Case studies in the design, analysis and interpretation of non-inferiority trials

Krishan Singh, Ph.D.

GlaxoSmithKline

Outline

- Introduction & Background
- Case Studies
  - Altabax – a topical antibiotic
  - Arixtra – an anticoagulant
  - Taxus Liberté – a medical device
- Summary

US Congressional Investigation

- September 2006: US Congressional Committee questions the FDA for use of non-inferiority trials as proof of efficacy for antibiotics due to concerns about
  - design and limitations of non-inferiority trials
  - difficulties in interpreting NI trials due to lack of internal validity in contrast to superiority trials
- Investigation triggered by post-marketing hepatic and cardiovascular adverse events observed with telithromycin
  - FDA withdraws approval for ABS and AECB
- Use of NI trials questionable for indications with high rate of self resolution
- No issues with use of NI trials for serious diseases such as CAP or complicated skin infections

Impact on Sponsors of New Drugs

- Increased scrutiny in the application of non-inferiority designs
- Protocol, study design and analysis plans previously reviewed and agreed by the FDA no longer acceptable
- Sponsors asked to provide rationale for non-inferiority trial and re-justification of margin
- additional/adequate and well controlled trial(s) requested to support approval of new drugs

Key Statistical Issues in the Design of NI Trials

- Choice of control group
- Constancy of control treatment effect
- Estimation and variability of control treatment effect
- Assay Sensitivity
- Selection of non-inferiority margin

History of Δ Selection

- FDA AI Division 1992 Points to Consider - Step Function Approach

Success Rate	Δ
90 - 100%	10%
80 - 89%	15%
70 - 79%	20%

- 1998 FDA Advisory Committee proposed:
  - Δ must be clinically relevant and indication specific
  - discuss with agency during protocol development
  - provide rationale for selection of control arm
- In 2001, the FDA adds disclaimer that PTC approach (step function) will be phased out

History of Δ Selection

- 1997 CPMP “Guidance on evaluation of AI products”
  - Δ = 10% for “common non-serious infections”
  - Smaller Δ for very high cure rates
  - Based on minimum clinically relevant difference

Altabax ®

- A new class of antibiotic for uncomplicated skin and soft tissue infections: SITL, SID & Impetigo
- 2 SITL and 1 SID NI trials, each against cephalexin (Δ = 10%, event rate 90%)
- Impetigo: one NI trial against fucidin (Δ = 10%, event rate 90%) and one placebo controlled trial
- 2004: SITL & SID protocols reviewed and agreed by the FDA including the non-inferiority margin
- Jun-06: FDA asks the sponsor to justify the non-inferiority margin
- FDA uses a 1984 mupirocin study to derive the treatment effect and concludes 10% Δ not justifiable

Results

Indication	Study	Population	T-C (%)	95% CI
SITL	I	PPC	-3.2	(-7.4, 0.9)
		ITTC	1.1	(-3.9, 6.0)
	II	PPC	-1.6	(-5.8, 2.6)
		ITTC	0.0	(-4.5, 4.6)
SID	III	PPC	-3.8	(-9.9, 2.3)
		ITTC	-3.4	(-9.7, 2.9)

- All three studies met the protocol defined objective (10% margin)
- SITL approvable - additional adequate and well controlled trial needed, implying need a placebo-controlled trial
- SID not approved

Issues

- Δ chosen based upon step function approach – guidance in force at the time
- No historical placebo controlled trials against cephalexin
- Unable to establish cephalexin effect and hence the non-inferiority margin
- Conclusion: must conduct a placebo controlled trial to support approval in SITL
- Problem/challenge: investigators not willing to participate in a placebo trial for ethical reasons
  - highly effective antibiotic with >90% success rate
  - not willing to expose patients to placebo
- Changes in study design issues under consideration for a placebo controlled study in order to meet regulatory acceptance and investigators' compliance

ARIXTRA®

- ARIXTRA®, an anti-coagulant already approved for a variety of indications
- Currently pursuing a new indication for the treatment of unstable angina/non ST-segment elevation (UA/NSTEMI)
- OASIS-5 - study supporting this new indication:
  - 20,000 patient, non-inferiority study comparing ARIXTRA to Lovenox; primary endpoint composite of death/myocardial infarction/refractory ischemia

OASIS-5: Interactions with FDA

- At End of Phase 2 meeting, FDA reviewed and provided feedback on study design and statistical methods:
  - patient population and sample size adequate
  - no comments on the non-inferiority margin
  - “for a non-inferiority...one trial is not sufficient to determine safety and efficacy…”
- Sponsor’s Understanding:
  - agency agreed with the non-inferiority margin
  - no mention if one non-inferiority study would not be sufficient

OASIS-5: Interactions with FDA (continued)

- To clarify the discrepancy, “Type A” meeting:
  - a single non-inferiority study could be adequate to support a new indication if issues such as choice of non-inferiority margin, possibility of changes in medical practice, comparability of patient populations, assay sensitivity are adequately addressed

- Sponsor confident that the chosen margin was conservative, and proceeded with OASIS-5

Supplement Submitted

- Supplemental NDA submitted included detailed justification for the margin and addressed complications noted earlier by the FDA

