CLOSER LOOK

MEMORANDUM

Novo Nordisk acquires Ziylo to accelerate glucose-responsive insulin development - August 24, 2018

Executive Highlights

- **Novo Nordisk recently acquired Ziylo in a renewed effort to develop glucose-responsive insulin for the treatment of diabetes.** Ziylo is a spin-off from the University of Bristol that develops synthetic glucose-binding molecules for therapeutic and diagnostic applications. The total payments in the deal could reportedly exceed $800 million for Ziylo, upon the achievement of development, regulatory, and sales milestones. Ziylo also received an upfront payment from Novo Nordisk, although the monetary amount was not disclosed.
- **Prior to acquisition, all ~20 employees of Ziylo were transferred to a new company called Carbometrics, to which Novo Nordisk has licensed the rights to develop non-therapeutic applications of the glucose-binding molecules.** Carbometrics will reportedly focus on the potential of the platform in CGM as well as collaborate with Novo Nordisk to optimize Ziylo's glucose-binding molecules.
- **We spoke to Dr. Marcus Schindler, Novo Nordisk's SVP of Global Drug Discovery, who shared that he hopes clinical trials begin within two to four years, with commercialization at least a decade away.** The Global Drug Discovery team at Novo Nordisk is now ~900 employees, with US research sites in Seattle and Indianapolis. Our report below includes our full interview with Dr. Schindler.
- **The GRI field seems to be gaining momentum, though we're cautiously optimistic at best, given the steep technical challenges in this arena.** Between JDRF/Gubra's recent partnership, Merck's advancement of a new candidate into phase 1 (based on what we heard at IDF), and Novo Nordisk's accelerated research in the field, we hope we are witnessing the tipping point in what many consider to be the next great development in insulin therapy.

Novo Nordisk recently announced the acquisition of Ziylo, a University of Bristol spin-off devoted to developing synthetic glucose-binding molecules for therapeutic and diagnostic applications. Novo Nordisk plans to pair Ziylo's molecules with its insulin platform to develop a glucose-responsive insulin (GRI).

Ziylo received an undisclosed upfront payment from the Novo Nordisk, and could potentially receive upwards of $800 million provided later development, regulatory, and sales milestones are met. In our initial assessment, this deal is a win for both sides, and we're excited by the momentum this could bring to glucose-responsive insulin R&D.

Prior to acquisition, all Ziylo employees (<20!) were transferred to a new company, Carbometrics, which now has the rights to develop non-therapeutic applications of Ziylo's glucose-binding molecules, with a focus on CGM. Going forward, Novo Nordisk will focus on unveiling the therapeutic potential of Ziylo's glucose-binding platform (GRI), while Carbometrics will focus on discovering its technological potential (CGM). According to Dr. Marcus Schindler, Novo Nordisk's SVP of Global Drug Discovery, this divide is reflected in the acquisition's structure and milestone payments, which are primarily centered on GRI development and commercialization.

Notably, Ziylo's website has already been taken down, replaced with redirects to Carbometrics and Novo Nordisk.

Ziylo is based on the work of Prof. Anthony Davis (University of Bristol), who has been developing synthetic glucose-binding molecules for more than 20 years; he was originally inspired by lectins, nature's carbohydrate-binding molecules.

Glucose-responsive insulin development is not without its technical challenges - after all, it's a tall order to create an insulin therapy that can turn "on" or "off" safely and reliably based on blood glucose-sensing. A quick glance at our insulin competitive landscape will show a number of discontinued GRI candidates.

Novo Nordisk's interest in Ziylo and in GRI allows for some (cautious) optimism; cautious because there's certainly still a long clinical road ahead before glucose-responsive insulin becomes a reality for patients, something they can pick up at the pharmacy. This acquisition also comes on the heels of a recent uptick in activity in the GRI field, which historically, has moved very slowly.

In June, JDRF and Gubra announced a one-year partnership to develop a GRI. At IDF 2017, Dr. J. Hans DeVries shared that Merck has advanced a candidate into phase 1, despite the earlier discontinuation of MK-2640 (another GRI). Presumably, Merck's new GRI is this unnamed candidate which showed preclinical efficacy in a poster at ADA 2017. To our knowledge, these two GRIs developed by Merck are the only two to ever reach the clinical stage, which further reflects the hurdles in this field.

