

DIABETES CLOSE UP

Diabetes Close Up, V3, #13

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Obesity and Cancer / 2Q Earnings Review

The short version

Update: In this issue! New links between cancer and obesity suggest that being overweight or obese is even worse for your health than we might've thought. Also, see our additional thoughts on 2Q03 earnings.

The longer version

1. Obesity and Cancer – Stronger Links, More Bad News

Obesity is bad for you, but how bad is slowly becoming clearer. Most of us are aware, even painfully aware, that over two thirds of the US population is overweight or obese. As the *Wall Street Journal* noted yesterday, this month's *Nature Reviews Cancer* reports that compared to normal-weight men, obese men are twice as likely to develop colorectal cancer and three times as likely to develop kidney cancer. Women, too, are at risk. Obese post-menopausal women are up to 50% more likely to develop breast cancer and 3.5 times more likely to develop endometrial, or uterine, cancer than their normal-weight counterparts. New research shows that in sum, obesity appears to be linked to about a dozen cancers, including breast and colon cancer.

Although precise explanation for the link between obesity and cancer remains uncertain, highly metabolically active regions of fat tissue are known to release free fatty acids and proteins that can prompt more insulin creation by the body, which may promote the type of cell division that leads to tumor growth. These free fatty acids can also cause chronic hepatitis, which can lead to liver cancer.

Obesity is increasing the incidence of the common as well as the not-so-common types of cancer, like esophageal adenocarcinoma, cancer of the lower esophagus, which is now one of the fastest-growing cancers in the U.S. Obesity can lead to acid reflux disease, in which acid from the stomach backs up into the esophagus and causes a premalignant lesion there, a harbinger of esophageal adenocarcinoma.

The second-largest cause of death in the United States, cancer is associated with significant health and societal costs as well. In 2003, approximately \$64 billion was spent to detect and treat cancer cases, while the estimate for lost productivity due to illness hovers over \$16 billion. Obviously, the growing incidence of obesity within the US population threatens to increase these statistics.

Activists have called for the federal government to accelerate (some would say create) its anti-obesity strategy, suggesting initiatives like a junk-food tax and a ban on advertising of junk food targeted at children as potential steps in the right direction.

Although historically, there weren't obvious links between obesity and cancer, there's been more action on the front recently. In mid-June, the American Diabetes Association (ADA), American Heart Association (AHA), and the American Cancer Society (ACS) announced a three-year campaign to inform Americans about ways to lower their risk of four leading causes of death: heart disease, cancer, diabetes, and stroke (nearly two-thirds of all deaths in the USA are attributed to these four diseases).

The new campaign features television commercials, radio ads, and print advertisements in both English and Spanish; the creative ads encourage Americans to "protect yourself from yourself." The initiative undertaken by the three health organizations is the first time that they have collaborated in providing a uniform set of health recommendations that people can follow. Their joint recommendations included:

- Be physically active
- Consume a healthy diet and maintain a healthy body weight
- Avoid tobacco smoke and refrain from smoking
- Visit a physician regularly

Although on some level, these recommendations may appear painfully obvious (so much so that some would wonder whether they can really change behavior), we applaud more attention in this direction, as visibility is painfully needed in our view. Additionally, the "Everyday Choices For A Healthier Life" program is the first time that screening advice for physicians has been provided by ADA, AHA, and ACS acting as a collective body. The uniform guidelines given include:

For Women & Men

- Blood pressure measurement: Starting at age 20, each regular healthcare visit, at least every 2 years
- Body Mass Index (BMI) measurement: Starting at age 20, each healthcare visit. Editor's note - this is a big change, and one that will promote valuable visibility on this front – to date, BMI has largely been ignored
- Blood cholesterol test: Starting at age 20, every 5 years
- Blood sugar (glucose) test: Starting at age 45, every 3 years. Editor's note – this is actually screened at age 40 in Canada, and we believe this starting age should be reduced in the US. High-risk groups also should be tested more frequently in our view.
- Colorectal screening: Starting at age 50, every 1 to 10 years.

For Women

- Undergo a clinical breast exam (CBE) every 3 years beginning at age 20
- Beginning at age 40, the CBE should be administered annually
- Annual mammography beginning at age 40
- Annual Pap test beginning at age 20
- At age 30, have a Pap test performed once every 1 to 3 years, depending on the test that the physician utilizes and on the results of Pap tests.

For Men

- Prostate specific antigen test & digital rectal exam: Beginning at age 50, ask the physician about the pros and cons of testing

AHA President, Dr. Augustus Grant, estimates that 1.5 million premature American deaths are caused by modifiable risk factors: excess body weight, poor diet, physical inactivity, and smoking. Positively modifying these behaviors can result in fewer Americans succumbing to any or all of the four chronic diseases. Furthermore, reducing the incidence of diabetes may lower the occurrence of the three other diseases, as it is known that having diabetes increases the odds that a patient will develop heart disease, cancer, and/or stroke. Recent research at Cambridge University shows, for example, that patients with diabetes are a striking three times more likely to develop colorectal cancer than people with normal blood sugar levels.

