Executive Highlights

We were honored to be in the company of some of the greatest minds in diabetes technology at the 6th International Conference on Advanced Technologies & Treatments for Diabetes (ATTD). Held in Paris, France from February 27 to March 2, attendance reached an ATTD record 2,000+, nearly tripling since the conference's 2008 inception in Prague with 742 attendees. We have watched the conference evolve significantly over time from Prague to Basel to Athens to London to Barcelona to Paris over the last six years as so much in diabetes technology has evolved; ATTD has done a terrific job of bringing together top researchers in very focused gatherings in successful meetings and it is no surprise that ATTD continues to receive such strong feedback and continues to see a higher number of attendees each year.

As we've come to expect, ATTD brought forth a wealth of new data. On the artificial pancreas side, multiple groups provided updates on ongoing outpatient closed-loop studies; (notably, in some ways, we felt like ATTD 2013 was a preview of ADA and even next year's major presentations). Earlier-stage closed-loop research focused on "fine-tuning" the AP – for example, adding activity monitors, incorporating pramlintide, speeding insulin absorption. Certainly, the academic community appears to be thinking creatively about how to innovate and optimize these systems with a mix of novel research along with incorporating available tools and technologies.

In some ways, ATTD 2013 was a meeting dominated by CGM. On the sensor side, we heard a slew of new accuracy data on Roche's prototype sensor, Medtronic's Enlite Improved, and Dexcom's AP version of the G4 Platinum, among others. We're glad to see so much emerging competition in the CGM arena, since that will translate into more options for patients, a heightened industry-wide drive to make compelling products that improve patient outcomes, and hopefully, greater penetration of the technology. At the same time, the magnitude of improvements with these next-generation sensors and improved algorithms reminded us that the field is still young and there is lots of upside that we hope will drive penetration (the memory for early-stage devices is unfortunately very long). We also felt that new companies, namely Roche and Becton Dickinson, were more forthcoming about their CGM projects and intent to enter the field as major market players, likely in no small part due to encouraging early research. In addition to data-driven presentations, KOLs partook in broader discussions on whether CGM has changed clinical practice, whether RCTs to date are representative of CGM, and how best to standardize study design and data reporting.

And while CGM and the AP were front and center, we also enjoyed presentations on a breadth of other topics, including insulins and insulin delivery, software, type 2 diabetes, and bariatric surgery.

This report contains our full coverage of ATTD 2013, divided into eight sections: 1) Artificial Pancreas; 2) Continuous Glucose Monitoring; 3) Blood Glucose Monitoring; 4) Insulin and Insulin Delivery; 5) Type 2 Diabetes, Obesity, and Bariatric Surgery; 6) Hospital Diabetes Care; 7) Pharmacotherapy, Telemedicine, Software, and Other; 8) Exhibit Hall. Below, we discuss the major themes and our big-picture takeaways from the conference, followed by our coverage of individual presentations. Talk titles highlighted in blue were not previously published in our daily reports, while talks titles highlighted in yellow represent just a small sample of some of the most memorable presentations we heard.

- **Interim results emerged from multiple ongoing outpatient closed-loop studies.** A highlight of the conference was Dr. Moshe Phillip (Tel Aviv University, Petah Tikva, Israel) and

his team's presentation of interim results for DREAM 4, the overnight home study investigating the MD-Logic Artificial Pancreas System in pediatric patients. Full results are expected at next year's ATTD. It was certainly an eventful conference for Dr. Phillip and colleagues, as the team's landmark DREAM 3 camp study results came out in the *New England Journal of Medicine* on day one of the conference. In the same session, Dr. Boris Kovatchev (University of Virginia, Charlottesville, VA) updated attendees on his team's partially outpatient study of closed-loop control, using a DiAs-enabled smartphone connected to a Dexcom G4 Platinum receiver (via USB cable) and a Tandem t:slim pump (via low-power Bluetooth). In the first five patients, the system appears to have responded well to meal, alcohol, and exercise challenges. Meanwhile, Dr. Roman Hovorka (University of Cambridge, UK) previewed encouraging glucose profiles from patients in his team's three (!) ongoing home studies using the FlorenceD closed-loop system – impressively, Dr. Hovorka bypassed transitional studies (e.g., in a diabetes camp or hotel) and progressed straight from the inpatient to the home setting. The ongoing home studies are taking place without remote monitoring (this would never happen here in the US) and even include an adult day-and-night trial. News wasn't uniformly positive for closed-loop studies, however, as Dr. Bruce Buckingham (Stanford University, Stanford, CA) showed very disappointing one-year data from a trial assessing the impact of closed-loop therapy in young people recently diagnosed with type 1 diabetes. We wonder whether two-year data will have more promising results, or perhaps whether newer-generation systems could have made a difference.

    - **In our view, the most key aspects to improve in the artificial pancreas are the speed of insulin action and the rapid glucose excursions seen after meals.** We believe incrementally better CGM and algorithms could nudge the needle slightly, but both have improved so much in recent years that truly substantial improvements in control will come with faster insulin (it's harder to imagine dramatically better CGM or algorithms changing the game whilst a 60-90 minute delay in peak insulin action exists; of course, improvements in both are very worthwhile to strive for, especially since faster insulin is undoubtedly coming). On the insulin absorption side, it was great to hear Drs. Howard Zisser and Eyal Dassau (University of California, Santa Barbara, CA) discuss preliminary results from use of MannKind's Afrezza (n=1) and Roche's DiaPort (n=6) in closed-loop insulin delivery. Both approaches had a very positive impact on postprandial glucose, and we look forward to more patients being tested by the time ADA rolls around in June. In terms of blunting postprandial rises, this year's ATTD did not have a huge focus on the use of adjuvant hormones. However, two presentations on pramlintide were of note: a closed-loop study out of Yale (pramlintide reduced postprandial excursions with significantly less insulin delivered) and one triple tracer study on the use of pramlintide in healthy individuals. We believe use of pramlintide and/or GLP-1 agonists is a ripe area for closed-loop research, especially as researchers look for ways to address high carbohydrate meals. We expect to see much more data come out, especially once phase 3 studies for liraglutide in type 1 begin.

- **ATTD 2013 was a big meeting for CGM, with new data and products shared by Roche, Medtronic, Dexcom, Abbott, BD, and others.** Roche drew lots of attention with never-before-seen data on its prototype CGM sensor – sensor readings were compared to the Accu-Chek Aviva meter to obtain an overall mean absolute relative difference (MARD) of 8.6% (n=30 patients; 7,039 data points). The study's methodology was somewhat controversial among attendees used to seeing YSI, so we'll be interested to see if this encouraging early accuracy data is confirmed in later studies. Meanwhile, Medtronic had an eventful meeting on the CGM front, displaying/discussing a plethora of CGM pipeline products: orthogonally redundant sensing in

partnership with the JDRF/Helmsley Charitable Trust, several algorithm improvements, the Enlite improved and Harmony sensors, and three new products on display in the exhibit hall (an integrated CGM sensor/insulin infusion set, a mobile hub that wirelessly sends pump and sensor data to CareLink and smartphone apps, and the recently CE Marked Sentrino critical care CGM). Competitor Dexcom showed off its exciting pipeline as well, offering the first look at Dexcom Share (remote monitoring), fresh data on the new AP version of the G4 Platinum sensor, and hot-off-the-press results from the G4 Platinum pediatric trial. Abbott was refreshingly outspoken about its new FreeStyle Navigator II, which has been under the radar since the low-key launch in Europe in fall 2012. The company provided a first-look at the updated receiver and 33% smaller transmitter, along with a review of the accuracy data (similar to the first-gen: a MARD of 12.3%). While BD did not share new data on its optical CGM sensor in development, the company expressed confidence in the science at this point, and emphasized the big goal going forward is to further miniaturize the system. We also heard new 90-day data (n=4) on Senseonics' implantable CGM, as well as the latest update on Glumetrics' intravascular critical care CGM.

- **Despite improvements in CGM accuracy, new products that complement the technology, and more companies entering the space, challenges remain.** First and foremost, penetration of CGM is still low, a point echoed by Dr. Irl Hirsch (University of Washington, Seattle, WA) in a presentation on use of CGM in the T1D Exchange. While more-frequent wear time is associated with a lower A1c, CGM use is still low at 9% overall and ~5% for people under 26 years old. The data prompted Dr. Hirsch to call for more research on making CGM desirable to use. We also enjoyed an excellent debate on whether the availability of CGM has changed the way we manage diabetes. Dr. John Pickup (King's College London School of Medicine, London, UK) argued that it has been very beneficial, though was honest in stating that RCTs have yet to produce substantial evidence demonstrating the value of CGM over SMBG with respect to severe hypoglycemia and quality of life. We sincerely appreciated his view that experiences in clinical practice are just as important as RCTs, though the payer perspective appears to remain very RCT-centric. Indeed, European reimbursement challenges were reviewed by his opponent, Dr. Joroen Hermanides (Academic Medical Centre, Amsterdam, The Netherlands) – France, for example, has no CGM reimbursement and both the UK and Germany provide reimbursement on a case-to-case basis. We're confident this will change in the coming years, especially as RCTs begin using newer gen devices that are more accurate and easier for patients to use and easier for HCPs to "teach".
- **Speakers questioned whether randomized controlled trials to date have been designed to appropriately access the benefits of continuous glucose monitoring.** Dr. Simon Heller (University of Sheffield, Sheffield, UK) suggested that the dearth of severe hypoglycemia events in CGM trials makes statistically significant reductions in severe hypoglycemia difficult to show. Dr. J. Hans DeVries (Academic Medical Center, Amsterdam, The Netherlands) noted similar challenges, which he attributed in part to the exclusion of patients with hypoglycemia unawareness in CGM trials. He posited that once CGM is formally studied in this patient population (two not-yet registered studies are on his radar), results will corroborate the benefits observed in clinical experience and observational studies. Problems characteristic of RCTs to date (e.g., that they are not designed to assess the effects of CGM on severe hypoglycemia, differing definitions of hypoglycemia, use of previous-generation CGM devices) are potentially compounded when included in meta-analyses. This is particularly

disconcerting when, as both Dr. DeVries and Dr. Heller noted, meta-analyses are the basis by which reimbursement authorities make decisions.

- **A number of presenters called for greater standardization in the development of glucose monitoring systems as well as the display of reports in practice.** Drs. Gary Thorpe (Gary Thorpe Associates Ltd, Birmingham, United Kingdom) and Guido Freckmann (Institute for Diabetes Technology, Ulm, Germany) urged caution when interpreting BGM accuracy comparison studies. A myriad of factors are capable of influencing accuracy results, including the number of samples, the type of sample (e.g., capillary vs. venous), the number of strip lots tested, and the comparison method – and that's just to name a few. Since regulatory processes alone do not guarantee meter accuracy (in part because companies submit their own data in the US), Dr. Thorpe saw an important need for well-conducted, independent accuracy comparisons. Dr. Freckmann took this one step further and envisaged a system of Centers of Excellence tasked with meter accuracy evaluations. We would love to see this. This same flavor of conversation emerged around the wealth of new sensor data presented. Should all sensors be compared to YSI? Roche's CGM presentation was a particular source of controversy, since the company's new sensor was compared to the Accu-Chek Aviva. Roche believes there are laboratory comparison methods superior to YSI (e.g., a perchloric acid deproteinization hexokinase comparison based on the "true" reference method isotope dilution mass spectrometry), but the question on our mind is can these be broadly implemented? Are meter comparisons acceptable in early-stage testing? And will regulators accustomed to YSI accept such a paradigm shift? On the data reporting side, an Abbott-sponsored symposium suggested that a universal, standardized summary report of continuous glucose sensor data, called the ambulatory glucose profile (AGP), could lead to easier data interpretation and help bring CGM data into clinical practice in a more meaningful way – this came just a day before an excellent joint publication from Bergenstal et al. in DT&T and JDST (for more information, see our report at https://closeconcerns.box.com/s/wvsp50bo4zqkakew7q61).
- **This year's ATTD brought a smattering of talks specifically addressing type 2 diabetes and obesity.** CeQur's PaQ insulin delivery device was a big hit in the exhibit hall following Dr. Thomas Pieber's (University Hospital of Graz, Graz, Austria) presentation of brand new usability data. A session on regional differences in type 2 diabetes treatment brought perspectives from China (Dr. Linong Ji), Europe (Dr. Cees Tack), India (Dr. Shashank Joshi), and the US (Dr. Irl Hirsch). Dr. Richard Bergenstal (International Diabetes Center, Minneapolis, MN) also discussed type 2 therapies in a session entitled "Treatment or Cure T2D" – GLP-1 receptor agonists were his clear favorite for optimizing A1c without weight gain or hypoglycemia. The session also included presentations by Drs. Dimitri Pournaras (Imperial College London, UK) and Dr. David Flum (University of Washington, Seattle, WA) on endoscopic alternatives to traditional metabolic surgery and the cost/benefits of metabolic surgery, respectively. Dr. Walter Pories (East Carolina University, Greenville, NC) also addressed metabolic surgery in one of our favorite presentations of the entire conference. He explored factors contributing to the under utilization of bariatric surgery in type 2 diabetes and obesity. Zeroing in on obesity therapies, we also heard from Aspire Bariatrics CEO Dr. Katherine Crothall who described the company's minimally invasive AspireAssist approach. Albeit small, we're glad to see some focus on type 2 diabetes and obesity at ATTD – the need is certainly huge, and we believe technology can help pave the way towards better outcomes.
- **ATTD's exhibit hall was replete with new product displays and timeline updates**. Medtronic's booth was front and center in the hall and a definite highlight. We saw three new products for the first time in person: an integrated CGM sensor/insulin infusion set, the recently

CE Marked Sentrino critical care CGM, and a mobile hub that wirelessly sends pump and sensor data to CareLink and smartphone apps ("Connected Care"). Meanwhile at the CeQur booth, sales representatives shared timeline details on the company's PaQ insulin delivery device for people with type 2 diabetes (EU launch in 2013-2014, preparing a 510(k) submission for US regulatory clearance). Updates abounded at other companies as well: Dexcom's booth emphasized the G4 Platinum's newly approved pediatric indication in the EU (US approval pending); Abbott had its updated FreeStyle Navigator II handheld on display, the first time we'd ever seen the new receiver in person (in contrast to the absence of a booth and no specifics on the device at EASD in October); Roche sales representatives indicated that the company is planning to submit the Aviva Expert blood glucose monitor with built in bolus advisor to the FDA this year (already available in the EU); Debiotech intends to outlicense its Jewel Pump after regulatory clearance; and Diasend is launching a mobile app later this year.

- **As much as the exhibit hall made us excited for the years ahead, so too did it remind us of the contrast in US and EU regulatory processes.** The discrepancy has led to companies employing a step-wise device submission strategy, whereby EU submission often occurs before US submission. We remain curious whether discussions about the safety-related shortcomings of the CE Mark process will translate into changes in the near-term, what those changes will look like, and whether they would have tangible effects on diabetes device submissions and approvals – would approvals take longer? Would they be less likely to occur? Would companies be more likely to submit in the US first? Would submission in the US become harder as gathering real-world data ex-US also becomes harder? Would independent safety and accuracy evaluations be required? Would changes in the EU motivate broader international changes? Especially in light of the EASD's recent statement urging an overhaul of the CE Mark system (see our *Closer Look* email at https://closeconcerns.box.com/s/af8pcu797hsw3qduw0ti), these questions are at the front of our minds.

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1. Artificial Pancreas

Session: ATTD Yearbook

CLOSING THE LOOP

Eyal Dassau (University of California, Santa Barbara, Santa Barbara, CA)

Of the 12 papers on closed-loop control in 2012, Dr. Eyal Dassau chose to discuss a survey of patient expectations for the artificial pancreas (van Bon et al.). "I am convinced that the closed loop is here and will be here to stay," said Dr. Dassau, but he highlighted this paper as a reminder that "ultimately the AP is for the patient." Indeed, he said that "patient perspectives and opinions must be considered as this technology develops" – not only algorithms, but also user interfaces and outcome metrics. Dr. Dassau then mentioned four major questions of near-term interest. These were: whether system individualization can be used to address inter- and intra-patient variability; whether sensors are accurate enough for closed-loop control (Dr. Dassau believes that they are, as long as we set conservative glycemic targets); whether sensor-based endpoints can be used for outpatient trials; and how best to design robust safety features for closed-loop systems. He also thanked Dr. Moshe Phillip's DREAM Consortium for their recent NEJM article and its "enormous impact on the field." Indeed, he expressed confidence that the results will help US researchers as they propose their own outpatient trials to the more conservative FDA.

Session: Closing the Loop at Home

DOES INTENSIVE METABOLIC CONTROL AT THE ONSET OF DIABETES FOLLOWED BY ONE YEAR OF SENSOR-AUGMENTED PUMP THERAPY IMPROVE C-PEPTIDE LEVELS ONE YEAR POST-DIAGNOSIS?

Bruce Buckingham, MD (Stanford University, Stanford, CA)

Dr. Bruce Buckingham unveiled long-anticipated – but sadly unsuccessful – one-year data from his group's randomized, controlled trial to preserve C-peptide levels in young people recently diagnosed with type 1 diabetes, through the use of hybrid-closed-loop therapy. The intensive group (n=48) received several days of inpatient closed-loop control within one week of diagnosis, followed by sensor-augmented pump therapy thereafter; the control group (n=20) received standard care with a different set of physicians. After one year, no statistically significant differences were seen in any of the metrics studied: C-peptide in response to a mixed-meal test, time course or peak level of C-peptide, percentage of

patients in the "honeymoon period" based on C-peptide levels, A1c, glycemic coefficient of variation as measured by CGM, percentage of time in CGM target zone of 70-180 mg/dl, or insulin dosage – whether the groups were analyzed as "intent-to-treat" or "per-protocol" (based on CGM usage). Dr. Buckingham maintained his trademark good humor and perspective as always, but he had clearly been hoping to share better news. During Q&A, two eminent researchers suggested that the two-year results might show significant differences in C-peptide (as occurred in the European ONSET trial of sensor-augmented pump use from diagnosis onward); nonetheless, Dr. Buckingham said that he does not expect much between-group difference to manifest during the remainder of the two-year trial. We wonder if more accurate CGM would have made a difference; we aren't positive which CGM was worn, but we believe it was the Medtronic Sof-Sensor combined with the Paradigm insulin pump.

Questions and Answers

Dr. Stephanie Amiel (Kings College London, London, United Kingdom): You showed data where you were looking at CGM values; some patients had data available for four days before starting on closed-loop therapy.

A: Patients were often consented at 2-3 days after diagnosis. At this point, we put them on blinded CGM. Everyone in the intensive group started hybrid closed-loop control within seven days of diagnosis, defined as when they first got insulin. There were some logistical issues in terms of when we got assigned the beds, nurses, etc. there was a physician and nurse at bedside at all times despite it being very close.

Dr. Peter Chase (Barbara Davis Center, Aurora, CO): Could you give us numbers of patients that no longer produced C-peptide? I am sure that Dr. Greenbaum's TrialNet dataset had a higher distribution of younger people. My memory of TrialNet is that about a third of older patients and roughly two-thirds of younger patients younger were not reaching the 0.2 threshold level of c-peptide. Isn't the really critical endpoint two years?

A: You are always the optimist. 20% in both groups had lost c-peptide at the end of one year. Will see a greater number lose C-peptide at two years; we are following subjects until two years out. I do not expect that we will see much difference.

Dr. Thomas Danne (Kinderkrankenhaus, Hannover, Germany): In ONSET, we had significant results only after two years. The higher percentage of kids who are in older age group, when you have a better chance of preserving C-peptide, the better your odds of positive results at two years.

Dr. Kaufman: Is there any relationship with diabetic ketoacidosis at onset? You are looking both to reduce hospitalizations and also for a link to c-peptide levels.

A: We did not see this.

Dr. Satish Garg (University of Colorado Denver, Aurora, CO): Did you look at the standard deviation and other indices of glycemic variability based on CGM data?

A: In one of the slides I showed coefficient of variation: standard deviation divided by mean. There was no between-group difference. But keep thinking! I want something to come out, at least one measure.

EFFICACY OF OUTPATIENT CLOSED-LOOP CONTROL

Boris Kovatchev, PhD (University of Virginia, Charlottesville, VA)

After reviewing the importance of modular design and quality control, Dr. Boris Kovatchev presented three outpatient feasibility studies of partially closed-loop control and/or remote glucose monitoring. The first trial, of a "range-control" system that supplemented patients' own diabetes control,

demonstrated successful communication among a DiAs phone, Dexcom's Seven Plus, Insulet's OmniPod, and an iPad application for remote monitoring (Diabetes Care, in press). The second was Dr. Bruce Buckingham's open-loop study of remote monitoring to reduce hypoglycemia at a diabetes camp (presented at EASD 2012). Thirdly, Dr. Kovatchev described an ongoing partially closed-loop study with an enhanced range-controller, Dexcom's G4 Platinum sensor, and Tandem's t:slim pump. In the first five patients, the system appears to have responded well to challenges like restaurant meals, alcohol, and 45 minutes of walking: mean low blood glucose index (LBGI) was dramatically reduced relative to open-loop control. He closed with a schematic of a future-generation closed-loop system. The system would be controlled by a smartphone running both medical and consumer operating systems as well as DiAs; this phone would communicate wirelessly with a Tandem pump and the Dexcom G5 'smart' transmitter. Also, the enigmatic Dr. Kovatchev noted, the system will contain "a secret ingredient that I will tell you about next year."

- **Dr. Kovatchev and his colleagues are midway through their latest outpatient study of hybrid closed-loop control.** The randomized, crossover-design study has no restrictions on meal size; restaurant dinners are mandatory, and alcohol is permitted. The protocol also includes light exercise (45 minutes of walking) as a hypoglycemic challenge. Patients spend 40 hours each under open- and closed-loop control. During both study conditions they use the same set of devices (see below); the only change is the setting on the smartphone controller.
    - **The study's first five subjects experienced good results in the primary endpoint, low blood glucose index (LBGI).** Dr. Kovatchev reviewed data from these subjects, all of whom were enrolled at the University of Virginia (see table below). He noted that this outpatient cohort's mean CGM (147 mg/dl) and time in the 70-180 mg/dl range (72%) were only slightly worse than in an inpatient study with "about the same system" (144 mg/dl and 77%, as reported in Breton et al., *Diabetes* 2012). The comparison is of course not quite apples-to-apples, but we agree with Dr. Kovatchev that the similarity is encouraging.

