State-of-the-Art Lecture:
Approval of New Diabetes Therapeutics

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Disclosures

G. Alexander Fleming

• Board Member/Advisory Panel/Consultant:

• Stock/Shareholder: Exsulin Corporation, Ammonett Pharma, Synagile,

• Other: Kinexum, principal
Overview
Approval of New Diabetes Therapeutics

• A little relevant history
• Where we are now in evaluating benefits and risks
• Challenges for diabetes development going forward
• Proposals for addressing them
FDA—the problem?
FDA is not the problem.

To the extent we are satisfied with current—

- Therapeutic choices
- Approved indications
- Current clinical outcomes
- Systems for developing therapies
Scope

• Inch wide and a mile broad
Regulatory Pathways for Marketing of Health Products in the USA

- **Dietary Supplement**
  - DSHEA

- **Food**
  - FD&C Act

- **Medical Food**
  - FD&C Act

- **Drugs**
  - PHS Act

- **Biologics**
  - FD&C Act

- **Devices**
The Saga of Diabetes Therapeutic Evaluation 1990-2010

350 BC

The Eon of controlling symptomatic glycemia (350 BC-1994)

1990

UKPDS benefits of glucose lowering in T2DM

1995

Explosion in Therapeutic Development: Metformin, PPARs, Insulin analogs

2005

Avandia meta-analysis

2010

Diabetes Therapeutic Development: Quo Vadis?

DCCT benefits of glucose lowering in T1DM

Vioxx

FDA CV Safety Guidance
The Saga of Diabetes Therapeutic Evaluation

The Eon of controlling symptomatic glycemia (350 BC-1994)
The Saga of Diabetes Therapeutic Development

DCCT
- Benefits of glucose lowering in T1DM

UKPDS
- Benefits of glucose lowering in T2DM

Effect of Intensive Diabetes Management on Macrovascular Events and Risk Factors in the Diabetes Control and Complications Trial

The Diabetes Control and Complications Trial (DCCT) was a multicenter, randomized, controlled clinical trial that demonstrated that intensive diabetes therapy delays the onset and slows the progression of retinopathy, nephropathy, and neuropathy in patients with insulin-dependent diabetes mellitus. This study presents the effect of intensive therapy on atherosclerosis-related events and associated risk factors. Patients (n = 1,441) between the ages of 13 and 39 years with insulin-dependent diabetes mellitus were randomly assigned to conventional or intensive diabetes treatment. The patients were free of cardiovascular disease at baseline. Patients with hypertension, hypercholesterolemia, or obesity were excluded. Average length of followup was 6.5 years (range 3.9 to 9). The study used standardized definitions of macrovascular events, verification of such events, and central laboratories for determination of lipids and the grading of electrocardiograms. The number of combined major macrovascular events was almost twice as high in the conventional therapy group (40 events) as in the intensive therapy group (23 events), although the differences were not statistically significant (p = 0.08). There were no differences in the cumulative incidence of hypertension. Mean total serum cholesterol, calculated low-density lipoprotein cholesterol, and triglycerides were significantly reduced in the intensive-treatment group (p < 0.01), as was the development of low-density lipoprotein cholesterol levels >160 mg/dl. Weight gain was significantly increased in the intensive-treatment group (p < 0.001). There were no differences in cigarette smoking habits, consumption of alcohol, or aspirin use between treatment groups. The reduction in some, but not all, cardiovascular risk factors suggests a potential beneficial effect of intensive therapy on macrovascular disease in insulin-dependent diabetes mellitus.

(Am J Cardiol 1995;75:894-903)
The Saga of Diabetes Therapeutic Development

DCCT benefits of glucose lowering in T1DM

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Explosion in Therapeutic Development: Metformin, PPARs, Insulin analogs


UKPDS benefits of glucose lowering in T2DM

Vioxx

The Diabetes Population Has Increased 86% in 10 Years

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

Eric J. Topol, M.D.

In May 21, 1999, Merck was granted approval by the Food and Drug Administration (FDA) to market rofecoxib (Vioxx). On September 30, 2004, after more than 80 million patients had taken this medicine and annual sales had topped $2.5 billion, the company withdrew the drug because of an excess risk of myocardial infarctions and strokes. This presents the largest prescription-drug withdrawal in history, but had the many warning signs along the way been heeded, such a debacle could have been prevented.
The Saga of Diabetes Therapeutic Development

Avandia meta-analysis

Vioxx

The NEW ENGLAND JOURNAL OF MEDICINE

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

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

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

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 on rosiglitazone, the Food and Drug Administration, and a clinical-trial database maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in a meta-analysis included a study duration of more than 3 years with a randomized control group not receiving rosiglitazone.