However, informing the public of behavior modification is an element of prevention. Unfortunately, national expenditures in chronic disease prevention is estimated to be less than 5% of total national health expenditures according to Dr. Eugene Barrett, President of the ADA. Thus, the three organizations will collaborate further by pooling their resources and expertise and encourage cooperation among insurers, healthcare providers, policymakers, and governments (federal and state) to increase funding for chronic disease prevention initiatives.

A free brochure specifically developed for the public can be obtained at the campaign website, www.everydaychoices.org, or by calling toll-free, 1-866-399-6789.

--Alka Tandon, Rick E. Ybarra, and Kelly L. Close

Sources:

Wall Street Journal - www.wsj.com
American Diabetes Association - www.diabetes.org
American Heart Association - www.americanheart.org
American Cancer Society - www.cancer.org
Center for Disease Control - www.cdc.gov
Cancerpage.com www.cancerpage.com
American Association for Cancer Research- www.aacr.org

2. Major pharmaceuticals report results for the June quarter.

- **Bristol Myers:** Bristol reported overall pharmaceutical sales that were generally weak. The Glucophage franchise certainly did nothing to help, as sales decreased 67% to \$79 million from \$240 million in 2003. Glucophage IR sales decreased 54% to \$12 million (from \$26 million), Glucovance sales decreased 59% to \$49 million (from \$116 million) and Glucophage XR sales decreased a whopping 90% to \$10 million (from \$102 million). Sales are down so sharply due to the impact of generics.

In discussing the pipeline, the company revealed that it expects to file for FDA approval of muraglitazar (a dual PPAR agonist) in the second half of 2004. With the recent FDA pronouncement on PPAR drugs, we can only assume that Bristol Myers has completed (or is nearing completion) of the necessary rodent toxicity studies. Additionally, the company announced that it expects to begin Phase 3 studies of its DPP-IV inhibitor in the second half of the year and that Basulin remains on track in its Phase 2 study. Basulin, developed in partnership with Flamel, is a controlled-release insulin that uses recombinant human insulin rather than an analog. Bristol will be hosting an analyst's day on November 17, and we would look for further pipeline updates at that time.

It is also worth noting that Bristol is facing challenges on numerous fronts – not the least of which is the patent expirations of many of its high-profile drugs. As part of its strategy to maintain growth, the company is moving away from mass-market and primary care products and moving toward specialty areas. It remains to be seen how this will impact their efforts in diabetes as diabetes shares many characteristics with both mass-market/primary care pharmaceuticals and specialty pharmaceuticals.

- **Aventis:** Aventis continues to make significant progress with Lantus. Sales of the insulin analog were up 96.5% worldwide (207M euros) and up 58.2% in the U.S. (123M euros). Lantus now has roughly 25% of the U.S. market and that number continues to grow.

Little was said about the pipeline – a fact we find somewhat surprising since Aventis has a robust stable of diabetes drug candidates. Readers should recall that Aventis is being acquired by the French pharmaceutical company Sanofi - a transaction which will likely close within shortly.

- **Glaxo:** Glaxo reported that global sales of Avandia/Avandamet grew 59% to £307M – with U.S. sales up 56% to £233M. During the conference call, the company pointed out that this year-over-year comparisons were aided by a weak year-ago quarter (caused by wholesaler inventory issues) and that the underlying growth was estimated to be about 23%. Sales in Europe were up 47% to £25M and international sales were up 90% to £49M. As the company mentioned, and these numbers certainly support, Avandia has become a significant growth driver for this company. Importantly, retail volume trends remain very strong and it looks as though 2004 will be an exceptional year for Avandia.

On the R&D front, the company had less to say. Avandaryl (a once-daily combination of Avandia and Amaryl) should launch within the next six months. What's more, the Company is optimistic that a "half-power" formulation of Orlistat (60mg) could be approved for OTC sales in 2006 or even sooner. Readers may recall that Orlistat is Glaxo's anti-obesity drug that works by blocking the body's absorption of fat. Orlistat has been ridden with side effect issues to date, though in a recently study, even at half-power, the drug appears to show significant improvement versus placebo (40%).

