



MEMORANDUM

**CC - Merck to acquire SmartCells, develop glucose-dependent insulin -
December 15, 2010**

Executive Highlights

- Merck and SmartCells today announced a definitive agreement for Merck to purchase SmartCells, a private company developing a glucose-dependent insulin formulation that is in preclinical trials.
- The deal includes upfront and milestone payments potentially worth over \$500 million.

Earlier this month, Merck and SmartCells announced a definitive agreement for Merck to acquire SmartCells, a Beverly, MA-based private company that is developing SmartInsulin, a glucose-dependent insulin therapy currently in preclinical trials. Merck will acquire all outstanding stock of SmartCells in exchange for upfront cash transfers and clinical and regulatory milestone payments, with the sum to potentially exceed \$500 million. Previously, SmartCells has relied on funding from NIH, JDRF, and four series of financing from various angel investors. By our estimates, these investments total less than \$20 million, suggesting that co-founder, president and CEO Todd Zion is very undiluted indeed. Merck's entry into insulin space differs from that of Pfizer, which recently partnered with Biocon to develop biosimilar versions of human and analog insulins. (See October 22, 2010 Closer Look). It will be interesting to see how and if other major companies come into the space; clearly both the 'more affordable' and the 'more innovative' strategies are seen as valuable. The Merck-SmartCells deal gives us confidence that glucose-dependent formulations are feasible long-term, though it remains to be seen whether these two companies will be the first (or the most successful) to launch a smart insulin - as we understand it, Bidel, Novo Nordisk, and others are all working on this front (presumably also the other major insulin manufacturers). Note that we had a slew of questions for management, but when reached, SmartCells CEO Todd Zion asked us to direct our questions to Merck since "they now own the company, the product candidates and the platform technology." We had not realized the deal had closed already! We were not successful in reaching Merck management to discuss but will update if we receive any additional information.

- **SmartCells is developing SmartInsulin, a once-daily glucose-dependent insulin therapy.** The technology was developed during co-founder Todd Zion's doctoral research at MIT, patented in 2003, and licensed to SmartCells from MIT in 2004. In the SmartInsulin formulation, insulin is bound to a biodegradable polymer that includes sugar groups. The insulin-polymer conjugate is coinjected with a multivalent glucose-binding molecule that can attach to the polymer's sugar groups, leading to an aggregate that prevents insulin from entering solution when blood glucose is low. During hyperglycemia, however, glucose binds to the glucose-binding molecule, displacing the insulin-polymer conjugate so that active insulin enters the bloodstream. During in vitro and in vivo studies, SmartInsulin has demonstrated a fast response to glucose challenges and negligible insulin leakage at normal blood glucose levels. Although human studies have not yet begun, SmartInsulin would be administered as a once-daily injection.
- **Other companies are also investigating smart insulins; most recently, Bidel displayed preclinical data on a self-regulating formulation of glargine (BIOD620) at the Diabetes Technology Meeting in November.** As a reminder, glargine (sanofi-aventis' Lantus) is soluble at low pH but not at physiologic pH, causing it to aggregate in the bloodstream for a slow release profile. Bidel's formulation includes ingredients that lower the pH of glargine in response to high glucose concentrations, thereby increasing glargine's solubility. In a swine model of

diabetes, BIOD620's pharmacodynamics were faster than Lantus' during hyperglycemia but equivalent during normoglycemia.

- **SmartCells has an exclusive license from MIT for its self-regulating release technology, which has potential applications in other endocrine disorders, cancer therapy, and drug-device combinations (e.g., drug-eluting stents).** We speculate that these non-insulin applications may have been one reason that Merck chose to purchase SmartCells rather than simply entering a licensing agreement (as in sanofi-aventis' partnership with CureDM to develop Pancreate; see April 13, 2010 Closer Look).

Close Concerns Questions

Q: When are human trials likely to begin?

Q: What is SmartInsulin's release profile during normoglycemia? Q: Would total daily insulin dose be reduced?

Q: Could SmartInsulin replace bolus insulin as well as basal insulin? How fast is the response time of the glucose-dependent release?

Q: Would solubility decrease between normoglycemia and hypoglycemia? Are rates of hypoglycemia significantly reduced in animal models?

Q: Why did Merck acquire the company and not enter a licensing agreement (e.g., sanofi-aventis and CureDM)?

Q: What role will the current leadership of SmartCells play in the company going forward?

Q: What premium if any would SmartInsulin likely carry, or would Merck price it the same in an effort to compete with the rapid acting analogs?

Q: How much of the deal consisted of upfront payments alone?

--by Joseph Shivers, Ben Kozak, and Kelly Close