DIABETES CLOSE UP

Diabetes Close Up, V3, #8
April 15, 2004
Abbott/J&J 1Q04 ~ Diabetes Asia/AACE/ADA Preview

T h e s h o r t v e r s i o n

1. **Happy tax day/Abbott and J&J report 1Q04**. Hope you all finished over the weekend or giddily deferred! In the meantime, Abbott and J&J have now both reported – a few quick thoughts with more details in our long version (Abbott Diabetes Care, Topamax, Obtech, etc.):
   - LifeScan sales hit a record $400 million for the quarter, a record, up 9% operationally.
   - The market still seems pretty anemic – LifeScan quoted market growth of 4.7% for meters and 2.1% for strips, as of 4Q. We don't think the meter market is growing that fast on a sustainable basis, but it would have benefited from TheraSense Flash strength in Q4 (initial quarter out). That strength should continue, particularly now that Abbott salespeople are detailing this excellent new meter. For the market, certainly, unit growth must be faster than dollar growth as we believe the market is still suffering from pricing pressure stemming from several sources, including product diversion, heavy competition, and grumpy managed care heavyweights.
   - US growth was flat to up-a-bit. MediSense sales were even, year over year – $52 million vs $52 million – while LifeScan's domestic growth rose 3% to $219 million. While 3% may not sound like anything to write home about, this represented LifeScan's best US performance since 4Q02.
   - International growth at both MediSense and LifeScan benefited from strong currency tailwind.
     - MediSense international sales of $90 million, down a bit from the last couple of quarters, rose over 18% in Q4, though after adjusting for the strong dollar, increased just 3%.
     - LifeScan international sales of $181 million represented a new quarterly international record, up 35%, and even after adjusting for currency, still rose a whopping 19%. This quarter's excellent international results were up 5% sequentially from last quarter's $172 million, which had also represented a record.
     - Product diversion still appears to be taking its toll on US sales (see DCU V3 #2). It's been difficult to measure the impact of the J&J letter to distributors warning them against such practices and while we imagine it didn't make things easier from the illegal distribution end, it's still clearly having an impact.
2. **Conference Preview – Diabetes Asia, AACE, and ADA**: We are SO excited! Schedules are out for Diabetes Asia (this weekend in Karachi, Pakistan), AACE (end of the month in April), and ADA (early June in Orlando) – Close Concerns will be at all … highlights inside.
3. **Conference Review – Diabetes UK 2004:** A bit on Diabetes UK 2004, which we generally found to be more rather than less slow.
4. **Media Watch – UK Press.** Was it a slow news day last Friday in the UK? All over the BBC, Guardian, etc. was news of Starbridge Systems micro-pump, a Wales company that received £140,000 funding from the National Endowment for Science, Technology, and the Arts to develop a prototype. What's that old saying '*If it sounds too good to be true …*' ? More inside on this new technology.
5. **Close Concerns reports:** Check out our website, we've added a report on the ADA's "*Novel Use of Gut Hormones*" conference last December. Approximately 150 doctors, scientists, and industry participants gathered at this special ADA session to discuss the role of GI hormones in diabetes, obesity, and energy homeostasis. While this report is summarized in *Diabetes 2004*, also available on the site, the detailed report is thirty-five packed pages! Let us know if you'd like the TOC. This report is $295; discounts available for private companies. For full time healthcare professionals, all our reports are priced at $25.

