CLOSER LOOK

MEMORANDUM

NIH announces four pivotal AP trials starting in 2017-2018: iDCL trial, Cambridge pediatric study, 670G vs. 690G, and BU-MGH bihormonal - February 9, 2017

Executive Highlights

- NIH officially announced ~$41 million in grants for four "pivotal" multi-center artificial pancreas trials starting in 2017-2018: (i) the International Diabetes Closed Loop trial (n=240, six months, serving as Tandem/TypeZero's pivotal); (ii) DAN05, a Cambridge pediatric trial in 6-18 year olds starting early this year (n=130, 12 months, using the Medtronic 640G/Enlite 3 and an Android phone); (iii) an IDC-Schneider's Children's collaborative comparing Medtronic's MiniMed 670G vs. MiniMed 690G in a crossover study starting in late 2017 (n=100, three months, adding auto-correction boluses into the 670G); and (iv) BU/MGH's bihormonal pivotal trial starting in mid-2018 (n=312, six months, iLet device with insulin+glucagon).
- All studies were funded and designed to serve as pivotal studies to support regulatory approval of commercial devices. (We're not sure of Cambridge's commercial plans.) Tampa's Jaeb Center will coordinate all the studies - thank you Dr. Beck!
- NIH emphasizes that these are "fully automated" devices that won't require mealtime bolusing, improving on the MiniMed 670G's basal-only insulin modulation. Of course, they will still require some user attention and involvement.
- These grants continue tremendous NIH commitment to this field, particularly in bridging the gap from academically-tested algorithms to commercial products. We hope these large, long, and independent trials (3-12 months) also build the evidence base around automated insulin delivery, positively influencing payer coverage. Combined, we estimate these trials will test nearly 100,000 patient-days of closed loop control.

Earlier this week, NIH officially announced four grants for pivotal artificial pancreas trials. The incredible ~$41 million in total grants, made possible through the Special Statutory Funding Program for Type 1 Diabetes, have been divided among:

- **The six-month International Diabetes Closed-Loop (iDCL) trial**, led by UVA's Drs. Boris Kovatchev and Stacey Anderson (n=240). This is expected to serve as Tandem/TypeZero's pivotal trial, supporting an expected late 2018 launch. The study has a "Research Site Training Protocol" that is now recruiting (n=40) and then a main phase that will start recruiting in a few weeks. We've known since last January that this study was NIH funded with a remarkable $12.7 million. Device details below!
- **DAN05, a Cambridge pediatric trial in 6-18 year olds** will start early this year. The 130-patient study will last an impressive 12 months (!) and use the Medtronic 640G/Enlite 3 and an Android phone running the Cambridge algorithm. This received ~$6 million from NIH.
- **A three-month crossover trial comparing the MiniMed 670G with the next-gen 690G (adding auto-correction boluses) led by IDC's Dr. Rich Bergenstal and DREAM's Dr. Moshe Philip**. The study will start in late 2017 and include 100 participants. This is a serious win for Medtronic/DreaMed to get this funded by NIH to the tune of ~$7 million.
- **BU/MGH's bihormonal pivotal trial will start in mid-2018, enroll 312 adults (18+ years), and last six months.** Dr. Damiano told us in October that this trial received $12 million

in funding to test the final integrated dual-chamber iLet device with insulin and a pumpable glucagon.

All studies were funded and designed to serve as pivotal studies to hopefully support regulatory approval of commercial devices. This is in line with our expectations for three of these studies, with the exception of Cambridge - we're not sure of Dr. Hovorka's commercial plans, but perhaps we'll hear more at ATTD. Tampa's Jaeb Center for Health Research will serve as the coordinating center for all these huge multi-center trials - what a gift to the field from the incredible Dr. Roy Beck and team.

