Closer Look

**7th International Conference on Advanced Technologies & Treatments for Diabetes (ATTD 2014)**

**February 5-8, 2014; Vienna, Austria; Day #1; Highlights - Draft**

## Executive Highlights

*Guten tag from Vienna, Austria, where Day #1 of ATTD 2014 just wrapped up! Today had just a few hours of sessions, and we heard plenty of updates from all areas of diabetes technology - glucose monitoring, regulatory approval, remote monitoring, insulin delivery, closed-loop control, and even smartphone-assisted carb counting.*

*A big highlight of the day was Abbott's standing-room-only corporate symposium on its next-generation sensing system, which will be a device in a new product category it is calling "Flash Glucose Monitoring." While much of the content refreshed similar sessions at IDF and EASD, Abbott confirmed its expectation for 2H14 CE Mark approval; shared new accuracy data from a six-lot prospective factory calibration study (MARD of 11% vs. fingersticks - crazy great, but maybe not surprising since this is based on the original Navigator technology, which was uber-accurate for its time); and discussed new design details (we love that). This continues to be a very exciting and promising new category of glucose monitoring technology. Also on the monitoring side, we heard a smattering of design details on Medtronic's next-gen Enlite sensor - most notably, the sensor has launched in six European countries. No accuracy data was shared, though we imagine the 80% reduction in implanted size and the new electrode pattern will improve the system's performance. It sure looked good under the glass in the Exhibit Hall.*

*This year's ATTD has a clear focus on the artificial pancreas, which was discussed at length in a conference-opening workshop on the EU's 7th Framework Program. Dr. Steve Lane (Commercial Director, Triteq, Hungerford, UK) provided an update on the progress of the AP@home project. The next step for the two-port (separate insulin and CGM sites) approach is an at home, 24/7, two-arm, randomized control trial of the University of Cambridge's system, which includes a FreeStyle Navigator CGM and a Dana SOOIL pump. The AP@home project is also working on a single-port system (single site for CGM and insulin infusion) in collaboration with Dexcom and Roche. A second in-clinic study of this prototype is set to begin in 1Q14. Wow is this field moving. We expect very good results from this system.*

*In a late-afternoon session on the artificial pancreas' safety, we heard growing consensus that mandatory remote monitoring might not be necessary and is likely not practical and in fact, may not even be advocated by FDA. Dr. Stacye Beck provided the FDA's perspective on the topic via webcast (budgetary constraints...this worked very well though!), pressing that not all safety mitigations used in clinical trials need to be implemented in products that are ultimately brought to market. An example is remote monitoring, which she characterized as useful in clinical trials (to ensure safety and to better understand the system) but perhaps less necessary once systems are on the market (obviously depending on the results of the trial). Immediately following her comments, Drs. Eran Atlas (Schneider Children's Medical Center, Petah Tikvah, Israel) and Thomas Danne (Kinder- und Jugend- Krankenhaus Auf der Bult, Hannover, Germany) debated whether remote monitoring will be required. As we've come to expect with such debates, Dr. Danne flipped to join Dr. Atlas in arguing against remote monitoring. Both contended that the value of remote monitoring was in practice much less than is often anticipated, and the effort required to conduct it is quite high. We believe remote monitoring is extremely useful in trials, nonetheless.*

*In insulin delivery, Ms. Leslie Lilly (CeQur, Marlborough, MA) presented new human factors data on CeQur's PaQ insulin delivery device - the study showed positive results regarding patients' happiness with ease of task completion and safety. We also appreciated seeing time-in-range data on PaQ, which clearly has some real potential to improve outcomes. See below for more, including Roche's handling study of the*

*Accu-Chek Insight, a futuristic automated carb counting software (via smartphone pictures!), highlights from the opening ceremony, and what we're looking forward to tomorrow.*