	Open-loop	Closed-loop
Daytime Hypoglycemic Episodes	6	1
Daytime LBGI	0.99	0.48
Nighttime Hypoglycemic Episodes	1	0
Nighttime LBGI	0.25	0.08

    - **The closed-loop system consists of a DiAs-enabled smartphone connected to a Dexcom G4 Platinum receiver (via USB cable) and a Tandem t:slim pump (via low-power Bluetooth).** (Dr. Kovatchev noted that the patient needed only the pump and the CGM sensor/receiver on their body; the smartphone and G4 receiver merely needed to be in the same room.) The DiAs smartphone runs an enhanced control-to-range algorithm designed by Pavia's Dr. Lalo Magni, as well as an insulin-on-board safety module developed by UCSB's Dr. Eyal Dassau and Dr. Frank Doyle.

OVERNIGHT CLOSED-LOOP CONTROL IN HOME SETTING

Roman Hovorka, PhD (University of Cambridge, UK)

The esteemed Dr. Roman Hovorka gave a snap shot of the Cambridge team's three ongoing home studies using the FlorenceD closed-loop system. FlorenceD was moved to the home setting in July; since then, his team has collected over 30,000 unsupervised, free-living hours on the system (in six months they have matched the number of closed-loop hours collected prior to the home studies). Impressively, given the team's confidence in their system and the wealth of simulation data they collected (over 100,000 nights worth), FlorenceD bypassed transitional studies (e.g., in a diabetes camp or hotel) and progressed straight from the in-patient to the home setting. The ongoing studies consist of an adolescent overnight trial (APCam06; n=16), adult overnight trial (Angela03; n=24), and adult day-and-night trial (AP@home02; n=18). At the time of his presentation, 13 patients had completed APCam06, three had completed Angela03, and three had completed AP@home02. Early results have shown positive benefits of FlorenceD (certainly, the individual patient glucose profiles that he displayed suggested as much); however, Dr. Hovorka was quick to remind attendees that the data presented was preliminary. Looking forward, Dr. Hovorka recognized that the size of the system, need to stop closed-loop control to deliver boluses, and limited battery life were limitations to use. We'll be interested to learn how the team intends to address these barriers moving forward.

- **As a reminder, the FlorenceD system consists of** the first generation Abbott FreeStyle Navigator CGM, the Companion (an investigational device to assist communication with the Navigator), a small bedside tablet running an MPC algorithm (in the day-and-night study this is worn in a carrying case on a belt), and a Dana R Diabecare pump (with Bluetooth connection). The interface is quite simple and involves turning the system on and off on the tablet. When the system is running, the control algorithm communicates insulin adjustments to the pump every 12 minutes and the CGM transmitter sends glucose information to the Companion every one minute. A physician first initializes the system, a process that requires entry of the patient's body weight and total daily insulin dose.
- **Study designs:** In a crossover design, adolescents in APCam06 are randomized to first receive either three weeks of overnight closed-loop control or three weeks of open-loop control. During closed-loop control, physicians stay close to the patient's home for the first 24 hours should they need to intervene. After this period, the three-week intervention period begins. Angela03 is similarly designed; however, the first 24 hours of closed-loop control take place in the CRC and the study's intervention periods are four weeks duration. In the AP@home02 trial, the first 24-hour period of both open- and closed-loop control occur in the CRC, followed by a seven-day period at home.
- **The Cambridge team is not employing remote monitoring during its home studies**. Risk is mitigated by appropriate training, a CGM calibration check prior to dinner, and reversion to open loop control if the system fails (e.g., sensor failure, communication with pump fails).

THE DIABETES WIRELESS AP CONSORTIUM (DREAM) INFRASTRUCTURE FOR ARTIFICIAL PANCREAS AT HOME

Tadej Battelino, MD, PhD (University Children's Hospital Ljubljana, Ljubljana, Slovenia) and Moshe Phillip, MD (Tel Aviv University, Petah Tikva, Israel)

With an NEJM publication on February 28, Dr. Tadej Battelino and his team's presentation of the DREAM project was an ATTD highlight. Dr. Phillip introduced the project, which investigates the MD-Logic Artificial Pancreas System in pediatric patients. The project is a four-step approach to bringing overnight closed-loop control to the home environment and is comprised of a feasibility study (DREAM 1), an inpatient overnight study (DREAM 2), an overnight study at a diabetes camp (DREAM 3), and an

overnight home study (DREAM 4). The control algorithm is based on fuzzy logic, which seeks to emulate the line of reasoning of diabetes caregivers by using if-then statements. DREAM 4 is currently underway, and Dr. Phillip was pleased to bring up his fellow researchers to present DREAM 3 results and interim DREAM 4 results. Neither Dr. Battelino nor Dr. Moshe Phillip (Tel Aviv University, Petah Tikva, Israel) spoke to future timelines for commercialization of the system during this presentation, however at ISPAD 2012 in October, Dr. Phillip remarked that a commercialized version could be on the market in the next two years – this would be an impressive and exciting feat indeed.

NOCTURNAL GLUCOSE CONTROL WITH AN ARTIFICIAL PANCREAS AT A DIABETES CAMP – STUDY DESIGN

Thomas Danne, MD (Kinderkrankenhaus auf der Bult, Hannover, Germany)

Dr. Thomas Danne provided detail on the MD-Logic AP system and DREAM 3 study. The MD-Logic AP (MDLAP) System is comprised of the Medtronic Paradigm Veo pump, Medtronic Enlite continuous glucose sensor, Bayer Contour-Link blood glucose meter, and a real-time remote monitoring system. DREAM 3 was as a transitional overnight closed loop study that took place at three diabetes camps located in Europe. Participants were randomized to two arms (overnight closed-loop control with MDLAP and open-loop control) in a crossover design study. Primary endpoints included the number of hypoglycemic events below 63 mg/dl, time below 60 mg/dl, and mean overnight glucose level. For a deeper dive into the study design and background on DREAM 1 and DREAM 2, see page 18 of our ATTD 2012 report at https://closeconcerns.box.com/s/c6run7lro5jt5p64tnpu.

NOCTURNAL GLUCOSE CONTROL WITH AN ARTIFICIAL PANCREAS AT A DIABETES CAMP – STUDY RESULTS

Thomas Danne, MD (Kinderkrankenhaus Auf der Bult, Hannover, Germany)

For those who hadn't yet read the NEJM paper published earlier in the week, Dr. Thomas Danne reviewed results from the DREAM 3 trial. As a reminder, this was the DREAM Consortium's crossover-design study of overnight closed-loop glucose control in young people at type 1 diabetes camps (n=54). Compared to open-loop overnight control with a sensor-augmented pump, use of the closed-loop system led to statistically significantly less hypo- and hyperglycemia. Dr. Danne attributed the success of closed-loop control mainly to some combination of three factors: the amount of insulin delivered (e.g., more insulin was given at night), the timing of insulin delivery (e.g., the closed-loop system commonly delivered a series of small boluses at night), and the presence of a sophisticated hypoglycemia alarm module (which was activated at a mean CGM value of 78 mg/dl, as opposed to 65 mg/dl for open-loop control). Areas of future improvement include alarm sensitivity (so that fewer carbohydrate interventions are required) and CGM accuracy (so that the sensors do not need to be recalibrated as often – in this study recalibration was required on roughly half of patient-nights for both open- and closed-loop control).

- **The final results of the DREAM 3 Trial included 54 children and adolescents with type 1 diabetes.** These participants had a mean age of 14 years, mean A1c of 8.0% ("as good as it gets" in the pediatric population, Dr. Danne said), mean duration of pump therapy 4.8 years, and a mean body mass index of 20.8 kg/m^2 (a "European" BMI, Dr. Danne quipped).
- **Compared to open-loop control with sensor-augmented insulin pumps, closed-loop control conferred statistically significant reductions in both time spent below 70 mg/dl and time spent above 180 mg/dl** (as measured by CGM). (Closed-loop control also

lessened the time that people spent above 140 mg/dl, but this change did not achieve statistical significance.) Dr. Danne further showed that closed-loop control led to significantly fewer hypoglycemic events. The reduction was seen whether hypoglycemia was defined at a threshold of 70 mg/dl (36 open-loop events vs. 12 closed-loop events) or 60 mg/dl (18 open-loop events vs. 6 closed-loop events).

- **The near-term success of single-hormone hybrid-closed-loop systems will depend on predictive hypoglycemia alarms and carbohydrate interventions, Dr. Danne said.** (He acknowledged that bihormonal systems were also an option, though he added that "in my mind, [the bihormonal approach] adds a lot of complexity and problems.") The total number of carbohydrate interventions was similar between nights of open- and closed-loop control: 25 and 26 interventions, respectively. These interventions tended to be slightly smaller with open-loop control (19.1 g) than closed-loop control (24.4 g). The rates of alarms were similar between groups, but the mean CGM value at the time of alarm was lower with open-loop control (65.2 mg/dl) than closed-loop control (77.7 mg/dl). Dr. Danne attributed this difference to the more-sophisticated alarm used by the closed-loop controller – intuitively, earlier warnings are more useful.
- **Dr. Danne addressed several limitations and potential criticisms of the study, including its use of CGM values as a performance metric.** On that point, Dr. Danne explained that CGM values can be retrospectively transformed based on their inherent probability of being above or below the actual glucose level (Hovorka et al., Diab Technol Ther 2012). This approach yields results that are theoretically more robust than the untransformed CGM values. The DREAM Consortium therefore re-analyzed their data after transforming the CGM values in this way; encouragingly, the benefits of closed-loop control remained statistically significant. Other limitations included the short duration (each patient was studied for only one night in each condition) and the short washout period between study nights (which is an issue because "hypoglycemia begets hypoglycemia," though results were similar whether patients underwent closed-loop control before or after open-loop control). Another issue was the frequent need to perform sensor recalibrations, as seen with both open-loop control (29 out of 54 study nights) and closed-loop control (26 out of 54 study nights). However, Dr. Danne said that "anyone running sensors during a camp" knows that recalibration is often needed – fewer recalibrations will likely be needed with future CGM systems.

HYBRID CLOSED-LOOP DAYS AND NIGHTS IN A DIABETES CAMP

Eran Atlas, MSc (Schneider Children's Medical Center, Petah Tikvah, Israel)

In a 24-to-36-hour diabetes camp study completed "basically a week ago," Mr. Eran Atlas and his colleagues evaluated a next-gen hybrid closed-loop system. They focused on what Dr. Atlas called the "two big pieces" critical for outpatient success: inter-device connectivity and CGM performance. Two sensors were evaluated: Medtronic's "Enlite Improved" – a version of the Enlite with modified electrode, transmitter software, and form factor – and Medtronic's "Harmony," which features two electrodes, an algorithm that selects which to use at a given time, and a transmitter communicating via Bluetooth low energy. Glucose control in the 18-patient study was good, similarly to that of earlier DREAM trials: no values were observed below 70 mg/dl, 64% were within 70-140 mg/dl, and 6% were above 180 mg/dl. As for CGM accuracy, during hybrid closed-loop control, mean absolute relative difference (MARD) were 13.4% for the Harmony and 15.6% for the Enlite Improved – still far from ideal in our view, but better than the DREAM Consortium's experience with the standard Enlite.

AN OVERNIGHT AUTOMATED CLOSED-LOOP, MD-LOGIC SYSTEM AT PATIENTS HOME

Revital Nimri, MD (Schneider Children's Medical Center of Israel, Petach Tikvah, Israel)

On behalf of the DREAM consortium, Dr. Revital Nimri presented interim results from the DREAM 4 Closed-Loop trial, which compares overnight glycemic control with the MD-Logic AP (MDLAP) system to sensor augmented pump (SAP) control in the patient's home. Dr. Nimri's analysis included data from 20 patients, five from a pilot feasibility study for the home study and 15 from the completed Israel site (the full DREAM 4 study will include 30 more patients, 15 from the Slovenia site and 15 from the Germany site). Interim results showed significant reductions in the number of nocturnal hypoglycemic events and duration of nighttime hours spent in hypoglycemia compared to SAP therapy. Further, MDLAP resulted in a significantly higher percentage nighttime hours spent in range (70-140 mg/dl). The interim results look promising and we look forward to the full results, which Dr. Nimri expects to emerge at next year's ATTD.

- **This randomized, crossover, single-blind study compares four consecutive nights of MDLAP control to four consecutive nights of SAP control;** the full study will enroll 45 patients across three sites (15 of 45 have completed). After an initial run-in period with the sensor and an assessment period to optimize pump settings, patients are randomized to four nights of either MDLAP or SAP control in a crossover design. The study is single blind such that the physician could not see whether patients were on open- or closed-loop control. As a reminder, MDLAP is comprised of the Medtronic Paradigm Veo pump, Medtronic Enlite continuous glucose sensor, Bayer Contour-Link blood glucose meter, and a real-time remote monitoring system.
- **Primary endpoint is time spent below 70 mg/dl and the percent of nights in which mean glucose is in range (90-140 mg/dl)**. Secondary endpoints include glycemic control variables (including other hypoglycemia-related metrics), artificial pancreas technical performance, and psychological endpoints (importantly, fear of hypoglycemia).
- **The interim analysis showed that patients on closed-loop control spent a significantly lower percentage of nighttime hours <70 mg/dl than patients on SAP control** (0.6% vs. 8.6%; p=0.001). The interim analysis recorded several hypoglycemic metrics, including the number of events and the area under the curve when hypoglycemia was defined to be <63 mg/dl and <70 mg/dl.

Hypoglycemia	MDLAP	SAP	P-value
Total Events <70 mg/dl	0	0.4	0.05
Total Events <63 mg/dl	0	0.3	0.002
Area Below 70 mg/dl	0.02	0.8	0.001
Area Below 63 mg/dl	0	0.33	0.0001
Low Blood Glucose Index	0.3	1.8	0.002

- **Further, patients spent a significantly greater percentage of nighttime hours in range (70-140 mg/dl) on closed-loop vs. SAP control (57.2% vs. 39.8%; p=0.03).**
- **MDLAP use resulted in a statistically significant decrease in fear of hypoglycemia (p=0.036), as assessed by the Children's Hypoglycemia Fear Survey, and overall**

satisfaction with MDLAP appeared high. On a scale of one to five, with five representing the highest score, patients responded with a mean score of 4.3 to the statement "I would like to use the AP for a long time." Further, "I would like immediately to use the AP" and "The AP alerts were accurate" scored 4.5 and 4.1, respectively. The latter is particularly encouraging given the potential frustrations and alarm fatigue associated to high rates of false alerts.

- **"Safe, safe, safe."** During Dream 4, no severe adverse events were observed – there were no episodes of diabetic ketoacidosis or severe hypoglycemia.

Questions and Answers

Dr. Fran Kaufman (Chief Medical Officer, Medtronic Diabetes, Northridge, CA): We appreciate the ability of the AP to be in the home. I wonder if we could use a common set of metrics that we could all be presenting over and over again in study to study so there could be internal logic as we interpret them all.

Session: Closing the Loop

EXERCISE INDUCED HYPOGLYCEMIA REDUCTION IN T1D: A FIRST STEP TOWARD CLOSED-LOOP SYSTEM

Satish Garg, MD (Barbara Davis Center, Denver, CO)

Dr. Satish Garg reviewed the in-clinic ASPIRE study of Medtronic's Veo pump with low glucose suspend – as a reminder, he presented on the study's results at ATTD 2012 and ADA 2012, and complete results were published in Diabetes Technology & Therapeutics *(Garg et al., 2012). He called it the "hardest study that I've done in the past three and a half decades in my life." Most interesting were some of his nuanced comments around the study's design and the interesting finding that "hypoglycemia begets hypoglycemia." As a reminder, the in-home ASPIRE study is currently underway in the US (ClinicalTrials.gov Identifier: NCT01497938).*

- **Dr. Garg reviewed the interesting finding that hypoglycemia begets hypoglycemia (presented in an oral at ADA 2012).** In ASPIRE, patients who underwent LGS-on experiments on their first study day recovered from hypoglycemia much faster than those whose LGS-on experiments came on the second study day (said differently, patients starting with LGS-off were still affected by the prolonged hypoglycemia induction from the first experimental day, even following the 3-to-10-day washout period). He called this a "very important lesson for future investigations," especially for crossover studies. He called for lengthening the washout period or considering alternatives to crossover designs. Dr. Garg hypothesized that depletion of glycogen and the failure of counter-regulation may have contributed to the hypoglycemia-begetting-hypoglycemia phenomenon.
    - **Two factors were significantly associated with the order effect: preceding cumulative induced hypoglycemia (number of minutes) and number of attempted experiments.** For example, take an individual that only required one initial experimental attempt and had ten days between the first and second crossover experiments. That patient had a lower likelihood of experiencing hypoglycemia the second time vs. those who had to repeat experiments and had fewer washout days.
    - **To read the full details of the ASPIRE study,** see the publication by Garg et al., in *Diabetes Technology & Therapeutics* (2012). To read our coverage of Dr. Garg's recent

presentations on ASPIRE, see pages 83-85 of our ADA 2012 report at https://closeconcerns.box.com/s/phnv2z6hpe8x4r81v1kw.

- **AP studies need to be done in individuals where it's likely to give the most benefit: those with hypoglycemia unawareness and a history of severe hypoglycemia.** Dr. Garg lamented that unfortunately AP studies (such as ASPIRE) have specifically excluded these populations. He went on to note that in almost all studies of CGM and pumps, these individuals are excluded.
- **When patients in the T1D Exchange are stratified by A1c, prevalence of severe hypoglycemia is identical** – ~6-9% of patients had severe hypoglycemia. Interestingly patients at an A1c of 6% and over 11% both had a 6% prevalence of severe hypoglycemia percentage.A1c and hypoglycemia from T1D Exchange. Dr. Garg noted this is a contrary to what is generally expected (and what was found in the DCCT): intensified management increases the amount of severe hypoglycemia.

Questions and Answers

Dr. Howard Zisser (Sansum Diabetes Research Institute, Santa Barbara, CA): You have data around the 50-70 mg/dl range for YSI and the sensor. What is the MARD? And what was the YSI on average when LGS kicked in?

Dr. Garg: In the full manuscript, we have published the mean blood glucose that was on the meter, on the sensor, and on the YSI. To answer the YSI vs. sensor glucose question, it was a difference of about 8 mg/dl – what you'd expect. But for many patients, we had to wait two or three hours – they spent all day in the clinic. Remember, the observation phase does not start until YSI goes down to 70 mg/dl. We had many times where blood glucose was 71 or 72 mg/dl for two hours. The protocol was so strict. That's the reason why many patients ended up staying longer.

Dr. Aaron Kowalski (JDRF, New York, NY): One of the concerns of FDA has been a decrement in A1c. JDRF has argued that is an unfair bar. It should be on the clinician and the patient to determine what they're willing to tradeoff. For instance, going from a 6.5% A1c to a 6.8% A1c is a fair tradeoff for a reduction in severe hypoglycemia.

Dr. Garg: In all my years of clinical practice, severe hypoglycemia, is more detrimental and more negative than anything – it doesn't allow you to intensify management. Patients are not willing to listen to you and won't come back into the clinic. I don't understand why FDA does not realize that reducing severe hypoglycemia is far more important than a small rise in A1c. I would go even farther than what you said – a rise from 7.5% to 7.8%. We need to be realistic. When you look at complications, they have significantly gone down. We need to be more realistic rather than having imaginary targets. [Applause]

Dr. Kowalski: I agree.

CLINICAL AND ENGINEERING ASPECTS OF IP INSULIN DELIVERY IN CLOSED LOOP STUDY – THE DIAPORT EXPERIENCE

Eyal Dassau, PhD (UCSB, Santa Barbara, CA),

Dr. Eyal Dassau presented preliminary results of the JDRF-supported closed-loop trial of Roche's DiaPort. The study is comparing fully closed-loop control (i.e., no meal announcement or pre-meal bolusing) using subcutaneous delivery to Roche's DiaPort (intraperitoneal delivery). For the six patients thus far, intraperitoneal delivery increased time-in-range by 27% (70-180 mg/dl) during the postprandial period and decreased average blood sugar from 193 mg/dl to 147 mg/dl. This translated to

a mean 59 mg/dl lower postprandial glucose peak. Dr. Dassau also noted that glucose turnaround following pump suspension was much faster. Still, the study's fully closed-loop nature meant control was not amazing – he cautioned that large unannounced meals are still a challenge, even with intraperitoneal insulin delivery. Moving forward, the team plans to further tune the closed-loop algorithm to optimize control with IP delivery. The results are encouraging, though also highlight that if ultra-fast insulin delivery was widely available tomorrow, we would still have room to improve the fully closed-loop

- **Dr. Dassau reviewed the design and implantation of Roche's DiaPort.** He showed pictures of the fairly short 30-45 minute implant procedure. The DiaPort is a transcutaneous port that enables Roche's Accu-Chek Combo insulin pump (worn externally) to deliver insulin directly into the intraperitoneal (IP) space. A single unit of IP-delivered insulin has a 10-minute absorption peak, as compared to 50-60 minutes for subcutaneous delivery. Also, a greater percentage of IP-delivered insulin is cleared by the liver, a route characteristic of endogenous insulin. "Yes, it's invasive," noted Dr. Dassau, and it's "probably not for everybody. But it's one option for people that want to try it." This study selected patients who had subcutaneous absorption problems and "IP was their last resort."
- **This 27-hour study compared closed-loop insulin delivery with Roche's DiaPort to subcutaneous delivery.** The system used Sansum's Artificial Pancreas System (APS) interface with a Dexcom Seven Plus CGM (there wasn't enough time to get Dexcom's G4), an Accu-Chek Spirit pump, and Zone-MPC control with a Health Monitoring System. Each patient serves as his or her own control group, using intraperitoneal delivery in one experiment and subcutaneous delivery in the other. Patients were admitted at 2 pm, closed loop began at 4 pm, and discharge occurred at 5 pm the following day. Unannounced meals (i.e., no pre-meal bolus or system input) were eaten at 7 pm (70-grams of carbs), breakfast at 8 am (40-grams of carbs), and lunch at 1 pm (70-grams of carbs). It's great to see such ambitious meal sizes to really challenge the system.
- **Preliminary results from six patients suggest IP delivery improves average blood glucose (193 mg/dl to 147 mg/dl) and reduces postprandial hyperglycemia.** The average postprandial peak was 59 mg/dl lower with IP delivery (range: 28-98 mg/dl), and patients spent 27% more time in the range of 70-180 mg/dl following meals. Nocturnal control was stable with both types of delivery. IP delivery required an average of 52 units, compared to 35 units for subcutaneous delivery.
- **This study of fully closed-loop control was intended to "push the envelope" and minimize patient burden.** Meals were unannounced and there was no pre-meal bolusing – certainly, either of those strategies, along with smaller meals, would have resulted in much better results.
- **"When you suspend the pump, you really suspend it."** Dr. Dassau explained that the DiaPort's fast-in, fast-out delivery (and relative lack of an insulin depot) means suspending the system can very quickly attenuate a rapidly declining glucose. This is in contrast to subcutaneous delivery, where suspending the pump does not raise glucose until about an hour later. This reminded us of yet one more reason why faster insulin delivery is so key for closed-loop control.
- **We respect Sansum's desire to minimize patient burden by developing an AP that does not require user intervention** – it's certainly a tough challenge given the current speed of insulin, but with emerging approaches to address slow delivery (MannKind's Afrezza [being tested in another Sansum study], BD's microneedles, Halozyme's PH20, InsuLine's InsuPatch,

and ultra-rapid-acting insulins from Novo Nordisk and Biodel, among others), it may not be quite as far fetched as was thought a few years ago.

