FOURSQUARE PARTNERS

Company: MannKind Corporation (MNKD)
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I reviewed fifteen year-old MannKind Corporation (MNKD) as a possible short investment since 1) it is conducting two Phase 3 trials for a dry powder, pulmonary insulin formulation called TechnoSphere/Insulin ("TI") based on very limited Phase 2 data and 2) the Company had a market capitalization of ≈ $870 million in mid-January (stock at $17.32, 50.2 million shares, $180 million cash at September end). On February 2, the stock closed at $18.00. MannKind will be reporting FYE results on February 6.

Founded by deep-pocketed Alfred (Al) Mann (M.S. in physics), the Company has been in stealth mode for most of its history having only come public in July 2004 at $365 million, pre-money (≈ $90 million raised). Post money, Mr. Mann owned 50.2 percent of MannKind. Al Mann founded Pacesetter, a mostly self-funded pacemaker company which was acquired by Siemens in 1985 for $150 million. In 1983, he founded and 70 percent financed Minimed, which became the top insulin pump company, worldwide. Medtronic acquired Minimed in May 2001 for $3.7 billion in cash.

In October 1998, I spent about three hours, one-on-one with Al at Minimed. He was broadly knowledgeable, well-studied in the relevant science, meticulous and scrupulous. Understated, he is nevertheless, quite impressive. [Text redacted by author]. Soon after my visit, Medtronic completed a $60 million equity investment in Minimed.

Conclusion: MannKind's short public tenure, preceded by over 13 years as a private firm has resulted in a less than transparent posture to new investors. Specifically, both Phase 3 trials in progress are essentially safety studies unsuitable for FDA registration. The Company provided no information in the press release about each trial's design. Three pivotal trials are planned to begin, within the next two quarters, which will evaluate the safety and efficacy of TI. Press releases describing MannKind's clinical development plans have been murky at best. Much of the relevant data has been disclosed on conference calls or at oral presentations, none of which are archived at the Company's website. Sell-side analyst reports (seven banks cover) may be the best source of data. Due to the relative opacity of MannKind's disclosure history, there is insufficient data to support either a buy or a sell recommendation at this time.

Finally, an extensive history is available for a product similar to TI, Pfizer/Nektar's Exubera (inhaled insulin). The first Phase 2 trial began in October 1996. In March 2005 an NDA was submitted and on January 27, 2006 the FDA cleared Exubera. Efficacy has never been an issue (although only ≈ 10 percent of the inhaled insulin enters the bloodstream). Demonstrating pulmonary safety after chronic dry powder delivery has proved to be the biggest hurdle at FDA. MannKind faces the same hurdle, plus two potential Big Pharma competitors (Lilly, Novo Nordisk) who are also in the race to be second to market.

TechnoSphere

Headquartered in Valencia, California (north of Los Angeles), MannKind also maintains a Clinical/Regulatory group in northern New Jersey (Paramus) and TI manufacturing/R&D in Danbury, Connecticut. Unlike Exubera, which is a simple powdered insulin/citrate buffer formulation, TI is insulin formulated with a non-metabolized carrier called TechnoSphere (a simple, inexpensive diketopiperazine derivative). The TechnoSphere composition-of-matter patent was issued in October 1994, so it will expire in 2011. Both formulations use recombinant human insulin. A 2002 clinical study (N=12) showed a slower onset of action (≈ 25 minutes, similar to sub-Q insulin) than that reported for Exubera (≈ 10 minutes). However, the two formulations were not directly compared. Also, both formulations depend on generating small particles (1-5 microns) of powdered insulin, which enables the drug to reach the deep lung where it is absorbed. Larger particles are trapped in the mouth and throat while particles much smaller than these are expired rather than absorbed.

Clinical Status

The first person received an insulin injection in January 1922. Three years later, pulmonary delivery was proposed. Progress has been slow ever since.

MannKind's clinical studies have been small and relatively brief. Overall, TI delivers insulin effectively and in dose-dependent manner. Only two Phase 2 studies have been reported. In one, roughly 60 Type 2 patients were treated with TI (titrated to ≈ 30IU/dose) and then, for only twelve weeks. Another 60 patients received placebo treatment. In the second trial, 180 patients were treated for only eight weeks but at four different insulin dosages (about 45 patients/dosage arm). Detailed results from the first study were presented in abstract form at ADA last June, but have not been formally published. I expect similarly detailed results from the second study (only top line data were reported on January 17) to be presented at ADA this June.