## Top 10 Highlights

**1. Abbott's ambitiously titled workshop on Flash Glucose Monitoring ("Advancing Towards the Next Frontier in Glucose Monitoring: 14-day, No-Calibration Sensors and AGP") drew a two-deep standing-room-only crowd.** Three updates were shared on Abbott's next-generation sensing system, which will be a device in a new product category called "Flash Glucose Monitoring." As a reminder, the goal is to be an alternative to BGM, while collecting continuous data for Ambulatory Glucose Profile reports. Most importantly, Abbott's Mr. Jared Watkin updated attendees on the slate of expected 2014 studies of the next-generation sensing system - an accuracy trial to support CE Mark approval (regulatory approval anticipated in 2H14 - on par with previous timelines) and two European multi-center, multi-country, randomized controlled trials to demonstrate improved glycemic control (one in type 1 and the other in type 2). The latter are intended to show real clinical outcomes, and we imagine would help drive data to support reimbursement in Europe. These could be quite tricky to design, since the parameters of the control group are not entirely obvious (How many fingersticks? What sort of retrospective review?) and the intervention group includes not only the device, but also the associated AGP download reports. While no timelines or details were shared on the US, we are optimistic Abbott has not given up on the FDA but working in the market (the EU) that will enable fastest time to commercialization. And boy are they moving …

- **Mr. Watkin also provided brand new (!) data from a six-lot factory calibration study** (the initial ENERGY study discussed at EASD only tested a single lot). The small study enrolled six patients with diabetes that each wore three sensors simultaneously over five days (Abbott has found that the full 14 days of wear are not necessary to get a sense of sensor stability/accuracy - this struck us as a bit surprising and we're trying to learn more on this). Overall MARD (vs. FreeStyle Precision fingersticks) using a lot-specific pre-determined (prospective) factory calibration was a solid 11%, with 84% of points in Zone A of the Parkes consensus error grid (for context, the initial ENERGY study found a MARD of 8.5% vs. YSI and 9.6% vs. fingersticks). If this factory calibrated accuracy of 11% holds up in the upcoming CE Mark accuracy study, it would represent truly impressive R&D and manufacturing capabilities. Abbott is continuing to hone and optimize the factory calibration scheme, as subsequent retrospective analyses have been able to slightly improve the initial calibration factors and reduce the level of error.
- **Mr. Watkin further disclosed a few never-before-shared design details of the next-generation sensing system.**
    - First, the system's sensor patch will be the size of a two-Euro coin - quite small and intended to be "simple," "low pain," and "low profile." This of course jives with the ambition to overcome some of the limitations of CGM and BGM.
        - As a reminder, this sensor patch will be worn for 14 days and will be fully disposable, meaning no reusable transmitter (it uses RFID and a limited memory chip to transfer up to eight hours of data, a real-time value, and trend arrow to the reader).
        - Interestingly, Abbott has found that traditional CGM users find the system "liberating," as they don't have to be close to the reader all the time in order to get the data stored (i.e., a patient can leave the reader at home while out of the house, and can still get all the continuous data as long as the sensor patch is scanned within eight hours). This is clearly another point of differentiation from traditional CGM.
    - The system's sensor patch is also "water resistant" (e.g., showering), can be scanned through patients' clothing (key for discretion), and transmits data to the reader in less than one second after a scan. Mr. Watkin showed some example screens from the color touchscreen reader, which included time in range graphs - this has been missing on CGM

receivers to date, so this is great to see. For more background on the system, see our EASD coverage.

- For context, the official name of Abbott's next-generation sensing system has not been released. While we have previously referred to this device as "Flash Glucose Monioring," Abbott has informed us that that term is the name of the new product category - not the name of this device.

**2. Via webcast, Dr. Stayce Beck gave the FDA's perspective on ensuring the safety of an artificial pancreas (AP) throughout its clinical development and market launch.** Patients would be proud and happy - Dr. Beck emphasized that researchers need to "come early" (begin conversations with the FDA early in the trial design stage), "be loud" (communicate with FDA and commercial partners), and "stay late" (in addition to working hard [which she noted researchers are doing], thinking ahead and designing systems so that they can be modified at a later date). Dr. Beck reassured researchers that safety mitigations used in a study are not necessarily required in the finally approved device, since the deeper experience gained in studies will help identify what precautions are actually necessary. One notable example was remote monitoring, which Dr. Beck characterized as useful in trials but likely not feasible in the real world. Overall, we were very encouraged by Dr. Beck's positivity for the AP: "We are very excited by the prospect of the artificial pancreas to mitigate the risks people with diabetes face everyday." In contrast, BSI, a Notified Body in the EU, was not able to give as much clear and actionable guidance on what the EU's regulatory perspective is on the AP. The EU presentation was somewhat disappointing overall, mostly discussing the nuances of device classification, risk analysis, and legal requirements.