Questions and Answers

Dr. Aaron Kowalski (JDRF, New York, NY): For obvious reasons, we think of type 1 diabetes as an insulin-centric disease. But the role of glucagon and amylin in the postprandial period is often ignored. We're trying to challenge the system with unannounced meals. But in people without diabetes, you have a cephalic insulin response. Perhaps you need a pre-meal bolus – especially given the DiaPort's intraperitoneal delivery – maybe there is important talking to liver that would happen.

Dr. Dassau: Yes. We really tested the water here. Maybe we made a mistake of trying to go for unannounced meals. Testing the envelope is engineering thinking. We would have had better results with a pre-meal bolus here. It's something to consider.

Dr. Howard Zisser (Sansum Diabetes Research Institute, Santa Barbara, CA): There's also the idea of combining inhaled insulin with intraperitoneal delivery. We don't have that much PK/PD data with IP. Inhaled insulin would allow us to get something in quicker to turn the liver off.

Dr. Yogish Kudva (Mayo Clinic, Rochester, MN): Have you looked at day-to-day variability in terms of the bioavailability of IP vs. subcutaneous? And there concerns regarding development of insulin antibodies?

Dr. Dassau: We haven't looked at the variability data – we don't have that data. We're just starting the research around that. Hopefully we can answer that better in the future.

Dr. Zisser: There is a subset of patients that develop high insulin antibodies. There is a certain cutoff level they won't do DiaPort implantation for. Occasionally, an explant is needed for someone who develops high antibody titers.

Dr. Roman Hovorka (University of Cambridge, UK): For the control algorithm, it seemed that you used different controllers. IP had lower glucose levels and was giving more insulin. Could some of the differences observed in IP delivery be related to the controller?

Dr. Dassau: You're right, we did make slight modifications between controllers. The insulins have different kinetics. That has to be taken under consideration in MPC. We need to analyze the data more and understand if it's more the controller or IP delivery. Yes the controller is more aggressive, but based on simulations, that was more the model of IP delivery than the aggressiveness of the controller.

Dr. Zisser: We need to wait to see what the insulin levels show. It might be delivering more insulin, but the insulin is not hanging around.

Dr. Hovorka: How did you tune the two controllers?

Dr. Dassau: We used simulations. We're not trying to beat the simulator using CVGA or time-in-range.

Q: Once the DiaPort is implanted, is there inflammation?

Dr. Zisser: So far, only 10 have been implanted. This is the second-gen DiaPort. They put a Dacron cuff on it. Ideally, some of the skin will grow in. Previously, there was a problem with skin infections. Occasionally the catheter becomes occluded, but that's just a simple office procedure.

Q: Can you talk about the catheter occlusion with the first-gen DiaPort?

Dr. Zisser: I have no direct experience with that. With the Medtronic implantable pump, there was occlusion and sometimes crystallization of the insulin, but that was U-400. Sometimes you got a fiber in the tip that you could flush off.

IN SILICO TESTING: THE GOOD, THE BAD AND THE UGLY

Roman Hovorka, PhD (University of Cambridge, Cambridge, UK)

Clinical testing during artificial pancreas development is resource and time intensive, explained the esteemed Dr. Roman Hovorka. In-silico testing stands to accelerate this process in three important ways. First, simulators can replace animal testing, which is required by the FDA. Second, simulator studies can help optimize the controller in terms of design control parameters and safety as well as predict controller performance. Third, simulators can be used to test the controller's robustness in challenging situations that investigators would not want to befall their patients in clinical testing (e.g., sensor error, user error, parameter misspecification). Dr. Hovorka reviewed the weaknesses and strengths behind the design of four simulators – Sorenson, Cambridge, Medtronic, and Virginia/Padova – with the underlying message that the quality of a simulator depends on the purpose it is being used for. As to the path forward, Dr. Hovorka believes that simulators need to make advancements in their models of meal absorption and intra- and interday variability. He envisions the future of in-silico testing to be based on "synthetic populations" built via stochastic "in silico experimental cloning," such that simulations can represent wider, more variable populations.

- **Replacing animal studies**: Only the Virginia/Padova simulator is accepted by the FDA for this purpose. As such, Dr. Hovorka characterized it as the only "good" simulator to use.
- **Optimizing the controller**: The appropriateness of the simulator depends on its ability to predict the outcome of clinical trials. Dr. Hovorka contends that the Cambridge, Medtronic, and Virginia/Padova simulators fall somewhere in the range of "good" to "bad," while the Sorenson simulator is "ugly" because the model represents a single, "average" subject, which would not represent a clinical study population.
- **Robustness testing**: Like with controller optimization, the quality of the simulator for this purpose depends on its ability to predict clinical outcomes. However, unlike with optimization, it needs to predict outcomes in what Dr. Hovorka calls the "outside envelope" (i.e., the extreme, challenging situations). For this, Dr. Hovorka believes that currently all simulators would be classified as "bad."

Questions and Answers

Dr. Howard Zisser (Sansum Diabetes Research Institute, Santa Barbara, CA): If two or three groups take the same clinical data and they use their own concepts to create simulators, how close do you think they would be to each other? How much does the data used to build the simulator affect the output?

A: It could be quite different. How you structure the simulator could have effects later on. Both groups will be able to fit the data well. The question is whether these models will represent what will happen clinically.

Q: How many subjects is sufficient to appreciate the variability?

A: I would be tempted to say in principle the same number you use for your study. But if I look at the pharmaceutical industry, they simulate the same trial not once, but a number of times with different subjects. There are random factors and random errors in these simulations.

Q: It appears that the simulator and control algorithms so far have been linked. Are simulators being used to analyze data across clinical trials that have used different control algorithms?

A: My understanding is that the Virginia/Padova controller has been used extensively by other groups. For our simulator, we also provide educational licenses and have centers using it in various settings.

Q: In AP@home, have you compared simulators?

A: We took the Padova/Virginia simulator and predicted the performance of our controller and vice versa. We have the data and it should be published – I think one of the reason it's not published is that we found differences between the real trials and differences between centers, where simulators would predict some centers well but not others. It's difficult to conceptualize why.

Dr. Boris Kovatchev (University of Virginia, Charlottesville, VA): You based your presentation of the Padova/Virginia simulator on a paper that does not represent the simulator. The simulator's model is based on 350 people and it has time variant parameters and other things not presented in the public domain.

Session: Artificial Pancreas Data Club Open Forum

USE OF A FUZZY LOGIC CONTROLLER DURING EXERCISE AND DURING A HIGH CARBOHYDRATE/HIGH FAT MEAL ON SEPARATE DAYS

Richard Mauseth, MD (Benaroya Research Institute at Virginia Mason, Seattle, WA)

Dr. Richard Mauseth described interim results of two fully closed-loop experiments using his group's fuzzy-logic controller. In the first experiment (n=3), patients ate pizza – a meal high in both carbohydrate (~120 g) and fat (~60 g) – on several separate days, with the controller's aggressiveness re-tuned on an individual basis between each visit. The postprandial excursions got dramatically smaller after the first round, but still pizza remains "difficult to handle" ("especially the Hawaiian – it's worse than the others"). In the second experiment (n=2), patients exercised for 30 minutes up to 70% of their V02-max. Dr. Mauseth showed results that looked favorable but said that the data were still too early to analyze. We admire this ambitious team for tackling high-fat, high-carb foods head-on; we think that such meals will pose some of the greatest challenges for any system that tries to handle all of a patient's insulin dosage. The next step is to prepare FDA submission of an updated control algorithm, which will be more aggressive when glucose levels are rising (or relatively high and flat). Dr. Mauseth and his colleagues will then enroll more patients in the exercise and pizza studies, which we understand to be funded by the same JDRF grant.

- **Dr. Mauseth reviewed his group's fuzzy logic controller, which is based on a dosing matrix** (Mauseth et al., JDST 2010). He graphically represented this matrix as a two-dimensional grid. Along one dimension were different glucose levels, and along the other dimension were different patterns of glycemic change. Thus each square in the grid corresponds to an insulin dose that would be given for a particular CGM trace. The controller's "degree of dosing aggressiveness" is defined by a number from called personalization factor (PF): lower PF means greater aggressiveness, and higher PF means less aggressiveness. Between each patient's visit in the pizza study, the controller's PF is being automatically changed according to an algorithm that seeks primarily to avoid hypoglycemia and secondarily to keep sensor glucose below 160 mg/dl.

- **In both experiments, the system consisted of:** two Dexcom Seven Plus sensors, an OmniPod, and the Sansum/UCSB APS closed-loop communication platform.

Questions and Answers

Q: Why did you have patients exercise to 70% of V02 max?

A: We originally had 80%, and the FDA told us we couldn't do it. That's why we had to take it down to 35-year-olds rather than 40-year-olds; FDA was concerned about cardiac problems.

AUTOMATED CLOSED LOOP CONTROL USING INHALED INSULIN TO MIMIC FIRST-PHASE PRANDIAL INSULIN

Howard Zisser, MD (Sansum Diabetes Research Institute, Santa Barbara, CA)

Dr. Howard Zisser described the first clinical study of inhalable Technosphere insulin (MannKind's Afrezza) as an adjunct to closed-loop control with a pump and CGM. He explained that the Sansum/UCSB researchers are seeking to develop an artificial pancreas that requires minimal interaction from patients. However, for fully reactive systems delivering subcutaneous insulin, even moderately sized meals (40-50 g carbohydrate) will cause significant hyperglycemic excursions and/or rebound hypoglycemia. They therefore tried augmenting their zone-MPC closed-loop control system with unannounced mealtime use of Technosphere, which has an "ultra-rapid" on/off profile that blunts postmeal excursions. This means that the closed-loop controller itself does not need to deliver as much insulin – in theory leading to less postmeal hyperglycemia and less risk of hypoglycemia. Compared to closed-loop control alone, the addition of Technosphere caused one patient's peak postmeal excursion to change from 64 mg/dl to 24 mg/dl. Dr. Zisser acknowledged that not all of the preliminary results are so "perfect." Nonetheless, he seemed excited to complete the 10-patient trial in the coming weeks and to report results in the coming year.

- **Dr. Zisser explained that Technosphere insulin can be difficult for type 1 diabetes patients to dose precisely when it is the sole source of insulin; however, he said that it could be a great addition to otherwise-closed-loop-control.** Doses of Technosphere come in increments of 10 units, which effectively translate to roughly 3-to-4 units given Technosphere's bioavailability of 30-to-40%. (Dr. Zisser said that this bioavailability probably varies between individuals but is probably fairly consistent among individuals.) This quantized dosing means that patients with type 1 diabetes cannot precisely match Technosphere insulin to carbohydrate intake although in theory they could match carbohydrate to TI dose. However, if patients augment closed-loop control by taking a minimum dose of Technosphere with any meal above a certain size (e.g., 30-to-40 g), then their postmeal excursions would be significantly blunted even before the controller can react. Thus the closed-loop control algorithm would not need to deliver as much subcutaneous insulin (which has a longer lag than Technosphere). Ideally, the result would be better time-in-range and less risk of hypoglycemia.

Questions and Answers

Q: Could you elaborate on the dose-dependency of Technosphere's glycemic effect?

A: Tomorrow I will show data where Technosphere cancels out postprandial peak altogether. In this study we are using the smallest possible dose, just to cancel out a bit of every meal. Insulin-resistant patients might use a higher dose.

Q: Is Technosphere dosage announced to the system's insulin-on-board (IOB) algorithm?

A: The IOB would know nothing, but in the case of glucose decline then you would get rate-of-change alarms. The goal of adding Technosphere to closed-loop control is that instead of having a rapid rate of rise, you would have a shallower-sloped rise, so the controller basically doesn't have to work as hard.

THE TYPE 1 DIABETES SIMULATOR: INCORPORATION OF STOCASTIC INTRA- AND INTER-DAY VARIABILITY

Chiara Dalla Man, PhD (University of Padova, Italy)

Dr. Chiara Dalla Man provided an update on her group's work to update the FDA-approved in silico type 1 diabetes simulator. Notably, her group is adding physiologically based intra- and inter-day variability in insulin sensitivity and carbohydrate absorption. This will allow researchers to run simulations of multiple meal, multiple day closed-loop experiments. Based on results from a Mayo Clinic/NIH study and the AP@Home CAT trial, Dr. Dalla Man showed how the researchers have clustered intra-day variation in insulin sensitivity into four groups: lower insulin sensitivity at breakfast (35% prevalence in the population, the most common), higher insulin sensitivity at breakfast (25%), higher insulin sensitivity at dinner (25%), and equal insulin sensitivity at breakfast, lunch, and dinner (15% prevalence in the population). Each virtual subject is randomly assigned to one of these four classes. Inter-day variation in insulin sensitivity will be randomly generated, meaning insulin sensitivity will change and deviate from the four aforementioned profiles. On the glucose absorption side, the CAT trial suggested that it is significantly faster at breakfast relative to lunch and dinner – Dr. Dalla Man noted that the difference stems from the high carb meal content at breakfast. Thus, high carb meals will be modeled with a 100% absorption rate, while lower carb meals will assume a 65% absorption rate. Dr. Dalla Man concluded that this work is especially important for simulations of longer ambulatory trials.

Questions and Answers

Q: You assign patients to four classes each time you run the simulation? Or permanently?

A: In the current version, we assign each subject. We can include this option to make subjects change in time, maybe in a longer period. We will try to do it. It's difficult to have data to do it in the proper way.

Dr. Kerstin Rebrin (BD, Franklin Lakes, NJ): Several people show breakfast is the hardest meal to control. But you had a group where breakfast had high insulin sensitivity. What could you say about that?

A: This is what we found in our trial – that breakfast has lower insulin sensitivity, in general. But this is not true for all the subjects. We had four possibilities.

RAPID DEVELOPMENT AND OUTPATIENT TESTING OF CLOSED LOOP APPLICATIONS USING THE DIAS AMBULATORY ARTIFICIAL PANCREAS PLATFORM

Patrick P. Keith-Hynes, PhD (University of Virginia, Charlottesville, VA)

Dr. Patrick Keith-Hynes, the developer of DiAs (UVa's Android-based artificial pancreas control platform), gave a general overview of how researchers can use the system in trials. The smartphone platform was designed to enable research and can wirelessly communicate with an insulin pump, a CGM, and multiple control algorithms loaded onto the device. It frees algorithm developers from having to know about many of the various aspects that go into the system: pump and CGM connectivity, building a backend database, user interface, etc. DiAs is covered by an FDA master file and has been

built in a modular fashion (i.e., separate apps on the phone), and a few modules can be replaced: the controller, meal activity, the constraint service, the safety service, and remote monitoring. The basic idea is researchers can take DiAs and "insert [a] control algorithm here." After UVa verification that the developer modules are communicating DiAs, researchers can submit to FDA and be off and running outpatient trials – sounds easy! We love the concept of this system as a research platform, since it speeds things up for everyone – FDA has a device on file it is familiar with (enabling faster IDE approvals), while researchers can easily write new algorithms, drop them into the device, and not have to worry about as many of the little things like device communication issues.

Questions and Answers

Q: Can you also modify the way the modules connect with each other?

A:I didn't stress that very well. Every blue dotted line [points to modular diagram in presentation] is an API. There's a standard way to communicate, but there is a fair amount of flexibility. All modules read out of the database.

Q: Have you thought about using the cellphone accelerometer?

A: We have added that to the most recent build of code. The first thing is that it can produce a whole lot of data really, really fast. We're still experimenting with how to filter the data and not store too much.

CLOSED-LOOP GLUCOSE CONTROL IN CRC USING INTRAPERITONEAL VS. SUBCUTANEOUS INSULIN INFUSION IN TYPE 1 DIABETES: PRELIMINARY DATA FROM THE JDRF/ROCHE DIAPORT TRIAL

Howard Zisser, MD (Sansum Diabetes Research Institute, Santa Barbara, CA)

Quipping that "subcutaneous insulin is malpractice" due to its slow, non-physiological route of absorption, Dr. Howard Zisser reminded the audience that intraperitoneal insulin has been shown to have a much faster on-/off-profile. With this in mind, he worked with Dr. Eric Renard to carry out a closed-loop study comparing Roche's intraperitoneal DiaPort 2 vs. subcutaneous pump use. Dr. Zisser explained that the 10-patient feasibility study recently concluded and that preliminary data would be presented on the following day by his colleague Dr. Eyal Dassau. He also noted that the results had several caveats (e.g., the control algorithm was not optimized for intraperitoneal dosing, the DiaPort-using patients in the study all had documented problems absorbing subcutaneous insulin, and the 40-70-g meals were relatively large for a fully closed-loop system to handle). These data reinforced to Dr. Zisser that faster insulin delivery alone won't guarantee better control. However, he emphasized during Q&A that ultimately an intraperitoneal approach "will give us better tools."

Questions and Answers

Q: Did you use the same algorithm for intraperitoneal and subcutaneous dosage? How did

A: The algorithm itself is the same, but it was tuned differently because we know that both the on- and off-profiles of insulin are different. In both cases the system was fully automated.

Q: How did the amount of insulin dosage compare between groups?

A: We gave more insulin in the IP group, but we think that this reflects the faster renal clearance of insulin.

Q: Do anti-insulin antibodies ever affect use of the DiaPort?

A: There is a cutoff beyond which DiaPort is not advised due to insulin antibodies. The peritoneum is an immune space. Patients who develop such antibodies with the DiaPort tend to have very high glucose levels during day, with hypoglycemia at night; occasionally an explant of the DiaPort is necessary due to the antibody titers.

Q: Have you looked at insulin data for the study?

A: Not yet. Dr. Jerome Place at Montpellier is the holder of this data, and we will look at it shortly.

Q: What is your protocol for dealing with hypoglycemia?

A: The controller has a predictive alarm; when this sounds, we will feed subjects 15 g of carbohydrate. With intraperitoneal dosing, when there is attenuation of the insulin, a glucose decline actually becomes noticeably less steep, due to the faster clearance. This can be tuned in future research. Intraperitoneal dosage won't guarantee better control, but it will give us better tools to achieve it.

HEART RATE ENHANCED CLOSED LOOP SYSTEM REDUCES EXERCISE INDUCED HYPOGLYCEMIA

Marc Breton, PhD (University of Virginia, Charlottesville, VA)

Dr. Marc Breton described a failing of typical control to range (CTR) closed-loop algorithms – namely, that they don't prevent exercise-induced hypoglycemia very well. His team investigated "exercise announcement" using a heart rate monitor, and the algorithm was able to reduce post-exercise hypoglycemia by 75% in a small pilot with ten patients. Additionally, use of the heart rate signal improved time spent in range throughout the day and night. The new system protects during exercise but doesn't preclude normal CTR at other times. A powered study is planned for the summer.

- **Control to Range (CTR) systems have been shown to reduce hypoglycemia risk, glycemic variability, average glucose, and increase the time spent in zone.** But CTR has failed to protect against hypoglycemia during and immediately after exercise.
- **The concept of this work is to announce exercise to the algorithm by adding a heart rate monitor in an attempt to avoid exercise-induced hypoglycemia.** The algorithm is manually triggered if heart rate goes 25% higher than resting (the heart rate monitor is not connected to the system). The rest of the closed-loop system is the current UVA DiAs system with OmniPod pump and Dexcom CGM. The pilot study consisted of n=10 adults with type 1 diabetes, who were very well controlled (average A1c of 6.9%), and who took part in either a conventional CTR overnight inpatient study or a similar study with an added exercise component. The study had a crossover design.
- **The exercise announcement reduced post exercise hypoglycemia, but it wasn't statistically significant because of the small size of the study.** Additionally, use of the heart rate signal improved time spent in range throughout the day and night. So the new system protects during exercise but doesn't preclude normal CTR at other times. A powered study is planned for the summer.

ASSESSMENT OF PRAMLINTIDE EFFECT ON GLUCOSE TURNOVER: IMPLICATIONS FOR A CLOSED-LOOP SYSTEM

Ananda Basu, MD (Mayo Clinic, Rochester, MN)

Pramlintide (Amylin Pharmaceuticals' Symlin,) could be an interesting additional hormone in a closed-loop system. In order for the algorithm to take this into account, Dr. Ananda Basu investigated its effect on glucose and insulin using a triple tracer technique on healthy adults. In this work, pramlintide delayed the meal rate of appearance as might be expected, but surprisingly also improved post-prandial insulin sensitivity and impaired beta cell responsivity (at least in the first seven subjects). Work on people with type 1 diabetes is underway.