The data for both trials are summarized below in the "raw DB" format:

Data From First Phase 2 of TI

12/22/04: PR; Ph 2b data; DB-PC in 123 Type 2 Pt.s at 21 US sites titrated from 6- to 48 IU before each meal; Of 107 completing 12wCOT (*13% D/O*), 90 evaluable; Baseline A1c=7.74 (6.6-10.5), so 2 groups (N=35 ≥ 8.0% (mean 8.72%, *A1c ↓1.37%*; p=0.0007) or N=55 <8.0%, (mean 7.18%, *A1c ↓0.43%*; p=0.0447); No SAE, no severe hypoglycemia; no pulmonary function change (FEV_1, FVC, DLco), no antibodies;

6/14/05:ADA (#357-OR); Ph 2b data; DB-PC in 119 Type 2 Pt.s; Mean dose in last 4 weeks was 30IU, before each meal as Diet/exercise ± TI; PCE is A1c ↓ from baseline; Also, mild hypoglycemia (Pt. reported) not SS different from placebo;
For ITT, placebo (N=42; *-0.32*, p=0.0028), Drug (N=48; *-0.76*, p=0.0001 and p=0.0019 vs placebo);
For A1c ≥ 8.0%, placebo (N=18; 8.52→8.01, *-0.51*, p=0.0094), Drug (N=17; 8.72→7.35, *-1.37*, p=0.0001 and p=0.0007 vs placebo);
For A1c < 8.0%, placebo (N=24; 7.16→6.98, *-0.18*, p=0.1292), Drug (N=31; 7.19→6.76, *-0.43*, p=0.0001 and p=0.05 vs placebo);
For ITT (LOCF), placebo (N=61; 7.78→7.47, *-0.31*, p=0.0020), Drug (N=58; 7.87→7.15, *-0.72*, p=0.0001 and p=0.0016 vs placebo);

Data From Second Phase 2 of TI

1/17/06: Ph 2b data as DB-PC, 4 dosages; 4wCOT on SOC, oral ± Lantus, then Lantus only and randomized; Post prandial glucose and A1c controlled;
Lantus, q.d. ± *TI* (14-, 28-, 42-, 56 units) at meals (t.i.d.) for *8wCOT*; N=227, ≈ 45/arm; No weight gain, no ↓ pulmonary function (FEV_1, DLco) or hypoglycemic events; Short treatment at 8wCOT, baseline A1c not given; At 56 units, A1c 0.79 below placebo (p=0.0002) and post-prandial glucose excursion of 34mg/dL (63% reduction from 92), p=<0.0001;

There is little question as to whether TI delivers insulin effectively. However, the safety data with respect to pulmonary function are inconclusive. These data are limited by a relatively small number of patients treated for a relatively short period. For comparison, Exubera's pulmonary function (FEV_1 and DL_{co}) safety database includes 2,498 adults with 1,698 treated for more than one year, 821 for more than two years and 153 treated for more than three years. A summary from Exubera's Package Insert follows:

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> "During the two-year clinical trials, individual patients experienced notable declines in pulmonary function in both treatment groups. A decline from baseline FEV_1 of $\geq$ 20% at last observation occurred in 1.5% of Exubera-treated and 1.3% of comparator-treated [*sub-Q insulin*] patients. A decline from baseline DL_{co} of $\geq$ 20% at last observation occurred in 5.1% of Exubera-treated and 3.6% of comparator-treated patients."

Exubera's Package Insert notes that decreased lung function was observed within several weeks of initiating treatment, but did not change over a two-year treatment period. Thus, the absence of an adverse effect of TI on pulmonary function after eight weeks might augur for a safe profile longer term. But, the data do not yet exist. To this end, the Company has initiated two Phase 3 trials primarily for safety and plans to add three more Phase 3 trials suitable for FDA registration.

Phase 3 Clinical Trials

MannKind has not posted any clinical trial information for TI at the NIH website, www.clinicaltrials.com. When asked, the CFO, Dick Anderson, said the Company saw no reason to do so. A search of 11 international clinical trial databases also revealed no trial information.

MannKind initiated its first Phase 3 trial in December 2004. Virtually no information about the trial design was included in the press release. Known as the "014" trial, treatment is planned for 280 Type 2 patients in Europe for six months. Patients are monitored for HbA1c and pulmonary function, but MannKind has not provided other relevant details such as primary and secondary endpoints or inclusionary/exclusionary patient enrollment criteria.

In late June, a second Phase 3 trial ("030") began in the US. It is an open-label, randomized trial of 1,900 Type 1 and Type 2 patients planned to treat patients for up to two years. Specifically, only 400 patients are planned to be treated for that duration. This trial is primarily designed to assess pulmonary function and would not be suitable for FDA registration on its own. The trial is operating under a Special Protocol Assessment (SPA) which includes a pre-specified statistical analysis package. Data from this trial are expected in mid-2008.

