DIABETES CLOSE UP

Diabetes Close Up, V3, #12
July 16, 2004
Abbott Diabetes Care ~ J&J ~ ConjuChem~ HHS on obesity

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

Update: In this issue!

- Commentary on second quarter blood glucose monitoring results – good new so far! Abbott Diabetes Care benefits big time from first quarter of TheraSense contribution and JNJ's LifeScan shows renewed strength;
- A follow up on our story yesterday re: disappointing Conjuchem results – the conference call allayed no fears. Back to the drawing board for ConjuChem … the call unfortunately didn't offer the new info for which we were looking but details inside on how our thoughts on the DAC compound are evolving.
- Very exciting news coming out of US Health and Human Services - it suggests, finally, that we're getting closer to moving beyond the nonsense that obesity shouldn't be perceived as a disease in any way, shape, or form.

Have a spectacular weekend!

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

1. **Abbott Diabetes Care results reflect added strength of TheraSense:**
   - Abbott Diabetes Care[1] benefited in a major way from its acquisition of TheraSense – domestic sales doubled year over year, rather than showing single digit growth - and international sales experienced a nice boost.
   - ADC 2Q sales reached $99 million, up 97%, while international sales grew to $98 million, up 25% (15% excluding the foreign exchange impact) – total 2Q sales of $196 million rose 53% (47% sans FX).
   - Although Abbott did not split out TheraSense's contribution, making it difficult to determine the incremental growth from the new acquisition, we do know ADC benefited from nearly an entire quarter of TheraSense sales, as the acquisition closed early in the quarter. We imagine that worldwide internal growth (i.e., former MediSense growth) was around 5%, give or take a couple of percent, and that domestic internal growth lagged internal international growth.
   - Management forecast 40% growth for ADC for Q3, which implies the company will exceed for the first time the $200 million sales mark this quarter. At the time that the TheraSense acquisition was announced, management had forecast growth of 30% for 2004 for the combined entity. Based on the combined results for 2Q and the 3Q forecast, we believe that early forecast will prove conservative; closer to 35% growth for 2004 would be our better bet, as the company continues to benefit from Flash, in particular, and from better visibility overall.

[1] The new name, ADC, combines old diabetes business MediSense and newly acquired TheraSense.

- Management discussed international expansion for FreeStyle (former TheraSense brand) products, which makes good strategic sense as ADC will benefit from the larger product portfolio. Management also noted it was encouraged by progress with Navigator, the continuous monitoring system submitted to the FDA in late 2003. As a sidebar, we note that there was extensive interest at the ADA in Orlando last month in Navigator.

2. **J&J/LifeScan achieves strong growth ~ not much news delivered on pharma front for diabetes/obesity but Topamax continues on roll**
   - LifeScan saw excellent growth in the second quarter, achieving sales of $236 million in the US, up a very impressive 37%, and $183 million internationally, up 17% on a reported basis (up 11% excluding FX). Worldwide, sales reached $420 million, up 27% (24% sans FX).
   - LifeScan benefited from easy domestic comparisons from 2Q03, which was a weak quarter. Still, the final worldwide tally of $420 million increased 5% from a quarter earlier and approaches $1.7 billion on an annualized basis. We call a moment of silence for perspective; it wasn't *so* long ago (2001) that LifeScan achieved its first $1.0 billion year in sales.
   - On the international front, LifeScan had a tough comparison and its 17% growth was actually the first quarter in the last eleven that growth below 20% was reported. We'll be curious to watch how both domestic and international growth settles out over the next few quarters, as this may have implications on the diversion front (see story from V#3, #2, January 16 for more on this topic).
   - While we believe industry unit growth for blood glucose monitoring will benefit from several major drivers moving forward (growing population of intensive users, greater hospital use, fewer places to 'hide' for users, sheer bloody continued growth of the disease, better diagnoses), pricing pressure concern remains and may heighten; more focus on this to follow.
   - On the pharma front, there was zero pipeline news on the obesity or diabetes front (nothing on ObTech, nothing on Topamax for obesity, nothing on J&J's PPAR in relatively early stage development), not that that was so surprising since the company typically doesn't say a lot before Phase 3. We do note that Topamax sales continue on a roll, increasing 27% worldwide; although the company doesn't have an obesity indication yet, we believe some patients still pursue – and get - off-label use, depending on physician approach.
   - Final odds and ends: 1) J&J closed the quarter with over $7 billion in cash. $7 billion! 2) Next pharma R&D day will be 2Q05.