- **It's well known that pramlintide reduces post-prandial hyperglycemia in type 1 diabetes, said Dr. Basu.** One reason is because it slows gastric motility.
- **Dr. Basu described an experiment to test the effect of pramlintide on meal appearance and insulin sensitivity.** Non-diabetic subjects with an A1c ~5% and normal gastric emptying were given 30 mcgs pramlintide and a mixed meal with 75 g carbohydrate. A triple tracer technique was used to determine the relative appearance of insulin, glucose, and glucagon compared to a control group.
- **For seven patients, the peak glucose was delayed and was lower with pramlintide.** Insulin was lower, as was glucose concentration in the pramlintide group. The peak appearance of the meal was delayed, but the area under the curve (total glucose exposure) was the same. Furthermore, endogenous glucose production was lower and glucose disappearance was delayed with pramlintide.
- **Surprisingly, insulin sensitivity was notably higher with pramlintide, and beta cell responsivity (an index of insulin secretion) was lower.** Obviously, patients with type 1 diabetes have no insulin secretion, and Dr. Basu has started working on type 1 studies that should help incorporate pramlintide into the closed loop.

Oral Presentations

PORTABLE GLUCOSE CONTROL WITH DAYTIME TREAT-TO-RANGE AND OVERNIGHT PROPORTIONAL-INTEGRAL-DERIVATIVE CONTROL IN ADOLESCENTS WITH TYPE 1 DIABETES

Trang Ly, MBBS, DCH, FRACP (Princess Margaret Hospital, Perth, Australia)

Dr. Trang Ly presented results from a study of Medtronic's Portable Glucose Control System 2 (PGCS2: Veo pump, two Enlite sensors, smartphone controller, RF-Bluetooth translator). The system employed treat-to-range control during the day and Proportional-Integral-Derivative (PID) control at night. Five adolescents with type 1 diabetes were tested during two 24-hour periods in the clinic. The efficacy and safety of the PGCS2 was compared to standard pump therapy under optimal conditions (in-clinic, regular meals with manual boluses, and 20 minutes of light exercise). Overall, time spent in the range of 70-180 mg/dl was comparable during the day between open loop therapy and closed-loop with Medtronic's treat-to-range system (74% vs. ~67% for open-loop control); however, overnight control was substantially better with closed-loop PID control (~90% vs. ~55% for open-loop control). Future studies will examine the system during missed meals (where Dr. Ly thinks the system will shine) and moderate intensity exercise.

- **The Medtronic Portable Glucose Control System 2 (PGCS2) consists of** a Veo pump, two Enlite glucose sensors, one-minute MiniLink transmitters, a Bluetooth-RF translator, and a proportional-integral-derivative with insulin feedback (PID-IFB) control algorithm operating

from a smartphone. PGCS2 operates 'treat-to-range' (TTR) for daytime glucose control and full closed-loop control overnight. TTR activates PID-IFB control when the sensor glucose is above or below a preset range – in this case, insulin infusion stayed at the pre-programmed basal rate when insulin levels were between 110mg/dl and 140mg/dl, decreased when glucose levels were <110 mg/dl, and was suspended when glucose <80 mg/dl. The patient commands full pre-meal boluses during TTR operation

- **Closed-loop control using daytime TTR and nocturnal PID were compared to standard open-loop pump therapy.** The Enlite CGMs were calibrated four times per day, light exercise was 20 minutes of walking, and patients manually bolused prior to meals and snacks. The study occurred in the CRC over 48 hours. Patients had a mean age of 26 years, a mean A1c of 7.5%, a mean duration of diabetes of 13 years, and a mean pump duration of 10 years.
- **Plasma glucose levels remained between 70 and 180mg/dl for 74% of the time under closed-loop control, comparable to ~67% time-in-range for open-loop control.** The most dramatic advantage of closed-loop control came at night, where ~90% of the time was spent between 70-180 mg/dl and ~65% between 70-140 mg/dl vs. ~55% and ~27% for open-loop control. Numbers are estimates based off unlabeled bar charts on the slides. P-values were also not clearly noted; only the nocturnal 70-140 mg/dl difference was starred as statistically significant.
- **The second stage of the study will test the PGCS2 when meal boluses are missed.** The subsequent third stage will examine the system's ability to respond to moderate intensity exercise.

Questions and Answers

Dr. Lori Laffel (Joslin Diabetes Center, Boston, MA): I was surprised that the system did not do that much better than the standard pump therapy in your study. It looked like there was a greater proportion of hyperglycemia on the days when treating to range than standard therapy.

A: I don't think that it's greater hyperglycemia. I think that the results are comparable. This system is not designed to be a fully closed-loop system. I think the true value of the system will be seen during studies of the missed meal bolus, because the system will probably work best as a backup system. The present study was simply designed to test whether the system works and makes the small changes it should make. These are optimal conditions. We know people don't always bolus.

Dr. Stuart Weinzimer (Yale University, New Haven, CT): I'm envious of the great toys you have that we want in the US. Perhaps you could do a controller effort analysis like Roman does. The combination of insulin feedback and IOB probably combine to turn off a lot of insulin secretion in the daytime. I think it is more hyperglycemia – I don't think it is comparable. You should look at the way those safety features combine.

A: Absolutely. There are things to modify, such as the gain and IOB. If we improve that, we may see more hypoglycemia. That's the tradeoff.

Dr. Laffel: During the day, you can recognize the hypoglycemia.

EFFECTS OF A FUNDAMENTAL CONTROL PARAMETER ON THE HYPOGLYCEMIA-HYPERGLYCEMIA MINIMIZER (HHM) SYSTEM

Daniel Finan (Animas Corporation, West Chester, PA, USA)

Mr. Finan examined the effects of an MPC algorithm tuning parameter, the "aggressiveness factor," (affects the speed and magnitude of response to changing blood glucose levels) on Animas' hypoglycemia-hyperglycemia minimizer (HHM) system. Twenty individuals were studied in "conservative," "aggressive," and "medium" categories over 24 hours of closed-loop control. Results indicated that the medium aggressiveness factor had the best trade-off between safety and therapeutic efficacy. The study also showed that with increasing aggressiveness, the larger doses were larger and more frequent, there was a decreased tendency to adhere to basal insulin levels, and there was increased readiness to decrease insulin below basal rates. Clinical results were consistent with simulation expectations. The final slide noted that "appropriate weight is being given to these conclusions with current regulatory guidance in mind."

- **Animas' HHM system pairs an insulin pump, a continuous glucose monitor, and a model predictive control algorithm.** The slides did not specify a CGM in this case, though historically it's been the Dexcom Seven Plus; we assume Animas will switch over to the G4 Platinum at some point (or already has).
- **This study investigated the "aggressiveness factor," an important tuning parameter in the MPC algorithm.** It affects the speed and magnitude of response to changing blood glucose levels. The system works by assigning penalties when there are values outside of the target range (above or below). Greater aggressiveness means more readily deviating from the basal rate. Conversely, more conservative aggressiveness tends to adhere to the basal rate. Since this was only a feasibility study, there was an emphasis on insulin dosing characteristics rather than on glucose outcomes.
- **Patients underwent closed-loop control under aggressive (n=5), medium (n=10), and conservative (n=5) tuning parameters.** Participants ate three study meals (breakfast, lunch, dinner) and corresponding insulin boluses were given.
- **The study demonstrated that medium aggressiveness had the best trade-off between safety and therapeutic efficacy.** As expected, with increasing aggressiveness, the larger doses were larger and more frequent, there was a decreased tendency to adhere to basal insulin level, and the readiness to decrease insulin below basal increased. No glycemic data was presented.

Questions and Answers

Dr. Laffel: Depending on the aggressiveness level, you were taking away or adding to basal?

A: This is a basal correction type system. Boluses for our system are given manually and mostly just for meals.

Dr. Laffel: How exactly does the aggressiveness factor affect insulin levels?

A: A basic summary is that as the aggressiveness factor increases, there is a greater willingness of the system to believe that the basal level is not correct.

MULTIVARIABLE ADAPTIVE CONTROL OF AN ARTIFICIAL PANCREAS WITHOUT MEAL ANNOUNCEMENTS

Ali Cinar, PhD (Illinois Institute of Technology, Chicago, IL)

Dr. Ali Cinar reviewed the results of a small fully closed-loop study in three patients (seven experiments). The study used an adaptive control algorithm with recursive modeling techniques. Quite uniquely, it also incorporated energy expenditure and galvanic skin response information from

BodyMedia's Sensewear armband. The presentation focused mostly on the algorithm's design and rationale; type of CGM and pump were not specified. Experiments lasted 10-32 hours and the algorithm was not informed of meals (up to 115 grams of carbs) or treadmill exercise (up to 185 bpm). Time spent in the range of 70-180 mg/dl was 75% overnight (12 am-7 am), 55% in the four hours following exercise, and 56% in the remaining time (two-thirds of the study). Time spent in hypoglycemia (<70 mg/dl) was fairly infrequent and ranged from 1-2% for the three periods specified. Overall, we're glad to see novel algorithm approaches that are trying to incorporate activity – it's a barrier to fully closed-loop control and will certainly need to be addressed in the long run. That said, this study's large meals and exercise without announcement made control quite challenging. We believe fully closed-loop control will continue to be very challenging until the speed of insulin improves significantly. Still, we salute Dr. Cinar for integrating energy expenditure information into his model, since even mild activity like walking can have a significant impact on blood glucose.

CLOSED LOOP INSULIN DELIVERY IN DIABETIC PIGS USING A SMART BIOMATERIAL DEVICE

M. Joan Taylor, PhD (De Montfort University, Leicester, UK)

This mechanical artificial pancreas has shown good results when implanted peritoneally in a pig model. The device releases insulin to the liver based on the glucose concentration, using a glucose sensitive gel that acts as a gateway for the insulin. The device has no batteries or moving parts; it's simple and refillable with insulin via ports. Early results show good glucose control in fasting and in response to a short-term glucose challenge.

- **At DeMontfort University, Dr. M. Joan Taylor is developing an implantable artificial pancreas using a novel glucose sensitive gel to provide closed-loop control.** The device doses insulin based on glucose concentration in the blood. The goal was to make the device specific to glucose, real-time, dose related, practical to use, and exhibit no down regulation over time.
- **The glucose sensitive gel, or "smart material," toggles between a gel and a sol depending on the presence of glucose. This large change in viscosity means that the smart material can be used both as a sensor and as the gateway to a reservoir of insulin.** The properties of the gel were carefully developed to be stable and to prevent contamination or immune system effects.
- **The device is located in a peritoneal site, allowing delivery of insulin directly to the liver.** There are no batteries, no moving parts, it is not biological, and it is easily refillable with insulin through a port.
- **In studies with diabetic pigs, the device was filled and glucose came down to the normal range in only five days.** The device also passed the pig equivalent of the OGTT, normalizing a glucose challenge within an hour. After insulin was removed from the device, the pig lost glucose control after 24 days (because of insulin still trapped in the gel).

PRAMLINTIDE ADMINISTRATION DURING CLOSED LOOP INSULIN DELIVERY IS ASSOCIATED WITH REDUCED MAGNITUDE OF PRANDIAL GLUCOSE AND GLUCAGON EXCURSIONS

Stuart Weinzimer, MD (Yale University School of Medicine, New Haven, CT)

Dr. Stuart Weinzimer presented study results from his team's investigation of pramlintide (analog of human amylin) administration on glucagon and glucose excursions. Ten subjects (mean A1c: 7.2%) underwent two 24-hour periods of closed-loop control: first without and then with 60-mcg pramlintide per meal. A three- to four-week outpatient dose escalation period preceded the closed-loop with pramlintide period. Each 24-hour test consisted of three meals (80-100 g carbohydrate) with no meal announcements. Pramlintide significantly reduced postprandial glucose excursions for all meals (p <0.001), breakfast (p=0.03), and lunch (p=0.003) compared to closed-loop control alone. This occurred with significantly less insulin delivered for all meals (p=0.005) and lunch (p-0.04). Further, because findings suggested that pramlintide blunted the 60-minute post-meal increase in glucagon, Dr. Weinzimer posited that the reduced glucose excursion was related to pramlintide's effect on glucagon.

Q: Was there any nausea?

A: Only among the study staff. [Laughter.] That is an excellent question. We did not have anybody who dropped out from nausea or other side effects but there was a definite reporting of diminution of appetite.

2. Continuous Glucose Monitoring

Session: ATTD Yearbook

CONTINUOUS GLUCOSE MONITORING

Bruce Bode, MD (Emory University, Atlanta, GA)

Dr. Bruce Bode provided a great over of the past year in CGM, breaking his presentation down into several key areas: 1) CGM in toddlers, children, and adolescents (benefits for parents, but no change in A1c or hypoglycemia); 2) patient or physician led CGM (no difference in A1c, more about cost effectiveness, contrary to JDRF and STAR trials); 3) the new Endocrine Society guidelines on CGM ("fairly straightforward," though Dr. Bode had a few critiques); 4) the ASPIRE study of Medtronic's Veo ("the data looks very good"); and 5) CGM in type 2 diabetes ("promising").

- **Data in toddlers, children, and adolescents suggest that CGM does not seem to have a significant benefit on A1c or hypoglycemia, but can help parents.** Dr. Bode hypothesized that one factor is parents' fear of hypoglycemia. One study looked at CGM use in a large database in Germany Austria (Ludwig-Seibold et al., *Pediatric Diabetes* 2012). While adults do very well on CGM and experienced a significant drop in A1c, this was not true with children and adolescents. Use of CGM was also low in this group, with just 4% of the database using it.
- **Dr. Bode reviewed the EVADIAC sensor study on patient- or physician-led CGM, noting it's a cost-saving approach** (Riveline et al., *Diabetes Care* 2012). In the physician-led group, doctors altered patients' recommended CGM wear frequency over time (i.e., patients started with 50% CGM usage [15 days per month]; by the end of the study, physicians recommended half their patients wear it all the time, and half should wear it 50% of the time). There was no significant difference in in A1c between the groups. However, the physician-led group used 35% less sensors. Dr. Bode highlighted that this finding was contrary to the JDRF and STAR trials – the more you use the CGM, the better you do. He felt it was useful from a cost-effectiveness standpoint.

- **The Endocrine Society Guidelines on CGM are "fairly straightforward," though Dr. Bode had a few critiques** (Phillip et al., *Pediatric Diabetes* 2012). The guidelines assert that real time CGM in the hospital setting has limited evidence from outcomes studies and the accuracy is not there. On the latter, Dr. Bode referred to a table compiling Clarke Error Grid analyses from various studies. He highlighted that they are "extremely good," leading him to conclude, "I'm not sure how they came to the accuracy conclusion." Turning to children and adolescents, the guidelines cite "strong evidence" that CGM is very beneficial to lower A1c and reduce hypoglycemia. However, in the three articles mentioned at the beginning of his talk, there was not good evidence of that. The guidelines cite weak evidence to support intermittent CGM use in the outpatient setting.
- **Dr. Bode briefly reviewed the ASPIRE in-clinic study data, which "looks very good"** (Garg et al., *DT&T* 2012). He highlighted the "tremendous" amount of work to complete the study, the beneficial impact of LGS suspension, and the solid ending blood sugars in the 90-100 mg/dl range.
- **Last, Dr. Bode mentioned Dr. Bob Vigersky's study on intermittent CGM use in type 2 patients not on prandial insulin** (a poster at ADA 2011 and published in *Diabetes Care* 2011). He highlighted the study's unique design, which gave patients CGM for two weeks on-one week off for four cycles (12 weeks total). The promising results at the one-year mark suggest participants made positive behavior changes. Dr. Bode concluded that use of CGM in type 2 diabetes is "promising." As a reminder, he is a co-principal investigator on a type 2 CGM study with Dr. John Buse entitled, "Examining The Role of CGM in T2DM" (ClinicalTrials.gov Identifier: NCT01614262). The study is notable because the enrolled type 2s are on oral therapies only. The 90-patient trial has an estimated primary completion date of December 2013. We cannot wait to see data.

DIABETES TECHNOLOGY AND TREATMENT IN THE PEDIATRIC AGE GROUP

Shlomit Shalitin, MD (Tel Aviv University, Ramat Aviv, Israel)

*Dr. Shlomit Shalitin described two papers about the impact of modern type 1 diabetes care for pediatric patients. First she summarized the findings of Rosenbaur et al. (*Diabetes Care *2012), who analyzed trends in metabolic control from the past 15 years. The overall population improved in a variety of respects, including rate of severe hypoglycemia and percentage of patients with A1c at or below the ISPAD goal of 7.5% (though DKA rates seem not to have changed much). These benefits cannot be entirely explained by advances in insulin therapy, said Dr. Shalitin; she noted that improvements in resources, organization, education, and attitudes may have played a role. Dr. Shalitin also reviewed DirecNet's recent randomized, controlled trial of CGM in type 1 diabetes patients from four to 10 years old (n=146; Mauras et al.,* Diabetes Care *2012). The technology was associated with high parental satisfaction, but its use was not linked to significant changes in A1c, time in range, time in hypoglycemia, time in hyperglycemia, or parental fear of hypoglycemia; severe hypoglycemia was rare in both groups. (Dr. Shalitin noted that such fears may have been a reason that parents did not use CGM data to tighten their children's glycemic control.)*

Session: Nothing New Under the CGM-Sky?

A NOVEL IMPLANTED GLUCOSE SENSOR

Todd Whitehurst, MD (Senseonics, Germantown, MD)

Dr. Todd Whitehurst shared new data on Senseonics' implantable fluorescent subcutaneous CGM sensor. As a reminder, it's boronic-acid-based, a bit smaller than an M&M, is inductively powered via RF using an on-body transmitter, and sends data using low energy Bluetooth from the transmitter to a smartphone app. Notably, Dr. Whitehurst showed data "fresh out of the clinic" from four patients who are halfway through a 180-day study of the sensor. The combined MARD was 12.5% (MAD of 15 mg/dl) relative to YSI, 81% of points were in Zone A (18% in Zone B), and accuracy has been consistent across the three months of the study. Fingerstick calibrations occurred prospectively twice per day, and the sensor has a 24-hour warm-up time. The sample size is admittedly small at this point, though we think the MARD data looks good at the three-month mark. We look forward to seeing if the accuracy holds up at the six-month mark, as well as what a pivotal study and regulatory path would look like.

- **The implantable sensor is inserted using Lidocaine and a blunt dissector in an approximately five-minute procedure.** Following implantation, patients must wait 24 hours before entering an SMBG calibration. On the first day, the sensor needs four fingerstick values, separated by two hours. From then on (days 2-180), it is calibrated twice per day using fingersticks.
- **The longevity of Senseonics' implant may be impaired by the immune system.** Dr. Whitehurst described how the formation of reactive oxygen species causes hydrogen peroxide to attack the boronic acid on the sensor. While the electronics last up to five years, the sensor's indicator life is limited by this immune attack.
- **To fight the immune system attack, Senseonics has applied a thin layer of platinum (10 nm) on the sensor's hydrogel surface.** This approach catalyzes the conversion of reactive oxygen species into water and oxygen, which is adequate to protect the indicator.
- **For more on Senseonics' CGM, see page 119 of our EASD 2012 full report at** https://closeconcerns.box.com/s/kt7rf3v6uy09x6t9ldke

Questions and Answers

Q: Why are you using a smartphone app for your monitor, and not a medical grade device?

A: Good question. We asked patients what they wanted. They didn't want to carry another device. All glucose calculation is done in the body worn transmitter. In meetings with the FDA, they have been open and have not seen that as a significant issue. In initial clinical studies, we will provide patients with an iPod touch. We anticipate regulatory approval to use smartphone.

Dr. Hans DeVries (Academic Medical Center, Amsterdam, Netherlands): Attempts like this have failed in the past. Can you speculate on the fundamental differences with your product?

A: The limit on our lifetime is the immune system attack against the sensor. We're overcoming this through several different mechanisms. Platinum is one of the strongest components to get longevity.

A NOVEL NEEDLE TYPE SENSOR

Michael Schoemaker, PhD (Roche, Mannheim, Germany)

Dr. Schoemaker presented "exciting and "very promising" clinical data on Roche's CGM, which was presented in much more detail on Day #1 of the conference. There's no question that this data has been the talk of ATTD 2013 on the CGM front – we've heard many buzzing about it in between sessions. In a 30-patient study, the sensor touted a mean absolute relative difference (MARD) of 8.6% when compared to Accu-Chek Aviva blood glucose meter (BGM) readings (n=7,039). Each patient wore two sensors simultaneously on the abdomen over a seven-day period that consisted of two induced glycemic swings; the study was performed in the inpatient setting. The sensor was initially calibrated two hours after the initial insertion, with two re-calibrations per day. Of the 7,039 CGM-BGM paired data points, 85% fell in Zone A of the Clarke Error Grid, with 14% in Zone B. When looking at individual sensor performance, an impressive 75%+ of sensors recorded a MARD ≤10% (it was great to see Roche also use this histogram approach, as we think it speaks to patients' experiences of "good' and "bad" sensors; it's one that Dexcom starting showing in presentations in the last year). Data also looked good in hypoglycemia (<70 mg/dl): in 573 paired CGM-BGM data points, MARD was 11.9%, 87% of readings fell in the Clark Error Grid Zone A, and 0.3% were in the B Zone. The induced glucose swings, which totaled 560 hours of data and resulted in 2,250 CGM-BGM paired points, resulted in 78% of readings in the Clark Error Grid zone A and 20.0% of points in zone B. The sensor recorded a MARD of 11% during this time period. Of the sixty sensors used, 59 lasted for seven days; of those 59 sensors, 100% of CGM data was captured. Dr. Schoemaker did not provide any indication as to when we might expect to see the first-generation system on the market, but for sure, we will closely follow Roche's progress to see whether future trials corroborate these initially promising results.

- **Dr. Schoemaker believes that the sensors' membrane material was the factor mainly responsible for the sensor's high accuracy**; however, he did not provide specific detail. Broadly, Dr. Schoemaker described three design elements important to accurate glucose monitoring that we assume are incorporated into Roche's design: 1) multiple working electrode spots to compensate for sub-millimeter scale heterogeneities and processes in the subcutaneous tissue; 2) the material and surface of the sensor coating, which Dr. Schoemaker primarily attributed the prototype sensor's accuracy to; and 3) a working electrode that contains the catalyst for hydrogen peroxide oxidation (and thereby reduces interference from other electrochemically active substances).
- **For much more detail on the data,** please see our ATTD Day #1 report at https://closeconcerns.box.com/s/pypcux2vn238a3qbjomr.

