Closer Look

MEMORANDUM

Aphios receives US patent for its oral insulin delivery technology

Executive Highlights

- Aphios Corporation has been granted a US patent for its oral insulin delivery technology, which encapsulates the insulin protein within biodegradable polymer nanospheres.

Massachusetts-based biotech Aphios Corporation announced today that is has been granted a US patent for its oral insulin delivery technology. The technology encapsulates the insulin protein within biodegradable polymer nanospheres (PNS), which protect the insulin from degradation within the stomach and transport it to the bloodstream. The oral insulin product has a bioavailability of 35-50% (which could be increased depending on the PNS design and insulin type) and an onset of action of less than 30 minutes. Aphios highlighted that the PNS' residence time within the stomach is "short compared to the insulin release rate from the PNS" (we presume this means that nearly all the insulin is released into the bloodstream rather than into the GI tract). Aphios noted that both the shell and the contained protein regulate the movement of the PNS from the gut to the bloodstream, and predicted that the combined characteristics of the shell and protein will significantly improve bioavailability. While the insulin product currently uses biosynthetic human insulin, management noted that the PNS technology can be applied to any insulin type. Aphios plans to find a partner before advancing the oral insulin technology into clinical development. While we are optimistic about the potential for oral insulin (the patient need is quite significant), we await further studies on Aphios' formulation to provide a greater understanding of the clinical implications, given the early stage of its development. A non-injectable insulin would change the diabetes game completely, so to speak, and at the moment, there is significant uncertainty regarding oral insulin, including dosing, action profiles, the risk of hypoglycemia, etc.

A number other companies are also investigating oral insulin candidates, and a summary of these development efforts is provided below. We are glad to see interest in oral insulin, as we would like to see prospects thoroughly vetted. As it stands, insulin is by far the most challenging (and, especially for prandial insulin, dangerous) drug for people with insulin to take, and the field could benefit from greater innovation in order to improve safety and other parameters that ultimately relate to adherence. We are happy to see scientists and researchers to be working on this front and believe much improvement in insulin awaits patients over the next decade, possibly even related to oral or glycemic- dependent insulin. Although we are not holding our collective breath in the near term, longer-term, we very much hope that as much progress will be made with prandial insulin, as has been made with basal insulin, and we hope that some progress in prandial insulin will be on the oral front, since so many patients could benefit from insulin who are not taking it.

- **A study in BB/Wor male rats (a model of insulin-dependent diabetes) showed that Aphios' nanoencapsulated biosynthetic human insulin (delivered using standard gavage method) significantly decreased glucose levels one-half hour, one hour, and two hours after administration** (further details not provided). A similar result was observed with injectable insulin (Protamine Zinc Insulin [PZI] from Lilly), but not with orally delivered injectable insulin (PZI). As a reminder, preclinical data is difficult to extrapolate to humans, and what has been seen before in diabetic rat models has often failed to be replicated in patients.
- **Aphios' Polymer Nanospheres (PNS) technology dissolves biodegradable biopolymers in SuperFluids (supercritical, critical, or near-critical fluids with or without polar cosolvents) and combines them with the insulin protein at operating pressures.** When

the mixture is decompressed (into an aqueous solution, liquid nitrogen, or an empty vessel), polymer nanospheres form around the insulin protein. The use of SuperFluids eliminates the need for organic solvents, which are traditionally used but have several negative effects. Aphios highlighted that the single-step PNS process is easily scalable and that it can be applied to a range of proteins because it is independent of size and molecular weight.

