CLOSER LOOK

MEMORANDUM

Renova Therapeutics to begin in-human trials of RT-200 gene transfer therapy for type 2 diabetes - October 17, 2016

Executive Highlights

- We learned from company representatives that Renova Therapeutics plans to commence in-human trials of a new urocortin 2 gene transfer therapy for type 2 diabetes. The candidate, RT-200, will enter a clinical study in 2017, with an IND submission expected in 2018 if results show efficacy.

This advancement of RT-200 comes on the heels of a publication from the laboratory of Renova Therapeutics co-founder Dr. Kirk Hammond, which demonstrated that urocortin 2 gene transfer normalizes blood glucose in insulin resistant mice. Renova recently highlighted positive preclinical findings for its novel urocortin 2 gene transfer therapy (RT-200). Spearheaded by Dr. Kirk Hammond, one of Renova's cofounders, the preclinical study involved one-time injection of a viral vector encoding the urocortin 2 gene into insulin-resistant rodents. The treatment increased insulin sensitivity, improved glucose homeostasis, reduced weight, and reduced fatty infiltration of the liver in two mouse models of insulin resistance. This insulin-sensitizing effect emerged within weeks of the gene transfer procedure and persisted throughout the study's three-month duration, which positions RT-200 as a promising potential therapy for type 2 diabetes, obesity, and nonalcoholic steatohepatitis (NASH). We learned from the company the first in-human trials of the urocortin 2 gene transfer procedure in individuals with type 2 diabetes are slated to begin in mid-2017. Dr. Richard McCloskey, Renova's VP of Clinical Development, shared in an interview with us that these in-human clinical studies should be wrapped-up by the end of 2017. If all goes well, Renova hopes to submit an Investigational New Drug (IND) application for RT-200 to the FDA in 2018.

- **RT-200 works by activating a subset of the genes that regulate blood glucose whose expression is dampened in some individuals with type 2 diabetes.** Introduction of the urocortin gene via viral vector initiates a cascade of transcriptional changes in the liver and muscle, ultimately improving glucose control. The mechanism is not completely understood yet - then again, having even partial knowledge of RT-200's molecular action makes it better-understood than many other drugs already on the market, as the esteemed Dr. Jaakko Tuomilehto (Dasman Diabetes Institute, Kuwait, and University of Helsinki, Finland) pointed out to us in a separate conversation.
- **It's too early to determine whether RT-200 will be powerful enough to restore insulin sensitivity in humans with a single injection, the way it did in mice.** Although we love the idea of a long-term treatment that requires only a single injection, multiple shots of RT-200 seem like a small price to pay if the therapy confers sufficient insulin sensitivity to help patients avoid countless insulin injections. As Dr. Tuomilehto explained, he envisions RT-200 working like a vaccine, with a few initial injections required over the course of a few days, followed by periodic boosters to maintain its effectiveness.
- **Drawing upon his vast expertise in diabetes and vascular disease prevention, Dr. Tuomilehto spoke to the greater implications of a gene transfer therapy for diabetes.** He pointed out that RT-200 - if it succeeds on the long road of clinical trials ahead and is brought to market - falls right on the line between treatment and cure. For older individuals with a long type 2 diabetes duration who present with profound insulin resistance, RT-200 will likely function as an insulin-sensitizing treatment. However, Dr. Tuomilehto elaborated that in younger individuals with less marked insulin resistance, the gene expression changes stimulated by RT-200 may be

sufficiently powerful to restore normal insulin sensitivity. In his view, RT-200 would ideally work as a preventative measure for people at risk of diabetes, compensating for abnormal patterns of gene expression before the actual onset of type 2 diabetes. We recognize we're quite a ways from a single-injection prevention tactic to give to all the millions of people with prediabetes worldwide, but we're extremely intrigued by this possibility and will follow RT-200 closely in its ensuing clinical trials.

- **Dr. McCloskey outlined four challenges to optimizing gene transfer therapy for clinical success:** (i) capturing the correct gene; (ii) identifying the correct target cell; (iii) finding the correct vector; and (iv) achieving a high transfection rate. In translating RT-200 from animal models to clinical use, Dr. McCloskey underscored that confronting each of these four challenges will be key.

-- by Abigail Dove, Payal Marathe, Sarah Odeh, and Kelly Close