T h e l o n ger v e r s i o n

Part 1: Abbott and J&J

1. **Abbott reported its final MediSense-only quarter April 8**, so things will become more interesting at the 2Q report – as of April 6, the closing date of its TheraSense acquisition, MediSense and TheraSense now exist as Abbott Diabetes Care (ADC). Alameda is the new headquarters for the joint entity. Quarter highlights:
    a. **As noted, MediSense US sales were virtually flat**. How'd we get 1% reported US growth, I wondered? 1Q03 was "slightly under" $52 million, while 1Q04 was "slightly over."
        i. We suspect after adjustments US MediSense sales might have risen a bit even if not reflected in the numbers – there are sometimes strange inventory quirks that seem to impact Abbott.
        ii. US numbers tend to be lumpy – last year, some quarters rose as much as 6% - a lot in 2003 – while other quarters fell as much as 4%.
        iii. MediSense had a tougher comparison in Q1, as a year ago, US sales rose 6%.
    b. **MediSense international sales** of $90 million, down a bit from the last couple of quarters, rose over 18% in Q4, though after adjusting for strong currency, rose just 3%.
    c. **The most interesting part of the results?** Hearing that Abbott expects ADC sales to reach $1.0 billion by 2006. By our take it's doable – by our math, this requires:
        i. The "former TheraSense" business to grow at least 20% in 2004 - the combined entity will book nine months of sales, minus six days
        ii. The base Abbott business to grow 5% in 2004
        iii. The combined businesses to grow 15% in 2005 and 2006. Although the market didn't grow anywhere near this in 2003, ADC will benefit from incremental sales from new products.
    d. **Management sounded excited about the TheraSense acquisition**, noting that TheraSense adds advanced technology, strong IP, and critical mass in global R&D and SG&A. Importantly, it enables Abbott to go after the premium (in our words, hyperintensive) segment. Even though this is a small percent of the total in absolute terms (low single digits?), it's a much higher percentage of revenue and profits.
    e. **Management said it would launch the combination Deltec pump and Freestyle blood glucose monitor** in the second quarter – we assume at the ADA in June. A single user interface will enable glucose monitoring and insulin management in one device. Very interesting idea – less hassle, though bigger device.
    f. **Management noted Navigator received expedited review from the FDA** – indeed, in a recent white paper, it highlighted innovative blood glucose monitoring devices at the agency currently (see DCU V3, #6). When we spoke with them later, it was noted that expedited review still had a big range in this area – six to eighteen months.
    g. **We'd love to comment on Meridia**, but we didn't get any results here, so we assume results were not notable for this obesity drug.
    h. **But so check it out, Glucerna** (nutritional shakes and bars) grew 40% in 1Q. New management at Ross is bringing good energy (karma, dare we say?) to the area.
2. **J&J reported April 13 with a nice uptick at LifeScan.**
    - **1Q04 results**: For the first time ever, LifeScan sales hit $400 million for the quarter, for a run rate of $1.6 billion. Total reported LifeScan sales grew 15%, while operational sales grew 9%.
    - **US sales** inched higher, rising 3% - although this may not sound incredibly positive, it's the highest quarterly domestic growth since 4Q02 - growth was negative in the first half last year, so it's an easier comparison, but still positive. In the current quarter (2Q04) LifeScan should show strong US growth since the 2Q03 comparison is a 27% loss.
    - **International sales** rose 19% operationally and 35% with help from the strong dollar. It's tough to know whether LifeScan is benefiting from product diversion or real international strength. Very little was noted about LifeScan on the call, except that LifeScan had made a "tactical decision" to try to growth international sales and that Ultra was key to those results. Mgmt also noted that UltraSmart had been launched in key countries in Europe and such expansion would continue.

We've actually heard that Bayer's Contour is doing pretty well in Europe – more after some channel checks.

- **In Q&A, management was asked to assess blood glucose market growth.** CFO Bob Daretta noted the company's belief that JNJ was not gaining market share. J&J quoted market growth of 4.7% for meters and 2.1% for strips, growth as of 4Q03 - we assume the higher monitor growth reflects at least in part the launch of Flash.
- **What else is going on at J&J on the diabetes/obesity/metabolic disease front?**
    - **On the pharma side, no news on Topamax's indication for obesity**, but it seems Topamax is probably being used off-label to some degree, and the question is just how much. Sales for the drug grew 38% operationally and 42% reported. No recent word on new formulation progress, but adverse events in the old obesity trial were troubling (the reason for the reformulation). Cognitive issues, we understand, were a worry.
    - **Management made a very quick allusion to strong gastric surgery** when discussing Ethicon Endo results - it has made very few references to its 2002 purchase of Obtech, a privately held Swiss company that markets the Swedish Adjustable Gastric Band (SAGB). Trials for this product are ongoing in the US, though we wouldn't expect to see the product before at least 2006.
    - **On the nutritional side, Splenda** continues to do incredibly well - it has a 45% share now in the tabletop sweetener market, which is pretty amazing given that it was launched in the consumer market only in 2000. JNJ recently announced it's available at all Starbucks, an obvious win on the visibility front. Excellent – now there's more reason than just wireless to go to Starbuck's …(if you're in San Francisco, check out my favorite coffee place, Tartine, in the Mission www.tartinebakery.com).

