



**Where Do We Stand?—
Unraveling the FDA Regulatory Pathway
for Diabetes and
Obesity Drug Approval**

Alexander Fleming, MD

Presenter Disclosure

Alexander Fleming, M.D.

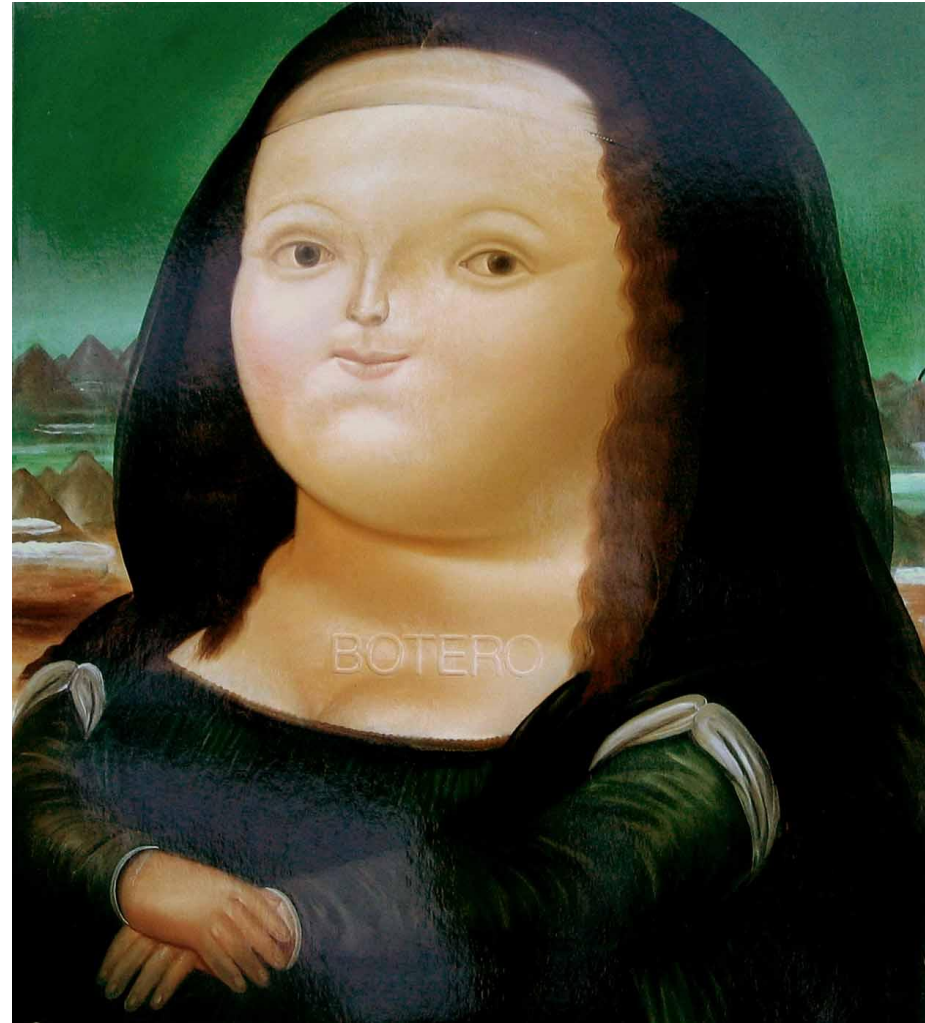
Board Member/Advisory Panel/Consultant:

Amgen, Andromeda, Arisaph, AtheroGenics (now Salutria), BCT, BioCon, Can-Am, Circ Pharma, Diasome, Elona, GI Dynmaics, Glenmark, Indigene, Integrium, Institute of Pharmaceutical Discovery, Isis, MannKind Corporation, Metabasis, N-Gene, Novartis Pharmaceuticals Corporation, Novo Nordisk, Inc., Orexigen, Plexxikon, ReceptorBio, Rhythm, Sanofi-Aventis, Sirtris, Takeda Pharmaceuticals, Teva, Time Cap, Vero, Zafgen.

Stock/Shareholder: Exsulin Corporation

Other: Kinexum, principle

A Tale of Two Therapeutic Indications





QUICK

NEWS

VIEW

MARKETS

PERSONAL FINANCE

TV

RADIO

MORE ▾

Related News: [Health Care](#)

Bristol Diabetes Pill Faces Safety Hurdle After Early Drugs Tied to Risks

By Elizabeth Lopatto - Jun 23, 2011 4:07 PM ET

Recommend

Tweet 46

Share

More

Bristol-Myers Squibb Co. and AstraZeneca Plc.'s new diabetes pill will probably face increased scrutiny from regulators and doctors after two rivals were tied to cancer and heart risks.