NIH emphasizes that these are "fully automated" devices that won't require mealtime bolusing, improving on the MiniMed 670G hybrid closed loop's basal-only insulin modulation - we agree that this is key for reducing burden and improving the daytime quality of life with these systems. However, these system will clearly still require user attention and involvement, so full automation is not perfectly accurate. Indeed, it will be very important to set expectations optimally; otherwise, it may set the wrong expectations about what these systems can do. We do think this message has been set and reiterated time and again, so ...

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We give tremendous kudos to NIDDK's Diabetes Technology Program Director Dr. Guillermo Arreaza-Rubín (following the scientific-technical aspects and progress of the projects), program official Dr. Andrew Bremer (following the clinical safety, efficacy, and administrative aspects of the trials), NIDDK Director Dr. Griffin Rodgers, and NIH Director, Division of Diabetes, Endocrinology, and Metabolic Disease Dr. Judy Fradkin - it's amazing to see this set of leaders and what they can make happen through such partnerships. These grants continue over a decade of tremendous NIH commitment to this field, now moving to bridge the gap from academically-tested algorithms to commercial products.

- **International Diabetes Closed-Loop (iDCL) Trial (NIH grant DK108483; $12.7 million).** The initial phase of the study is called a "Research Site Training Protocol" (n=40) on ClinicalTrials.gov (now recruiting) and uses a smartphone running the TypeZero inControl algorithm, a Tandem pump, and Dexcom's G5. The study's main protocol (n=240; six months) has been approved by FDA, but the team will hold recruitment to allow the training study to finish. The main phase will start with the same smartphone system, but then switch to a fully embedded system with a Dexcom G6 sensor-integrated Tandem t:slim X2 pump that incorporates TypeZero's inControl algorithms directly into the touchscreen pump (basal modulation + automatic correction boluses). As we've covered previously, the iDCL trial is expected to serve as the pivotal trial for Tandem's second-gen automated insulin delivery system, slated for a late 2018 launch if things go well. We first learned about this NIH funding one year ago. The NIH press release notes that a second six-month study will recruit from the 180 US participants of this main protocol to test an alternative algorithm (Harvard's Zone MPC).
    - **Estimated Study Completion Date:** 2Q18 (per an email exchange with Dr. Kovatchev).
    - **Primary outcomes:** CGM-measured metrics between baseline and 6-months - superiority in CGM-measured time below 70 mg/dl, and non-inferiority in CGM-measured time above 180 mg/dl.
    - **Comparator:** Pump + CGM.
    - **Population:** 14+ years old, use of an insulin pump for at least six months, A1c level <10.5% at screening.
    - **Study Sites:** University of Virginia Center for Diabetes Technology, William Sansum Diabetes Center, Stanford University, Barbara Davis Center, University of Colorado, Harvard University (Joslin Diabetes Center), Mayo Clinic, Icahn School of Medicine at Mount Sinai, University of Montpellier, University of Padova, Academic Medical Center (Amsterdam).