Questions and Answers

Dr. DeVries: It's exciting data, but the proof is in the pudding: a comparative study vs. other CGMs. Can you comment?

A: We have done comparative studies with other sensors, but I haven't shown this data here today.

Dr. David Klonoff (Mills-Peninsula Health Services, San Mateo, CA): What about the sensor chemistry allows you to be this accurate, especially in hypoglycemia – it's really good data.

A: We don't know. It's the choice of materials that's the hardest things to explain. It's trial and error and the sensor architecture.

DEXCOM: THE NEXT GENERATION

Tom Peyser, PhD (Dexcom, San Diego, CA)

Dr. Tom Peyser represented Dexcom during this packed CGM session, devoting the first half of his presentation to a review of the G4 Platinum pivotal study data (similar to his presentation during Dexcom's corporate symposium at EASD 2012) – he asserted that the currently available G4 Platinum fits with his presentation's title, since the performance and accuracy do represent a major advance over the Seven Plus. Most notable was Dr. Peyser's discussion of Dexcom's future pipeline – specifically, he gave new details on Dexcom Share (remote monitoring), highlighted the insulin pump partnerships with Tandem and Animas (hopefully within the next year), and shared data on the G4 AP version. He also addressed the "time lag" associated with publications on CGM accuracy, which have not included the G4 Platinum. Dr. Peyser gave a much more detailed presentation later on in the day, which included a more extensive Q&A – those interested should scroll down to that section of the report.

- **Dr. Peyser displayed a graphical illustration of how Dexcom Share will work, the first time we we've ever seen a description of it.** The graphic displayed the Dexcom Share device (a cradle that holds the G4 Platinum sensor and plugs into a power outlet) at a patient's bedside. Data from the G4 Platinum is then sent via the cradle (using Bluetooth) to a nearby smartphone (the picture displayed a phone on the nightstand, right next to the Share device). That phone then uploads the data to the cloud, where it can be monitored by parents/caregivers through push notifications or SMS text messages. The picture showed a father on a business trip in a taxi, checking his phone with a sigh of relief this his daughter's blood glucose was 150 mg/dl. As of Dexcom's 4Q12 call, this product will be submitted to FDA in 3Q13.
    - **We're very excited to see Dexcom getting into remote monitoring, since we think many, many parents will appreciate this.** Share is of course a first baby step, since the G4 Platinum must be physically inserted in the cradle, which must be plugged into the wall, which must have a nearby phone to send the data to the cloud. Certainly, Gen 5 is much more ambitious, since sensor data will go right from the transmitter to a smartphone.
- **With Dr. Claudio Cobelli's group at Padova, Dexcom is developing an AP version of the G4 with special algorithms; early data suggest further accuracy improvement.** The G4 Platinum sensor and transmitter will be the same, and only the algorithms on the receiver will be different algorithms. Dr. Peyser characterized the algorithm efforts as "denoising." The device will be made available to investigators under an IDE or equivalent hopefully by the end of this year.
    - **Overall MARD declines from 13.2% with the G4 Platinum to 11.6% with the G4AP.** Dr. Peyser also noted that the G4 AP brings a "significant compression" in the sensor MARD distribution, as standard deviation of MARDs declines from 6.7% to 4.1%. Dr. Peyser showed an example of a sensor tracing from the G4 Platinum pivotal study to which the new G4AP algorithm had been applied. The MARD improved from 12.7% on the first day with the G4 Platinum algorithm to 7.2% with the G4AP algorithm. Overall, he called the new algorithm "quite a breakthrough."
- **"Hopefully within the next year," Dexcom will be integrated with the Animas Vibe and Tandem t:slim.** As of Dexcom's 4Q12 call, J&J and Dexcom are finalizing the PMA for the Animas Vibe and expect to submit by the end of 1Q13 (based on the G4 Platinum's slightly less than 180-day review, a 2013 approval could still be possible). Meanwhile, the Tandem partnership does not have an official timeline, though we would guess it will be filed sometime this year. Dr. Peyser did not mention the dissolved partnerships with Insulet and Roche.

- **Dr. Peyser reviewed a few recent publications on CGM accuracy and showed how the G4 Platinum and G4AP stacked up.** The short answer: very positively and always comparable to or better than the competition. The publications included Drs. Damiano and Russell (*Diabetes Care* 2013) comparing the FreeStyle Navigator, Dexcom Seven Plus, and Medtronic Guardian; Dr. Hovorka et al. (*DTT* 2013) comparing the Navigator and Seven Plus on the frequency of large errors; and Dr. Luijf et al. at DTM 2012 and ATTD 2013 comparing the Navigator, Enlite, and "prototype G4" (i.e., the version formerly used with the Animas Vibe in Europe, not the more advanced and more accurate G4 Platinum). Said Dr. Peyser, "There *is* a time lag problem with CGM": it's not the lag between blood glucose and interstitial fluid glucose, it's the lag between the development of sensor technology and publications (i.e., published papers cannot keep up with the pace of new technology).

Questions and Answers

Q: On noble metals, what is more noble than platinum? Will that be used for Gen 5 or 6?

A: It's a difficult question. There is great vogue in the marketing world for platinum. In the United States, there is Bud Light, a beer brand with "less calories, more taste" called Bud Light Platinum.

BD GLUCOSE BINDING PROTEIN SENSOR UPDATE

Kerstin Rebrin, MD, PhD (BD, Franklin Lakes, NJ)

In one of the company presentations we were most looking forward to, Dr. Kerstin Rebrin provided an update on BD's glucose binding protein (GBP)-based optical CGM sensor. She did not share any new data on the system, but revealed the product development pathway and current status. The system is in its second-generation "mobile version," which is being used in two clinical studies: a 24-hour study through UVA/JDRF in 12 patients (a poster here at ATTD) and a 29-patient, three-day study in Canada under Dr. Aronson. Dr. Rebrin expressed confidence in the science at this point, and emphasized the big goal going forward is to further miniaturize the system (i.e., "the wearable size of an infusion set"; the mobile version still looked fairly large in the picture shown). Once miniaturized, BD plans to conduct safety and effectiveness studies. In early tests of the system, BD's sensor has shown great accuracy (a consistent ~9-11% MARD in hypo- normo-, and hyperglycemia), fast warm-up time (under 30 minutes), and a little lag (about five minutes). The company is certainly taking a data driven, patient-centric approach; we hope to see more accuracy data shared soon.

- **BD's CGM has a three-stage product development path.** The first generation was a "table top version" to demonstrate proof-of-concept in the first clinical study (12 hours, 40 subjects at Profil; published by Judge et al. in *DTT* in 2011). The second-generation is a "mobile version" being used in current preclinical and clinical development studies. The slide specifically noted a 24-hour UVA/JDRF study (n=12), which is a poster here at ATTD 2013; she did not disclose any data from this study, though our full report to come will contain all the details) and a three-day study in Canada under Dr. Aronson (n=29). A picture showed the on-body component of the mobile version (presumably the transmitter and other electronics), which looked roughly comparable in size to a deck of cards (a three inch by three inch square). The third product stage pictured an artist's rendering of a much-miniaturized commercial product version, resembling an infusion set. BD will conduct safety and effectiveness clinical studies with this version.
- **Dr. Rebrin discussed some of the advantages of BD's proprietary technology:** low sensor warm up time ("definitely less than 30 minutes" – in a canine study of 36 sensors, the sensor was stable after 10 minutes), a sensor lag time of about five minutes ("which can be

corrected"), and per the first-generation study by Judge et al., consistently good accuracy in hypoglycemia, normoglycemia, and hyperglycemia (~9-11% MARD). The CGM is also not impacted by commonly known interferences like acetaminophen.

- **One key part of BD's CGM is the measurement of two wavelengths of light: the blue band and the green band.** The signal response is improved by employing the ratio of green over blue spectral bands, with a consequent reduction in noise.

Questions and Answers

Dr. David Klonoff: Is there a problem in using the ratio of two signals?

A: No, it has positive effects. It looks like we can remove a lot of the noise.

NEW ADVANCES IN CGM

Joe Bugler, MSc (Abbott Diabetes Care, Alameda, CA)

Mr. Joe Bugler devoted his presentation to Abbott's FreeStyle Navigator II, which launched quietly in Europe prior to EASD 2012. The company's new sensor aims to improve the user experience of the original FreeStyle Navigator and the updated FreeStyle Navigator Quick Start (shorter warm-up). Navigator II has a totally different receiver and a 33% smaller transmitter; otherwise, the sensor technology and measurement methods are the same as the previous version. Consequently, the accuracy is nearly identical: a MARD of 12.3% and 84% of points in Zone A of the consensus error grid (n=2,843 total). We think the form factor updates are great for patients and are very glad to still see Abbott actively developing CGM (especially considering the historically strong enthusiasm for the accurate Navigator). Mr. Bugler unfortunately did not discuss plans for submission of the FreeStyle Navigator II to the FDA, or details on the company's next-generation sensor (per the Abbott 4Q12 call, a pivotal trial is expected to start in 2013, and EU launch is expected by the end of 2014).

- **The FreeStyle Navigator (FSN) II includes an updated receiver design and a 33% smaller transmitter.** Updates to the receiver include a thinner form factor, a color display (vs. monochrome previously), a rechargeable battery, and USB connection to a PC (rather than Bluetooth). FSN II is similar FSN Quick Start in that it includes a shorter warm up, one more required glucose calibration, and a new glucose algorithm. Mr. Bugler emphasized that the glucose sensing technology in FSN II remains the same. The receiver also still contains a built-in FreeStyle Lite blood glucose meter.

FreeStyle Navigator Design History				
FreeStyle Navigator (FSN)	10-hour start up	Four BG calibrations over five days	Version 1 glucose algorithm	Osmium-GOD sensor chemistry
FSN Quick Start and FSN II	1-2 hour start up	Five BG calibrations over five days	Version 2 glucose algorithm	Osmium-GOD sensor chemistry

- **Mr. Bugler discussed a two-week study comparing the accuracy of FSN II to SMBG (FreeStyle Lite) in the home setting.** The study included 31 patients enrolled at two clinical sites in the United States. Patients were 61% type 1, 39% type 2, with a mean age of 48 years.
    - **MARD was 12.3%, with 84% of points in Zone A of the consensus error grid** [95% CI: 84-90%] and 16% in Zone B (n=2,843 total) – this data is right on par with previous studies of the Navigator. In those seven studies, percent in Consensus Zone A ranged from 73-90% with FreeStyle Navigator I and 87-89% with FreeStyle Navigator Quick Start. MARDs were in the 10-13% range for all studies.
- **To illustrate the impact of lag time, Mr. Bugler showed an interesting graph plotting CGM bias as a function of glucose rate of change.** When the Navigator arrow displayed a rate of change from -1 to 1 mg/dl/min, mean percent bias was nearly zero. However, when rates of change exceeded ±2 mg/dl/min, sensor bias jumped substantially to ±15%. By removing rapidly changing glucose values, sensor bias declines, and the percentage of values in Zone A rose slightly to 87%.
- **In three studies of the Navigator, SMBGs per day declined from a baseline average of 4-5x/day to 1-2x/day after the study.** We think this speaks to the power of accurate CGM to reduce the hassle of SMBG. Additionally, when patients have confidence in the readings and the sensor is running accurately, fewer SMBGs are needed (although CGM is not approved for dosing insulin, we believe many patients do it when they feel the CGM accuracy is on par with actual blood glucose).

REDUNDANCY: THE FUTURE OF CGM AND THE PATHWAY TO THE ARTIFICIAL PANCREAS

Rajiv R. Shah, MS (Medtronic Diabetes, Northridge, CA)

Mr. Rajiv Shah discussed some of the CGM improvement initiatives in Medtronic's pipeline, which include a focus on redundancy (multiple sensors or orthogonal sensing) and intelligent diagnostics. These approaches have shown an ability to improve the accuracy and reliability of CGM. His discussion was mostly theoretical, though a smattering of examples demonstrated nice improvements in MARD using these approaches. He closed by noting that the "future is bright" and a redundant, intelligent sensor system is a "precursor to what's required for the AP."

- **Medtronic has tested placement of a number of equally sized sensors on a probe smaller than its current Enlite.** The redundancy helped correct for deviations in sensor response: on one side of the probe, both sensors performed as they should, while on the second side, noise and local anomalies obscured the signal.
- **Medtronic has developed intelligent diagnostics that detect sensor issues and take corrective action.** The company has a new body worn instrument that connects to redundant sensors and measures "sensor health." Depending on how close the different sensor values resemble each other and how that compares with expectations, the system assigns a sensor fidelity metric and a weight to each sensor. Those are combined in a fusion algorithm to provide a composite reading. Mr. Shah provided two examples from human feasibility studies. In the first, two separate sensors had a MARD of 15%. When they were combined, the composite MARD was 11.5%, better than the average of the two. A second example was similar: MARDs of 12.8% and 10.6% dropped to a composite of 8.9%.

- **To accomplish this, Medtronic has developed a new silicon microchip in the last couple of years.** It allows for connection of up to five sensors. The redundant intelligent sensing electronics monitor sensor health and finds faults before they become failures.
- **One useful application of this system is a sensor start up.** Mr. Shah explained that some sensors take longer than expected to stabilize. Smart diagnostics could figure out when a sensor has stabilized, and only then would it prompt for a glucose calibration. In one test without an intelligent startup, a sensor had a 26% MARD. With intelligent startup and redundancy, MARD declined to 10%.
- **Medtronic's orthogonal glucose oxidase/optical sensor for the AP is in preclinical studies and is moving forward to human feasibility studies.** The optical sensor is GBP based. As a reminder, this is in partnership with JDRF and the Helmsley Charitable Trust. Mr. Shah emphasized that this approach is essential for the closed loop, where sensing requires a solution for all anomalies.

Oral Presentations

DEVELOPMENT OF AN ORTHOGONALLY REDUNDANT GLUCOSE SENSOR SYSTEM

Anu Bansal (Medtronic Diabetes, Northridge, CA)

Ms. Anu Bansal shared snapshots from in-vitro and animal studies of Medtronic's orthogonally redundant glucose sensor system, which combines an electrochemical sensor with an optical sensor. Since June 2012, product development has been supported by JDRF and the Helmsley Charitable Trust in hopes that this redundant CGM system could be more reliable and accurate than current devices – a potential boon for the artificial pancreas. Ms. Bansal noted that the optical sensor itself is already small enough to be combined with a Sof-Sensor at the same insertion site. The external portion of the sensor is still quite large (several times the volume of the MiniLink transmitter to which it is attached); both the internal and external components are being further miniaturized. Ms. Bansal indicated that the electrochemical and optical sensors appear generally accurate in in-vitro, rat, and dog studies, though she said that the optical sensor is more susceptible to noise – a drawback that Medtronic engineers hope to address with improvements in sensor design, inter-component connectivity, and/or data-processing algorithms. We share Ms. Bansal's excitement at the progress in the past 10 months and hope that Medtronic, JDRF, and the Helmsley Charitable Trust can soon bring an effective sensor into clinical research.

- **The optical sensor measures glucose concentration using fluorescence resonance electron transfer (FRET).** The main body of the sensor is a fiber-optic column with a 250-micron diameter. In its last 500 microns or so, the sensor bulges out to a 380-micron diameter (to make room for the sensing chemistry inside). The very tip of the sensor is a glucose-permeable membrane, which allows glucose to diffuse in and come in contact with the sensing molecules. The two main molecules are the glucose-binding protein MBL, which is conjugated to a fluorescent dye (the fluorophore), and the glucose-like molecule dextran, which is conjugated to another dye (the quencher). When light travels down the sensor's fiber-optic column, it excites the MBL-conjugated fluorophore and produces a fluorescent signal. However, when glucose concentration is low, most of the MBL is bound to dextran. This means that most of the fluorophores are close to quenchers, which hide most of the fluorescent signal. By contrast, when

glucose concentration is high, glucose displaces dextran. With dextran and the quencher no longer bound close by, the fluorophores shine more brightly, and so a stronger fluorescent signal is produced.

- **Sharing images and a video, Ms. Bansal described the prototype of the combined electrochemical/optical sensor.** Because the fiber-optic column is so thin (and potentially becoming smaller yet), it can be co-located with the Sof-Sensor inside a modified insertion needle. (After insertion, the two sensors remain co-located in the subcutaneous space.) The external portion of the sensor consists of a modified MiniLink transmitter attached to another piece of electronics, the "reader." The first generation of the "reader" has roughly three times the footprint of the transmitter and is roughly fivefold thicker off the body. Ms. Bansal also showed an image of a second-gen reader that is intermediate in size between the gen-one reader and the MiniLink, and she said that further miniaturization is being attempted. The reader contains a rechargeable battery with a run-time of 17 days, a printed circuit board (PCB) that can interact with both sensing technologies, and a narrow-band spectrofluorometer ("the heart of the optical sensing method").
    - **The spectrofluorometer is composed of an LED that shines light into the fiber-optic column, as well as two photodetectors to receive the fluorescent signal that travels back from the sensor's tip.** One photodetector measures the signal from the MBL-conjugated fluorophore (which is supposed to be proportional to the concentration of glucose, as described above). The other photodetector measures a separate fluorescent molecule, which is not involved in the glucose-binding kinetics and thus can be used as a measure of "noise" that is unrelated to glucose. Ultimately, it is the "optical ratio" of these two fluorescence signals that gets translated back into an estimate of glucose concentration.

CONTINUOUS GLUCOSE MONITOR USE IN CLINICAL PRACTICE: A REPORT FROM THE T1D EXCHANGE CLINIC REGISTRY

Irl Hirsch, MD (University of Washington, Seattle, WA)

In this excellent and data-heavy talk, Dr. Irl Hirsch described the CGM-using patients in the Helmsley Charitable Trust's T1D Exchange clinic registry. The analysis included 12,088 registry participants who completed a year-one follow-up visit. Of these, 1,089 (roughly 9%) were considered CGM users (i.e., they had used real-time CGM during the past month). Relative to the registry as a whole, the CGM-using population was disproportionately white, female, privately insured, pump-using, high in socioeconomic status, and with low A1c. Prevalence of CGM use was roughly 5% among registry participants under 26, as compared to roughly 20% among registry participants older than 50. The split among Medtronic and Dexcom was roughly 50/50 overall among both adults and pediatric populations, even though Dexcom sensors are not FDA-approved in patients under 18. Among patients using CGM at their time of enrollment in the registry, one-year rates of discontinuation were high for Dexcom (29%) and higher still for Medtronic (47%). Incidence of severe hypoglycemia within the past three months was rather high regardless of whether patients used CGM (5-12%, with higher rates in older patients), but Dr. Hirsch emphasized that the comparison is tricky, given that many people start using CGM precisely because they already *experience frequent hypoglycemia. Few patients downloaded their CGM data every week (~6%), but real-time CGM features were considered useful by the vast majority of patients (e.g., over 90% for trend arrows). Also, as indicated in many past studies, more-frequent CGM use was*

associated with lower A1c. Dr. Hirsch concluded that future research should focus on how to make CGM more desirable so that more patients can benefit from its long-term use – hear, hear!

- **This observational analysis included 12,088 participants who had completed a year-one follow-up visit in in the Helmsley Charitable Trust's T1D Exchange of leading clinical centers; of these, 1,089 (9%) were considered CGM users.** (According to the researchers' definition, CGM users were those who had used real-time CGM during the past month.) The majority of people in the analysis were younger than 18, and over 25% were younger than 12. We note that, as with any analysis of the T1D Exchange, the results may not be representative of the overall population of people with type 1 diabetes (e.g., quality of care is probably higher) – but the massive, granular, expanding dataset is nonetheless one of the best views possible into how people live with their disease in the US.
- **Relative to other participants in the T1D Exchange, the CGM-using population had higher percentages of people who were:** older than 18, female, non-Hispanic whites, privately insured, living in households with annual income of $75,000 or more, and using pumps. (Of the 531 wearers of Medtronic CGM who used pumps, 98% used Medtronic pumps; among the 416 wearers of Dexcom CGM who used pumps, Medtronic's share was 32%). Broadly, we would be quite curious to see a comparison of CGM users and non-users that controls for these demographic differences, though of course every observational analysis is inherently limited in distinguishing correlation from causation.

	CGM Users (n=1,089)	**Non-users (n=10,999)**
<18 years old	30%	62%
Female	57%	50%
White (non-Hispanic)	91%	84%
Private Insurance	90%	76%
Annual Household Income $75k	67%	51%
Pump Use	86%	58%

- **Slightly more than half of CGM users wore their devices for at least six days per week,** and roughly one-fifth used CGM less than 3.5 days per week.

	Frequency of CGM Use		
Age	**<3.5 d/wk**	**3.5-<6 d/wk**	**≥6 d/wk**
<13 (n=176)	27%	20%	53%
13-25 (n=208)	33%	26%	41%
≥26 (n=624)	19%	20%	62%

- **Mean A1c was lower among CGM users than non-users, and lower among more-frequent CGM users than less-frequent CGM users.** Dr. Hirsch analyzed users according

to whether their weekly use was below 3.5 days, from 3.5 to less-than-6 days, or 6 days or more. Mean A1c values for these respective groups were 7.9%, 7.6%, and 7.3% – a highly statistically significantly relationship with wear-time. However, we calculate that even among the users wearing CGM least frequently, mean A1c was lower than for non-users (7.9% vs. 8.3%). We suspect time in zone would be even more different but of course that is impossible to measure.

	Mean A1c		
Age	**CGM Users**	**Non-users**	**P-value**
<13	7.8%	8.2%	<0.001
13-25	8.1%	8.6%	<0.001
≥26	7.2%	7.6%	<0.001

- **Dr. Hirsch reported that market share was split at 50/50 between Medtronic and Dexcom for the population of CGM users as a whole, and he noted that Dexcom CGM products were used by 48% of CGM users under 18 years old – despite not being FDA-approved in this population.** Use of CGM was much more common among people 26 years old or older, but the analysis included mostly participants younger than 26.