--by Kelly Close

Part 2: Conference Previews

1. **Diabetes in Asia:** We just received the final schedule for this conference in Karachi, Pakistan, where Close Concerns will be this weekend.
    a. **Insulin will be widely discussed,** starting with the opening session, "Insulin Therapy-2004; Basic needs or Sophistication?" Pierre Lefebvre, whom we last heard at EASD, will lead this session – he's the incoming International Diabetes Federation head and a powerhouse. (Interesting tangent – IDF 2006 was supposed to be in Korea in 2006 but was cancelled. No new venue yet www.idf.org but getting the scoop is a goal.)
    b. Other sessions of note will focus on diabetes nephropathy, ethnicity implications, diabetes care in the hospital setting, and new concepts in diabetes management.

2. **AACE** (www.aace.org): This happens April 28 – May 2, in Boston. It is a jam-packed few days. Among the sessions of note, some particularly outstanding selections:
    a. **Allen Spiegel and Donald Bergman (AACE president)** on "The NIH Research Agenda for Prevention of Obesity and Diabetes"
    b. **Irl Hirsch** on "Intensive Inpatient Diabetes Management"
    c. **Alan Moses** on "Technology in DM Monitoring and Treatment: Where Are We and Where Are We Going?"
    d. **Regina Herzlinger** on "Reimbursement for Healthcare Services: What's Next After Managed Care?"
    e. **Aaron Vinik and Lois Jovanovic** on "Clinical Aspects of Diabetic Neuropathy"
    f. **F. Xavier Pi-Sunyer and Jeffrey Mechanick** on "Clinical Approaches to Obesity"

3. **ADA** (www.diabetes.org): This happens June 4-8 in Orlando – last day for a discounted fee is April 23. Among the sessions of note, some that look most excellent to us include:
    a. **Michael Bliss** on the discovery of insulin
    b. **David Kendall on the Use of TZDs** (this will be meaty and great – Kendall is an outstanding speaker. He'll be arguing advantages and someone unnamed (who would want to go against Kendall? Though the CVD points on TZDs are unsettling) will be arguing disadvantages.

c. **Lori Laffel** (brilliant Joslin doctor) on "Epidemiology of Diabetes Complications – Changing Trends over Ten Years"
d. **James Gavin, David Marrero, and Lawrence Blonde** on "Tools for Diabetes Prevention and Control."
e. **Satish Garg, Howard Wolpert, and Mary Korykowski** on "Practical Approaches to Insulin Therapy"
f. **Alan Cherrington and others** on "Evolving Concepts of Incretin Action"
g. **David Ludwig and others** on "Glycemic Index: What we Know, Don't Know, and Need to Know"
h. **Richard Rubin, Stuart Chipkin, Matthew Riddle, and Irl Hirsch** (get here twenty minutes early to grab a seat, with this lineup) on "Pharmacologic Treatment of Type 2 Diabetes"
i. **Fran Kaufman and Samuel Gidding** on "To Treat or Not to Treat, That is the Question: Lipids and Diabetes in Childhood"
j. **Rury Holman and others** on "Preventing Cardiovascular Disease in Type 2 Diabetes: Trial Data"
k. **Bariatric Surgery: Before and After**
l. **Progress on the New Standardization and Values for the A1C Test**
m. **Islet and Gut Hormone Connections**
n. **Treatment of Metabolic Syndrome**
o. **ACE vs ARB for Prevention and Treatment of Renal Disease**
p. **Advances in Peripheral Vascular Disease**
q. **Hypoglycemia Unawareness**
r. **Oral Agents During Pregnancy – Is it Time for Guidelines**?
s. **Pay for Performance: Linking Reimbursement to Diabetes Outcomes**
t. **Sources of Surrogate Beta Cells**

Part 3: The Diabetes UK Annual Professional Conference took place late last month in Birmingham, UK. Approximately 2000 healthcare professionals, researchers, industry exhibitors and patient advocates gathered for an intensive three days of lectures, poster presentations, and exhibits. While there is some excellent stuff going on overseas on the diabetes front, and while we know – and met more – impressive clinicians and scientists - we don't find that the UK is necessarily on the cutting edge, largely due to reimbursement issues and a general unwillingness to pay, period, for anything beyond the basics[1]. So sometimes, you think a conference will be amazing, and it is – other times, you pick out what was intriguing, but offerings are slimmer. This was more of a proverbial "other" time. Select highlights:

The conference kicked off with a very good joint symposium with the British Hypertension Society, "Hypertension: from Cells to Care," chaired by Jiten Vora and Kennedy Cruickshank.