- **DAN05, Cambridge Pediatric Trial (NIH grant DK108520; ~$6 million).** Recruitment for this 12-month pediatric pre-pivotal study (n=130; ages 6-18) will begin "early this year" according to the NIH press release and should wrap up by September 2018 according to Clinicaltrials.gov. The closed loop system will consist of Medtronic's MiniMed 640G pump and Enlite 3 CGM sensor with an Android phone running Cambridge's MPC algorithm. In September, Cambridge was awarded £4.6 million to run a year-long trial investigating use of the artificial pancreas in type 1 children ages one to seven (no start timing has been provided). We're not sure of the team's commercial plans, but assume this will study will help inform those going forward.
    - **Estimated Primary Completion Date:** June 2018.
    - **Primary Outcome:** A1c at 12 months.
    - **Comparator:** Pump alone (no CGM).
    - **Population:** 6-18 years old, use of an insulin pump for at least 3 months, A1c 7.5%-10%
    - **Study Sites:** Stanford University, Barbara Davis Center, Yale, International Diabetes Center at Park Nicollet, University of Cambridge, and The Leeds Teaching Hospitals NHS Trust.
- **IDC-Schneider's Children's Collaboration testing Medtronic's MiniMed 670G (PID algorithm) vs. MiniMed 690G (PID + Fuzzy Logic) (NIH grant DK108611; $7 million).** Drs. Rich Bergenstal (Minneapolis) and Moshe Philip (Israel) will lead this multi-center crossover study (n=100; ages 14-30; six months) comparing the FDA-approved MiniMed 670G hybrid closed loop with basal-only modulation (full launch in May-October in the US and internationally) with the next-gen MiniMed 690G - as a reminder, this adds the DREAM fuzzy logic algorithm on top of hybrid closed loop to bring automatic correction boluses (key for covering meals). According to Clinicaltrials.gov, the study is slated to begin in early December 2017 and wrap up in late June of 2020 - we assume the latter is very conservative, since each participant will only need six months to get through the study. Participants will be randomly assigned to 670G or the 690G Fuzzy Logic system for 12 weeks, followed by a four-week washout period, and a crossover to the opposite arm for 12 weeks. The primary outcome is percent of time in hyperglycemia (blood glucose >180 mg/dl) during the day, while secondary outcomes cover time in range, hypoglycemia, glycemic variation, and A1c. The results will show the benefit of adding the Fuzzy Logic algorithm on top of the 670G's basal-only algorithm. Notably, the FDA is actually listed as a collaborator on ClinicalTrials.gov.
    - **Estimated Primary Completion Date:** December 31, 2019
    - **Primary Outcome:** CGM-measured time >180mg/dl from 7 am-11 p, 12 weeks for each arm of the crossover.
    - **Comparator:** MiniMed 670G
    - **Population:** 14-30 years old, MDI or pump (with or without CGM) users with type 1 diabetes for at least one year, A1c of 7%-12%.
    - **Study sites:** Yale, University of Florida, Joslin, International Diabetes Center, Hannover Medical School, Schneider Children's Medical Center, and University of Ljubljana.
- **BU/MGH's Bihormonal Pivotal Trial (NIH grant DK108612; $12 million).** The six-month pivotal trial (n=312; 18+ years) of the bihormonal iLet Bionic Pancreas (insulin + glucagon) is slated to begin in mid-2018. Prior to the pivotal trial, the team will run bridging studies to show that the iPhone-driven research platform is similar to the integrated iLet device. IDEs for both insulin-only and bihormonal bridging studies will be submitted by the end of May, enabling a study start by mid-July and running into September 2017. Meanwhile, Beta Bionics is also looking to commercialize its insulin-only bionic pancreas in parallel, with a six-month pivotal trial slated for the end of 2017 or early 2018. Dr. Damiano and team shared with us a week ago that Beta Bionics (the public benefit corporation commercializing the iLet) has partnered with Novo Nordisk and received a $5 million investment from the insulin giant, mirroring Lilly's investment about a year ago.

- **The bihormonal trial is obviously not yet posted on ClinicalTrials.gov**, though we assume the team still plans on A1c and percentage of CGM measurements <60 mg/dl as the primary outcomes. The NIH funding application cites 480 participants (8+ years, A1c <11%), though the actual NIH press release only notes 312 adult (18+ years) participants. We assume the latter is the plan for now but are following up with Dr. Damiano.

Close Concerns Questions

Q: Will these trials all result in commercial products? Which will make it market the fastest, and which will offer the greatest improvement in glycemia + diabetes burden (particularly during the day)? Which will be easiest to train providers on? Which will patients like the most? Will the target market for these products change at launch vs. three years vs. five years out?

Q: What primary outcomes are most persuasive to payers, who are they real gatekeepers of these technologies?

Q: Will payers interpret closed loop studies on a device-by-device basis, or take the whole evidence base into account - e.g., could a 670G pivotal trial be used to support reimbursement for a Tandem/TypeZero product?

Q: What is the right comparator group for a pivotal artificial pancreas study, given the goals for expanding the market and getting broad payer access?

Q: What are the remaining gaps in automated insulin delivery research?

-- by Brian Levine, Adam Brown, and Kelly Close