To be sure, a viable glucose-responsive insulin would be a game-changer for diabetes care and a *tremendous* win for patients. Many view GRI as the next great development in insulin, some going so far as to say that a glucose-responsive insulin would be a functional and non-invasive "cure" for diabetes. A safe and effective GRI could reduce injection burden and daily diabetes burden for patients (i.e. less "work" required to dose insulin); it might also lower hypoglycemia risk and postprandial glucose excursions.

While we remain curious about the specifics of this acquisition deal, we do overall see it as a win for both companies:

What Novo Nordisk Gets...	What Ziylo Gets...
▪ Ziylo's entire glucose-binding patent suite ▪ Clear path to GRI development without an entirely new insulin - an opportunity to leverage their own developed insulins into GRIs by augmenting with Ziylo's molecules	▪ An unspecified upfront payment and milestone payments which together could exceed $800 million ▪ Rights to develop glucose-binding molecules for diagnostic and CGM applications ▪ Collaboration with an established player in the insulin market and a leading player in the diabetes industry

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Research Timeline and Competitive Landscape

- **In our conversation with Novo Nordisk SVP Dr. Schindler (see the full interview below), he shared an aim to begin clinical trials within two to four years, with commercialization at least a decade away.** While GRIs don't have a great track record of reaching the clinical stage, Novo Nordisk has reportedly been following Dr. Davis' work for some time now, and we imagine that the project's potential has been carefully evaluated. Novo Nordisk's preclinical candidate joins 11 others (10 of which are also preclinical) in our competitive landscape. As we see it, the GRI field is too young to speculate how Novo Nordisk's accelerated research will affect competitors**.**
- **The Ziylo acquisition certainly fits in with growing interest in GRIs from both manufacturers and patients.** During the diaTribe Foundation's annual Musings Under the Moon "Next-Gen Diabetes" discussion at ADA, Sanofi's North American Head of Diabetes and Cardiovascular Ms. Michelle Carnahan shared her A-HA moment from the past year. She had asked a group of parents and patients what they were most excited about in diabetes. The responses included connected care, beta cell treatment, and GRIs. Ms. Carnahan astutely pointed out the key theme connecting these therapies: they all have the potential to bring normalcy to the lives of people with diabetes, reducing diabetes "work" so to speak. We found this message incredibly compelling, and we hope it serves as motivation for continued investment in glucose-responsive insulin.

Mechanism of Action

- **While the precise scientific mechanism underlying Novo Nordisk's candidate was not revealed, glucose-binding has so far been a pipedream for GRIs.** As we understand it, the high-level idea behind Novo Nordisk's product is that insulin will be inactive when attached to Ziylo's glucose-binding moiety and active when the amalgamation interacts with a glucose molecule in the blood. This mechanism theoretically allows for insulin activity proportional to glucose concentration (i.e., "carb-sensing"), similar to a functioning pancreas. To provide scientific granularity on Novo Nordisk's approach and the difficulties associated with this mechanism, we reached out to Oxford's Prof. Rury Holman and Newcastle University's Prof. Philip Home, two leaders in this field:
    - **Prof. Rury Holman:** "Two particular issues are worth noting for 'smart' insulins. Substantially more insulin than needed will have to be administered to provide a 'reservoir' that can be called on, a substantial proportion of which is likely to be metabolized before it is used (a cost issue). If the glucose sensing mechanism is affected by other issues (e.g., fever), it could result in inappropriately increased insulin activity and hypoglycemia (a safety issue)."
    - **Prof. Philip Home:** "The lectin-enhanced disposal concept, which seems to have struggled at Merck (and others), has the unattractive features of needing an expensive-to-produce insulin and getting the disposal-glucose-response curve sufficiently sensitive to competing glucose concentration, while having a molecule which retains insulin activity at its own receptor. There are other approaches of course, such as using glucose-binding to a lectin-insulin adduct in a way which changes the access of the insulin molecule to its receptor (i.e., decreased access when glucose is lower). There are problems with that too, however, because insulin is cleared through its receptor, so with a half time sufficient to fill the insulin space (VD) of about 25 min, the effect is negated by concentration changes. One could alter insulin receptor kinetics dependent on glucose-binding, but that is tiger country as B10-Asp showed."
- **According to the company announcement, Novo Nordisk is explicitly focused on mitigating hypoglycemia with its GRI, which should ultimately reduce hyperglycemia as well.** If hypoglycemia were eliminated, insulin doses could be increased to more effectively

manage hyperglycemia. The need for GRIs to address hypoglycemia (the more serious, immediate risk associated with insulin therapy) before hyperglycemia is a well-acknowledged notion; back in 2016, JDRF sponsored a day-long workshop on GRIs (then known as "smart" insulins), during which this point was repeatedly emphasized.