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
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Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Room 7-77
Rockville, MD 20857-7000
E-mail: Comm@fdacommunications.dhhs.gov
Phone: 888-463-6532
Web: www.fda.gov/CDER Comm
http://www.fda.gov/medwatch
The Saga of Diabetes Therapeutic Development 2010→

- **Risk of Cancer Associated with Insulin Therapies**
- **TIDE**
- **Avandia III FDA Advisory Committee

2009

- **Risk of Thyroid Cancer Associated with Liraglutide**
- **Risk of Bladder and Breast Cancer Associated with Dapagliflozin**
- **Incretins’ Risks of Pancreatitis and Pancreatic Cancer?**

2010

- **Risk of Cancer**
- **avandia vs. pioglitazone trial stopped**
- **OAD results reported**

2011

- **Avandia III**
- **FDA Advisory Committee**

2013

- **FDA**
- **Safety: FDA Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes in Europe**

2014

- **FDA Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes in Europe**
- **FDA**
- **ClinicalTrials.gov**
- **The Lancet**
- **The New England Journal of Medicine**
- **U.S. Food and Drug Administration**

[Additional context and details about each event and their implications are provided in the full document.]

[Image and text content are analyzed and restructured for clarity and coherence.]
Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study

L. G. Hemkens, U. Grouven, R. Bender, C. Günster, S. Gutschmidt, G. W. Selke, P. T. Sawicki

Abstract

Aims/hypothesis
The aim of this cohort study was to investigate the risk of malignant neoplasms and mortality in patients with diabetes treated either with human insulin or with one of three insulin analogues.

Methods
Data were provided by the largest German statutory health insurance fund (time-frame: January 1998 to June 2005 inclusive), on patients without known malignant disease who had received first-time
Safety

Victoza (liraglutide [rDNA origin]) Injection: REMS - Risk of Thyroid C-cell Tumors, Acute Pancreatitis

[Posted 06/13/2011]

AUDIENCE: Endocrinology, Family Practice

ISSUE: Novo Nordisk reminded healthcare professionals of important safety information about Victoza (liraglutide [rDNA origin]) injection required in a Risk Evaluation and Mitigation Strategy (REMS). The letter is being sent because a recent assessment of healthcare providers showed that some primary care providers are not fully aware of the serious risks associated with the use of Victoza.

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Additionally, in clinical trials studying Victoza, there were more cases of pancreatitis in patients treated with Victoza than in patients treated with comparators.

BACKGROUND: FDA may require a REMS for newly or already approved prescription drug product when FDA judges that a REMS is necessary to ensure the benefits of a drug outweigh the risks of the drug. Victoza is
FDA rejects novel diabetes drug over safety fears

The US Food and Drug Administration has said that it will not approve first-in-class diabetes drug dapagliflozin until more trial data become available. Talha Khan Burki reports.

Last month, US regulators informed AstraZeneca and Bristol-Myers Squibb that they are not yet able to approve dapagliflozin, an oral antidiabetic drug on which the two companies are partnered. In a joint press release, AstraZeneca and Bristol-Myers Squibb disclosed that the US Food and Drug Administration (FDA) had requested “additional clinical data to allow a better assessment of the benefit-risk profile of dapagliflozin” (in particular, induced hepatic toxicity). Whether this is an ascertainment bias or something more worrying remains to be seen. “There is a lot of angst about all drugs related to diabetes in terms of cancer risk”, explains Rob Andrews from the University of Bristol, UK. “The main concern with dapagliflozin is bladder cancer.”

“The main concern with...
One million UK diabetics set to benefit from new drug dapagliflozin

The National Institute for Health and Care Excellence will announce it is recommending dapagliflozin for some people with type 2 diabetes.
The US Food and Drug Administration (FDA) today approved a novel glucose-lowering agent, canagliflozin (Invokana, Janssen Pharmaceuticals) for the treatment of adults with type 2 diabetes.

