



Muraglitazar

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Disclosure

Consulting: AstraZeneca, Abbott, Atherogenics, Bayer, Lipid Sciences, Wyeth, Novartis, Pfizer, Sankyo, Haptogard, Hoffman-LaRoche, Kemia, Takeda, Kowa, Sanofi-Aventis, Protevia, Novo-Nordisk, Eli Lilly, Kos, GlaxoSmithKline, Forbes Medi-tech, Vasogenix, Vascular Biogenics, Isis Pharma, Viron Therapeutics, Roche, and Merck–Schering Plough

Lectures: AstraZeneca and Pfizer

Clinical Trials: AstraZeneca, Eli Lilly, Takeda, Sankyo, Sanofi-Aventis, Pfizer, Atherogenics, and Lipid Sciences.

Companies are directed to pay any honoraria directly to charity.
No personal reimbursement is accepted for any relationships.

Muraglitazar

A case study of the challenges of FDA drug safety evaluation when considering for approval the first agent in a new pharmaceutical class

PPARs: A Quick Primer

- Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear transcription factors that modulate gene expression.
- Therapeutic agents that target two distinct families of PPARs (α and γ) have been introduced.
- The fibric acid derivatives fenofibrate and gemfibrozil are weak PPAR α agonists, modulate lipid metabolism, lowering serum triglyceride levels and increase HDL-C.
- The PPAR γ agonists (pioglitazone and rosiglitazone) increase insulin sensitivity - used as anti-diabetic agents.

Dual PPARs: A Promising Approach?

Because both hyperlipidemia and insulin resistance promote atherosclerosis in diabetics, pharmaceutical companies have sought to develop dual α and γ PPAR agonists.

However, four dual PPARs failed during clinical testing due to varied and serious toxicities - ragaglitazar (Novo Nordisk), farglitazar (GSK), MK-767 (Merck) and TAK559 (Takeda).

Unfortunately, a literature search revealed not a single publication detailing the toxicities leading to discontinuation of development of these four agents.

Muraglitazar (BMS) Advisory Panel Scheduled

- Muraglitazar, developed by Bristol Myers Squibb, is the first dual PPAR to come before an FDA Advisory Committee.
- Because of an interest in this class of drugs, I review the briefing materials posted Sept. 8, 2005 on the FDA website.
- The FDA briefing materials reveal a striking and consistent pattern of excess death and major cardiovascular events.
- I assume that the advisory panel will not approve this agent in the presence of such a strong adverse safety signal.
- Since four previous dual PPARs failed in late stage trials, I consider whether any glitazar will make it to market

FDA Advisory Committee (September 9, 2005)

Muraglitazar presented to nine panel members, including diabetologists, patient and consumer representatives.

The sole permanent panel cardiologist is recused for conflict of interest (BMS consultant).

The FDA briefing material include a thorough safety review, which are provided to panel well in advance, and posted on the FDA website September 8.

FDA reviewer presents a slide show to the advisory committee with a comprehensive safety review.

An Excerpt from Written FDA Safety Review

All-cause and cardiovascular mortality: An imbalance of total and cardiovascular deaths was noted in the muraglitazar clinical program, with 19 of 3226 (0.59%) deaths in muraglitazar-treated subjects... as compared to two of 823 (0.24%) pioglitazone-treated subjects and one of 591 (0.17%) placebo-treated subjects (all type 2 diabetics). There were nine (of 3226) cardiovascular deaths in muraglitazar-treated subjects, one (of 591) in the placebo group, and none (of 823) in the pioglitazone-treated subjects.... The cardiovascular deaths seen in the clinical program were due to myocardial infarction, stroke, or sudden death.

Further Excerpt from Safety Review

Cardiovascular events, not including CHF: As with cardiovascular deaths, an imbalance in cardiovascular adverse events (defined as coronary disease and stroke) was seen in the Phase 2 and 3 studies pooled; primarily driven by the glyburide add-on study, in which there were 11 (of 384) cardiovascular-related AEs in the muraglitazar groups and none (of 199) in the placebo group. The other studies, while demonstrating a *numerical increase* in events in the muraglitazar groups over comparators, have too few events and too small a difference between groups to draw conclusions. Furthermore, a clear pattern in terms of a unifying diagnosis, common finding, or clinical presentation of these cardiovascular events has not emerged. Therefore, the risk of cardiovascular events with muraglitazar treatment (independent of fluid retention and congestive heart failure) is difficult to establish from the clinical studies.