Finally, three pivotal Phase 3 clinical trials for TI are expected to begin this half. They are as summarized below:

Q1/06E: Ph 3 begins ("102"; *pivotal*) in 650 Type 2 Pt.s as premixed insulin vs *TI* for 1yCOT;
Q2/06E: Ph 3 begins ("009"; *pivotal*) in 650 Type 1 Pt.s as basal insulin (i.e., Lantus) vs *TI* for 1yCOT;
Q2/06E: Ph 3 begins ("103"; *pivotal*) in 550 Type 2 Pt.s as oral drugs vs *TI* for 1yCOT;

Competition/Insulin Supply

Overall, Pfizer/Nektar's Exubera has set the bar for FDA approval of pulmonary insulin. The efficacy portion of any NDA submission only needs to show non-inferiority to injected (subcutaneous) insulin. The primary clinical endpoint in Type 1 or Type 2 patients will rely on HbA1c measurements. Large, multi-year studies will be required to demonstrate relative safety via two lung function assays, FEV_1 (forced expiratory volume, in liters, in 1 second) and DL_{co} (diffusion capacity for carbon monoxide) both of which decrease with worsening lung function.

At least two other competitors are racing MannKind to become the second FDA approved inhaled insulin. Fifteen year old Aradigm (ARDM) was partnered with Novo Nordisk (June 1998; #1 insulin source WW), but sold the entire project to Novo in September 2004. Having recently improved the delivery device, Novo plans to re-initiate Phase 2 trials of its AERx insulin system this quarter. Thus, Novo is over three years from FDA approval. More advanced and closer to MannKind in clinical development is Lilly/Alkermes's AIR/Insulin, which began two Phase 3 trials, primarily for safety, this past summer. Thus, Lilly/ALKS and MannKind are at about the same stage of clinical development. MannKind anticipates the FDA to clear its NDA in 2008.

One less recognized problem for all pulmonary insulin providers is insulin supply, which has been constrained, WW, for several years. There are three manufacturers of the world's insulin, Novo Nordisk, Lilly and Sanofi-Aventis (via its Hoechst unit). Specifically, Pfizer/Nektar's insulin is made in a German facility that started as a JV between Pfizer and Hoechst. Similarly, Medtronic's pumps (via its Minimed acquisition) use insulin manufactured by Aventis/Hoechst as well. Novo Nordisk, given its stumbles with Aradigm, may simply decide to abandon the AERx project (a walk-away fee to Aradigm is likely) in order to partner with MannKind, which, of course, still needs an insulin supplier.

In summary, pulmonary insulin does not solve a medical problem but may address a subset of the Type 2 patient population that should be on insulin, but isn't. Given the relatively poor efficacy of pulmonary insulin delivery and WW supply constraints, cost-of-goods is a major element affecting adoption. Pfizer has indicated that it expects Exubera to sell at ≈ 3 times the per-day cost of sub-cutaneous insulin. Reimbursement may also figure into the puzzle. Ironically (fortuitously?), any potential investment in MannKind can probably wait until actual market data are in for Exubera.

Risk Assessment

- *Downside risks:*

  If Exubera does not do well, MannKind is likely to suffer in parallel. Pulmonary insulin is a completely new market. As good an idea as it sounds to the lay investor, high costs and non-superiority to subcutaneous insulin may hinder adoption. In the end, the pulmonary delivery of insulin may be a solution in search of a problem.

  Low delivery efficacy of 10-30%, at best, raises the per diem cost of goods and may create a supply problem for the API (rhu-insulin).

  Broad adoption over the next two years may reveal more significant pulmonary function decline than was observed during clinical trials. Press coverage of even a few cases of pulmonary fibrosis, for example, would have a severely negative impact, especially with increased attention on adverse events in general due to Merck's Vioxx debacle.

  Mannkind is a medical device company with its first product not expected to be on the US market until 2008. Few companies of this ilk could sustainably support a $900 million market capitalization in an environment where the market is untested, the clinical risks are still a work-in-progress and the regulatory scrutiny over safety has never been tougher.

- *Upside opportunity:*

  MannKind needs to sign a supply agreement with one of the three insulin manufacturers. Doing so is likely to advance the stock, near term. Novo Nordisk is the most likely partner. An out-and-out acquisition of MannKind is also possible. Medtronic should not be counted out.

  Al Mann is perceived as having the golden touch (Pacesetter, Minimed) although few are aware of his other endeavors including Advanced Bionics (cochlear implant), CTL Immunotherapies (acquired by MannKind), Second Sight Medical (artificial retina) and MRG (Medical Research Group, acquired by Medtronic in the Minimed deal) with sensors and pumps. Al is focused and patient, but he hasn't been cloned and, at 80, he won't live forever (sadly).

  Analysts are optimistic on Exubera's potential. Good news for Exubera is good news for MannKind. Unfortunately, the inverse will also be true.