# Trial-design in biosimilar research: Equivalence or non-inferiority design

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## Overview

- The place(s) of the clinical efficacy and safety trial(s).

- The principles of clinical non-inferiority or equivalence trials.

- Designs and equivalence margins for biosimilars.

- Switching and designs.

- Concluding remarks.

# Place(s) of clinical efficacy and safety trial(s)

EMA Guidances on biosimilars:

- "Generally, the aim of clinical data is to address slight differences shown at previous steps and to confirm comparable clinical performance of the biosimilar and the reference product."

- "Efficacy trials of biosimilar medicinal products do not aim at demonstrating efficacy *per se*, since this has already been established with the reference product."

# Place(s) of clinical efficacy and safety trial(s)

Contrasts with "general" non-inferiority trials.

- A *minimal requirement* ….is that we must be confident that the test product would have been shown to be efficacious if a placebo controlled trial had been performed.

- "…an appropriate choice of margin will ….. provide assurance that the test product is not substantially inferior to the reference" (exclude differences of clinical importance).

- Superiority not excluded

- Statistical and clinical reasoning

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# Example: Flixabi as biosimilar for infliximab

*A randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of SB2 compared to Remicade in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy.*

Primary efficacy endpoint: Proportion of patients achieving clinical response (ACR20) at Week 30.

Expected responder rates: 57%     (from meta-analysis)

Two-sided equivalence margins:     (-15%, 15%)

Results (*per-protocol*):

| Treatment | Flixabi | Remicade |
|---|---|---|
| N | 231 | 247 |
| Response rates | 64.1% | 66.0% |

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# Confidence interval approach

*From random effects meta-analysis*

Estimated treatment effect: $E_{Remicade} - E_{Placebo}$

0

$\Delta$

(----------|------------)

**90% Confidence interval**
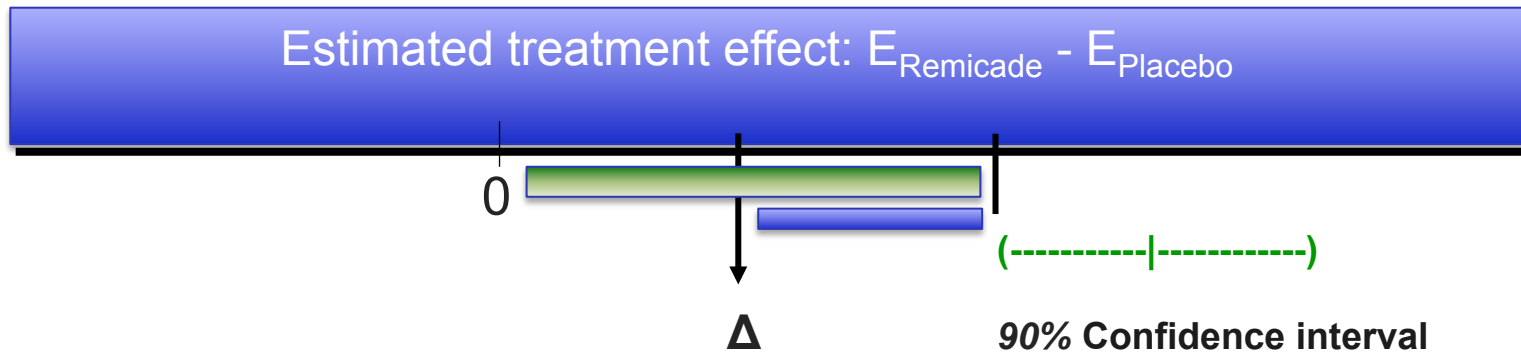
Difference between Remicade and Placebo: 33%

*90% Confidence interval:*                                 (28%, 38%)

*(95% Confidence interval:*                                *(27%, 39%)*

"Preserve at least 50 % of treatment effect." $\Delta = 15\%$

(follows in essence FDA guidance on non-inferiority)

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# Confidence interval approach

Non-inferiority or equivalence  (note: the larger the better)



Estimated treatment effect: $E_{Flixabi} - E_{Remicade}$

$-\Delta$          0          $\Delta$

Non-Inferior  Equivalent

Ref Non-Inferior

-10.3 % (---- -1.9%|-----------) 6.5%

(-----|-----)

(-----|-----)

(-----------------|-----------------)

(-------------------|-------------------)

(--------------------|--------------------)

(--------------------|--------------------)

(--------------------------|--------------------------)