- **Several other companies have oral insulins in early to mid-stage development (listed below in order of late to early stage development).** These companies include Tamarisk, Biocon, Oramed, Diabetology, Novo Nordisk, and Transgene Biotek.
    - **Las Vegas based Tamarisk Technologies is developing a nanoencapsulated oral insulin (brand name: O'insula), which appears close to regulatory filing outside the US, though we remain skeptical about its current approval chances given a lack of clinical data.** Tamarisk notes that the Serum-Specific Nano-Encapsulate (SSNe) particles that surround the insulin protein are 100% resistant to GI fluids and can easily cross the gut membrane (further preclinical information is available at http://www.tamarisktechnologies.com/Reports/ORAL-INSULIN-REPORT.pdf). Tamarisk is currently conducting one clinical trial (n=1,029) comparing O'insula to standard care (details not given); the trial is being performed outside the US (location not specified) and Tamarisk plans to release the study results in February 2013. Management has highlighted plans to complete phase 3 testing by the end of 2012 and to market O'insula by mid-2013 - both forecasts apply to locations outside the US that were not specified. Given that Tamarisk has not been successful in licensing O'insula to another company, Tamarisk will presumably manage O'insula's commercialization on its own. Should Tamarisk adhere to this timeline, oral insulin could potentially reach the global market much sooner than expected, though we question whether global regulatory agencies will be convinced of O'insula's safety and efficacy given the lack of clinical data.
        - **Earlier this year, Tamarisk submitted a request to the FDA to skip phase 1 and phase 2 trials (!),** with the rationale that the SSNe technology has already received a GRAS ("generally recognized as safe") determination from the FDA and is already used in the food industry - GRAS substances do not require premarket FDA approval, but the status is limited to the substance's intended conditions of use; thus the GRAS determination likely does not extend to the use of SSNe for insulin delivery, and we presume that the FDA would apply the same safety and efficacy standards to O'insula as it would to any diabetes product (or perhaps a higher standard given the lack of precedence for oral insulins). It is unclear whether and how the FDA has responded to Tamarisk's request. However, management has noted that Tamarisk plans to file O'insula with the FDA in January 2013. As noted, we remain skeptical about its approval chances at present, given that no clinical trials have been performed within the US and that the clinical development program appears quite small (~1,000 participants).
    - **Biocon's prandial oral insulin IN-105 is currently in phase 2/3 and will be further studied in upcoming global phase 2 trials.** Tamarisk Technologies' CEO Dr. Daniel DeBrouse previously expressed doubt that Biocon's non-encapsulated oralinsulin could effectively cross the intestinal tract membrane. However, Biocon management recently explained that IN-105 has a modified insulin backbone that prevents degradation in the intestinal tract and a molecular structure that promotes easy transportation across the gut membrane. IN-105 has prompted commercial interest, as Biocon recently announced an option agreement with BMS for the candidate; however, at present no development deal has been made (for details, please see our Biocon F2Q13 report at http://www.closeconcerns.com/knowledgebase/r/3cc1ad21). Biocon will present at the upcoming JP Morgan Healthcare Conference (on Monday, January 7 at 10:30 am in

Elizabethan A/B 120) and will hopefully provide further details on IN-105's development at that time (Our JP Morgan 2012 conference preview is available at http://www.closeconcerns.com/knowledgebase/r/8664ff48).

- **Biocon will be conducting global phase 2 trials for IN-105 -** these will likely help BMS make its decision on whether to exercise the option and will better inform the design of potential studies that BMS could perform. As stated during its F2Q13 earnings update, Biocon expects to conduct multiple studies in a staged manner over the next two years to help further characterize IN-105's clinical profile. ClinicalTrials.gov currently lists one phase 1 trial of IN-105 of "unknown status" that was last updated August 2010. The trial was designed to compare IN-105 to Lilly's insulin lispro and was scheduled to enroll 28 type 1 patients and complete in February 2011.
- **The last publically reported data on IN-105 was from a "proof of concept" phase 3 study that was presented at JP Morgan 2011**. The study randomized 264 patients poorly controlled on metformin to either IN-105 or placebo. IN-105 did not meet the primary efficacy endpoint of achieving a placebo-adjusted A1c reduction of 0.7%, though it did meet multiple secondary efficacy endpoints, including statistically significant reductions in postprandial glucose and a "significant drug effect in many subsets." IN-105 was associated with no "clinically relevant" hypoglycemia (not defined), no serious adverse events, no immunogenicity, and no weight gain (for details, please see our JPM 2011 report at http://www.closeconcerns.com/knowledgebase/r/b8ac0d19).

- **Oramed Pharmaceuticals' insulin capsule ORMD 0801 remains in phase 2.** On December 11, 2012, Oramed announced that it had raised $5.6 million to fund phase 2 trials of its oral insulin capsule in the US. Oramed stated that in the "upcoming weeks," it plans to file an IND with the FDA for a phase 2 trial that will enroll 147 type 2 patients in several centers in the US (further details on the study design were not disclosed). This company has been working on oral insulin for some time and has not had results that have prompted significant confidence historically.
  - **The most recent public data for ORMD 0801 was published as a poster at the 2012 Diabetes Technology Society Meeting.** In a phase 2a, single- blind, open-label trial of eight patients with uncontrolled type 1 diabetes (baseline A1c 7.5%-11%), ORMD 0801 was added on top of patients' usual insulin regimens three times daily (45 minutes before each meal) for 10 days. Blood glucose was monitored by blinded CGM for five days before and during the treatment period. During the oral insulin treatment period, patients experienced a 16.6% reduction in glucose area under the curve; more frequent readings <70 mg/dl (1.99% vs. 0.45% in the treatment vs. pre-treatment phases); and a 24.4%reduction in glucose readings >200 mg/dl compared to the pre-treatment period. No adverse events were reported. These results suggest that the orally administered insulin was successfully and safely delivered to the blood stream.
  - **Oramed also reported from a phase 2b study in 2010.** The six-week study randomized 29 type 2 patients to ORMD 0801 (n=21) or placebo (n=8) and primarily assessed safety. Investigators observed no serious adverse events and only two cases of mild hypoglycemia during the study. ORMD 0801 treatment led to statistically significant decreases in insulin and C-reactive protein levels, while both markers were increased with placebo.
- **Diabetology is developing two oral insulins (Capsulin OAD and Capsulin IR)** in phase 2 for people with type 2 diabetes and for people with type 1 diabetes or late-stage type 2 diabetes, respectively. The company is also investigating an oral therapy, Combulin,

which combines insulin with an insulin sensitizer (the two agents were not specified). Combulin is currently in preclinical development for the treatment of type 2 diabetes.

