Implementing the Large Simple Trial and Appropriate Technologies to Efficiently Evaluate Cardiovascular Safety of Chronic Therapies

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The Large Simple Trial

- LST is not a new concept
- Follow on indications have been approved by FDA on basis of LSTs
- The proposed LST_{III} does not/cannot take the place of a standard phase 3 trials aimed at characterizing general safety and efficacy

This trial is possible:

THE OLD ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Assessment of cardiovascular safety of Metanormin: a randomised, double-blind, active-controlled trial

The Metanormin Trial Group

25,234 patients

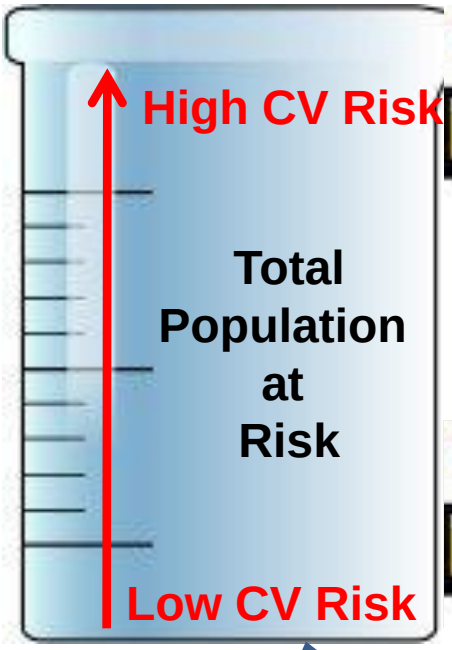
Background: Metanormin reduces hyperglycemia in type 2 diabetes apparently through reducing oxidative stress and inflammation. Our aim was to assess the cardiovascular safety of metanormin compared to a commonly used anti-diabetic therapy, sitagliptin, in people with T2DM patients

Methods: 25,234 patients were randomly assigned to metanormin groups (n=12,601) or sitagliptin treatment (n=12,633) in addition to standard of care. Enrollment began in July, 2013; this event-driven trial was stopped in August, 2014, after the prespecified number of primary outcome events had occurred. The composite primary endpoint was time to first occurrence of cardiovascular death, resuscitated cardiac arrest, myocardial infarction, or stroke. Glycemic control was targeted to achieve a mean glucose level of 124 mg%.

Findings: All randomized patients were included in the efficacy analyses. Metanormin and sitagliptin groups did not differ (136 events in the metanormin group vs. 142 in the sitagliptin group; hazard ratio 0.96, 95% CI 0·89—1·01, p=0·98). Glycemic control between treatment groups was comparable.

Interpretation: Metanormin and sitagliptin treatment do not differ in cardiovascular safety. Since sitagliptin has previously been shown to be neutral in affecting cardiovascular outcomes, metanormin is concluded to be neutral in its effects on cardiovascular outcomes.

Crux of the Problem: Enough CV Events



Patients at high CV risk have higher event rates but are much harder to find

N=5,000

High risk 4.0% per year event rate*

Time to recruit 2 years

Minimum Time to 200 MACE events ~3 years

Recruitment Over years

Conventional Enriched Trial Approach (RCT)

N=25,000

Moderate: 0.75% per year rate*

Time to recruit <0.5 years

Minimum Time to 200 MACE events ~1.3 years

Recruitment over weeks

Large Simple Trial Approach (LST)

*Event rates represent, respectively, lowest and highest rates seen in major T2DM trials

What is necessary and sufficient for an acceptable CV safety study for T2DM?

- Informed consent
- Integrity of randomization
- Confirmation of adequate drug exposure
- Parity of glycemic control between treatment groups
- Reliable CV event ascertainment
- Expert event adjudication
- Adequate number of MACE events
- Assurance of comparable glycemic control
- 21 CFR part 11 compliant e-system
- Ability to verify key source documents

Proposed LST_{III} Approach—General Principles

- Sufficient number of clinical sites (1,000-5,000) averaging ~5 patients/site over a 6 month enrollment period
- Investigators are recruited by a simple web-based form
- Patients enroll by web or phone
- Patient incentives include free medication and reimbursement of clinic visit costs
- Simple protocol relies on randomization to balance groups
- Assigned drug is distributed by mail from central pharmacy
- Patient has personal website for entering comments, accounting for drug, finding help.
- Web based EDC for site, patient and third party data
- Onsite monitoring and event review performed as requested by adjudication committee

LST_{III} Actionable Data Strategy

- Key End Point results collected and triggered automatically
- Alerts programmed
- Safety forms pre-populated to minimize data discrepancies
- Auto-encoding of medical terms
- ECG, angiograms, and lab results transmitted electronically
- Timely CEC adjudication
  - Read Only Permissions can be given to adjudicators to see pertinent data within the EDC system.
- DSMB review, if needed, can be as frequent as required
  - Adjudicated and un-adjudicated data within the EDC system available in real time

RCT vs. LST: Comparison of Key Features

Trial Features	Randomized Control Trial (RCT)	Large Simple Trial (LST)
Phase	III	III
1^{o} Basis of recruitment	Investigation site	Patient referral
Incl/Excl criteria	Generally restrictive	Essentials only
Site qualification	By Monitor visits	Web training
Investigators	Experienced	Clinical Care providers
Drug distribution	Pharmacy Controls	CTM Vendor centrally
Source verification	100%	Limited, targeted
AE and Con Med verification	100%	Limited
Clinical Laboratory	Central	Local lab, limited
ECG Reading	Central	Local, subset central
MACE Adjudication	100% Central	100% Central
CV adjudication data packet	Extensive	Reduced to key measures
Medication compliance	Conventional pill counting	Electronic pill boxes

RCT vs. LST- Trial Performance Data

	RCT*	LST
Phase	III	III
Patients		
Total Required	5 to 8,000	20 to 32,000
CV Risk Group	High	Moderate
MACE events/year	4 %	0.75
% T2 population eligible	<10%	>90%
Concomitant Rx	Restrictive/monitored	Less Restrictive
Timelines		
Investigators, Sites	200 to 400	5,000
Patients/site	20 to 30	4 to 8
Months to Enroll	24	6
Months to Accrue Events	36 to 48	18
Costs ($)		
per patient	16 to 22,000	3 to 5,000
Total (site, lab, report)	80 to 176	60 to 160

*Based on results of a recent CV outcome study

Take Home Points

- Finding non-inferiority in a poorly designed and conducted safety trial is of no value
- Credibility of any T2DM CV safety trial depends on ascertaining:
  - unbiased accrual of CV events
  - drug exposure
  - parity of glycemic control
- All of these necessary and sufficient attributes are achievable in a LST_{III}

Questions to FDA

- Could the LST approach be acceptable for assuring CV safety and benefit of T2DM drugs?
- If yes, could a T2DM drug NDA be filed, reviewed, and approved subject to confirmation of no CV harm by a credible LST of CV outcome?