Age	Prevalence of CGM Use	Dexcom / Medtronic Share
<6 (n=425)	5%	77% / 23%
6-12 (n=3,238)	5%	49% / 51%
13-17 (n=3,482)	4%	42% / 58%
18-25 (n=1,879)	6%	40% / 60%
26-49 (n=1,747)	22%	55% / 45%
≥50 (n=1,317)	20%	48% / 52%

- **A high proportion of CGM users was no longer using CGM at their one-year visit to the registry.** Discontinuation was especially common among Medtronic users and people who were aged 13-to-25-years at enrollment.

Medtronic users' rates of discontinuation at one year visit			
Overall (n=649)	**<13 yrs** (n=132)	**13-25 yrs** (n=159)	**≥26 yrs** (n=358)
47%	55%	69%	34%

Dexcom users' rates of discontinuation at one year visit			
Overall (n=442)	**<13 yrs** (n=159)	**13-25 yrs** (n=358)	**≥26 yrs** (n=277)

29%	38%	50%	20%

- **Roughly half of the registry's CGM users reported checking their blood sugar less frequently when wearing CGM,** though roughly 10-20% said that they performed fingersticks more often when wearing CGM.

	Change in Frequency of Blood Glucose Checks When Wearing a CGM		
Age	**Less often**	**No change**	**More often**
<13 (n=188)	49%	41%	10%
13-25 (n=242)	52%	33%	15%
≥26 (n=659)	51%	28%	21%

- **Turning to adverse events, Dr. Hirsch reported that regardless of CGM use, similar percentages of participants had experienced at least one severely hypoglycemic episode in the past three months.** Recent diabetic ketoacidosis was numerically less prevalent among users of CGM.

	Frequency of ≥1 Severe Hypoglycemic Event in Past Three Months	
Age	**CGM Users**	**CGM Non-Users**
<13	4.8%	5.6%
13-25	9.9%	7.7%
≥26	11.5%	11.7%

	Frequency of ≥1 DKA Event in Past Three Months	
Age	**CGM Users**	**CGM Non-Users**
<13	3.2%	6.9%
13-25	7.0%	9.0%
≥26	1.8%	3.1%

- **Beyond the real-time display of glucose values, a variety of CGM features were rated by most users as "helpful" (rather than "not helpful" or "somewhat helpful") – though few participants downloaded and reviewed their data on a weekly basis.** The prevalence of "helpful" ratings was higher for real-time features – e.g., arrows showing the direction of change (91%), high or low alarms (82%), falling or rising glucose alarms (73%), using sensor values for insulin dosage (57%). Retrospective features were widely considered helpful as well, though by lower percentages of patients – e.g., retrospective analysis to change insulin

(62%), retrospective analysis to manage exercise (63%), and retrospective analysis to change food (45%). The percentage of participants who downloaded and reviewed their CGM data at least once per week was low among all age groups presented: people younger than 13 (8%), aged 13-to-25 (10%), and 26 and older (5%).

ACCURACY AND RELIABILITY OF CURRENT CGM SYSTEMS: A DIRECT COMPARISON

Yoeri Luijf, MD, MSc (Academic Medical Center, Amsterdam, The Netherlands)

Dr. Yoeri Luijf reprised his presentation from DTM 2012, sharing data on a head-to-head-to-head comparison of the Abbott FreeStyle Navigator I, the Medtronic Enlite, and the Dexcom G4 Version A (i.e., the version used with the Animas Vibe in Europe, not the more advanced G4 Platinum available in the US). During the in-clinic portion of the study on day one, the G4A's accuracy was significantly worse than that of the Navigator and Enlite (as measured by mean absolute relative difference, MARD). However, during the home-use period that followed, the Navigator and G4A had statistically similar accuracy, and the Enlite's was significantly worse. (Dr. Luijf thus hypothesized that the G4A's warm-up time may be longer than indicated by the manufacturer.) Sensor longevity was also assessed; all three sensors had median lifetimes longer than their respective indicated wear times, but accuracy for sensors that outlasted their indicated wear-time was significantly better for the Dexcom sensor than Abbott's or Medtronic's. During Q&A at DTM 2012, Dr. Luijf said that the researchers will conduct a follow-up study using the G4 Platinum, with the in-clinic portion of the study conducted on day three rather than day one to ensure that all three sensors have fully warmed up. He called CGM "the Achilles heel of closed-loop systems," a comment we felt was not quite on the mark. To date, some of the biggest obstacles in closed-loop have been rapid post-meal glucose excursions and rapid drops in blood glucose during and after exercise – in our view, these challenges are really insulin absorption/action problems more than issues with CGM accuracy and lag (i.e., faster insulin could more quickly attenuate postprandial hyperglycemia and intra- and post-exercise drops in blood glucose). Still, we agree that CGM does need to get more accurate, and appreciate Dr. Luijf's desire to scientifically and independently test system accuracy.

- **The study enrolled 20 patients with type 1 diabetes, who were simultaneously fitted with three different CGM sensors: the Abbott FreeStyle Navigator I, the Medtronic Enlite, and the Dexcom G4 version A** – i.e., the sensor approved for use with the Animas Vibe in Europe, not the more-advanced G4 Platinum. On the first day of sensor wear, patients stayed in the clinical research center for a glycemic challenge (breakfast with an insulin bolus that was delayed and then increased). Reference blood glucose values in the clinical research center were taken with YSI. After this in-clinic portion, one of the three sensors was randomly removed so that patients would need to wear only two sensors for the rest of the study. Each patient then wore those two sensors at home, taking fingerstick blood glucose measurements for reference. To assess sensor longevity, patients wore each sensor for as long as they could until apparent technical failure or two consecutive days of mean absolute relative difference (MARD) greater than >25%.
- **During the clinical research center (CRC) portion of the study on day one, the Dexcom G4 A had significantly worse YSI-matched accuracy than either the Abbott FreeStyle Navigator I or the Medtronic Enlite** (which were not statistically different from each other). This same pattern was seen in sub-analyses of glucose values below 100 mg/dl and between 100 and 200 mg/dl. For glucose values above 200 mg/dl, however, accuracy did not significantly differ between the sensors.

YSI-matched accuracy in clinic on day one

	MARD	SD
Navigator I	16.5%	14.3%
G4A	20.5%	18.2%
Enlite	16.4%	15.6%

MARD = Mean absolute relative difference; SD = Standard deviation

- **The median range of sensor longevity was 8.5 days for the Abbott FreeStyle Navigator, 10 days for the Dexcom G4 A, and 8.0 days for the Medtronic Enlite.** Maximum observed sensor lifetime was 26 days for the Navigator, 82 days for the G4A, and 15 days for the Enlite. (Dr. Luijf noted that three of the Dexcom sensors lasted for over 40 days, though he emphasized that these were outliers.) As a reminder, the indicated wear time is five days for the Navigator I, seven days for the G4A, and six days for the Enlite.
- **During the study's home phase, accuracy within labeled wear time was statistically significantly worse for the Enlite than the Navigator or G4A; beyond labeled wear time, the G4A's accuracy was best by a significant margin.** Accuracy during home use was assessed by comparison to self-monitoring of blood glucose (SMBG) fingerstick values.

SMBG-matched accuracy at home

	MARD during specified lifetime	MARD after specified lifetime
Navigator I	14.5%	18.9%
G4A	16.5%	15.6%
Enlite	18.9%	30%

MARD = Mean absolute relative difference

Questions and Answers

Dr. Lori Laffel (Joslin Diabetes Center, Boston, MA): On the first slide, the CRC data looked like the responsiveness of the Dexcom sensor was the closest to glycemic excursions.

A: That's the danger of showing one single patient. I took one single sensor trail to illustrate the story. It's not the result of the trial.

Dr. Laffel: In the patient wearing the Dexcom for 82 days, what did the skin or site look like? Did that person bathe?

A: It was an Italian [laughter]. I don't want to say anything about that. I did not see the patient myself. I asked the clinician, and the patient was completely covered in bandages and had the glue residue. The site was not infected – it was amazing the sensor kept functioning. We're trying to figure out what is so special about this patient.

USING ACTIVITY MONITORS TO IMPROVE CGM SENSOR ANOMALY DETECTION

B. Wayne Bequette, PhD (Rensselaer Polytechnic Institute, Troy, NY)

The indefatigable Dr. B. Wayne Bequette described an algorithm to detect a drop in CGM signal when patients roll over at night (pressure induces sensor attenuation [PISA]). It's important to handle this, particularly for appropriate pump shutoffs. In his study, which incorporated a heart rate monitor and accelerometer into an artificial pancreas system, it appears that PISA happens more than 3% of the time during the night.

- **Pressure induced sensor attenuation (PISA) is a phenomenon where individuals roll over on their CGM sensor during sleep,** reducing the CGM signal accuracy and affecting closed loop performance. PISA has certain characteristics that allow it to be detected – for example, there is a non-physiological rate of change in the CGM signal at the outset. Dr. Bequette has developed a PISA detection algorithm based on these characteristics. However, this algorithm is designed for overnight conditions. So he decided to deactivate PISA detection when patients were awake.
- **Dr. Bequette described a small study (n=23; 1,140 hours of CGM data) of the PISA algorithm**, using a closed loop system with a Medtronic pump and Dexcom CGM. He also added a heart rate monitor and an accelerometer, which can sense waking and sleep.
- **The algorithm detected 0.2% PISA during the daytime and 3.3% PISA at nighttime.** Closed-loop algorithms can take this into account – it's important to understand if rapid CGM changes are physiologic or not so we can have better pump shutoffs at night. Detection of whether or not a person is asleep becomes vital for non-typical sleep schedules, such as overnight or multi time zone travel, or shift work.

Corporate Symposium: Clinical Experience with the Dexcom G4 Platinum and Future Applications (Sponsored by Dexcom)

PEDIATRIC EXPERIENCE WITH DEXCOM G4 PLATINUM - SENSOR PERFORMANCE AND CLINICAL APPLICATION

Bruce Buckingham, MD (Stanford University, Stanford, CA)

Dr. Bruce Buckingham shared the accuracy data from the recently completed G4 Platinum pediatric trial (n=176 at six sites in patients 2-17 years old). Each patient wore two G4 Platinum sensors, one unblinded at home (compared to the Verio IQ BGM) and both blinded for in-clinic testing vs. YSI. Overall, the G4 Platinum was clinically accurate and tracked well to home use of the Verio IQ meter: MARD vs. the Verio IQ was 15% (n=16,318). Most surprising to us was the comparison of the Verio IQ to YSI: MARD was 13% (n=2,514), a higher level of inaccuracy than we had thought. This made us wonder how much CGM accuracy could be improved with use of much more accurate meters. There was no difference in G4 Platinum accuracy in pediatrics in daytime vs. nighttime, age, insertion site (buttocks and abdomen in the pediatric study, vs. abdomen only in adult studies), or use of adhesives. Said Dr. Buckingham, "It seems that subcutaneous measurements give you subcutaneous glucose values" regardless of who is being measured or the CGM's placement. G4 Platinum was also well tolerated in pediatrics, with <5% skin reactions. As a reminder, the PMA supplement for a pediatric indication has been submitted to the FDA and Dexcom expects a 2H13 approval. Dr. Buckingham closed with a review of his inspiring remote monitoring study first presented at Dexcom's corporate symposium at EASD 2012. He noted the high level of enthusiasm for the G4 Platinum ("All the families in our studies really liked wearing this. They really felt like they could trust it") and the rate of true alarms (in that study, "80% of the time when it said it was low, it was low").

- **Dr. Buckingham also reviewed the data that supported the G4 Platinum's recent CE Mark in children as young as two years old.** The 30-patient study compared CGM to SMBG values in patients 2-17 years old. Overall MARD from 40-400 mg/dl was 15%, nearly identical to the 14% seen in adults. Mean absolute difference for CGM ≤80 mg/dl was 21 mg/dl in pediatrics vs. 11 mg/dl in adults. Clarke Error Grid A-Zone values were nearly identical, at 76% for pediatrics and 79% for adults. Sensor life (up to 7 days) was 94% in adults vs. 81% in pediatrics. The striking difference in study size here in the US (n=176) vs. this EU study (n=30) really underscores the disparate regulatory expectations and it crystalizes just how high the barriers to entry are in the US when it comes to commercializing a CGM.

Questions and Answers

Q: Do you plan to test the remote monitoring system at home with parents?

A: We have an NIH grant in to do that. Whoever is in here that evaluates that, it would be nice if you would fund it. [Laughter]

Q: In the first part, you said the CGM was at least as accurate as the meter, or even more?

A: One of important things is testing the meter against YSI. But then Dexcom is calibrated against the meter, so it's only as good as the meter is accurate. The meter had a bias high; if you calibrate the Dexcom, it also has a bias high. Better and better meter technologies will really improve CGM. We think of parents at home looking at the values and comparing them to a test against the meter. There was a very good correlation. They felt it was right on a lot of the time. Day one is still a little rocky. But on days two, three, four, five, and six, the MARD goes down, and that's really nice to see.

Q: Is there data comparing Dexcom between pediatric patients on MDI and CSII?

A: When doing the JDRF study, we took MDI and CSII patients. Both showed an improvement. A lot of the time, when we have someone on MDI and put them on a sensor, after a few months, they prefer to go on a pump. They're seeing so much more information. The pump allows them to make adjustments more frequently.

Q: You had good local tolerance of the Dexcom G4 at different sites on the body. How long is it possible to maintain CGM in such young children with not very much space – six months, one year, or more?

A: The whole thing is user interface. How easy is it to insert. How fearful is someone of insertion? The easier the insertion and the easier to carry around, the better. The new device is really slick. It fits into the iPod motif that kids like. They aren't getting adhesive reactions and site reactions. I think we'll see an improvement. We aren't seeing these data gaps. We do these studies like the JDRF CGM trial with one set of technology. Now we've moved forward with better sensors and insertion. By the time you evaluate something, you're behind.

DEXCOM CGM TODAY AND IN THE FUTURE

Tom Peyser, PhD (Dexcom, San Diego, CA)

Dr. Tom Peyser followed his presentation from earlier in the day with a broader discussion of CGM, Dexcom's G4 Platinum, and future products. Most notable was his discussion of Dexcom's future pipeline – specifically, he gave new details on Dexcom Share (remote monitoring), highlighted the insulin pump partnerships with Tandem and Animas (hopefully within the next year), shared data on the G4 AP version, mentioned that Gen 5 is currently in clinical studies, and highlighted that the SweetSpot system

will hopefully be here in the next year. He also addressed the "time lag" associated with the G4 Platinum (only five to seven minutes) and with publications on CGM accuracy in general. Dr. Peyser closed by emphasizing that G4 Platinum represents a new level of accuracy and performance, and the hope is that the improved user experience will inspire more patients to use CGM on a regular basis. While he believes that "we still don't have a gold medal – wait for Gen 5 or Gen 6 for that – we're at a level we can smile about." We agree.

- **The JDRF CGM trial was "hailed as a landmark study, but we must take into account that it was an early stage of CGM."** In Dr. Peyser's view, the trial underestimated the true potential benefit of CGM, as the glycemic benefit was quite small compared to what we see today. At that time, it was difficult to achieve sustained use since CGM readings were often wrong, and early devices were inaccurate and hard to use. Patient and HCP reactions were also mixed. Using an Olympics analogy, Dr. Peyser called early CGM devices "a bronze medal," not a gold.
- **"We're finding lag times for the G4 Platinum compared to blood glucose measurements of five to seven minutes.**" To Dr. Peyser, this suggests that the issue of CGM lag that is commonly discussed is perhaps not warranted with the G4 platinum. A study funded by the Helmsley Charitable Trust at the Mayo Clinic will use radiotracers to obtain a precise measurement of physiological CGM lag time. Results are expected next year.
- **Dr. Peyser displayed a graphical illustration of how Dexcom Share will work, the first time we we've ever seen a description of it.** The graphic displayed the Dexcom Share device (a cradle that holds the G4 Platinum sensor and plugs into a power outlet) at a patient's bedside. Data from the G4 Platinum is then sent via the cradle (using Bluetooth) to a nearby smartphone (the picture displayed a phone on the nightstand, right next to the Share device). That phone then uploads the data to the cloud, where it can be monitored by parents/caregivers through push notifications or SMS text messages. The picture showed a father on a business trip in a taxi, checking his phone with a sigh of relief that his daughter's blood glucose was 150 mg/dl. As of Dexcom's 4Q12 call, this product will be submitted to FDA in 3Q13.
    - **We're very excited to see Dexcom getting into remote monitoring, since we think many, many parents will appreciate this.** Share is of course a first baby step, since the G4 Platinum must be physically inserted in the cradle, which must be plugged into the wall, which must have a nearby phone to send the data to the cloud. Certainly, Gen 5 is much more ambitious, since sensor data will go right from the transmitter to a smartphone.
- **With Dr. Claudio Cobelli's group at Padova, Dexcom is developing an AP version of the G4 with special algorithms; early data suggest further accuracy improvement.** The G4 Platinum sensor and transmitter will be the same, and only the algorithms on the receiver will be different algorithms. Dr. Peyser characterized the algorithm efforts as "denoising." The device will be made available to investigators under an IDE or equivalent hopefully by the end of this year.
    - **Overall MARD declines from 13.2% with the G4 Platinum to 11.6% with the G4AP.** Dr. Peyser also noted that the G4 AP brings a "significant compression" in the sensor MARD distribution, as standard deviation of MARDs declines from 6.7% to 4.1%. Dr. Peyser showed an example of a sensor tracing from the G4 Platinum pivotal study to which the new G4AP algorithm had been applied. The MARD improved from 12.7% on the first day with the G4 Platinum algorithm to 7.2% with the G4AP algorithm. Overall, he called the new algorithm "quite a breakthrough."

    - **Dr. Peyser implied during Q&A that Dexcom might be able to make the G4AP commercially available to patients.** Unfortunately, the FDA will require a "large-scale clinical study," so it's not clear to us if Dexcom will pursue this in advance of Gen 5.

- **"Hopefully within the next year," Dexcom will be integrated with the Animas Vibe and Tandem t:slim.** As of Dexcom's 4Q12 call, J&J and Dexcom are finalizing the PMA for the Animas Vibe and expect to submit by the end of 1Q13 (based on the G4 Platinum's slightly less than 180-day review, a 2013 approval could still be possible). Meanwhile, the Tandem partnership does not have an official timeline, though we would guess it could be filed as soon as this year. Dr. Peyser did not mention the dissolved partnerships with Insulet and Roche.
- **Dr. Peyser mentioned that Dexcom's Gen 5 sensor (sending data to a smartphone) is currently being tested in clinical studies.** He showed a picture of the mobile app that receives the CGM data and displays values and trend graphs. As a reminder, Gen 5 will use a new transmitter with the G4 Platinum sensor. As of Dexcom's pipeline update at JPM 2013, Gen 5 is expected to launch in late 2014-2015.
- **The SweetSpot web-based data management platform was also a brief topic of discussion, which will "hopefully" be here in the coming year.** Dr. Peyser emphasized how this will appeal to physicians, who will have an easier time accessing patient data. As of 3Q12, goal was FDA submission by end of 2012. We have not been updated on SweetSpot platform progress since.
- **Dr. Peyser reviewed a few recent publications on CGM accuracy and showed how the G4 Platinum and G4AP stacked up.** The short answer: very positively and always comparable to or better than the competition. The publications included Drs. Damiano and Russell (*Diabetes Care* 2013) comparing the FreeStyle Navigator, Dexcom Seven Plus, and Medtronic Guardian; Dr. Hovorka et al. (*DTT* 2013) comparing the Navigator and Seven Plus on the frequency of large errors; and Dr. Luijf et al. at DTM 2012 and ATTD 2013 comparing the Navigator, Enlite, and "prototype G4" (i.e., the version formerly used with the Animas Vibe in Europe, not the more advanced and more accurate G4 Platinum). Said Dr. Peyser, "There *is* a time lag problem with CGM": it's not the lag between blood glucose and interstitial fluid glucose, it's the lag between the development of sensor technology and publications (i.e., published papers cannot keep up with the pace of new technology).

Questions and Answers

Q: So in the G4AP, the only difference is the algorithm?

A: We do hope to make it available for everybody. In the US, there's a small barrier to jump over called the FDA. It's reasonable, but we have to run a large-scale clinical study. We'd have to show the same kind of clinical results. We can make it available earlier under an IDE to AP groups for investigational use only. At that time, we can put in place the regulatory filings to make it more available commercially.

Dr. Gerard Reach (Avicenne Hospital, Bobigny, France): On the slide you showed us on lag time, it seemed that when glucose level went up, you had 5-7 minutes of lag time. When blood glucose decreased, there was no lag at all. Did you observe this consistently? That may have theoretical significance.

A: We're looking at that now. There's been a lot of work done on this issue for several decades. Some of earliest and best work was done by you at the dawn of the CGM era. At the Mayo Clinic, Drs. Basu and Kudva will shed a lot of light on this. We will be instrumenting their studies with sensors. It's a great

question and something we're very interested in. The point in showing this was to say that lag time in CGM, at least with Dexcom, should not be considered an obstacle to patients.

Q: What changed with the G4 Platinum?

A: The sensors are better. They're smaller, they've gotten faster, and the algorithms are better. In our case, we put a lot of effort in the transition from Seven Plus to G4 in increasing the signal to noise. There's not as much smoothing and filtering, which is a major source of delay. We don't do very much smoothing or filtering with the G4 Platinum.

Q: Accuracy improves at days three, four, five, six, and seven. Why?

A: Great question. For day one, the accuracy might be at 14-16%. Interestingly, most sensors get worse as a function of time because of biofouling. The scientists at Dexcom have built a highly biocompatible membrane. We don't see much biofouling. So on day one, it's 14-16%, on Day four it's 11%, and on day seven it's probably 11%. There are two things happening: one is, the sensor is stabilizing in the body. Any kind of wound response is beginning to abate. The second is that algorithm is starting to learn as we put more and more calibration numbers in. It's just doing better.

Q: What do you think about using sensors longer than seven days?

A: We find commercially that many patients use the device for longer than seven days – perhaps 10 days or 14 days. We did a study with Dr. DeVries with an early G4 version. The last patient came to the clinic wearing the sensor for 82 days. Andy Balo and I were frantic. He was duct taping the sensor to his abdomen. We are looking at an expanded indication for up to 10 days or 14 days, but that's in the future.