The Panel Meeting

- The sponsor (BMS) emphasizes lipid and glucose lowering effects, minimizing safety concerns.
- The committee members ask virtually no detailed or probing questions about the CV outcome data!
- The panel votes 8:1 to approve muraglitazar as monotherapy and 7:2 to approve use with metformin.
- They vote 7:2 *against* approval in combination with sulfonylureas, requesting more data.
- The meeting ends at 2:05 pm and everyone heads to the airport.

Sleepless in Cleveland

- Mid-afternoon September 9, the news media report that the panel recommended approval of muraglitazar. Wall Street analysts predict >\$1 billion in peak annual sales.
- I am truly stunned and once more review the FDA briefing document, confirming a strong safety signal.
- My colleagues and I rapidly analyze mortality and morbidity data from the publicly disclosed studies, and quickly submit a manuscript to JAMA for peer review.
- The editors post the manuscript on the web October 17 as an emergency, just five weeks following panel meeting.

Muraglitazar Clinical Development Program

CV 168006 104 weeks monotherapy		CV 168018 24 weeks monotherapy		CV 168021 24 weeks +glyburide		CV 168021 78 weeks +metformin		CV 168025 26 weeks +metformin							
mura 0.5 mg	236	mura 2.5 mg	111	mura 2.5 mg	191	mura 2.5 mg	233	mura 5 mg	587						
mura 1.5 mg	236	mura 5 mg	114	mura 5 mg	193	mura 5 mg	205	Pio 30 mg	572						
mura 5 mg	236	Placebo	115	Placebo	199	Placebo	214								
mura 10 mg	236	<table border="1"> <thead> <tr> <th colspan="2">Totals</th> </tr> </thead> <tbody> <tr> <td>Muraglitazar <5 mg</td> <td>2374</td> </tr> <tr> <td>pio or placebo</td> <td>1351</td> </tr> </tbody> </table>								Totals		Muraglitazar <5 mg	2374	pio or placebo	1351
Totals															
Muraglitazar <5 mg	2374														
pio or placebo	1351														
mura 20 mg	236														
pio 15 mg	236														

Muraglitazar Studies: Baseline Characteristics

	Monotherapy Studies		Combination Therapy	
	Muraglitazar (N=729)	Comparators (N=366)	Muraglitazar (N=1409)	Comparators (N=985)
Age	53.5	52.5	55.1	54.6
Male N (%)	57.2%	54.1%	51.4%	50.8%
White N (%)	81.6%	79.2%)	87.2%	89.1%
Body Mass Index	31.2	31.5	31.3	31.7
HgbA1C (%)	8.1	8.2	8.1	8.1
Systolic BP	129	129.4	131	131.4
Diastolic BP	79.7	80.1	80.3	80.4
LDL-C (mg/dL)	123.7	128.4	113.1	112.3
HDL-C (mg/dL)	43.0	43.7	45.4	45.6
Statin use (%)	20.3%	17.5%	24.3%	24.2%

Results: Common CV Composite Endpoints

<i>Endpoint</i>	<i>Mura n (%)</i>	<i>Controls n (%)</i>	<i>RR</i>	<i>95% CI</i>	<i>p value</i>
All cause mortality or nonfatal MI	27/2374 (1.14%)	7/1351 (0.52%)	2.21	0.96-5.08	0.06
CV death or nonfatal MI	19/2374 (0.80%)	5/1351 (0.37%)	2.17	0.81-5.83	0.12
All cause mortality plus nonfatal MI or stroke	35/2374 (1.47%)	9/1351 (0.67%)	2.23	1.07-4.66	0.03
CV death + nonfatal MI or Stroke	27/2374 (1.14%)	7/1351 (0.52%)	2.21	0.96-5.08	0.06
All cause mortality+nonfatal MI, stroke, TIA, or CHF	50/2374 (2.11%)	11/1351 (0.81%)	2.62	1.36-5.05	0.004
CV death + nonfatal MI, stroke, TIA, or CHF	42/2374 (1.77%)	9/1351 (0.67%)	2.69	1.30-5.53	0.007

Results: Individual Components of Composite

<i>Endpoint</i>	<i>Mura n (%)</i>	<i>Controls n (%)</i>	<i>RR</i>	<i>95% CI</i>	<i>p value</i>
All cause mortality	16/2374 (0.67)	3/1351 (0.22%)	3.05	0.89-10.47	0.08
CV death	8/2374 (0.34%)	1/1351 (0.07%)	4.57	0.57-36.53	0.15
Fatal or nonfatal MI	15/2374 (0.63%)	9/1351 (0.30%)	2.14	0.71-6.46	0.18
Fatal or nonfatal stroke	9/2374 (0.38%)	2/1351 (0.15%)	2.57	0.55-11.89	0.23
Fatal or nonfatal TIA	5/2374 (0.21%)	1/1351 (0.07%)	2.85	0.33-24.4	0.34
Adjudicated CHF	13/2374 (0.55%)	1/1351 (0.07%)	7.43	0.97-56.83	0.053

Muraglitazar Analysis: Limitations

- Because access limited to data from publicly disclosed sources, analysis unable to employ more powerful time-to-event approach.
- Relatively small number of events result in rather broad confidence intervals.
- BMS did not submit any data from long term extension studies for the advisory panel meeting.

