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
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):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Flixabi</th>
<th>Remicade</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>231</td>
<td>247</td>
</tr>
<tr>
<td>Response rates</td>
<td>64.1%</td>
<td>66.0%</td>
</tr>
</tbody>
</table>
Confidence interval approach

From random effects meta-analysis

- Difference between Remicade and Placebo: 33%
- 90% Confidence interval: (28%, 38%)
- 95% Confidence interval: (27%, 39%)

“Preserve at least 50 % of treatment effect.” Δ= 15%

(follows in essence FDA guidance on non-inferiority)
Confidence interval approach

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

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

Two-sided 95% Confidence interval
Key conditions for non-inferiority and equivalence 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.
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)
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)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Bemfola</th>
<th>Gonal-f</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>249</td>
<td>123</td>
</tr>
<tr>
<td>Mean nr of oocytes</td>
<td>10.85</td>
<td>10.58</td>
</tr>
<tr>
<td>SD</td>
<td>5.11</td>
<td>6.06</td>
</tr>
</tbody>
</table>

Difference

<table>
<thead>
<tr>
<th>Mean nr of oocytes (ZIP analysis)</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean nr of oocytes</td>
<td>0.27</td>
<td>(-1.34, 1.32)</td>
</tr>
</tbody>
</table>

{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.
## Similar biosimilar.....Ovaleap

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Gonal-f</th>
<th>Ovaleap</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>145</td>
<td>152</td>
</tr>
<tr>
<td>Mean nr of oocytes</td>
<td>12.0</td>
<td>12.2</td>
</tr>
<tr>
<td>SD</td>
<td>6.8</td>
<td>6.8</td>
</tr>
</tbody>
</table>

### Difference

<table>
<thead>
<tr>
<th>Mean nr of oocytes</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ZIP analysis)</td>
<td>0.03</td>
<td>-0.76, 0.82</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Remsima</th>
<th>Remicade</th>
</tr>
</thead>
<tbody>
<tr>
<td>N ALL-R</td>
<td>302</td>
<td>304</td>
</tr>
<tr>
<td>PP</td>
<td>248</td>
<td>251</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Response rates</th>
<th>Remsima</th>
<th>Remicade</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL-R</td>
<td>60.9%</td>
<td>58.6%</td>
</tr>
<tr>
<td>PP</td>
<td>73.4%</td>
<td>69.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL-R</td>
<td>2%</td>
<td>(-6% 10%)</td>
</tr>
<tr>
<td>PP</td>
<td>4%</td>
<td>(-4%; 12%)</td>
</tr>
</tbody>
</table>
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.
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 substantially 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.