    - **The general development track for GRIs (addressing hypoglycemia first, followed by hyperglycemia) is reminiscent of closed loop insulin delivery.** In closed loop systems, predictive low glucose suspend first mitigated hypoglycemia by reducing basal insulin, followed by the introduction of basal modulation moderating some highs (currently seen in Medtronic's 670G hybrid closed loop). Looking ahead, auto-boluses will diminish postprandial highs - the holy grail of closed loop technology. In our view, this seems to be a fair template and a potentially strong way of balancing safety with efficacy as GRIs evolve.

Global Drug Discovery

- **Novo Nordisk's Global Drug Discovery team is now comprised of ~900 people (!) with US research sites in Seattle and Indianapolis, all led by Dr. Schindler.** In his words, "it's a nice and significant critical mass with which we can address a wide variety of metabolic issues" - an exceedingly modest evaluation! Dr. Schindler mentioned a recent investment in a new Novo Nordisk Research Center in Oxford to focus on type 2 diabetes and its associated comorbidities and extolled the obesity work being done in Seattle with Novo Nordisk's VP of Obesity Research Dr. Kevin Grove. Novo Nordisk also has a type 1 diabetes research center in Seattle led by VP Dr. Matthias vom Herrath. While many of these cities are research hubs, Dr. Schindler noted that it is also important "to go to the places that don't necessarily get the headlines" when looking for partners, as evidenced by the Ziylo (University of Bristol spin-out) acquisition.

Carbometrics and Glucose-Binding Molecules in CGM

- **In our view, the Ziylo acquisition worked very well for employees; this small company (<20 employees) just created Carbometrics, which is now a new company (that seems very similar to Ziylo - presumably it's all the same employees) that were at Ziylo except the young company is now collaborating with a well-established industry player and retains the rights to explore its glucose-binding technology in non-therapeutic applications.** Carbometrics will reportedly follow two primary projects: (i) a collaboration with Novo Nordisk to optimize glucose-binding molecules; and (ii) development of glucose-binding molecules for diagnostics and CGM. According to Dr. Schindler, all Ziylo employees were transferred to Carbometrics prior to acquisition, and none will be directly associated with Novo Nordisk. As such, Carbometrics is essentially Ziylo, minus the rights to explore its glucose-binding molecules in GRIs.

    - **Carbometrics' ambition to explore glucose-binding molecules in CGMs is a well-established principle.** According to Bigfoot CPO Dr. Bryan Mazlish, both Senseonics and Profusa currently use this technology in their CGMs. That said, not all attempts to marry these ideas have been successful. Back in 3Q14, BD ended its JDRF/ Helmsley-partnered CGM program, which also used glucose-binding proteins to determine glucose concentration. We certainly hope that Carbometrics strikes success with this work, although we note that Novo Nordisk's digital health collaboration history is not overly inspiring. Novo Nordisk previously cancelled a GLP-1 microneedle patch collaboration with Zosano, and we have heard little about its partnerships with IBM Watson and Glooko since their announcements in late 2015 and early 2017, respectively.

Interview with Dr. Marcus Schindler (SVP of Global Drug Development, Novo Nordisk)

Q: An acquisition of Ziylo seems like a pretty big decision - the company is young and curious. What drove the decision?

A: The development of glucose responsive insulins is a key strategic area for Novo Nordisk. Novo Nordisk has acquired Ziylo to gain exclusive access within therapeutics to Ziylo's GBM technologies. The area of research is attractive, and the majority of insulin companies are pursuing various ways of developing glucose responsive insulins.

Q: Can you give us any background on carb sensing?

A: Ziylo glucose-binding molecules are synthetic molecules that were designed by Professor Anthony Davis at the University of Bristol. These stable, synthetic molecules exhibit an unprecedented selectivity to glucose in complex environments such as blood. The technology is built on over 20 years of research pioneered by Professor Anthony Davis' group at the University of Bristol and originally inspired by nature's carbohydrate-binding molecules (lectins).

Q: How will the Carbometrics spin-out work?

A: The Ziylo employees have prior to the acquisition been transferred to a new company called Carbometrics that has entered into a research and collaboration agreement with Novo Nordisk. Novo Nordisk has full rights to Ziylo's glucose-binding molecules for therapeutic use. Carbometrics has licensed rights to develop non-therapeutic applications of glucose-binding molecules, with a focus on developing continuous glucose monitoring applications.

Q: Could you help us better understand the acquisition structure? What are the milestones associated with the $800 million payment?