Canagliflozin is the first in a new class of drug, an oral inhibitor of sodium glucose cotransporter 2 (SGLT2). Inhibition of SGLT2 reduces resorption of glucose in the kidney, resulting in increased urinary glucose excretion, with a consequent lowering of plasma glucose levels as well as weight loss.
An elevated fasting plasma glucose level is an independent risk factor for adverse cardiovascular outcomes. Basal insulin secretion is required to maintain fasting plasma glucose levels below 100 mg per deciliter (5.6 mmol per liter), and an elevated fasting plasma glucose level indicates that there is insufficient endogenous insulin secretion to overcome underlying insulin resistance. The correction of this deficiency may reduce cardiovascular outcomes.
Avandia review by FDA examines whether dangers were overdrawn

June 05, 2013 | By Melissa Healy

Three years after the Food and Drug Administration was taken to task for overlooking safety problems with the diabetes drug Avandia, a panel of FDA advisors met Wednesday to open a two-day review of the research that guided the agency's actions.

The meeting's first day brought an exhaustive and often testy dissection of research on Avandia, whose generic name is rosiglitazone. Drawing on an analysis prepared by a team at Duke University Medical School, FDA staff experts
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 by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability...
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Odds ratio for myocardial infarction 1.43 (95% CI 1.03-1.98)

Odds ratio for cardiovascular death 1.64 (95% CI .98-2.7)
# Diabetes Cardiovascular Guidance

<table>
<thead>
<tr>
<th>Upper Bound of 95% CI for Risk Ratio</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.8</td>
<td>Inadequate to support approval</td>
</tr>
<tr>
<td>&gt;1.3 but &lt;1.8*</td>
<td>Postmarketing trial(s) needed to show definitively &lt;1.3</td>
</tr>
<tr>
<td>&lt;1.3*</td>
<td>Postmarketing cardiovascular trial(s) generally not necessary</td>
</tr>
</tbody>
</table>

Cl=confidence interval
*with a reassuring point estimate
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:**

- 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 clinical benefit

- Neutral/equivocal data will be punished by the market (e.g. Zetia)

*All risk is back loaded but investment is front loaded*
This study has been terminated

FDA has place the trial on full clinical hold
Lessons Learned from Avandia et al

- Epidemiologic studies and meta-analyses are always hypothesis generating.
- These are useful tools but their limitations must be respected.
- Some findings from these non-prospective approaches have had “over stated” and “overly accepted”
- Consequences—some good, but some bad and some ugly

Going forward—
- Let’s be careful
- Let’s remember
Evaluating Diabetes Drug Safety: Going Forward

• Not just about CV safety anymore
• Just going to get harder
• Cancer signals raised for almost all classes of diabetes drugs
• Much tougher to resolve than CV safety—
  – Long latency
  – More confounding
  – Low event rates
Just a few points about evaluating benefits
Glucose lowering

- HbA1c is the regulatory primary efficacy endpoint
- For lots of good reasons

![Graph showing the benefit of lowering HbA1c](image)
What about post prandial glycemic control?

- Glucose levels after meals may be very important
- Evidence is—
  - Mechanistic
  - Epidemiologic
  - Prospective

Preliminary Communication

Activation of Oxidative Stress by Acute Glucose Fluctuations Compared With Sustained Chronic Hyperglycemia in Patients With Type 2 Diabetes

Louis Monnier, MD; Emilie Mas, PhD; Christine Ginet, MD; Françoise Michel, MD; Laetitia Villon, MD; Jean-Paul Cristol, MD; Claude Colette, PhD
A predicament:
Postprandial glucose control only accounts for about one third of overall glycemic control as reflected by HbA1c

- Postprandial glycemic control is not accepted as a validated primary efficacy endpoint
- This has led to relatively less clinical and commercial value being put on intervening against this target
Evaluating Efficacy Summary

• HbA1c will continue to be the primary efficacy end point
• Other measures of glycemia are not likely to become primary endpoints
• Benefits on clinical outcomes will not be required on approval but will have to eventually be demonstrated for a product to be successful.