Muraglitazar: Our Conclusions

- In muraglitazar-treated patients, there was at least a doubling of relative risk for every major adverse cardiovascular event, compared with pioglitazone or placebo.
- The magnitude and consistency of this hazard seemed highly unlikely to represent chance alone.
- Although not presented, muraglitazar had no useful efficacy advantages over existing agents (pioglitazone)
- Muraglitazar should not be approved without a larger randomized cardiovascular morbidity-mortality study.

August 22, 2001

Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors

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ASPIRIN AND NONSTEROIDAL anti-inflammatory agents (NSAIDs) have proven analgesic, anti-inflammatory, and antithrombotic properties but also have significant gastric toxicity. The gastrointestinal toxicity appears to be related to cyclooxygenase 1 (COX-1) inhibition.¹ In 1990, Fu et al² detected a novel COX protein in monocytes stimulated by interleukin, and a year later Kujubu et al³ identified a gene with considerable homology to COX-1.

Identification of this COX-2 protein

Atherosclerosis is a process with inflammatory features and selective cyclooxygenase 2 (COX-2) inhibitors may potentially have antiatherogenic effects by virtue of inhibiting inflammation. However, by decreasing vasodilatory and antiaggregatory prostacyclin production, COX-2 antagonists may lead to increased prothrombotic activity. To define the cardiovascular effects of COX-2 inhibitors when used for arthritis and musculoskeletal pain in patients without coronary artery disease, we performed a MEDLINE search to identify all English-language articles on use of COX-2 inhibitors published between 1998 and February 2001. We also reviewed relevant submissions to the US Food and Drug Administration by pharmaceutical companies.

Our search yielded 2 major randomized trials, the Vioxx Gastrointestinal Outcomes Research Study (VIGOR; 8076 patients) and the Celecoxib Long-term Arthritis Safety Study (CLASS; 8059 patients), as well as 2 smaller trials with approximately 1000 patients each. The results from VIGOR showed

Muraglitazar

<i>Endpoint</i>	<i>mura</i>	<i>cont</i>	RR
CV death	8	1	4.57
Fatal or nonfatal MI	15	9	2.14
Fatal or nonfatal stroke	9	2	2.57
Fatal or nonfatal TIA	5	1	2.85
Peripheral Vascular	NR	NR	NA
Totals (unique patients)	32	8	2.28

Vioxx (VIGOR)

<i>Vioxx</i>	<i>naproxen</i>	RR
6	6	1.0
23	8	2.88
11	9	1.22
2	0	NA
6	1	6.0
42	17	2.47

Muraglitazar: Challenges and Lessons

- Development programs typically study relatively healthy subjects with less severe disease than the intended population, resulting in few safety events.
- Pharmaceutical companies rarely publish *safety* data from Phase II-III studies and virtually never publish the findings if they suggest an adverse safety signal.
- Most muraglitazar studies not published, nor even registered.
- Accordingly, publicly disclosed data from FDA website may represent the only comprehensive source for safety analysis at the time of approval.

Muraglitazar: Challenges and Lessons

- FDA is well-intentioned, but underfunded, overworked and must rely on external panels for advice.
- Panels sometimes perform very well and sometimes perform very poorly, as in the case of muraglitazar.
- Pharmaceutical sponsors attempt to dazzle advisory panels with efficacy claims (comparisons to submaximal doses of pioglitazone), while minimizing safety concerns.
- Companies come very well-prepared and frequently bring well-remunerated, prominent “spokesmodels” to advisory committee to impress the panelists.

Muraglitazar: Epilogue

- Two days before our JAMA manuscript appears, FDA issues an “approvable” letter, but subsequently requests more robust safety data from longer trials.
- In denying immediate approval, a potential public health catastrophe averted.
- Bristol Myers Squibb announces termination of marketing agreement with Merck.
- Company announces that it is considering dropping further development of muraglitazar.

How Can FDA Improve Drug Evaluation?

- The Agency should consider requiring registration of trials before consideration for approval or labeling.
- For all trials, study agreements must require investigator access to data and publication of results.
- The Agency needs greater help from academic organizations to improve the quality of advisory panels.
- When safety signals are observed, randomized trials are essential, not so-called “pharmacovigilance” studies.
- The Agency should “raise the bar” when considering the first agent in a new class.



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