1. **John Petrie termed the pathophysiology of hypertension as more than a consequence** – as, in fact, a "jigsaw puzzle" of initiating, sustaining, and modifying factors
2. **Rury Holman (a complete powerhouse), summarizing the findings of the UKPDS follow-up study re hypertension, described the risk factors of HDL, LDL, glycemia, blood pressure, and smoking as a "deadly quintet**."
    a. In 1987, a subset of UKPDS participants was selected for a blood pressure control study. In the follow-up, they're being observed but no effort is being made to influence their therapy. Thirty-six percent are on three agents to reduce blood pressure. Sorrowfully, only 17% of hypertensive type 2s have actually attained 130/80, the recommended goal.
    b. As we heard at the Canadian Diabetes Association conference, combo therapy is king, or if it isn't king yet, it's becoming king. Addressing blood pressure may require three different agents. Although to start, it doesn't seem to matter hugely whether you use ACE inhibitors or β-blockers as long as you're addressing the problem (with drugs). (The CDA, by the way, was our favorite conference last year – we love all meetings, but there,

[1] As such, we deem one of the conference highlights the performance by ABBA tribute band Björn Again : >.

based on our unscientific survey, we found more doctors love to sit down and have a pint than anywhere else! That's the best …)

3. **According to Bryan Williams, persistent myths interfere with aggressive blood pressure management in diabetic patients**. Among them:
    a. That TZDs may worsen outcomes (he says they don't)
    b. That β-blockers are dangerous (he says they're not)
    c. That calcium-channel blockers are bad (he says they're good)
    d. That renovascular complications are so common there's no point in treating them (he says, of course there is)
4. **Neil Poulter drove home the point that type 2s with blood pressure >140/90 ought to be on drugs**. Cholesterol should be <4.0 mmol/L (~154m g/dL!!) or statins should be initiated. Sounds pretty intense, but indeed, the Heart Protection Study, out last year, implied that all people with diabetes over 40 should be on statins no matter *what* their cholesterol. (Let us know if you'd like more info on this – a fascinating study.)
5. **Takeaways**:
    a. Increased CVD risk of diabetes can be all but eliminated by lowering blood pressure.
    b. Choice of initial therapy appears irrelevant.
    c. Evidence that ARBs like Losartan and ACE inhibitors can help prevent nephropathy does not mean they should be simply used alone - repeat, monotherapy may not be enough.

On day 2, the session "Monitoring/Treatment in Type 2 Diabetes" brought several interesting oral poster presentations. For example, E. R. Pearson examined whether sulfonylureas or metformin should be used to treat non-obese type 2 diabetic patients. The hypothesis: non-obese patients would do better on metformin, obese patients on sulfonylureas.

1. In the study, the metformin group started out slimmer and lost a little more weight.
2. Sulfonylureas were used in bigger patients and that group gained some weight.
3. Conclusion: metformin seems to reduce insulin resistance to the same absolute degree in the obese and the non-obese; non-obese patients do better on metformin.

Day 3 brought more on "**Insulin Therapies**."

1. E. L. Lim shared data on 76 type 1s who had been switched to insulin glargine (Lantus™) between August 2002 and June 2003.
    a. Sixty-three percent of patients took less total daily insulin, but 37% needed more insulin when taking glargine
    b. HbA1c improved in 62% of patients, did not change in 5%, and increased in 33% (mean SD reduction of 0.4%: 9.1%→ 8.7%). We think this is really interesting. While the increase seems worrying, we think it's equally important to look at glycemic variability overall. If it is reduced, maybe the rise in A1C isn't that big an issue. We'll be studying this question more in the coming months.
2. Guys', King's, and St Thomas's Hospitals in London made an excellent case for initiating pump therapy in patients classically contraindicated for psychological reasons.
    a. Patients with emotional problems and problematic diabetes control saw improvements in quality of life as well as fewer episodes of diabetic ketoacidosis than with MDI.
    b. Psychiatric support and commitment from the diabetes care team contributed greatly to positive patient outcomes.
    c. The conclusion was that CSII can work in patients who would normally be disqualified on grounds of mental health. So what surprised us the most about this was that this was even any question. Pump therapy is extremely difficult to get approved in the UK; use of Lantus first is typically required, and generally patients need to be doing pretty badly in terms of A1C to quality.

