DIABETES CLOSE UP

Diabetes Close Up, V3, #11
July 15, 2004
ConjuChem ~ PPARs

The short version

1. **Update:** I've been on an extended time away, and am today writing from Helsinki. It's gorgeous here – I'm wishing we could import the midnight sun concept. In the meantime, lots has happened of late – ConjuChem trial data and PPAR chaos are the topics today – upcoming, recent blood glucose monitoring results discussion. To it!
2. **ConjuChem**: Re: data released yesterday on the company's Phase 2 monotherapy trial, we found it difficult to draw meaningful conclusions due to high nausea/dropout and study design/results presentation. Overall, the results appear disappointing, though it's early and we look forward to hearing more detailed findings on the call today (www.conjuchem.com; 8:30 am EST). Main takeaways below, more details inside.
    a. Very high drop out rate at 54%. Ninety-four of original 206 finished trial. Nausea was a major side effect.
    b. Endpoints difficult to interpret. We were surprised to see area-under-curve for post-meal glucose as the primary endpoint. Other results, including A1C, fasting blood glucose, and weight were tough to assess in light of nausea. Further muddying interpretation, the study results for the treated groups[1] were all shown compared to the "not treated" group, rather than compared to baseline.
        i. Straight-line average of the four treated groups implies an A1C drop of ~1.0% compared to NT group. Closer to a ~0.5% drop may be better way to interpret in the absence of baseline data – the NT group had an unexplained 0.5 increase in A1C.
        ii. We're not sure why results are shown that don't indicate baseline comparisons *as well as* placebo – we saw this problem with LAF-237 results at ADA as well, which is very frustrating. We'd love some baseline comparisons on the call, but we aren't optimistic.
    c. Dosing was problematic, particularly in 1x/week group where only 35% got to target dosing levels.
    d. Weight dropped for all groups, including NT group, about 2.5 kg, compared to 2.3 kg at 4 weeks. The question about whether this is caused by nausea is bound to arise, especially since these are only 12-week results and since nausea doesn't necessarily appear to improve. It would be very interesting to see data for patients who didn't suffer from nausea.
3. **PPAR Update:** Late last week, Ligand announced news that is meaningful to the diabetes drug marketplace:
    a. Ligand announced that FDA concerns regarding cancer had led the agency to require all companies developing PPAR compounds to complete 2-year rodent safety / toxicity studies before progressing with long-term human studies (studies longer than six months in duration). This new FDA guidance covers all PPAR compounds (alpha, gamma, and dual) and will effectively end clinical investigation of these compounds until the relevant safety studies are performed and the FDA is satisfied that the compounds are safe.
    b. Companies directly affected by this FDA action include Ligand (and its partner, Lilly), Bristol Myers (and its marketing partner Merck), Aventis, Glaxo, and Johnson & Johnson. At present, as far as we know, only Ligand has publicly commented on this FDA action and noted that it will delay their compound by 18 – 24 months. While it is likely that most companies will have roughly the same experience, it is also possible that one or more companies had already begun a two-year rodent cancer/safety study. In such cases, the delay could be less than two years. We will update this as company releases and our own due diligence permit.
    c. In the meantime, we see this news as at least a minor positive for companies that are the furthest along in the development of non-PPAR compounds. See more detailed comments inside.

Company	Compound	Regulatory Status
Amylin/Lilly	Exenatide	Filed NDA late June, 2004
Novartis	LAF-237	Phase 3
Novo Nordisk	Liraglutide	About to enter Phase 3
Merck	MK0431	About to enter Phase 3

[1] There were four treated groups who had various dosing regimens – once per day, three times per week, twice per week, and once per week.

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

1. More on ConjuChem

A few more detailed points on ConjuChem's data, from our before-the-call perspective. Hopefully much will be delineated on the call this morning.

- **Safety/Drop outs**: Only 46% of the 206 people finished the trial; 36% dropped out at titration and another 18% after maintenance. Nausea was the major side effect, prompting ~18% of the dropouts. Other dropout reasons were consent withdrawal (17%), insufficient efficacy (14%), and "other" (5%). Would be nice to know how the dropouts were divided across the dosing groups and what percentage of patients suffered no nausea.

- **Dosing** obviously an issue in 1x/ week group, if only 35% got to full dose. Tolerability in other groups will be key to assess, although it's conclusions are tough to make for small groups (especially after the dropouts).

- **Primary endpoint results**: We were surprised to see area under the curve used as primary endpoint. We gather this was to assess post-prandial glucose levels; unfortunately, as noted earlier because comparisons were made to the NT cohort and not baseline, it's hard to draw meaningful conclusions. 30% sounds promising, though we don't know what AUC changes were for NT set.

- **Other endpoints - A1C**:

    - For A1C endpoint as well, the company compared the treatment groups to the "no –dose" group, not to baseline, which limits the conclusions that can be made, especially since the no-dose A1C actually rose 0.5. Once you adjust for this, it would seem that the group that took the drug once a day had a closer to a 1% A1C reduction, the three times a week had closer to a 0.6 A1C reduction, the twice a week a ~0.4% A1C reduction, and the once a week looks to have had no A1C reduction. Obviously this is speculation and we would like to see the results as well as the distribution of results.

    - Surprisingly, the company didn't communicate what percent had an A1C that was "normalized[2]" or less than 7%. After 28 days treatment, these were 80% and 27%, respectively, of first 80 patients (would be interesting to know what percent dropped out of that group). As a reminder, the first 80 patients had an A1C drop of 0.8%.

- **Other endpoints - weight**:

    - Here the NT group also lost weight – we were not sure if the comparison was to baseline and we will look for that answer on the call. The weight loss seems impressive and fairly consistent across groups though we would like information on starting weights to assess weight loss in percentage terms.