Bristol-Myers Squibb Co and AstraZeneca's new diabetes pill will probably face increased scrutiny from regulators and doctors after two rivals were tied to cancer and heart risks.



Orexigen® Therapeutics Provides a Regulatory Update on Contrave® NDA

Jun 03, 2011

Orexigen® Therapeutics Provides a
Regulatory Update on Contrave® NDA

SAN DIEGO, June 3, 2011 /PRNewswire/ -- Orexigen® Therapeutics, Inc. (Nasdaq: OREX) announced today that it recently met with the Food and Drug Administration (FDA) regarding the New Drug Application for Contrave® (naltrexone HCl/bupropion HCl) extended-release tablets for the treatment of obesity, including weight loss and maintenance of weight loss.

**WEIGHT LOSS
DRUGS—
THE OLD
DAYS**

- Long tradition of old drugs without FDA approval
- Dexedrine and other stimulants were approved for short term weight loss
- Phentermine still approved for “short term” weight reduction

Fen-Phen and Dexfenfluramine

MARCUS L. HANSEN

- **Fen-Phen was very popular and fairly effective**
- **Dexfenfluramine was developed as an NME version of Fen-Phen**
- **Both products removed from the market because of valvulopathy**

Vioxx!



The NEW ENGLAND JOURNAL of MEDICINE

[HOME](#) | [SEARCH](#) | [CURRENT ISSUE](#) | [PAST ISSUES](#) | [COLLECTIONS](#) | [HELP](#)

PERSPECTIVE

Volume 351:1707-1709 October 21, 2004 Number 17

Failing the Public Health — Vioxx, Merck, and the FDA

Eric J. Topol, M.D.

Vioxx – Lessons Learned

- **Limitations of nonclinical toxicology models**
- **Systematic adjudication and analysis of CV events**
- **Limited sensitivity of pooled CV safety data prior to approval**
- **Limited value of epidemiologic data**

Avandia



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Volume 356:2457-2471 June 14, 2007 Number 24

vious

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

Background Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

Methods We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained

FDA CV Safety Guidance

Guidance for Industry **Diabetes Mellitus — Evaluating** **Cardiovascular Risk in New** **Antidiabetic Therapies to** **Treat Type 2 Diabetes**

Additional copies are available from:

*Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
E-mail: druginfo@fda.hhs.gov
Fax: 301-847-8714
(Tel) 301-796-3400
<http://www.fda.gov/cder/guidance/index.htm>*

FDA CV Safety Guidance

- **Applies to all T2DM drugs**
- **Generally requires >6000 additional patients in phase 3**
- **Must confirm degree of no harm prior to drug approval and greater degree of no harm post-approval**

A Sponsor's viewpoint – The Type 2 Diabetes Guidelines And Implications For Drug Development

DIA Meeting, Washington, October 2010

Anders Svensson MD, PhD

Head of Global Clinical Development – Metabolism

F. Hoffmann – LaRoche Ltd, Basel, Switzerland

HbA1c is no longer sufficient for approval

Evidence demonstrating the lack of a CV risk is mandated

- **Summary of FDA/EMA Guidance:**

- Sponsors will need to show pre-approval that the upper bound of 2-sided 95% CI for the risk ratio of the incidence of CV events is <1.8 using the meta-analysis of Phase 2/3 trials (FDA), and “as far as possible, exclude that the new drug increases the risk of macrovascular complications, e.g. cardiovascular disease” (EMA).
- Long term studies (at least 18-24 months (EMA) or minimum 2 years (FDA). Number of patients not clear.

- **Consequences for Pharma:**

- Substantial increase in the size, length and cost of pivotal T2D packages
 - Event driven pivotal trials - cost increase 2-3X for PhIII; in the range of \$500-700 million
 - Given the cost & time – this investment **must deliver evidence of positive benefit**
 - **Neutral / equivocal data will be punished by the market (cf Zetia and ENHANCE)**
 - *All risk is back loaded but investment is front loaded*

Implications for Pharma:

HbA1c is no longer sufficient for approval
Evidence demonstrating the lack of a CV risk is mandated

• Summary of FDA/EMA Guidance:

- Sponsors will need to show pre-approval that the upper bound of 2-sided 95% CI for the risk ratio of the incidence of CV events is <1.8 using the meta-analysis of Phase 2/3 trials (FDA), and "as far as possible, exclude that the new drug increases the risk of macrovascular complications, e.g. cardiovascular disease" (EMA).
- Long term studies (at least 18-24 months (EMA) or minimum 2 years (FDA). Number of patients not clear.