**3. A "debate" between Drs. Eran Atlas (Schneider Children's Medical Center, Petah Tikvah, Israel) and Thomas Danne (Kinder- und Jugend- Krankenhaus Auf der Bult, Hannover, Germany) on the need for a remote monitoring system in the artificial pancreas (AP) suggested that there is not much to argue - both voted that it should not be a mandatory safety feature.** Dr. Atlas asserted that remote monitoring does not provide the expected level of safety, as its ability to effectively identify any severe event is often overestimated. He further reasoned that it is not practical to perfectly follow the AP readings of up to 20 million users (the number of people with type 1 diabetes in the world - this estimate is on the high side of what we had previously understood type 1 prevalence to be) from either a cost, usability, or infrastructure perspective. Dr. Atlas went as far as to say that remote monitoring can actually reduce the safety of an AP - it can fail on the connectivity side as well as in device integration. Dr. Atlas continued, however, to note that remote monitoring is a good "pair of training wheels" as the AP progresses from feasibility and translational studies into real world use. Additionally, remote monitoring can help patients improve their diabetes management through the data it collects, giving patients and their loved ones more peace of mind as they start using the technology. In concluding, Dr. Atlas felt that remote monitoring could be a beneficial optional feature. Dr. Danne was supposed to argue in favor of remote monitoring, but flipped to the 'CON' argument and pressed that patients want an AP that can look after itself and is hassle-free. Similar to Dr. Atlas, he contended that the value of remote monitoring was in practice much less than is often anticipated, and the effort required to conduct it is high. Although some complained that it really wasn't a "debate", it was great that Dr. Danne even took the CON side in our view and we found the session extremely illuminating overall. We will be returning in our full report to discuss more about different safety features discussed.

**4. In the tail end of Medtronic's case-based workshop, we heard a bit about the "next-gen Enlite sensor" (previously called "Enlite 2" or "Enlite Enhanced").** In new news, we learned that that next-gen Enlite has already been rolled out in six European countries - this had not been publicly disclosed before today. As of the last update at EASD 2013 in September, the product had just received a CE Mark. It was disappointing not to hear any accuracy data (none has been shared to date), though the Medtronic rep emphasized the product's major improvements over the original Enlite: 1) an 80% reduction in implanted size; 2) a new sensor adhesive to reduce skin irritation; 3) a new electrode pattern with the goal of more consistent performance throughout the sensor life (not quantified); and 4) an improved sensor to transmitter connection (the same clamshell transmitter from prior generations is still being used). We expect the smaller size and electrode redesign would improve sensor performance, particularly early in the sensor life

- it will valuable to see data to quantify this assertion. Moving forward in Europe, Medtronic plans to "replace" the current Enlite with the next-gen Enlite. No timeline was given for when the conversion would complete or when any US submission might occur.

**5. Dr. Steve Lane (Triteq Innovations) described the current status of the EU's 7th Framework AP@home program, including timeline updates.** The AP@home project currently consists of two prototype configurations of a two-port artificial pancreas (separate CGM and pump sites) - the University of Virginia's Diabetes Assistant and the University of Cambridge's closed-loop system (see our IDF and DTM reports) - and a single prototype of a one-port artificial pancreas (CGM and insulin infusion at a single site). According to Dr. Lane, the next step for the two-port AP@home is an at home, 24/7, two-arm, randomized controlled trial of the Cambridge two-port configuration, which uses an Abbott FreeStyle Navigator CGM and a Dana SOOIL pump. The study will last an impressive three months and will enroll 30 patients at six centers. The trial is expected to complete in July 2014 (quite soon!), and the primary outcome will be change in A1c. Meanwhile, the single-port approach has been tested in an open-loop, in-clinic study, and a second in-clinic trial using the AP@home platform is to begin in 1Q14. In speaking to Dr. Lane after the presentation, he indicated that the one-port system is a collaboration between Dexcom and Roche.