3. **Conjuchem: Phase 2 Study Results – Is It Apples-to-Apples or Lemons**? On July 14, Conjuchem announced results from its Phase 2 monotherapy study of its DAC GLP-1 compound; the following morning, the company hosted a conference call to add color to the results.

   Historical revisionism at work? It's an efficacy study… No! It's a proof-of-principle study …We were surprised to hear the company management on the call characterize this Phase 2 study as more of an exploratory study to guide future clinical studies, rather than a more typical Phase 2 efficacy study. While we acknowledge the possibility that we misinterpreted previous management intention and tone, we did not hear the Company characterize this study as a "proof of principle" study when they provided their (we would characterize as dramatic) interim update in April. While management can of course be expected to present things in the best possible light, we believe credibility has been stretched.

The huge dropout problem drew the most interest, followed by the nausea problems. While company management attempted to downplay this, like many, we found huge level of patient dropouts in the study alarming. A total of 112 patients quit the study, out of total enrolment of 206. While 36 patients quit due to the nausea, we are more concerned by the fact that 29 quit due to a lack of efficacy (and 21 of these quit during the initial stage when everyone received treatment). An additional 36 patient dropouts were characterized as withdrawals of consent. The company characterized this as an issue of convenience, since the injections were administered at a doctor's office. This would be hard to believe for a drug patients were excited about and that was showing efficacy. A sidenote: on the April call, management characterized the nausea as improving, not worsening; although that call was based on fewer patients at only four weeks, that was also that call that was called because the results were perceived as "material" by management.

We found the company's characterization of nausea as endemic to all GLP-1 drugs as too general in nature as it implies that all GLP-1 drugs see a similar nausea profile, which has not been true to date. While it's true that all GLP-1 drugs have shown some nausea, none has shown this much. Amylin's exenatide, for example, was studied over 52 weeks (versus 12 weeks in this study) and had nowhere near as great a problem with nausea or patient dropouts due to nausea.

Regarding the dropout rate, we note that trials for AIDS drugs, cancer drugs, and other drugs with truly unpleasant side effects don't show nearly this high a level of drop-out (consider ISIS' drug that is injected into the eye). One conclusion was that the patients didn't see value in continuing – it's hard to justify continuing a trial if you don't think the drug is helping.

Incomplete data remains an issue. In addition to the drop out and nausea issues, we continue to be troubled by the presentation of efficacy data (or lack there of). The decision to use area-under-curve post-meal glucose as the primary endpoint is unusual. Since this is not a common primary endpoint, comparison to other studies is challenging. While the data presented is positive (a 30% reduction versus those not receiving treatment), the absence of baseline comparison and a relatively high p-value are causes for some concern.

HbA1c, fasting blood glucose, and weight loss were secondary endpoints, and were presented only in comparison to the not-treated group and only on the basis of completion. While the presented HbA1c data is positive (down 1.5% versus placebo in the once-daily group and down 1.1% versus placebo in the every-other-day cohort), netting out the effect of a rise in HbA1c in the non-treated group tempers enthusiasm. In addition to this data, we would like to see baseline data for respective groups, which was not given on the call – we are not sure why.

Weight reduction and fasting plasma glucose results showed similar strength – weight loss ranged from 2.4kg to 2.7kg across the treatment groups and average FPG was down by almost 30% - and were again difficult to interpret given the absence of baseline[2] data. We understand the value of presenting data versus a placebo, but we believe it is important to also show the data versus a baseline – presenting one without the other presents interpretation problems. On a practical level, there is another reason to present baseline data – healthcare professionals and patients care about how absolute HbA1c levels and FPG levels will

[2] In addition to comparison to its "placebo" group – we do understand placebo effect is key to net out, although usually the placebo effect causes patients to improve, not decline further!

improve. While we understand that's not the purpose of this study, we maintain that while it's critical from a regulatory perspective also to see how patients do versus others not taking the drug, presenting both sets of data solves the problem.

A fix? ConjuChem does believe it has a fix to the problem. It appears that the severe nausea is caused by "free" compound that doesn't immediately bind to albumin in the body after injection; roughly 85% binds immediately, while the remainder becomes "free" in the bloodstream and binds to cystine (what else happens with the remainder?). The company believes this can be alleviated by a different reconstitution solution and the company intends to pursue this in a new Phase 1 study. Phase 1. Yes, so timing assumptions will undergo some changes.

Best in class? Not so fast. While we are not discounting the possibility that this compound could ultimately be a meaningful competitive entry, it appears that Conjuchem has a long way to go to achieve their oft-discussed 'best in class' goal.