IV. The final session, "Working in Partnership: joint sessions with lay members of Diabetes UK" raised some interesting issues related to diabetes in young people.

1. Soon the UK National Institute for Clinical Excellence (NICE) will release new guidelines for managing type 1 and type 2. The UK's issues concerning diabetes overlap with many areas of debate

in the US, but the National Health Service's administrative structure and priorities influence care and treatment more than one might expect. We'll be watching to see what develops. Issues that arose:

a. How do we address huge gaps that exist in the evidence base?
b. What can be gained from continuous monitoring? (The UK is much further behind the US on this front.)
c. What other information is available on long-acting insulin analogs?
d. How should novel insulin regimens be used in children under 5?
e. Should metformin be used in overweight teens?

-- By Melissa Ford and Kelly Close

Starbridge Systems Insulin "Micropump," Swansea, Wales

Starbridge Systems, a Wales company, recently received £140,000 funding – and loads of British press![2] - from the National Endowment for Science, Technology, and the Arts to develop a prototype micropump, possibly before year-end. At first blush, we are skeptical, for the following reasons:

- Insulin molecules are too large to be delivered through the skin at a reliable rate. Jet injectors never really took off, after all. Skin functions as a barrier to keep foreign objects and substances out of the body. Absorption of anything through the skin varies depending on both external conditions and the type of skin. We're not the scientists, but … a needle so tiny that it can be inserted by applying a patch seems unlikely to penetrate deeply enough to bypass all layers of skin and to reach optimally absorptive tissue.
- Insulin is a C-peptide hormone. Individuals' sensitivities and requirements vary much more with insulin; one unit of rapid-acting insulin might make one person's blood glucose decline by 40 mg/dl but another person, even at nearly the same height and weight, could require .5, 1.5, or 2 units of insulin to experience the same change.
- Audience – these micropumps are geared toward type 2's. On the one hand they're the obvious audience: 1) insulin resistance is common among type 2 patients, lowering risk of severe hypoglycemia; 2) they are more likely to have some counter-regulatory hormones; and 3) may have less variation in basal needs. But on the other hand most type 2 patients using insulin need more insulin than most type 1s. Their relatively higher insulin requirement would seem to imply that a three-day basal supply might be much harder to squeeze into a patch-type device unless the insulin is highly concentrated. Whether the insulin will be absorbed well via micropump at any concentration also remains a question.
- Rates of flux (not linked to blood pressure) vary in tissues throughout the body. Blood appears to moves more slowly in tissue just below the skin's surface, where a tiny, minimally invasive needle might go. But externally introduced insulin should circulate in the bloodstream as soon as possible after administration. One must stick a needle or cannula well into subcutaneous tissue to reach the bloodstream quickly, but intravenous and intraperitoneal delivery remain the fastest ways to change blood glucose A flat or even adjustable basal rate that won't show some change in blood glucose within an hour of being adjusted is not a logical advance, in our view.
- Only mimicking non-diabetic physiology brings us closer to optimal metabolic control. If insulin were made in subcutaneous tissue, then a transdermal patch might be a positive. Insulin is, unfortunately, a C-peptide hormone made in just 2% of the pancreas. Even injecting or infusing subcutaneously, the best widely available ways of delivering insulin to date, may not be the optimal way to receive it but it seems to us to make much more sense than a patch, barring major advances.

-- By Melissa Ford and Kelly Close

[2] www.guardian.co.uk/uk_news/story/0,3604,1188687,00.html ; www.cti-wales.com/eng/casestudies-detail.php/CID=99~MID=; http://news.bbc.co.uk/1/hi/health/3617501.stm; http://thescotsman.scotsman.com/health.cfm?id=411892004

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