
95% CI	(49.14, 53.96)	(42.92, 57.65)	
ORR ratio of T/C			0.926 (0.772, 1.110)

- The non-inferiority of T is not demonstrated because the lower limit of the ratio of ORRs $< 0.824 = M2$
- Similar analysis is performed for full analysis set and also using the central (BIRC) RECIST data and there also NI of T is not demonstrated.

Take away messages

- A non-inferiority trial is reasonable when a new treatment has some property sufficiently favorable that physicians, and their patients, would be willing to sacrifice some degree of benefit relative to an already approved therapy.
- Correct interpretation of NI trial involves carefully examining the design, the execution as well as the analysis and results of the trials.
- We need to be careful in choosing the active control to avoid Biocreep.

The use of non-inferiority trials is likely to increase. Clinicians should not accept the term ‘non-inferior’ at face value. It is important to be aware that ‘non-inferior’ does not mean ‘equivalent’ or ‘similar’ or ‘as good as’. Non-inferiority means the new treatment is not unacceptably worse than standard treatment

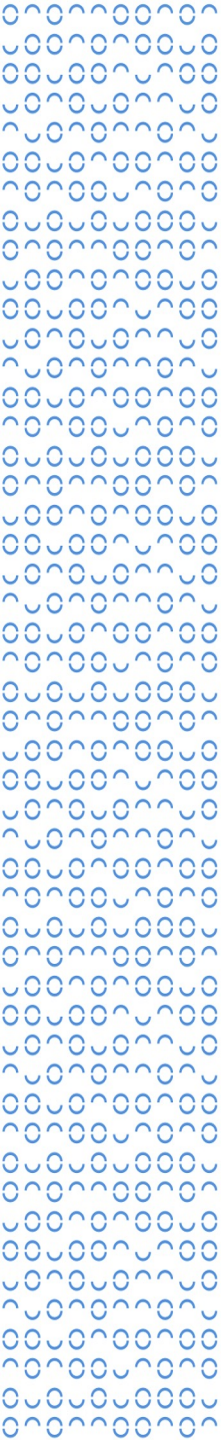
REFERENCES

<https://www.fda.gov/media/78504/download>

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-choice-non-inferiority-margin_en.pdf

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3510268/>

<https://heart.bmj.com/content/106/2/99>



Thank you

Do you have any questions?



Anubrata Kundu

Sr. Statistical Programmer

Novartis Healthcare Private Limited

Hyderabad, India

Email: anubrata.kundu@novartis.com