• Consequences for Pharma:

- Substantial increase in the size, length and cost of pivotal T2D packages
 - Event driven pivotal trials - cost increase 2-3X for PIII; in the range of \$500-700 million
 - Given the cost & time - this investment must deliver evidence of positive benefit
 - Neutral / equivocal data will be punished by the market (cf Zetia and ENHANCE)
 - All risk is back loaded but investment is front loaded

- Event driven pivotal trials – cost increase 2-3X for Phase 3; in the range of \$500-700 million
- Given the cost and time – this investment must deliver positive benefit
- Neutral/equivocal data will be punished by the market (e.g. Zetia)

All risk is back loaded

but investment is front loaded

Sibutramine (Meridia™)



- **Weight loss indication approved 1997**
- **Blood pressure and heart rate effect known at time of approval**
- **CV outcome trial required in Europe showed drug associated with excess CV events**
- **FDA Advisory Committee recommended withdrawal**

FDA Panel Endorses Contrave Weight-Loss Drug



(ABCNEWS.com)

AUTO START: ON | OFF



By EMILY P. WALKER MedPage Today Washington Correspondent
Dec. 8, 2010

SILVER SPRING, Md. -- An FDA advisory committee has voted 13-7 that the modest weight-loss benefits of an investigational combination of naltrexone and bupropion -- marketed under the brand name **Contrave** -- outweigh the drug's blood pressure risk.

Facebook Recommend 48
Email icon | Facebook icon | Twitter icon



Orexigen® Therapeutics Provides a Regulatory Update on Contrave® NDA

Jun 03, 2011

Orexigen® Therapeutics Provides a Regulatory Update on Contrave® NDA

SAN DIEGO, June 3, 2011 /PRNewswire/ -- Orexigen® Therapeutics, Inc. (Nasdaq: OREX) announced today that it recently met with the Food and Drug Administration (FDA) regarding the New Drug Application for Contrave® (naltrexone HCl/bupropion HCl) extended-release tablets for the treatment of obesity, including weight loss and maintenance of weight loss.

Opportunities for FDA to Address Major Issues:

- **Innovate ways to get good clinical data – faster and more meaningful and affordable**
- **Restructure the regulatory process**
- **Change priorities and incentives within FDA**
- **Improve the general understanding of what's involved in developing health products**

Opportunities for FDA to address major issues:

- ✓ Innovate ways to get good clinical data – faster and more meaningful and affordable
- ✓ Restructure the regulatory process
 - Change priorities and incentives within FDA
 - Improve the general understanding of what's involved in developing health products

This Trial Is Possible:

THE OLD ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Assessment of cardiovascular safety of Metanormin: a randomized, 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