Plan B – Drug combos may help the cause: The company is currently conducting a study of DAC GLP-1 in combination with metformin. Apparently nausea is not so much of a factor in combination (because there is less drug administered) and there is an improvement above that which would be expected from metformin alone. The company hopes to produce results from this study before year-end and we are eager to see this data and hope that it will be presented in more comprehensive fashion than this round of data. It seems probably now that DAC GLP-1 will first see the light of day as a combination therapy, at which point doctors may choose to prescribe it off-label as a monotherapy if efficacy can be shown without side effects.

The Future – Don't Queue The Fat Lady Just Yet: We are disappointed with this study, but not all is necessarily lost. There remains some reason to believe this compound can ultimately show some efficacy, though not necessarily that it could be *better* than competing products. If the nausea problem can be resolved, which stands now as a major if, there may be no reason that this compound can't compete. The question, of course, is timing. It will take time for the reformulated drug to move through trials – time that will allow other purveyors of GLP-1 compounds to gain a strong beachhead in the marketplace. If Conjuchem does decide to go with a different formulation of DAC GLP-1 (presumably to moderate the nausea to more acceptable levels), it is probable that the FDA would require them to essentially start over – meaning a new Phase 1 and Phase 2 study. Should the company decide to go this route, it could be 18-24 months or even longer before the company could hope to start a Phase 3 study. Tough news for a mid-summer report. We do look forward to hearing more on July 28 at the company's R&D symposium in New York, where Dr. Daniel Drucker will be on hand, a figure widely perceived as among the very smartest in the GLP-1 business. Stay tuned, as we will be.

4. **HHS**:
   - **So there's been a big problem in the US for some time on the obesity drug/device coverage front** – basically, it's that problems with weight often need to prompt other issues like cardiovascular problems, diabetes diagnoses (diabetes complications) before patients can get any help with the underlying problem, which has to do with weight. This is very related to another issue we've been consumed by, which is why the country often seems more focused on addressing acute problems (for example, amputating legs) rather than taking a preventive approach (for example, urging blood glucose control). So all of

this is reductive, we know, but ! There is some good news, as was reported by the WSJ and NYT late this week.

- **In essence, Tommy G. Thompson**, Secretary of Health and Human Services, announced that Medicare's new coverage policy would enable better coverage of anti-obesity interventions if scientific/medical evidence show effectiveness in improving outcomes.
- **As the HHS press release explains**, www.hhs.gov/news/press/2004pres/20040715.html the new policy from CMS (Centers for Medicare & Medicaid Services) "removes language in the Medicare Coverage Issues Manual stating that obesity is not an illness". This step allows requests that Medicare review medical evidence to determine whether specific treatments related to obesity would be covered by Medicare.
- **Although there is all sorts of language** in the release that suggests this won't result in any major changes, we see this as an important philosophical step forward and believe that functionally this could result in patients being looked after sooner and better so that things don't have to become *really* bad before anything can be done.
- **We'll be re-visiting this issue** after we do more research but for now, we certainly view it as a positive from a public health perspective and also a positive for companies with drugs and devices that address obesity. Inamed with its Lap-Band is the major one that comes to mind in terms of commercial products, and companies with drugs that address obesity should ultimately benefit from this as well. Most of these are in clinical trials currently; obesity drugs currently on the market prompt so many side effects that we don't see this decision impacting their sales.

5. **Final observations**:
   - **AADE takes place in Indianapolis from August 10 – 14**. Melissa Ford and I will be there – if you haven't decided whether to go, let us know, and we'll send you our preview "best of" schedule.
   - **Free time this weekend**? Live in a major US city? Go see "Super Size Me," Morgan Spurlock's successful sleeper documentary, a vigilante version of an FDA drug trial in which McDonald's, not Big Pharma, is under scrutiny. The film examines the obesity epidemic in the US, the health issues it has raised, and the culprits for its continuance in our prosperous, fat, country. Through the video journal of writer/director Spurlock, audiences live vicariously on a strict "McDiet" for one month. The result is near liver failure from fat deposits, a cholesterol level increase from 168 to 230 mg/dl, a 25-lb. weight gain, chest pains, and depression. An extreme example, yes, but high entertainment and good learning too. See our detailed review online at www.closeconcerns.com under newsletters/reports/reviews.
   - **Apologies for the late arrival of this edition of DCU**. I'll be back to the grindstone come Monday but right now I'm still on holiday and writing from Sweden's Archipelago, where Internet access has been spotty, but where the midnight sun is still being thoroughly relished.
   - **On that note,** please relish *your* weekend!

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