    - Notably, after 28 days, the weight loss had been 2.3 kg, so the fact that the weight loss now is 2.2 - 2.7 kg seems positive.

    - It will be important to watch to see if these 12-week results can be sustained; inability to sustain weight loss is a common problem.

    - The question about whether this is caused by nausea is bound to arise and it will be interesting to see this addressed.

[2] Unclear how this was defined.

- **Other endpoints - fasting plasma:** Again, this was compared to NT group, which we assume had artificially high fasting glucose given 0.5 increase in A1C. We will listen carefully to assess whether improvement versus baseline is noted, which may be closer to 15% than 30%. This had been reported 24% improvement at 28 days treatment. A 15-20% decrease in fasting blood glucose, of course, is still positive, particularly when considered that this is monotherapy and other agents may be added to regimen that would address fasting blood glucose (more than, for example, post-prandial glucose levels).

--by Kelly L. Close

2. More on PPARs:

Late on Thursday (July 8), Ligand Pharmaceuticals announced news that will likely have a meaningful impact on diabetes drug marketplace. Ligand announced that FDA concerns regarding cancer had led the agency to require all companies developing PPAR compounds to complete 2-year rodent safety / toxicity studies before progressing with long-term human studies (studies longer than six months in duration). This new FDA guidance covers all PPAR compounds (alpha, gamma, and dual) and will effectively end clinical investigation of these compounds until the relevant safety studies are performed and the FDA is satisfied that the compounds are safe.

As a quick reminder, PPAR (peroxisome proliferator-activated receptor) drugs target intracellular receptors that regulate glucose and lipid homeostasis within the body. In essence, PPAR-gamma agonists help re-sensitize the body to insulin. What's more, dual-PPAR agonist drugs have looked especially promising as they offer the hope of effectively lowering glucose without the troublesome weight gains associated with many medications currently on the market.

While the timing of FDA pronouncements is never predictable, this particular event is not a complete surprise to us. As we noted to our subscribers in our June 6 piece on PPAR compounds, many PPAR drugs showed disturbing and unusual cancers in rodent test subjects, which we felt the FDA would not simply overlook. We believed it was quite likely that the FDA would step in and require companies to investigate possible carcinogenic effects of PPAR agonists in greater depth before allowing them to progress further in the regulatory process.

This FDA decision is clearly bad news for all companies developing PPAR compounds, but it may turn out to be a long-term blessing in disguise. By acting now, the FDA avoids placing itself in the position of recalling approved drugs or refusing to approve drugs that have already been through lengthy and costly trials, only for a cancer problem to come to light in follow-up studies or clinical experience. This is still the Rezulin era, after all. While pipeline delays are always punished by the stock market, it is certainly better for everyone concerned to get to the bottom of this problem immediately. A two-year rodent[3] study is considerably cheaper than a Phase 3 human study and if the rodent studies reveal insurmountable problems or risks, the affected companies and prospective patients will be better off for knowing sooner than later.

It should also be noted that the FDA's guidance on this toxicity study is nothing out of the ordinary. Two-year studies are common when studying possible carcinogens -- due in part to the fact that a mouse's natural lifespan averages out to about two years. While it would certainly be bad news for the mice to die early in the study, it is necessary to look out over two years to ascertain whether there are problems late in the mouse's lifespan (and, by extension, late in the human's lifespan) – especially since a PPAR-type drug would likely be taken daily for the duration of the patient's life after a diagnosis of type 2 diabetes. In studies such as these, it is common practice to administer a normal intended dose (weight-adjusted, of

[3] Why use mice versus, say, primates? The mouse model is the most widely-recognized and accepted pre-clinical model, mainly because of its versatility. Unless research has reached the point of being ready for clinical trials, many investigators steer clear of using primates. They expensive to maintain and can be unpredictable. While roughly speaking, it costs approximately $2/day/cage to house and maintain mice, the price is closer to $12-$15/day for large primates. Additionally, not too many lab personnel know how to properly handle primates, which can jeopardize the animal's well being and ultimately the research.

course) to a population of rodents and observe them over a two-year period while simultaneously giving excessive doses to other populations. These comparative studies help determine a dosing level that practically "guarantees" a cancer outcome (a process similar to the normal LD50 process of assessing the toxicity of compounds).

Companies directly affected by this FDA action include Ligand (and its partner, Lilly), Bristol Myers (and its marketing partner Merck), Aventis, Glaxo, and Johnson & Johnson. At present, only Ligand has publicly commented on this FDA action and revealed that it will delay its compound by 18 – 24 months. While it is likely that most companies will have roughly the same experience, it is also possible that one or more companies had already begun a two-year rodent cancer/safety study. If such is the case, the delay could be less than two years. We will update this as company releases and our own due diligence permit.

In the meantime, we expect this news to give a minor boost to companies far along in the development of non-PPAR compounds. To name several, Amylin (Exenatide –recently submitted NDA to FDA), Novartis (LAF-237 – Phase 3), Novo Nordisk (Liraglutide – about to start Phase 3), and Merck (MK0431 – about to begin Phase 3) all have advanced non-PPAR compounds. Positives we see for these companies:

- With most PPAR drugs on hold for approximately two years, these drugs may garner a little extra time to shine with less competition, assuming their own regulatory paths proceed as expected.
- Perhaps even more helpfully, we believe the delay of PPAR drugs will reduce the noise level in the market.

For those interested in a broad overview of currently-under-development diabetes drugs, a copy of the current diabetes drug pipeline is included in our ADA review report, which will be available in the coming weeks. If you would like more information on contents, please inquire at info@closeconcerns.com.

--By Stephen Simpson and Kelly L. Close

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Many thanks to Stephen Simpson and Melissa Ford for help in researching and writing this newsletter.