Q: When will we get to no calibration at all?

A: We're actively working on that. There are two goals for future gen sensors. I cannot say if it will be Gen 6 or Gen 7. One is no calibration, and the other is a replacement claim. We're approaching a level of accuracy and performance where we can start thinking about that.

Q: You talked about the importance of patients' confidence in the results of sensor. Did you survey patients about their confidence?

A: We didn't. That's an interesting question. A paper just came out from Dr. Polonsky in *Diabetes Technology and Therapeutics*. It was looking at user satisfaction with CGM – that's exactly the thing someone like that should explore with the G4 Platinum. Hopefully, he and others will do so. Anecdotally, patients really like the device. I visited with Dr. Buckingham during the camp study. There were 120 kids at the camp, and only 20 had the sensor, and that was a real issue. Many kids were unbelievably demanding to have a sensor. I think it was the pink and blue colors.

Corporate Symposium: After More Than a Decade, CGM is Still a Niche Product. How Can it Fulfill the High Expectations of Patients and Health Care Professionals? (Sponsored By Roche Diagnostics)

PROS AND CONS DEBATE: THE AVAILABILITY OF CGM HAS ALREADY CHANGED THE WAY WE MANAGE DIABETES – YES

John Pickup, MD (King's College London School of Medicine, London, United Kingdom)

When posed with the question, "Has the availability of CGM already changed the way we manage diabetes?" Dr. John Pickup argued the affirmative. Dr. Pickup urged the audience to consider the value of CGM according to experiences in clinical practice, not just by the data presented in RCTs. We were happy to hear this; it has been frustrating not to see better data in RCTs but unsurprising since they all use older technology than is now approved. Dr. Pickup explained that RCTs have yet to produce substantial evidence demonstrating the value of CGM over SMBG with respect to severe hypoglycemia and quality of life; however, he argued that this lack of data was largely because trials designed to appropriately test these outcomes have not been done. He believes that for patients with disabling hypoglycemia on MDI or CSII, "CGM is the only logical option short of islet or pancreas transplant." Evidence from every day practice, he said, shows that severe hypoglycemia can be reduced and that quality of life can be improved with CGM. Along with his colleague, Dr. Pickup has been collecting UK patient narratives of experiences with real-time CGM. He presented a collection of stories which characterized CGM as "life-saving," "a wonderful tool," and "fantastic." Of course, he said, CGM is not without its limitations and patients recognized this too ("I must remember these are not infallible pieces of kit," said one user). However, he concluded, like many of the patients in his survey, that if understood for its limitations, CGM has benefits that outweigh its drawbacks. In the words of one patient, "changing the sensor is quite fiddly – but then so is opening a bottle of Champaign (similar cost/benefit ratio)."

PROS AND CONS DEBATE: THE AVAILABILITY OF CGM HAS ALREADY CHANGED THE WAY WE MANAGE DIABETES – NO, NOT YET

Joroen Hermanides, MD, PhD (Academic Medical Centre, Amsterdam, The Netherlands)

"I am going to tell you that CGM doesn't work," said Dr. Joroen Hermanides. "It's not an easy task." In the debate as to whether CGM has already changed the way we manage diabetes, Dr. Hermanides argued that it has not, not yet. He explained that diabetes has many faces and many names, and for the vast majority, CGM has not significantly impacted care. He divided patients with diabetes according to their respective diabetes type and considered the available evidence for each group. First, he noted that there has been a paucity of data assessing the value of CGM in patients with type 2 diabetes and CGM use during pregnancy. In critical care situations, he interpreted the data available to be mixed. While he saw potential for CGM with respect to preventing hypoglycemic events, he believes that the evidence does not show that CGM improves overall glycemic control. Further, in his own study assessing CGM in the hospital (Hermanides et al., Diabetes Technol Ther *2010), he commented that CGM inaccuracy and the resulting false hypoglycemic alarms "drove the nurses mad." Next, Dr. Hermanides looked at patients with type 1 diabetes. He presented two review studies. He used the first to show that CGM use has demonstrated significant A1c reductions vs. SMBG but that patients with high baseline A1c and who frequently use CGM are the ones who benefit most (Pickup et al.,* BMJ *2012). He used the second to show that CGM does not reduce the risk for severe hypoglycemia (Langendam et al.,* Cochrane Database Sys Rev *2012). The audience took issue with this latter statement in the Q&A discussion that followed due to the analysis' use of early-generation CGM devices and the impact of CGM education and training on results. Dr. Hermanides believes that the value of CGM is, for the time being, restricted to the motivated, compliant, reimbursed patient with type 1 diabetes who currently has poor glucose control and who can tolerate the device. In order for CGM to broadly impact the way diabetes is managed, he called for technical improvements, more clinical trials, and better reimbursement.*

- **Dr. Hermanides reviewed the challenging CGM reimbursement environment in Europe** (according to data by Heinemann et al., *J Diabetes Sci Technol* 2012). France, for

example, has no CGM reimbursement and both the UK and Germany provide reimbursement on a case-to-case basis.

Reimbursement Criteria	
France	No reimbursement
Germany	Individual cases
Israel	- Children with hypoglycemia (0-8 years) and/or poor control - Children with hypoglycemia (8-18 years) - Adults with hypoglycemia unawareness
The Netherlands	- Adults with A1c >64 mmol/mol (>8%) - Pregnant women with diabetes (type 1 and type 2) - Children
Slovenia	- Patients <8 years old - Pregnancy (type 1 and type 2 on intensive insulin therapy) - Severe hypoglycemia or hypoglycemia unawareness
Spain	Limited use of CGM systems is allowed for diagnostic or investigational purposes in advanced diabetes centers
Sweden	Pump patients with: - A1c >86 mmol/mol (>10%) - Two or more severe hypoglycemic events/year - Children testing > 10 times/day
Switzerland	- Type 1 diabetes patients using a pump and with A1c ≥64 mmol/mol (≥8%) - Frequent potentially life-threatening hypoglycemia - Brittle diabetes with emergency room/hospital visits
UK	Case-by-case basis

PANEL DISCUSSION

John Pickup, MD (King's College London School of Medicine, London, United Kingdom) and Joroen Hermanides, MD, PhD (Academic Medical Centre, Amsterdam, The Netherlands)

Dr. Eric Renard (Montpellier University Hospital, Montpellier, France): What kind of patient would you absolutely use CGM for and what patient would you never use CGM for?

Dr. Hermanides: I would doubt its use for a patient with type 2 diabetes.

Dr. Renard: No CGM for type 2 patients?

Dr. Hermanides: If they are motivated, perhaps, but for starters they are not reimbursed anywhere in Europe.

Dr. Renard: In spite of your being against CGM, do you sometimes by error prescribe it? [Laughter from audience.]

Dr. Hermanides: I have seen patients that have improved fantastically and they are the type 1 patient.

Dr. Renard: Any type 1 patient?

Dr. Hermanides: Type 1 patients with high A1c.

Dr. Renard: John?

Dr. Pickup: I would prescribe CGM to the patient who failed to achieve satisfactory control with all other measures tried. And who agrees to a trial of CGM. Particularly, I would use it for the patient with disabling hypoglycemia, where my experience is that dramatic effects in changing quality of life has been achieved. While it may not happen in everybody, it happens sufficiently often to be very encouraging. The same rule applies to who you don't give CGM to. And that's the patient who doesn't want to go on CGM, who doesn't want that extra technology.

Dr. David Price (Executive Director, Clinical Research, Dexcom): In the Cochrane meta-analysis, why did they exclude GlucoWatch?

Dr. Hermanides: I'm not sure.

Dr. Price: They reported that those products are no longer on the market. On all studies you showed, they used products from the three manufacturers that are no longer on the market. Each manufacturer has products available with improved performance and reliability. It should translate into more people using and trusting the devices.

Dr. J. Hans DeVries (Academic Medical Center, Amsterdam, The Netherlands): I did Cochrane, maybe I can answer this question. GlucoWatch is fundamentally a different device and they retracted it from market. I agree, the current manufacturers (Dexcom, Abbott, Medtronic) are putting new devices on the market and making new generations and I also agree, to some extent, that the newer versions are better than the older versions. However, I put forward that these increases are little steps and we make a lot of little steps, but this is not like the invention of Penicillin. They are getting better, but they need to get even more so.

Q: As a pediatrician, we continuously treat patients with a continuous sensor and in our experience, I would hesitate very much with current meta-analysis results. You're not just testing sensors, you're testing education, correction factors, pump settings… It's very complicated. I think we need to account for that. You should also reward the training. It's not a pharmaceutical pill. It has as much to do with the implementation and skill of the clinic. Do you do regular downloads? Do you try to improve treatment on a weekly basis? I would very much more be in touch with the presentation by Dr. Pickup. CGM needs improvements, but stay a bit a way from meta-analyses where there is no clarification on pump settings and training.

Dr. Pickup: I agree, meta-analysis is a dangerous tool and there is much to be said about the misuse of it. We try to use meta-analyses for selecting the patients who might do best, not for summarizing the evidence base. That's the misunderstanding, including Cochrane, who put out reviews that don't tell physicians what they want to know. These treatments are a package, just like MDI. There is education, SMBG, enthusiasm of the doctor… It's not just the isolated technology; it's the whole business of how we use it. In a lot of my patients' comments, they said that their training wasn't very good, so that is a clear area to be improved.

Dr. Hermanides: Meta-analyses don't say everything, but especially in CGM trials, we are often testing the whole package.

ADVANCES IN CGM TECHNOLOGY AND ITS BENEFITS FOR PERSONALIZED DIABETES MANAGEMENT

Michael Schoemaker, PhD (Roche Diabetes Care, Mannheim, Germany)

Dr. Michael Schoemaker presented never-before-seen clinical data on Roche's glucose sensor prototype, which touted a mean absolute relative difference (MARD) of 8.6% when compared to Accu-Chek Aviva blood glucose meter (BGM) readings (n=7,039). The study cohort was comprised of 30 patients with type 1 diabetes. Each patient wore two sensors simultaneously on the abdomen over a seven-day period that consisted of two induced glycemic swings; the study was performed in the in-patient setting. The sensor was initially calibrated two hours after the initial insertion, with two re-calibrations per day. Of the sixty sensors used, 59 lasted for seven days and of those 59 sensors, 100% of CGM data was captured. Of the 7,039 CGM-BGM paired data points, 85.1% and 13.8% fell in the Clark Error Grid zone A and zone B, respectively. When looking at individual sensor performance, more than 75% of sensors recorded a MARD ≤10%. Of the 573 paired CGM-BGM data points in hypoglycemia (blood glucose ≤70 mg/dl), 87.3% of readings fell in Clark Error Grid zone A and 0.3% in zone B. MARD was 11.9% in this glucose range. The induced glucose swings, which totaled 560 hours of data and resulted in 2,250 CGM-BGM paired points, resulted in 77.8% of readings in Clark Error Grid zone A and 20.0% of points in zone B. The sensor recorded an MARD of 10.6% during this time period. Dr. Schoemaker did not provide any indication as to when we might expect to see the first-generation system on the market, but for sure, we will closely follow Roche's progress to see whether future trials corroborate these initially promising results.

- **Thirty patients with type 1 diabetes each wore two sensors each on their abdomen during the seven-day study**. Sensors were initially calibrated two hours after insertion, then re-calibrated twice daily (once in the morning and once at night, regardless of blood glucose at the time). The study was an in-patient study, though participants were allowed to move freely. By design, the study induced a glucose swing on day 2 and day 3, once via a high glycemic index breakfast and once via an altered and delayed insulin dose.
- **Patient characteristics**: The cohort was comprised of 15 males and 15 females. Twenty-two patients were on CSII and eight were on MDI. The cohort had a mean age of 47 years (range: 21 to 63 years), BMI of 26.9 kg/m^2 (range: 21.6 to 41.4 kg/m^2), time since diagnosis of 23.4 year (range: 5.8 to 11.7 years), and A1c of 7.7% (range: 5.8 to 11.7%).
- **Blood glucose measurements were taken by the Accu-Chek Aviva meter ~17 times per 24-hour period;** during glucose swings, measurements were taken every 15 minutes. The study also performed laboratory glucose measurements by perchloric acid deproteinization hexokinase comparison, such that ~1.6 readings were taken per 24-hour period.
- **Fifty-nine of 60 sensors lasted for the seven-day trial**, which translated to a 98.3% sensor survival rate. The sensor that did not last through the trial was removed "due to obvious malfunction;" no additional detail was provided. Of the 59 sensors that lasted over the seven-day period, the data reporting percentage was 100%.
- **Based on paired CGM-BGM readings, 98.9% of data points fell in the Clark Error Grid A + B zone** (n=6963 of 7039). Five hundred and seventy three data points were ≤70 mg/dl, 4,518 points were >70 mg/dl and ≤180mg/dl, and 1,948 points were >180 mg/dl.

Zone	n	Percent
A	5991	85.1%
B	972	13.8%

C	-	-
D	75	1.1%
E	1	0.0%
Total	7039	100.0%

- **Over the entire glucose range, MARD was 8.6% when compared to BGM**. Zeroing in on individual sensor performance, 75% of sensors recorded a MARD ≤10%; five sensors recorded an MARD ≤6%. All sensors had a MARD ≤13%, with the exception of one sensor that recorded an MARD of 19%. On day one, mean MARD was 10% (range: 4.9 to 20.3%) and the top 25% of sensors had a MARD of ≤7.8%. Compared to the laboratory method, the sensors recorded a MARD of 8.1% over the seven-day study (n=682).
- **Percent absolute relative deviation (PARD) over the entire glucose range was 7.6%** (n=282,047). For background, PARD quantifies the absolute relative deviation between two CGM sensors running simultaneously on one patient. Dr. Schoemaker said that currently marketed CGM systems have PARDs ranging from 15.3-16.0%, with the caveat that this data is quite difficult to find in the literature.
- **In hypoglycemia (≤70 mg/dl; n=573), MARD was 11.9% and 87.6% of paired CGM-BGM readings falling in the Clark Error Grid A+B zone**. (PARD was not provided for the hypoglycemic range.)

Zone	Percent
A	87.3%
B	0.3%
C	-
D	12.4%
E	-
Total	100.0%

- **During the glucose swings, the sensors recorded a MARD of 10.6% with 97.8% of paired CGM-BGM data points in the Clark Error Grid A+B zone**. During periods of glucose swings, PARD was 8.0%. The glucose swings accounted for 560 hours of data collection and 2,250 paired CGM-BGM data.

Zone	Percent
A	77.8%
B	20.0%
C	-
D	2.2%
E	-
Total	100.0%

- **Dr. Schoemaker believes that the sensors' membrane material was the factor mainly responsible for the sensor's high accuracy**; however, he did not provide specific detail. Broadly, Dr. Schoemaker described three design elements important to accurate glucose

monitoring that we assume are incorporated into Roche's design: 1) multiple working electrode spots to compensate for sub-millimeter scale heterogeneities and processes in the subcutaneous tissue; 2) the material and surface of the sensor coating, which Dr. Schoemaker primarily attributed the prototype sensor's accuracy to; and 3) a working electrode that contains the catalyst for hydrogen peroxide oxidation (and thereby reduces interference from other electrochemically active substances).

Questions and Answers

Dr. Renard: Your sensor is really astonishing. It's a prototype, but please don't change it too much. [Laughter from the crowd.] What was the major improvement that resulted in the improved accuracy? Is it a matter of biocompatibility? What, in your opinion, is its most striking difference?

A: It's the right choice of the membrane material. Biocompatibility is very important and it has two meanings. On the one hand, biocompatibility is a given – it is highly regulated because you have to make sure the sensor does not do harm to the body. The other side is that the sensor is doing what it is supposed to do – that is the other part. All the sensors in the market are certainly biocompatible. Otherwise, the authorities would never have approved them. You have to find the right material for both aspects.

Dr. Renard: There were discrepancies between sensors. You showed one was accurate, and another was not so good. Is that due to the location of the sensor or improvements you have to do on manufacturing?

A: We think it's physiological effects. We placed sensors in the abdomen. There are physiological artifacts, possibly from sensor insertion.

Q: What kind of range of SMBG was there for calibration? It looked like calibration points were done in euglycemia. Did you try calibration at hyper- or hypoglycemic points?

A: We are doing this of course because we want to learn more about the effect of calibration. What I showed was one morning and one evening calibration regardless of high glucose or low glucose.

Q: It was prospectively done?

A: It's hard to explain. The analysis was done retrospectively but we've used prospective calibration. The data would look same if we had it running on line.

Q: CGM is in the subcutaneous tissue, but blood glucose meters measure the blood. Did you correct for this difference?

A: No. We are not aware of any correction factor.

Q: Would difference in internal circulation impact results in accuracy of the CGM?

A: The blood circulation? No, we haven't looked at that.

INSIGHTS FROM A GERMAN PEDIATRIC DIABETES PRACTICE – HOW CAN ADVANCED CGM TECHNOLOGY HELP TO IMPROVE DIABETES MANAGEMENT IN THE PEDIATRIC AGE GROUP?

Ralph Ziegler, MD (Praxis Dr. med Ralph Ziegler und Kollegen, Münster, Germany)

Dr. Ralph Ziegler discussed CGM's potential to improve pediatric care. He explained that CGM can be used to gain more information about critical situations, like what precedes hypoglycemic events. Even

though patients may not respond or may not respond appropriately to the additional data provided by CGM, at least, said Dr. Ziegler, they get the chance. Looking forward, he called for more precise sensors as CGM is increasingly being used as a diagnostic tool and especially as patients are using CGM to make decisions – while he recognized that CGM is not approved for this indication, he said that the reality is that most patients do make decisions based off their CGM. With precise sensors Dr. Ziegler believes that CGM can help patients, help parents, provide peace of mind for parents and other caretakers, and provide insights about diabetes therapy improvements.

Corporate Symposium: From Innovation to Action: Improving Your Patients' Outcomes (Sponsored by Medtronic)

A PROSPECTIVE VIEW OF IMMINENT CGM TECHNOLOGIES

Rajiv Shah, MS (Senior Engineering Director, Medtronic Diabetes, Northridge, CA)

Mr. Rajiv Shah gave a whirlwind pipeline update on behalf of Medtronic. He discussed the company's development work on the Enlite Improved continuous glucose sensor, Integrated Sensor & Set, Actionable CGM, Orthogonal Redundancy, and Connected Care Device – he concluded his presentation with a demo of the latter! (His slides made clear that these products were not CE Marked.) Medtronic's technological approach to sensor development is founded on the premise that if sensors fail, they need to "fail safe." As such, Medtronic's "actionable CGM" is designed to obtain glucose information from multiple sensors and determine which sensor is reporting most accurately. Through redundant sensing that draws information from slightly different microenvironments, Medtronic hopes to avoid sensor inaccuracy caused by localized effects. However, because it's possible that there are sensor failures specific to electrochemical sensing, Medtronic is also developing orthogonal redundancy in collaboration with JDRF, such that both electrochemical and optical sensors are used. Said Mr. Shaw, "our singular focus is the artificial pancreas. We are building CGM with that end in mind."

- **Enlite Improved**: Medtronic's next-generation sensor features myriad design improvements over the Enlite: 1) 80% smaller implant volume; 2) circular electrode array (40 micron diameter) that allows for more uniform plating than the rectangular array of the Enlite; 2) removed cannula, which the company felt had a deterrent to rapid sensor start up; and 3) new overtaping accessories that are meant to better hold the sensor on the body. (He commented that the device will likely get a different name when it comes to market; no timeline details were given.)
    - **Enlite Improved Algorithm**: Mr. Shaw explained that raw glucose values are processed by the Veo pump's algorithm; however, the Veo is not optimized for the Enlite Improved. The sensor will still function with the Veo's algorithm, but the company expects better performance when it launches pumps with the new Enlite Improved version.

Algorithm	Sensor	n	Mean-ARD	Median-ARD
Veo	Enlite	87	17.22%	11.95%
	Enlite Improved	118	12.06%	8.47%
Enlite Improved	Enlite Improved	118	10.99%	7.60%

- **Integrated Sensor & Set**: This product incorporates an insulin infusion catheter and a CGM sensor separated via a split needle design; however, from a functional point of view, Mr. Shaw feels it is equivalent to a single insertion. In initial feasibility studies, the company has not seen interferences between the infusion and sensor, even with large boluses. We got our first in-person look at the system at Medtronic's Exhibit Booth on Day #1 (see page 15 at https://closeconcerns.box.com/s/pypcux2vn238a3qbjomr): from a top view of the integrated set, it looked like a Mio infusion set fused with the clamshell-shaped Guardian/Enlite transmitter.
- **Actionable CGM**: Actionable CGM employs redundant electrochemical sensing and real-time electrochemical impedance spectroscopy to identify and de-emphasize the input from a failing sensor. Mr. Shaw showed that on a single CGM sensor, glucose information obtained from the front surface of the sensor vs. the back surface of the sensor can deviate. He believes this confirms that cells in close proximity to the sensor contribute to sensor failures and justifies redundant sensing, even when sensing is separated by just a two mm space (the separation distance between the front and back of the sensor insertion).
- **Orthogonal Redundancy**: Mr. Shaw described Medtronic's efforts with JDRF to take traditional electrochemical sensing and interface it mechanistically with optical based sensing. He deferred to Medtronic's oral presentation on the topic later that day (see talk entitled "Development of an Orthogonally Redundant Glucose Sensor System").
- **Connected Care Device**: This cellular-enabled tabletop device captures glucose data and moves it to the cloud via a GSM network. From here, information is automatically uploaded to CareLink (someone who has this device would never have to use the CareLink USB again, he said). To conclude his presentation, Mr. Shaw demoed the system. He displayed simulated sensor output on his iPad, and then generated a failure in the connected pump – a notification appeared in the corner of the iPad and a text was sent to his iPhone. With Medtronic's Connected Care and Dexcom's Share (Dexcom's remote monitoring system; FDA submission slated for 3Q13) in development, CGM seems to be taking important strides in wireless data transmission and connectivity.