Two-sided 95% Confidence interval
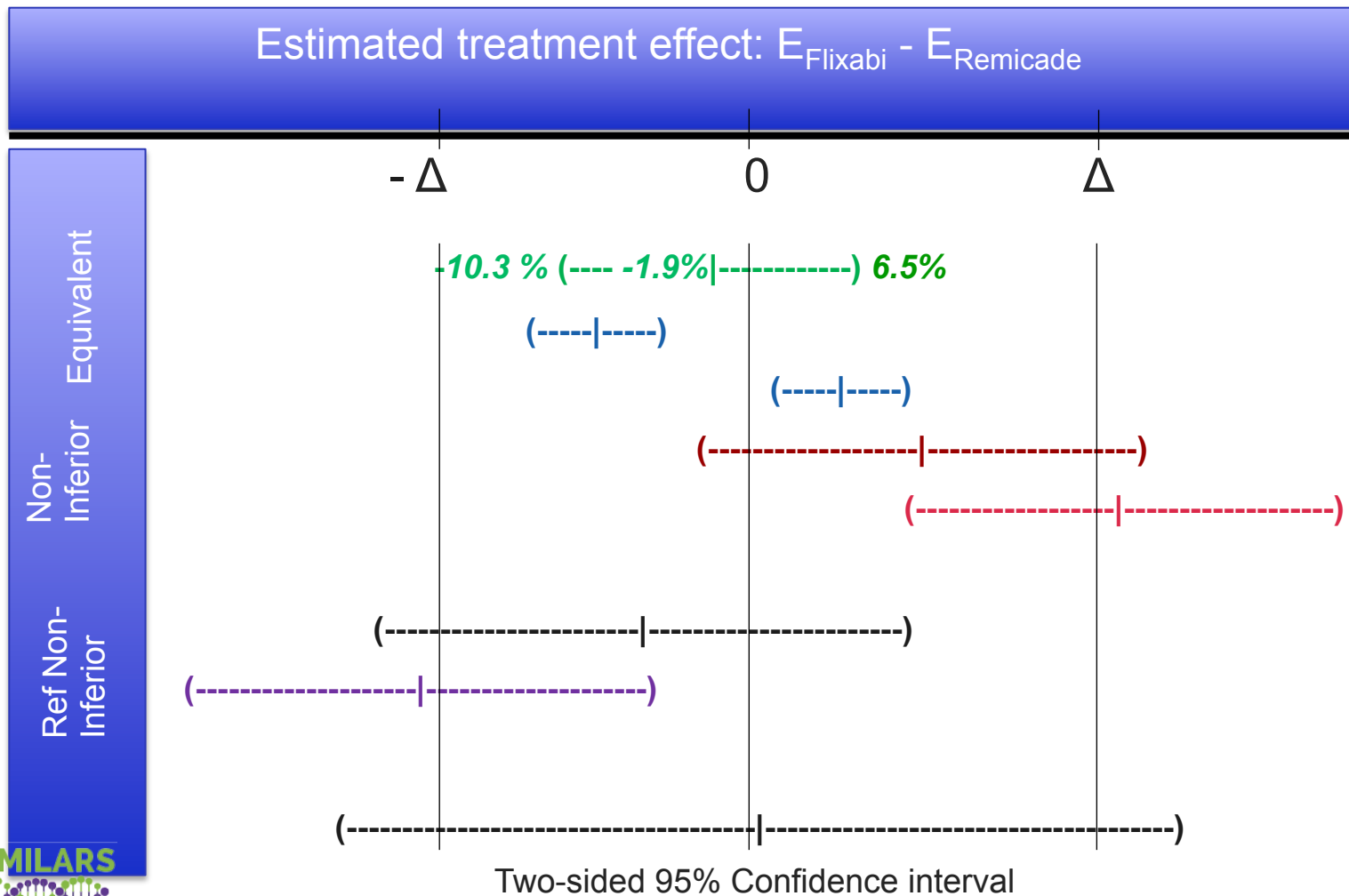
# Key conditions for non-inferiority and equivalance trials

- Assay sensitivity (addressed in guidance)
    - Choice of endpoint
    - Choice of study population
    - Sample size
    - Analysis & analysis population

- Constancy (relevant for biosimilars?)

# Non-inferiority or equivalence for biosimilars

- Demonstrating (absolute or relative) efficacy is not the primary objective.

- From the principle of stepwise approach to reducing uncertainty:
  - Any difference demonstrated may cast doubt on biosimilarity.

- *Equivalence is the preferred design.*

- Non-inferiority may require smaller sample sizes
  - At the cost of stronger assumptions that need to be proven.

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# Example (2): Bemfola as biosimilar to follitropin alpha (recFSH)

Stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT).

+ Other indications.

Reference product: Gonal-f (Serono)

# Bemfola main study

Efficacy, safety and tolerability of Bemfola compared to Gonal-f in women undergoing assisted reproductive technologies

Primary objective was to demonstrate equivalence.

Primary endpoint: Number of oocytes retrieved.

Randomisation in 2:1 ratio.