- FDA issues approvable letter
  - In establishing the effect of the active control based on historical studies, limited consideration given to accounting for between-study variability
  - FDA recalculated the effect size accounting for variability to come up with a narrower margin (1.06 vs 1.185).
  - With an upper confidence interval of 1.13, study couldn't be considered a positive study

Sponsor Response

- Sponsor response to the non-inferiority margin
  - Margin chosen was strict yet clinically meaningful
  - Approach used to define the pre-specified NI margin of 1.185 using fixed effects meta-analysis methodology is the most appropriate
    - FDA used random effects methodology which has limitations when applied to meta-analyses of small # of trials and trials with low event rates
  - Across multiple efficacy endpoints and timepoints, the high degree of consistency further supports that there is no reason to suspect departure from non-inferior efficacy between the two drugs
  - Concludes…margin was conservative and appropriate and the strength of the clinical data supports non-inferiority
- FDA and sponsor discussion continues!

Key Learnings

- Importance of obtaining regulatory agency agreement upfront
- Justification of non-inferiority margin is crucial, including methodology used to compile historical trials and meta analysis used to derive the estimate of active control effect
- A single non-inferiority study to support a new indication or approval of a new drug carries significant risk

TAXUS® Liberté

- TAXUS® Liberté – a coronary stent (medical device) recently approved by the FDA in Oct 2008
- A paclitaxel-eluting stent system to improve luminal diameter for the treatment of *de novo* lesions in the native arteries
- TAXUS ATLAS: pivotal phase III study supporting this indication
  - 871 patient, single-arm, non-inferiority trial to compare TAXUS Liberté Stent to TAXUS Express Stent in subjects indicated for PCI or CABG
  - Objective is to demonstrate non-inferiority of TAXUS Liberté to TAXUS Express using case-matched historic control data derived from TAXUS IV (662 patients) and TAXUS V (329 patients) *de novo* studies
  - Primary endpoint for the study is 9-month target vessel revascularization (TVR) rate®
  - Non-inferiority margin is 3%

Results

	TAXUS Liberté	TAXUS Express	Difference (Upper 95% CI)	p-value	Δ
PP	7.95% (68/855)	7.01% (67/956)	0.94 (2.98%)	0.0487	3%
ITT	8.03% (69/859)	7.14% (69/967)	0.90 (2.94%)	0.0454	3%

- Since upper bound of the 95% CI < 3%, sponsors claims non-inferiority is demonstrated with p-value < 5%
  - Wald's method used to calculate the CI
  - Methodology defined upfront in the protocol and agreed by FDA

- WSJ reported, per several reputed academic statisticians, Wald method is flawed as it "overstates the certainty" of clinical results
  - Variance must be estimated assuming true difference is 3%, not 1% as observed, which gives the upper bound of the 95% CI as 3.0183% (p-value = 0.0515) => non-inferiority can not be claimed

Regulatory Comments

- FDA's medical device branch: WSJ analysis raises "good question" but declines to comment on the trial or the Liberté Stent, and calls the calculation approach "a standard methodology"

- Studies designed to satisfy FDA's medical device branch are generally much less rigorous than those for US approval of drugs – in part due to a 1997 federal law that requires device manufacturers for the "least burdensome appropriate means" of proving new device works
  - Active control NI trials are required only for novel devices
  - Non-inferiority margin based on consensus between the sponsor and the agency (objective performance criteria)
  - For all other devices, single arm, case-matched historic control trials are acceptable

Selection of Δ

- Information should be obtained from:
  - preferably from multiple placebo controlled trials with same design, population etc as NI trial
  - single placebo-controlled trial – may be acceptable
  - single/multiple trials with different designs – questionable value
  - no information to estimate Δ_1 – hard to justify NI trial

- Precision and constancy of control effect is critical in defining Δ_1 and in turn Δ_2

Major Challenges

- What if no placebo controlled data exist?
- Indications where treatment effect is modest but not precisely known?
- Serious indications with low incidence?

Suggested Solutions

- Consider superiority trial design as an alternative to NI trial design – stronger evidence and potentially smaller sample size
- If no serious harm in delaying treatment, it may be possible to randomize patients to placebo with early escape/rescue
  - If no improvement at early blinded assessment, treat as treatment failure and switch to standard care
- Three arm design: test drug, active control and placebo
  - Not necessary to predefine margin
  - Built-in assay sensitivity
  - Tests both superiority and non-inferiority
- Compare Test drug (target dose) against Test Drug (low/ineffective dose) which could address ethical concerns

Summary

- Many issues in the design and interpretation of non-inferiority trials
- Choice of active control: to prevent potential “bio-creep”, active control should be consensus standard of care
- Selection of non-inferiority margin is critical: must be based on both clinical judgment and statistical consideration
- Selection of margin should reflect uncertainties in the evidence on which selection is based and should be conservative
- Consider alternate designs when historical information on control effect is of concern

References

1. Wall Street Journal: Boston Scientific Stent Study Flawed by Keith J Weinstein, November 4, 2008
2. Summary of Safety & Effectiveness Data for Taxus Liberté available at: http://www.fda.gov/cdrh/pdf6/P060008.html
3. Guidance for Industry: Coronary Drug-Eluting Stents at: http://www.fda.gov/cdrh/ode/guidance/6255.pdf