How will we do that?
The Case of Aleglitazar

• Going straight to a CV Benefit trial

Media Release

Roche to commence phase III trials with innovative treatment designed to lower cardiovascular risk in diabetes patients with recent heart attack
SYNCHRONY study published in The Lancet supports cardio-protective potential of aleglitazar

Roche today announced it will start Phase III clinical investigations for aleglitazar, its innovative PPAR co-agonist R1439 which is uniquely designed to reduce cardiovascular morbidity and mortality in high risk patients with type 2 diabetes. This decision is supported by data from the Phase II SYNCHRONY study published today in The Lancet\(^1\) and announced at the American Diabetes Association (ADA) in New Orleans, US. The phase III programme is
Large outcome studies like SYNCHRONY—

• Can also serve to support the approval of new indications, like—
  – Metabolic syndrome
  – Diabetes prevention
  – Primary cardiovascular prevention

• But, these are enormously expensive and risky trials

How can we practically go forward?
Two approaches for enabling development of diabetes treatments and preventions

1. Very large controlled trials in the healthcare setting
2. Stepwise regulatory approvals
The LST is a prospective, randomized trial that appropriately addresses clear clinical endpoints

LST is not a new concept....
A Dozen or More LSTs Used for Regulatory Objectives

GISSI-2  ISIS-2  CURE  BALANCE  ZODIAC

Comparative Mortality Associated With Ziprasidone and Olanzapine in Real-World Use Among 18,154 Patients With Schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC)

Objective: The authors compared 1-year mortality rates associated with ziprasidone and olanzapine in real-world use.

Method: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) was an open-label, randomized, postmarketing large simple trial that enrolled patients with schizophrenia (N=18,154) in naturalistic practice in 18 countries. The primary outcome measure was nonsuicide mortality in the year after initiation of assigned treatment. Patients were randomly assigned to receive treatment with either ziprasidone or olanzapine and followed for 1 year by unblinded investigators providing usual care. A physician-administered questionnaire was used to collect baseline demographic information, medical, and psychiatric history, and concurrent medications were collected.

Results: The incidence of nonsuicide mortality within 1 year of initiating pharmacotherapy was 0.91 for ziprasidone (N=9,077) and 0.90 for olanzapine (N=9,077). The relative risk was 1.02 (95% CI: 0.76-1.39). This finding was confirmed in numerous secondary and sensitivity analyses.

Conclusions: Despite the known risk of QTc prolongation with ziprasidone treatment, the findings of this study failed to show that ziprasidone is associated with an elevated risk of nonsuicide mortality relative to olanzapine in real-world use; the study excludes a relative risk larger than 1.35 with a high level of confidence.
The Large Simple Trial

- LSTs have been accepted by FDA to approve follow on indications
- An LST could be used to satisfy FDA’s CV safety guidance but it cannot take the place of a standard phase 3 trials aimed at characterizing general safety and efficacy
An LST can achieve all the necessary elements of a conventional phase 3 trial

- 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
Contrasting Features of the LST

• Conducted within healthcare networks
• Patients and their physicians participate using simple, easy to use documentation
• Electronic technology supports efficient capture, processing, and adjudicating of data
• Low per patient cost enables very large trials that can be
  – completed sooner,
  – with greater interpretability,
  – in the targeted population
Instead of a single, one-size-fits-all drug approval system, we need...
A step-wise approval system

- **High risk orphan indication**
- **Conditional approval based on surrogate outcome**
- **Approval restricting use because of a safety concern**
- **Unrestricted approval**
Such a Staged Approval Approach—

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

How could this work?
OXIMA®
(amidoxime nicotinate)
Tablet 200 mg

INDICATIONS

OXIMA® is indicated as an adjunct to metformin/diet to lower the blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be controlled by standard therapy.
We do need to get beyond indications that just palliate the late stage manifestations of a complex disease.

INDICATIONS AND USAGE
GLUCOPHAGE® is indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes mellitus.
Population Targets for Therapeutic Development:

Diabetes and obesity are the easily identifiable populations that we treat when they reach late stages.

Let’s look at it in another way-
Increasing evidence points to the importance of metabolic and nutritional factors as root contributors to most causes of mortality.

These risk factors can be eliminated or modified.
What could we call this constellation of metabolic and nutritional disorders, which could be targeted with one or more therapies?

How about?....

“Metabesity”
How do we get there?

PROGENSA®
(Resenoprenol)
Tablets 500 mg

INDICATION
Progensa® is indicated for persons 40 years of age and older as a means of increasing life span and slowing age-related decline in quality of life and function.
Targeting therapies for disorders in the metabesity constellation –

We can’t get there from here

(as things are)