- **The most recent data on Capsulin OAD were phase 2 results published in the January 2010 issue of *Diabetes, Obesity, and Metabolism*.** The study compared the PK/PD profiles of Capsulin OAD and regular human insulin (Novo Nordisk's Actrapid) in 16 type 2 patients previously on oral antidiabetic medications. During two six-hour isoglycemic glucose clamp studies, the participants received either Actrapid (12 U) or Capsulin OAD (150 or 300 U); both Actrapid and Capsulin OAD increased the glucose infusion rate, though values for Actrapid were higher than those for Capsulin OAD, suggesting that Capsulin OAD was not as effective at clearing glucose from the blood stream. At the post-study visit, investigators observed significant reductions in A1c, body weight, and triglyceride levels with Capsulin OAD. The article is available at http://onlinelibrary.wiley.com/doi/10.1111/j.1463-1326.2009.01146.x/abstract.
- **Diabetology has released phase 2a data for Capsulin IR from a UK study that completed in July 2005.** Eight type 1 patients were given a single dose of Capsulin IR 150 IU, followed by a single dose of Capsulin IR 300 IU five to 28 days later. Measurements for blood glucose and plasma insulin concentrations were taken every 15 minutes for up to eight hours after each dosing. Data from the six participants who completed the study showed that Capsulin IR treatment led increases in insulin levels and decreases in blood glucose levels that were dose dependent, with the Capsulin IR 300 IU dose providing a mean 29 mg/dl decrease in glucose (baseline not given).
- **In July 2012, Diabetology entered into a partnership with India-based USV Limited to develop and commercialize Capsulin for the Indian market.** Under the agreement, USV will oversee Capsulin's development program and commercialization, and Diabetology will receive milestone payments and royalties on product sales based on development, regulatory, and commercial achievements. It appears that this partnership covers both Capsulin IR and Capsulin OAD. Estimates for development timelines were not provided.

- **Of note, Novo Nordisk is developing two oral basal insulin analogs in phase 1: OI1362GT (NN1954) and OI338GT (NN1953).** No ongoing studies are currentlylisted on ClinicalTrials.gov. Novo Nordisk's interest in the area lends an air of credence to the field, although we also believe their culture is to leave virtually no stone unturned, so their interest in an area is just the first step. Also, the real arena where oral insulin is probably more needed is prandial, because basal insulins are already quite easy to take and will become only more so with Novo Nordisk's degludec.
  - **Both NN1954 and NN1953 use Merrion Pharmaceuticals' GIPET delivery technology.** As background, in November 2008 Novo Nordisk signed a development and licensing agreement with Merrion for the development and commercialization of oral insulin, in particular the prandial oral insulin NN1952 (which has been discontinued). The agreement could be worth up to $58 million (in addition to royalties on sales) if development, regulatory, and sales milestones are achieved. In December 2009, Merrion received a $2 million milestone payment for the initiation of a phase 1 study for NN1952, which had an estimated complete date of May 2010 (for details, see our *Closer Look* at http://www.closeconcerns.com/knowledgebase/r/e518d2b5). Since then, development of NN1952 has been discontinued because of unacceptable interactions with food.

- **In December 2010, Novo Nordisk announced that it had entered into a development and licensing agreement with Emisphere Technologies** to develop and commercialize oral formulations of Novo Nordisk insulins using Emisphere's Eligen technology. Under the agreement, Emisphere was eligible to receive up to $57.5 million in milestone payments, pending development, regulatory, and sales success. While oral insulin is listed in Emisphere's pipeline as a product in "active development," the Eligen technology is currently not licensed for use with insulin. However, Novo Nordisk signed a separate agreement with Emisphere in June 2008 to develop oral GLP-1 agonists, and two of Novo Nordisk's current oral GLP-1 candidates use the Eligen technology (NN9924 and NN9927; both phase 1 - a third phase 1 candidate [NN9926] uses GIPET technology). Emisphere's website also lists an oral insulin under "past development programs," suggesting that the company had previously pursued another oral insulin with little success.
- **As a reminder, in 2001 Novo Nordisk established a partnership with Aradigm to explore the potential for inhaled insulin.** However, the program was terminated after the commercial failure of Pfizer's Exubera. Novo Nordisk still invested far less money than other big pharmaceutical companies in inhaled insulin - the company's interest could be characterized, perhaps, as primarily a hedge though it is difficult to speculate on this front, of course.

- **Transgene Biotek Limited lists an oral insulin candidate (TBL-1001OI) in preclinical development.** So far, we have heard little information on this candidate.

- **Several companies have not provided a recent update on their oral insulin candidates,** and it is unclear whether development has been discontinued. These include Diasome Pharmaceuticals (HDV-insulin) and Access Pharmaceuticals (cobalamin [vitamin-B12]- bound insulin).

-- by Nina Ran, Jessica Dong, and Kelly Close