Equivalence margin for difference in mean number of oocytes retrieved: (-2.9, 2.9)

(1) Difference of up to 3 oocytes not clinically meaningful

(2) Accounting for poor responder rate

# Bemfola: Results (per protocol)

| Treatment | Bemfola | Gonal-f |
|---|---|---|
| N | 249 | 123 |
| Mean nr of oocytes | 10.85 | 10.58 |
| SD | 5.11 | 6.06 |

| Difference | Estimate | 95% CI |
|---|---|---|
| Mean nr of oocytes (ZIP analysis) | 0.27 | (-1.34, 1.32) |
| {Full Analysis Set | 0.29 | (-1.29; 1.34) } |

# Bemfola remarks

- The equivalence margin for Bemfola [-2.9, +2.9] is tighter than has been used in the registered Elonva (modified recFSH with a longer half-life) equivalence trial comparing Elonva with recFSH (Puregon); [-3, +5]).

Evaluation beyond primary endpoint(s)

- A higher incidence of OHSS was noted for Bemfola: Bemfola (22.1%) vs. Gonal-f (13.0%).

- The higher proportion of AMH levels ≥ 24 pmol/L in the baseline characteristics of the Bemfola group could have contributed to this higher OHSS incidence in the Bemfola arm.

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# Similar biosimilar…..Ovaleap

| Treatment | Gonal-f | Ovaleap |
|---|---|---|
| N | 145 | 152 |
| Mean nr of oocytes | 12.0 | 12.2 |
| SD | 6.8 | 6.8 |

| Difference | Estimate | 95% CI |
|---|---|---|
| Mean nr of oocytes (ZIP analysis) | 0.03 | -0.76, 0.82 |

Remarks

The number of OHSS cases was small, 4 cases (2.7%) in the Gonal-f group and 7 cases (4.6%) in the Ovaleap group.

# Similar biosimilar…..Remsima

Phase 3 study to demonstrate equivalence in efficacy and safety of CT-P13 compared with Remicade when co-administrated with methotrexate in patients with active RA.

Primary efficacy endpoint: Proportion of patients achieving clinical response (ACR20) at Week 30.

Expected responder rates:                50%       (postulated)

Two-sided equivalence margins:      (-15%, 15%) (meta-analysis)

"Although the proposed margin of ±15% could be considered clinically relevant, it was accepted by the CHMP in the context of a biosimilarity exercise, since it is also based on physicochemical, biological, and PK comparisons. "

# Similar biosimilar…..Remsima

| Treatment | Remsima | Remicade |
|---|---|---|
| **N**  ALL-R | 302 | 304 |
| PP | 248 | 251 |

**Response rates**

| | Remsima | Remicade |
|---|---|---|
| ALL-R | 60.9% | 58.6% |
| PP | 73.4% | 69.7% |

| Difference | Estimate | 95% CI |
|---|---|---|
| ALL-R | 2% | (-6% 10%) |
| PP | 4% | (-4%; 12%) |

## Switching and designs: switch from…….

Perspective of market authorisation of a new drug

*Evidence based decision* of allowing physicians to add a new drug to their treatment options.

*Provide information* to guide the prescribing physician.

Perspective of treating physician

*Evidence based decision* for the (current, next) patient to treat, selecting from the available treatment options.

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# Switching and designs

Interchangability, substitution, *switching* definitions.

- In principle needs estimates *at the individual patient level.*
  - Which parallel-group designs cannot provide.

- Cross-over designs that include the switches to be evaluated.
  - T -> R, R -> T, but also R->R, T->T as comparison.
  - Designs are (well) known.

- Not always applicable to clinical biosimilar setting, and (to my knowledge) not really "tested" yet.

- Differences, and margins on equivalence different interpretation.

## BIO-SWITCH Example (Ref: NTR5279, trialregister.nl)

To explore the effect of switching treatment from Remicade® to infliximab biosimilar (Inflectra®, Remsima®) on efficacy, safety and immunogenicity in patients with rheumatoid arthritis (RA), spondyloarthritis (SpA) or psoriatic arthritis (PsA) *in daily clinical care*.

**Design:**

Exploratory, observational before – after prospective cohort.

**Switch group:**

Currently Remicade treated patients willing to switch.

**Control group:**

Currently Remicade treated patients who will not switch.

## BIO-SWITCH Example (Ref: NTR5279, trialregister.nl)

- In line with close monitoring of shared decision to switch.

- Submitted to CCMO for approval:
  - Does not fall under WMO (intervention not substiantially different from care, informed shared decision).

- Of course limitations in study design, but "real world evidence" of shared decision switching strategy.

- Different from similarity evaluation.

## Concluding remarks: Designs for biosimilarity

- Equivalence design preferred above non-inferiority design.

- Margin setting follows "classical" non-inferiority guidance.
  - Fairly strong statistical justification
  - Fairly weak clinical justification

- Nevertheless, data appear robust (results well within margins, across sensitivity analyses and secondary endpoints).

- Variation across studies of reference product seems at least as large as differences with biosimilars.

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