- **Triteq is developing is a small, battery-operated device that runs a closed-loop algorithm and communicates with the associated CGM and insulin pump.** The device is intended as an alternative to having a smartphone run the control algorithm, which Dr. Lane stated would be difficult to get approved. The Triteq device has four-buttons, as well as audible, visual, and vibratory alarms that can be modified to optimize patient-device interaction. For example, patients could potentially input meals, exercise regimes, and manually-given boluses into the algorithm using the buttons. It is our understanding that the device was purposefully designed in a flexible manner so that it could accommodate future improvements. Triteq has also developed a CGM translator, a device that a CGM receiver slides into (the slide showed a FreeStyle Navigator). The translator enables CGM data within the receiver to be communicated via Bluetooth rather than through a USB.

**6. In a session sponsored by CeQur, Ms. Ellie Strock (International Diabetes Center, Minneapolis, MN) presented CGM data from patients wearing the PaQ insulin delivery device for two weeks.** There was no significant difference pre- and post-wear, although there was a trend toward increased time in range, decreased time above range, and slight (but not clinically meaningful) increased time below range. CGM traces demonstrated increased time in range for all three patients shown and reduced total daily dose in two of the three patients - one patient saw time in range (70-140 mg/dl) increase from 13% to 78% (!). Specific results are outlined in the table below. While we assume that these patients were hand picked for use in this presentation, we were still very encouraged to see the early data from a very short-term study. In the same session, Ms. Leslie Lilly (CeQur, Marlborough, MA) also presented valuable new human factors research on PaQ. Patients ranked the PaQ a 6.6/7.0 on ease of task completion and the safety of the device, which was quite positive to hear. Additionally, Ms. Lilly broke each category into four different sections to further determine where patients felt the most confidence; overall, patients ranked the ease of bolus dosing with and without distraction very high, marking each at 6.9/7.0. Assembling PaQ got the lowest task completion score at a 5.9/7.0. On the safety side, all ratings were quite high: Preparing the device for use (6.7/7.0); delivering bolus doses with and without distraction (6.8 and 6.4/7.0); and interpreting communication signals (6.4/7.0). We'd love to know how patients "weight" the importance of each of these sections.

**Table 1. Time in range before and after CeQur use, and change in total daily insulin dose**

| | Time in range (70-140 mg/dl) pre-PaQ use | Time in range (70-140 mg/dl) post- PaQ use | Change in total daily dose (post-PaQ - pre-PaQ; units) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Patient #1** (baseline A1c: 7.9%) | 61% | 64% | -13 |
| **Patient #2** (baseline A1c: 7.7%) | 19% | 42% | 1.8 |
| **Patient #3** (baseline A1c: 8.1%) | 13% | 78% | 3.0 |

**7. Dr. Guido Freckmann (University of Ulm, Germany) presented results from a handling study of Roche's new Accu-Chek Insight insulin pump system.** The results - originally presented at DTM 2013 - demonstrated that patients using the Accu-Chek Insight were able to perform five of ten tasks (quick bolus delivery; insulin pump cartridge filling system; changing of the cartridge, infusion set, and cannula; connecting a new infusion set to the pump; and editing a basal profile) in the fewest number of steps vs. six other pumps (Tandem's t:slim; Dana's Diabecare; Medtronic's Paradigm Veo; Roche's Accu-Chek Spirit Combo; J&J's Animas Vibe; Insulet's OmniPod; and Roche's Accu-Chek Insight). For each task, the number of steps for each pump was counted by two different investigators, and pictures of each step were entered into an Excel spreadsheet. All pumps were programmed using the same parameters. This study had several questionable limitations that give pause to the results. First, the exact number of steps was not specified, making us wonder just how they were counted and relatively compared (we also wonder if each investigator got the same number). Second, the Insulet OmniPod patch pump was deliberately excluded, an unfair move in our view given this pump's high ease of use. Third, we believe time to complete tasks is a more important and fair metric than number of steps, as some pumps have faster user interfaces than others (though perhaps more "steps"). Also, more recently approved pumps have more steps given the FDA's crackdown on human factors and device safety - comparing old and new pumps on steps alone is not quite apples to apples.

- **For background, the Accu-Chek Insight meter is a next-gen pump with a meter remote. Roche plans to begin the product's launch in Austria in March 2014.** The company also plans to file the device with the FDA later in 2014. For more updates on Roche, please see our 4Q13 financial report.