A: Novo Nordisk has paid an upfront payment and will potentially later pay earn-outs. The earn-outs consist of contingent milestone payments based on the achievement of certain development, regulatory and sales milestones. The upfront and other detailed financial terms have not been disclosed.

Q: Are any members of the Ziylo team moving to Denmark?

A: The scientists we have been working with have been moved to Carbometrics, and we will continue to work closely together on the Ziylo chemistry. We will conduct research on glucose responsive insulins in Bristol and our research sites in both Måløv, Denmark and Oxford, UK.

Q: How fast could we see this product in humans? On the market?

A: I'd love to see it in humans as soon as possible. Two to four years from now we hope to be in clinical development, and then you have a full blown clinical program which will take time. Maybe ten years, ten years plus it could be released.

Q: Is there anything in particular about this technology that you think makes it more likely to succeed than previous GRIs?

A: As of right now it's important to note that the candidate is still very much in the research stage. That said, we think that the chemistry that Ziylo has created has an amazing potential to be attached to insulin to make it "glucose sensing." The glucose sensing element interacts with the insulin to determine if it is active or not, giving the molecule amazing potential.

Q: We were not expecting this acquisition, and we were wondering if you could give any more background?

A: It's been a really interesting story. Novo Nordisk and our peers have been working on GRIs for a very long time and one of our scientists - a protein chemist - has been following Dr. Anthony Davis' work. That's how we got to know about this chemistry and the Ziylo company. Not long ago, we realized that the chemistry may be

suitable to couple with the insulin molecule, and we had a conversation to see if the two companies could work together.

Q: That's interesting to hear about the scientific scouting. Could you say any more about that?

A: Sure. We all know sort of know the scientific hotspots. Bristol certainly has not really been on the map, but it's important for us to invest. We just invested in Oxford establishing a research center on type 2 diabetes and associated comorbidities. It's important to go to the places that don't necessarily get the headlines. We're quite active in all sorts of levels to figure out who we could potentially work with.

Q: How big is your group (Global Drug Discovery) now?

A: My team is roughly 900 people, and we work in diabetes and obesity, as well as NASH and atherosclerosis as of recently. In addition to this, several hundered people globaly are working on research technologies. You know we have a site in Seattle that works a lot on obesity with Dr. Kevin Grove and on type 1 with Dr. Matthias von Herrath. For me it's a nice and significant critical with which we can address a wide variety of metabolic issues.

Q: We attended a JDRF meeting a couple of years ago and it definitely seemed like there was a path to working out hypoglycemia before hyperglycemia, but I think patients will expect "smart" insulins to address both. What are your thoughts on this? We are all very interested about the carb sensing piece.

It's really a great point - we haven't described the scientific mechanism yet. The main thing is to abolish the risk of hypoglycemia. Ultimately, we want better disease management to bring people closer to their goals.

Q: Carbometrics is doing all of the tech part - that wasn't part of the initial or 800 million in milestone payments?

The entire Ziylo team moved over to Carbometrics to work on CGM which is currently not within our applications. We own the entire patent estate of Ziylo but hve licensed the rights for all non-therapeutic uses of glucose-binding molecules including applications in diagnostics and glucose monitoring to Carbometrics. The deal structure and milestone payments are focused on glucose responsive insulin.

Q: Is the size of the company about the same? Under 20?

Yes - that's roughly the size of the company. None of the Ziylo employees are now Novo employees

Q: Is there anything you think we missed or that you are particularly excited about?

A: What I'm quite proud of is that we're investing in the insulin space where. To at least have the division and ambition to bring a totally new value proposition to physicians, patients, and payers makes me very excited and I think that Novo is a great place to do this.

Close Concerns' Questions

Q: Where was Ziylo valued by Novo Nordisk prior to acquisition? The company had less than $10 million in funding, with only $1.4 million in public funding when it was acquired. How much did Novo Nordisk pay up front?

Q: How will the mechanism of Novo Nordisk's GRI candidate compare with that of Merck's phase 1 candidate (the only clinical-stage glucose-responsive insulin, as far as we're aware)?

Q: Down the line, how would payers reimburse glucose-responsive insulins? Will GRIs escape the overwhelming pricing pressure plaguing the insulin market (both basal and prandial) today?

Q: How would glucose-responsive insulins compare to fully automated closed loop systems?

Q: How much could one's diet and lifestyle affect the injection burden of glucose-responsive insulins?

--by Peter Rentzepis, Payal Marathe, and Kelly Close