- **Roche:** R483 was the real story with Roche's pharmaceutical diabetes business for this quarter. Roche noted that phase 2 studies of R483, a "novel TZD" in development, were in and that the results look positive. From the ADA abstract, R483 appeared to offer a better way to target PPAR-gamma, as it looks to have higher affinity and binding. However, in light of the new guidance by the FDA on all PPAR drugs in development, Roche said it will wait for further long-term toxicity data to come in before making firm Phase 3 plans. Sounds like they are already in midst of rat studies, and they will have data in 2005.
- **Lilly:** Lilly reported that second quarter diabetes care sales grew 5%. Humalog sales were up 12% to \$285M, Humulin sales were up 1% to \$259M, and Actos sales were down 3% to \$112M. All in, sales of diabetes medications totaled \$675M (versus \$640M a year ago and \$681M in the first quarter).

Looking at the pipeline, an NDA has been filed with the FDA for Exenatide (this drug is partnered with Amylin Pharmaceuticals). Although the company made no specific comment on its pulmonary insulin program, the company did say that "*a decision is*

coming up” regarding the product. We would assume that this would be a go/no-go decision as the product should be near the end of Phase 2 testing.

- **Pfizer:** For the second quarter, the diabetes news from Pfizer is about the future. The company remains enthusiastic about its Exubera inhaled insulin product. A pooled analysis of two one-year studies showed no “clinically important” negative pulmonary functions and the company (and its partners Aventis and Nektar) remain on track.

Pfizer’s press release had more on diabetes than usual - possibly because Mannkind was on the road talking up inhaled insulin of its own, Technosphere: *"Diabetes is a growing health problem that currently affects about 150 million people worldwide and is projected to affect about 300 million people by 2025. More than 30 percent of people with type 2 diabetes will eventually need insulin. The injection requirements of current insulin therapies are a huge barrier to its use. Exubera demonstrates glucose lowering equivalent to insulin injections and improved glycemic control as compared to oral agents used alone."* It is not clear to us the source of the 30 percent – seems a low estimate given the recent JAMA edict that only ~35% of type 2 patients experience good control.

- **Novartis:** While Novartis said nothing about diabetes during the conference call, there was information pertaining to LAF-237 (the company’s DPP-IV inhibitor) on the slides shown during the call. In a one-year extension study, the drug showed sustained efficacy in metformin-treated patients. It appears that FDA submission should still happen circa 2006.
- **Merck:** Merck also had little to say about its diabetes program. They have begun Phase 3 studies of MK0431 (a DPP-IV inhibitor) and expect to file for approval sometime in 2006. Merck also eschewed discussion of muraglitazar and whether or not additional toxicity studies will be needed to comply with the new FDA directive on PPAR drugs.
- **Commentary:** Business in the big pharma space is going pretty much to plan with no major surprises from any of the players. We would point out, however, that there appears to be an odd trend toward ignoring diabetes in many of the conference calls and presentations. For example, Lilly devoted significant time and attention to Cialis (a \$32M drug in the second quarter), but said nothing about Humulin or Humalog – both of which generate over 8x more revenue. While we understand that cancer drugs, cholesterol drugs, and impotence drugs are the “sexy” topics in the market right now, we believe it’s unusual that a market as large as diabetes receives comparatively so little attention.

2. Blood Glucose Monitoring – Roche continues to grow while Becton Dickinson continues to struggle.

- **Roche** continues to report strong sales in its blood glucose monitoring business, with sales up 12% (in local currencies). Accu-Chek Compact was the strongest product, while the market has responded favorably to the introductions of Accu-Chek Go and Accu-Chek Advantage III. With Roche now manufacturing its meters in China, we would expect its blood glucose monitoring business to become even more profitable over time as the cost of goods declines.

Based on successful pilot studies in the Netherlands, the company is optimistic about its new insulin pump (D Tron) and expects to roll out in the United States before too long.

While the U.S. pump market is starting to look a bit crowded, we believe there's lots of room left for penetration to grow. Roche's marketing and product design prowess should make the company a meaningful competitor in the space, once it gets past FDA woes.

- **Becton Dickinson** continues to have its issues in the blood glucose business. Sales for the second quarter were roughly \$11M (flat-to-down sequentially) and the company has lowered its full-year guidance to the low-\$40M range (versus \$50M initially). Strip usage appears to be stable and the company currently derives about 40% of its sales from Medtronic customers. The company maintains that its earlier recall has set them back by roughly one quarter and that revenues would have been in the mid-teens had it not been for the overhang of the recall. While the company did post a modest gross profit, the diabetes business as a whole showed a net loss of roughly \$16 million.

--Stephen Simpson and Kelly L. Close

Diabetes Close Up is a newsletter highlighting notable information and events related to selected companies with diabetes/obesity businesses. This newsletter is put forth as an unbiased commentary on the industry. If you have any suggestions or comments regarding content, please contact info@closeconcerns.com. If you would like to 1) unsubscribe; 2) receive a monthly digest rather than real-time updates; 3) add a name to the DCU mailing list; or 4) offer any suggestions or comments regarding content, please write to info@closeconcerns.com.

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