**8. Dr. Stavroula Mougiakakou (University of Bern, Bern, Switzerland) introduced attendees to the cool GoCarb smartphone-based carb counting system.** GoCarb is an EU-funded project that uses machine learning and computer vision to automatically and quickly calculate the carbohydrate content of a meal from a pair of user-captured smartphone pictures, allowing more precise bolus insulin dosing in type 1 patients. Users start by taking two pictures of a plate of food, making sure to include a credit card-sized reference object from two different angles. An algorithm recognizes the food types on the plate, calculates the volume of food, and combines the data to calculate the carbohydrate content of the meal. That information, combined with a blood glucose reading and insulin on board data, is used to generate a recommendation for bolus insulin dosing. In early non-clinical testing of the system with real meals, GoCarb's mean absolute error rate was seven grams per meal, well below the 20-gram maximal error allowance pre-specified by the research group (given how notoriously difficult carb counting is, even for experts, this is pretty good accuracy). The system will be moving into testing with patients in September of this year; this phase is expected to run for approximately one year. As an early foray into the application of computer learning to diabetes care, the GoCarb understandably has limitations and room for improvement - all the food on a plate must be visible to the smartphone camera, and we imagine that mixed foods will be difficult for GoCarb to analyze. Nonetheless, as a starting point, GoCarb is quite exciting, as it meets a major area of unmet need for people with diabetes. We're very excited to try it.

**9. The day ended with the official opening ceremony, kicking off the ATTD 2014 scientific program that begins tomorrow.** Conference co-chair Dr. Moshe Phillip (Tel Aviv University, Petah Tikva, Israel) shared that over 2,100 attendees (and counting) from 83 countries are attending this year's seventh ATTD - the conference has grown tremendously in the past few years (~400 attendees were at the inaugural in 2008 in Prague), and we give great credit and thanks to the renowned Dr. Phillip and co-chair Dr. Tadej

Battelino (University Children's Hospital, Ljubljana, Slovenia) for organizing such a consistently outstanding meeting full of so much technology learning. As we understand it from a valuable conversation with Dr. Philip and Dr. Battelino in the Exhibit Hall this evening, this year's conference was even preceded by two "ATTD schools," which brought together young healthcare providers (as students) in a program led by diabetes KOLs.)

- **The opening ceremony's keynote speaker, Dr. Raimund Weitgasser (Paracelsus Medical University, Salzburg, Austria), surveyed a number of topics in diabetes technology during his address**. He touched briefly upon Google [X]'s new contact lens-based glucose monitoring project (read our *diaTribe* article for background), noting that the road to commercialization is likely to be long and challenging (we don't think anyone, including Google, would debate that). He also emphasized the need for "smart" patient empowerment tools, as the projected rise in diabetes prevalence could overload the capacity of the healthcare system. We appreciated data from a six-month video-based intervention (Patienten Fuchs, of Patient Fox) that led to a 0.9% A1c reduction (baseline 7.6%; n=103 type 2 diabetes patients; no comparator arm) - although the intervention was somewhat onerous (two hours a week, once a week), we applaud efforts to develop tools that can empower and educate patients to take control of their own care.
- **After Dr. Weitgasser's lecture, we were serenaded by a most beautiful string quartet playing Mozart's Eine Kleine Nachtmusik and the Vienna Blood Waltz by Johann Strauss II.**

**10. ATTD 2014 is off to terrific start, and there's a lot more to come over the next three days - see our preview for everything we're looking forward to.** Tomorrow, we are especially excited for a powerhouse closed-loop session to start the day (Drs. Peter Chase, Bruce Buckingham, Thomas Danne, and Frank Doyle); new data from Tandem on patient reported outcomes and training time with the t:slim; a pumps and sensors session that will include the great Drs. Irl Hirsch and John Pickup; a powerhouse Sanofi sponsored symposium on BGM (Drs. Lutz Heinemann, Boris Kovatchev, David Klonoff, and Bill Polonsky); an afternoon session with Dr. Howard Zisser on patch pumps, Dr. Francine Kaufmann on real-life challenges with sensor-augmented pumps, and Dr. Bruce Bode on basal insulin; and what looks like an excellent (and somewhat provocative) Dexcom G4 Platinum corporate symposium to close out the day (Drs. Jay Skyler, Hans DeVries, Steve Edelman, and Ed Damiano). Stay tuned for our coverage!

*-- by Adam Brown, Hannah Deming, Hannah Martin, Manu Venkat, and John and Kelly Close*