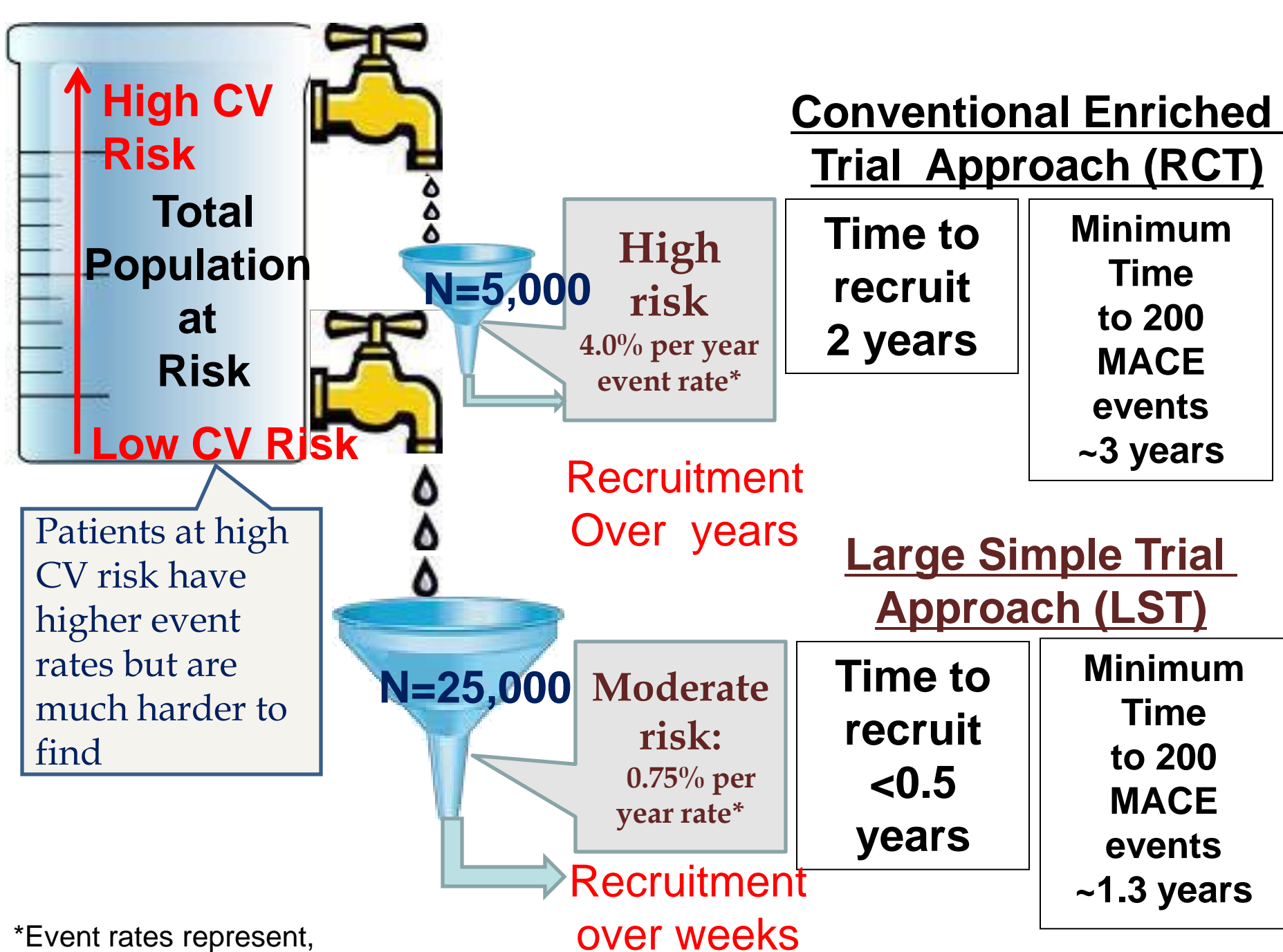
Methods: 25,234 patients were randomly assigned to metanormin groups (n=12,601) or sitagliptin treatment (n=12,633) in addition to standard of care. Enrollment began in July, 2013; this event-driven trial was stopped in August, 2014, after the prespecified number of primary outcome events had occurred. 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.

An Opportunity for FDA and Industry: Embrace the Large Simple Trial

- **LST is not a new concept**
- **Follow on indications have been approved by FDA on basis of LSTs**
- **LST does not/cannot take the place of a standard phase 3 trials aimed at characterizing general safety and efficacy**
- **The objective is to minimize the time and cost involved to creditably answer a single question**



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

RCT vs. LST comparison

| | <u>RCT*</u> | <u>LST</u> |
|---------------------------|-----------------------|------------------|
| 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 | \$16,000-22,000 | \$2,000-3,000 |
| Total (site, lab, report) | 80 to 176 | 60 to 160 |

*Based on results of a recent CV outcome study

Take Home Points about LST:

- **LST can be as credible as any conventional phase 3 trial**
- **LST taps the large pool of patients and physicians who would not otherwise engage in trials**
- **LST can allow less frequent adverse events to be evaluated in shorter time and with far less expense**
- **LST can also be applied to showing benefits (not just adverse effects) and can be used in any therapeutic area**

For Regulatory Approval, Instead of Having to Scale a Single High Mountain....



...A Step-Wise Approach is Needed



Such a Staged Approval Approach—

- Is already provided at FDA under the regulations (Subpart H)**
- Would enable a more achievable benefit to risk relationship for initial approval**
- Reduce time and cost to market**
- Allow very large outcome studies to be done earlier and with more favorable economics**
- Would increase development of metabolic and other chronic disease therapies**

FDA – the Enemy?