SUCCESS IN THE NEXT STEPS TO PREVENT HYPOGLYCEMIA

Thomas Danne, MD (Kinder- und Jugendkrankenhaus Auf der Bult, Hannover, Germany)

The highly-regarded Dr. Thomas Danne presented an overview of technologies for hypoglycemia prevention, focusing on Low Glucose Suspend (LGS). Poignantly he started his talk with an emotional recollection of a 25-year old patient who had recently died after she had started to live alone. The cause was most likely nocturnal severe hypoglycemia. Understandably, the fear of hypoglycemia is very high for patients and even higher for parents. LGS is intended to reduce hypoglycemia excursions and reduce the time spent in hypoglycemia by suspending insulin when glucose reaches a target threshold. LGS is implemented in the Medtronic Veo pump. Dr. Danne presented studies that clearly demonstrated that LGS works safely, and implied that it could help save lives, such as his patient's. The next step is Predictive LGS (PLGS), which suspends when hypoglycemia is predicted rather than attained. Again, a small clinical trial of this new technology indicated that it appears safe and effective.

- **The fear of hypoglycemia is significant, even though the risk of death is relatively small.** Maternal 'fear of hypoglycemia' score is 2.9 versus 1.9 for adults with diabetes. With experience of a severe hypoglycemia event, the maternal score rises to 3.2.

- **Low glucose suspend (LGS) means that basal insulin is suspended below a preset glucose threshold, and it's also not possible to give a bolus. LGS is intended to improve patient safety by avoiding prolonged severe hypoglycemia. LGS is implemented in the Medtronic Veo pump.** The ASPIRE trial studied LGS in an in-clinic setting, and showed clearly that the system avoids time in hypoglycemia. But it was a difficult trial because "hypoglycemia begets hypoglycemia" – patients who experience a severe hypoglycemic event are much more likely to have subsequent severe hypoglycemia, which has implications for the design and interpretation of a crossover study of this type. The CareLink database of ~50,000 patient days for nearly 1,000 patients, showed that LGS was safe and effective. Work performed by Dr. Danne's team demonstrated that LGS reduced hypoglycemia and time spent in hypoglycemia without changing average glucose.
- **Dr. Danne gave specific examples of patients who had avoided dangerous situations because of LGS.** It was sobering to think that LGS might have avoided a tragedy. (But more practically, one patient had set their threshold at 40 mg/dl – too low to be of much help, and another had set such tight tolerances that it over-alarmed.)
- **The next step would be to predict future hypoglycemia and suspend insulin in advance of going low. This is known as Predicted Low Glucose Suspend (PLGS).** The PILGRIM study was designed to assess this concept. The study included an exercise component to generate mild hypoglycemia (under close supervision) and the system was shown to work as expected. In the future, Dr. Danne expects to see predictive LGS as part of overnight closed loop control in a treat to range mode.

Questions and Answers

Dr. Bergenstal: Why don't people respond better to alarms?

A: It's a real life thing – it's human nature. People will ignore alarms if they are used to them. It is a real source of concern.

Q: What are the right settings for the threshold?

A: We had a patient for whom 70 mg/dl was too late, and we had to change it to 80 mg/dl in order to prevent hypoglycemia. So it can vary by patient.

Q: Teachers tell kids to turn alarms off in class – so we have a problem during the day too.

A: Absolutely correct. This technology can really help.

Q: Blood glucose can fall precipitously with exercise. In this case LGS can fail to prevent hypoglycemia because CGM can't respond fast enough.

A: True but in every single case we investigated, PLGS prevented severe hypoglycemia without any carb intervention. We had an ICU set up next door because everyone was so concerned, but from 17 patients at least, I am feeling confident that LGS can handle exercise reasonably well.

Q: Have you had enough experience to see if fears of hypoglycemia are alleviated by LGS and PLGS?

A: It's very difficult to answer because we need real life experience rather than in-clinic trials. My personal impression is yes - it does relieve concerns with both kids and their parents.

MANAGING TYPE 1 PREGNANCY

Helen Murphy MD, PhD (University of Cambridge, Cambridge, UK)

Pregnant women with diabetes have normal risk of delivering a live birth, but complications due to diabetes are common and rise rapidly with A1c during pregnancy. Giving women advice before becoming pregnant is the best thing HCPs can do to influence outcomes. The use of CGM in pregnancy is becoming more common, but trials do not give a uniformly rosy picture. That's because there are massive changes in carbohydrate metabolism and insulin PK/PD during pregnancy and it's very difficult to control post-meal excursions. New technology such as sensor augmented pumps and closed-loop control should help to address this issue.

- **Even decades after insulin was introduced, maternal mortality was 10-20%. And infant mortality was up to 40%. It's only more recently that people with diabetes can have relatively normal pregnancy outcomes. But the single most important thing HCPs can do for women with diabetes is give advice on avoiding unplanned pregnancy.** That's because there is a well-known relationship between A1c and major congenital malformation. An A1c of 6.5% during pregnancy gives a risk of major malformation of 1 in 33, while an A1c of 9.5% has a 1 in 10 risk. Development of the organs happens so early that it's clear that patients need to optimize their A1c prior to conception.
- **In a Diabetes Care study (2010), women with diabetes were deliberately and consistently "bombarded" with pre-pregnancy care information, with positive results.** This intervention was associated with an average A1c reduction in pre-pregnancy of about 0.9% and about 0.5% in the first trimester. But despite this, only 50% could achieve an A1c below 7.0% pre-pregnancy.
- **Although the risk of delivering a live baby is now the same for people with diabetes as with the general population, the risk of complications is still high, and glucose control in late pregnancy is actually getting worse.** In the UK from 2006-2009, the percentage of babies who were large for gestational age (LGA) or who displayed macrosomia was 40-50%, those delivered preterm was 33%, and those admitted to neonatal care 40%. Looking at the Nordic countries, glucose control in mid to late pregnancy appears to have gotten worse over the last twenty years. Rates of emergency sections, neonatal admissions, and macrosomia have stayed high, while BMI of women has increased over the same time period.
- **In pregnancy, we've seen the use of retrospective and real-time CGM, the use of pumps and CGM together, and now we are starting to see closed-loop trials in pregnancy.** In studies, women with type 1 diabetes who used CGM had 60% time in zone at the end of their pregnancies, compared to about 75% for type 2 women. Another study showed that retrospective CGM positively influenced A1c in subsequent pregnancies and the lowered risks of complications. A recent trial of real-time CGM hasn't had such strong results, presumably because of good baseline A1c and poor compliance. So there is clearly more to understand about the particular situation of pregnancy.
- **The JDRF-funded CONCEPT trial is an n=324 multi-center open label trial of CGM for pregnancy in women with type 1 diabetes.** The trial seeks to understand whether real-time CGM will have enough of an impact on A1c to improve infant outcomes.
- **The key appears to be managing post-prandial excursions.** Pregnancy per se does not alter the blood glucose impact of higher carb meals. But women do become more insulin resistant, particularly after meals. It also takes 30 minutes longer for insulin to be absorbed. So there is a huge variability of carbohydrate metabolism and insulin kinetics changes during pregnancy. This

is very difficult for patients to understand and predict, so CGM and the closed loop will allow for more personalized insulin delivery.

Questions and Answers

Q: What percent of carbohydrates is recommended for pregnant women in the UK?

A: At breakfast, 30-40 g of carbohydrates seems to be well tolerated. We advocate smaller carb loads to prevent post-prandial hyperglycemia. We are aiming for 180-200 g of carbohydrates per day, so we need to have five to six smaller meals/snacks.

Q: Isn't the time right to be doing sensor augmented pump therapy trials in pregnancy?

A: Yes, it's taken a long time to get funding for even real-time CGM work. But we need to do that trial.

Q: Any changes in boluses in late pregnancy?

A: The most important thing is getting the insulin in early. This is challenging, and closed loop will have a lot to offer in this regard. We have only 10-20% of patients who can do this properly, and even they are not consistent.

Q: What insulins do you use? (Not all are approved.)

A: I use the fastest acting insulins, in the largest doses, as early as possible. We tend to be conservative in pregnancy, but I explain the risks to the women.

3. Blood Glucose Monitoring

Session: ATTD Yearbook

SELF-MONITORING OF BLOOD GLUCOSE – AN OVERVIEW

Satish Garg, MD (University of Colorado Denver, Aurora, CO)

Dr. Satish Garg opened the ATTD 2013 yearbook session with a topic on the minds of nearly everyone in the healthcare system: cost. Specifically, he mentioned Medicare/Medicaid's decision to cut SMBG reimbursement to $15 per 50 strips as of 2014, and he said that UK decision-makers are considering a switch back to urine strips ("I thought many of us want to go forward to CGM, but people still talk about going back"). He questioned these strategies given that only about 20% of healthcare costs go toward drugs and medical equipment combined, with some 80% spent on services ("the overall cost may be more related to hospitals than pharma companies"). Dr. Garg then shifted gears to call for an end to gender disparities in diabetes care, as well as greater investment in mobile-health interventions (especially given the increasing ratio of diabetes patients to care providers). Finally, he acknowledged the ongoing controversy about the utility of SMBG in type 2 diabetes – a debate that he anticipates will continue until "we have a large, INDEPENDENT, randomized, controlled trial" on the matter.

Oral Presentations

INTEGRATED STRIP-FREE SMBG TECHNOLOGY (ACCU-CHEK MOBILE) IMPROVED PATIENT'S ADHERENCE TO RECOMMENDED TESTING AND GLYCEMIC CONTROL - RESULTS FROM THE EX-ACT STUDY

Alberto Maran, MD (University of Padova, Italy)

Dr. Alberto Maran showed trial results for the Accu-Chek Mobile (Roche), which is an integrated "strip-free" SMBG device. In the ExAct trial, the Mobile device improved number of tests/day by 0.37 and lowered A1c by 0.27% compared to a single strip control device. The concept is that a more convenient meter encourages more testing and therefore tighter control.

- **SMBG adherence is low. But Dr. Maran believes patients would test more frequently if SMBG was easier, more discreet, and less painful.** Sixty percent of people with type 1 diabetes perform three tests or less a day (i.e., less than the ADA recommendation). Approximately 40% of those with type 2 diabetes don't test enough according to guidelines. One additional SMBG test per day is associated with an A1c reduction of 0.32% for those with type 1 diabetes (taking three or more injections).
- **The primary objective of the ExAct study was to explore whether an integrated strip-free SMBG system (Roche's Accu-Chek Mobile) would change testing frequency compared to a single-strip system.** All 332 patients analyzed were non-adherent (i.e., they performed less tests than recommended.) ExAct was a four-country, six month study with three planned visits.
- **There was a statistically significant difference in tests/day between the two meters.** The Mobile group had a 0.48 tests/day increase and an improvement from control of 0.37 tests/day. This was after adjusting for testing frequency at baseline, country, device group, and visits.
- **The Accu-Chek Mobile group saw an average decrease in A1c of 0.27% compared to control.** There was also a greater decrease in A1c for type 2 patients, those taking 0-50 units insulin per day, those >65 years, and patients who didn't change dosing strategy during the trial.

International Fair of New Technologies in Diabetes

INTEGRITY APPLICATIONS: IS IT A REALITY OR JUST ANOTHER DREAM?

Avner Gal (CEO, Integrity Applications, Ashkelon, Israel)

Dr. Avner Gal, representing Integrity Applications, discussed GlucoTrack, which is a non-invasive blood glucose monitor. The device is clipped to the earlobe and uses three independent measurement types to determine glucose. The ear clip is calibrated for each patient in a process that takes up to two hours. This is repeated every six months, when the clip is replaced. Although the accuracy of the GlucoTrack does not meet the ISO standard for blood glucose monitoring, Dr. Gal takes the view that since compliance is expected to be higher than fingersticks, it can result in better outcomes for patients. He concluded that although there are limitations, a non-invasive glucose monitor is indeed feasible.

- **The hope of Integrity Applications is to bring to market a non-invasive device with acceptable accuracy that will encourage more frequent testing.** Well-known issues with invasive testing are cost and pain, leading to poor compliance.
- **The principle behind the device, known as GlucoTrack, is to combine three simultaneous measurement channels – ultrasonic, electro-magnetic and thermal.** A proprietary algorithm calculates the glucose reading and it is displayed on a handheld device (there is an audible prompt for people with vision impairment). Dr. Gal claimed that this approach increases reading accuracy, has a reduced susceptibility to environmental variability, and increases robustness and repeatability.
- **GlucoTrack is clipped to the earlobe, and the measurement takes about one minute.** The ear clip is calibrated for the patient once for its entire lifespan (which is 6 months per earclip). Calibration takes less than 2 hours.
- **A clinical trial showed that GlucoTrack is not as accurate as invasive devices, and doesn't yet meet the ISO 15197 standard.** It realized 96-97% in Zones A and B in the Clarke Error Grid, with an A Zone of about 47%. But Dr. Gal suggested that this is to be expected given the maturity of strip technology. Furthermore, if the patient uses the device to test glucose much more, it may result in a better outcome. In the clinical study, patients said that the device was easy to use and they were more likely to use it more frequently than conventional methods.

Corporate Symposium: How Accurate Glucose Measurement, Meter Functionality, and Sophisticated Decision Support Technology Translate Into Clinical Utility (Sponsored by Roche Diagnostics Gmbh)

ANALYTICAL PERFORMANCE OF BLOOD GLUCOSE METERS: WHY IS IT THAT COMPARATIVE ACCURACY EVALUATIONS FREQUENTLY YIELD DIFFERING RESULTS?

Gary Thorpe, PhD (Gary Thorpe Associates Ltd, Birmingham, United Kingdom)

Dr. Gary Thorpe's presentation armed conference attendees with a checklist for assessing comparative accuracy studies of blood glucose meters. These studies are important to diabetes care, explained Dr. Thorpe, because the CE Marking process alone does not guarantee meter accuracy. According to the oft-cited Freckmann study (Freckmann et al., J Diabetes Science Technology *2012), 20% of CE-marked systems do not meet current ISO standards and 50% of CE-marked systems are not expected to meet the proposed ISO standards (95% within ±15 mg/dl for <100 mg/dl and ±15% for >100 mg/dl). Diving deeper, 37% of low-cost systems do not meet current standards and 73% of low-cost meters are not expected to meet proposed ISO standards. As Dr. Thorpe reviewed the number of study design elements that can potentially influence comparison results, he concomitantly made clear that accuracy comparison is a sophisticated science that needs to be undertaken carefully. Dr. Thorpe further complicated study interpretation by reminding conference goers that accuracy is just one part of a system's performance. When translating meter performance to the real world, usability, training, and other factors also need to be considered. Certainly, even with Dr. Thorpe's checklist in hand (listed below), accuracy comparison studies should be interpreted with caution.*

- **Comparison method**: Reference method, said Dr. Thorpe, is commonly used ambiguously. When looking at the method used in a comparative accuracy study, it is important to consider whether the comparison method has traceability to higher-order methods, whether the study used

the manufacturer's standing measurement procedure, and of course, to realize that there can be accuracy differences between methods.

- **Comparing "like with like" samples**: Capillary and venous blood glucose levels should not be assumed equal – he noted that these samples can show differences of 2% and postprandially, differences of 30%.
- **Number of samples**: Dr. Thorpe advocated for at least 100 fresh capillary samples (which would translate to 200 data points as ideally, each sample should be tested in duplicate).
- **Spread of glucose concentrations**: While he recognized the difficulty in obtaining very high and very low glucose blood samples, Dr. Thorpe emphasized that studies need to have a sufficient spread of results spanning the analytical range. He recommended adhering to the stipulations put forth put forth by ISO 15197:

Percentage of Samples	Glucose Concentration
5%	<50 mg/dl
15%	>50 - 80 mg/dl
20%	>80 - 100 mg/dl
30%	>120 - 200 mg/dl
15%	>200 - 300 mg/dl
10%	>300 - 400 mg/dl
5%	>400 mg/dl

- **Accuracy criteria**: This point covers how accuracy data is displayed. To name a few, Dr. Thorpe called for a clinical accuracy assessment such as Parkes or consensus error grid analysis and a summary of results identified as acceptable by current guidelines.
- **Number of strip lots**: Dr. Thorpe noted that ideally, studies would use at least three lots and at least 200 strips from at least 10 different vials. While a constant bias by strips could be tolerable, a variable one is not, he said. By analyzing multiple lots, studies can gain some insight into this.
- **Full details provided**.
- **Independency**: We certainly agree on this point and see a striking need for an independent, robust evaluation of the newest commercially available meters.
- **Concordance with ISO 15197.**

ANALYTICAL PERFORMANCE, METER FUNCTIONALITY, AND DECISION SUPPORT TECHNOLOGY DETERMINE THE CLINICAL UTILITY OF GLUCOSE INFORMATION

Matthias Schweitzer, MD (Roche Diabetes Care, Mannheim, Germany)

Dr. Matthias Schweitzer discussed how glycemic data can be made more clinically useful in this high-level talk, which he supplemented with references to many recent Roche-sponsored studies. He spoke in favor of strict standards on glucose meter device accuracy but also emphasized that "total system

performance" depends on a wide variety other factors such as labeling, support, and education. Dr. Schweitzer also highlighted the utility of products with "medical functionalities," such as meters with integrated test strips (ExAct Study, ATTD 2013) or an integrated bolus calculator (ABACUS study, Diabetes Technology Meeting 2012). He briefly reviewed the fundamental importance of glucose data at every step of the patient/provider "Diabetes Management Loop" and noted that Roche has studied how interventions at any single step can improve glycemic control. Finally, he looked forward to automated solutions that will make diabetes management interventions more sustainable and comfortable – everything from streamlined data capture to insulin-titration software to the artificial pancreas.

THE IMPACT OF INTEGRATED STRIP-FREE SMBG TECHNOLOGY ON PATIENT ADHERENCE TO RECOMMENDED TEST FREQUENCIES – RESULTS FROM THE EXACT TRIAL

Alberto Maran, MD (University of Padua, Padua, Italy)

Despite the glycemic benefits associated with frequent SMBG, many patients with type 1 diabetes test their blood sugar only three times per day (or less). However, testing frequency has been shown to increase with use of the Accu-Chek Mobile, which has its test strips built into the meter itself (Mast et al., JDST 2010). To further study the meter's effects, Dr. Alberto Maran and colleagues conducted the ExAct trial in four European countries. This cluster-randomized trial included 332 adults with type 1 or type 2 diabetes who at baseline were "nonadherent" (A1c above 7.0% and testing frequency less than 3.25 tests per day); these participants were randomized to use either the Accu-Chek Mobile or any traditional "single-strip" BGM. After six months, patients in the Accu-Chek Mobile group had a significantly higher mean test frequency (adjusted between-group difference of 0.37 tests per day) and significantly greater A1c reduction (adjusted between-group difference of 0.22%) – benefits that were roughly consistent at both three and six months.

Questions and Answers

Dr. Schnell: Did you ask the patients using the integrated system how they felt about it and what they saw as key advantages? Did they see an advantage for themselves?

A: I think that patients were keen to carry on with the new devices in terms of reliability and practical lifestyle. To increase the number of tests per day, we must ensure that testing is easy to perform and accurate.

Dr. Schnell: Was education comparable between the two groups?

A: Yes.

Corporate Symposium: Technology: Contributing to Diabetes Management Today and Tomorrow (Sponsored By Sanofi)

EFFECTIVE CLINICAL DECISION MAKING THROUGH TRUST IN THE NUMBERS: ACCURACY AND STANDARDIZATION IN SMBG

Guido Freckmann, MD (Institute for Diabetes Technology, Ulm, Germany)

Echoing sentiments expressed by Dr. Gary Thorpe earlier in the day, Dr. Guido Freckmann called for cautious interpretation of meter accuracy evaluations. Similarly, Dr. Freckmann made clear that a CE

Mark does not guarantee accuracy. The new ISO standards will hopefully move meters towards greater accuracy independent of any CE Mark or FDA process change, and to Dr. Freckmann's knowledge, these could come into effect in the next month (95% within ±15 mg/dl for <100 mg/dl and ±15% for >100 mg/dl). He examined the various methodological components that can impact accuracy results (e.g., reference method, number of strip lots). Citing Dr. Thorpe's "checklist" and accompanying study assessing the quality of publications evaluating the accuracy of blood glucose systems (Thorpe, Diabetes Technology & Therapeutics *2013), Dr. Freckmann showed that most studies to date fail to implement an appropriate evaluation process. As such, he urged that when interpreting study results, don't just read the conclusion, read the method. To remedy this methodological inconsistency in accuracy evaluation, Dr. Freckmann recommended that Centers of Excellence be tasked with standardizing and conducting accuracy evaluations.*

EMPOWERED TO TAKE CONTROL: HOW TECHNOLOGY IS CHANGING THE LIVES OF PEOPLE WITH TYPE 1 DIABETES

J. Hans DeVries, MD (Academic Medical Center, Amsterdam, The Netherlands)

Dr. Hans DeVries believes that the role of the physician in treating a patient with diabetes should be to offer the right tools to empower the patient. His tool kit consists of common goal setting, education, and technologies and the remainder of Dr. DeVries presentation focused on the latter. He reviewed the Debiotech product and meta-analysis findings related to CGM. For detail on Debiotech, see our Day #1 Exhibit Hall report at https://closeconcerns.box.com/s/pypcux2vn238a3qbjomr. Turning to CGM, he believes that the technology has reached a stage where it has changed the way we manage diabetes and where meta-analyses can be done on CGM RCTs to gain reimbursement. Meta-analyses to date have shown A1c reductions with CGM over standard of care, but have not show reductions in severe hypoglycemia. However, explained Dr. DeVries, the patients who stand to benefit the most, those with hypoglycemia unawareness, have not been studied in clinical trial. Observational studies and clinical experience suggest that CGM will yield substantial and impressive reductions in severe hypoglycemia. "We just need to study these patients formally," said Dr. DeVries, and encouragingly, two studies are underway to assess hypoglycemia in this patient subgroup – the New Zealand trial and a trial by the VU Medical Center in Amsterdam (both have yet to be registered). Looking forward, Dr. DeVries noted the importance of demonstrating cost-effectiveness of these technologies. Currently, CGM costs $100,000 per quality-adjusted life year, and this is reflected by the poor reimbursement situation in Europe.

BLOOD GLUCOSE MONITORING IN TYPE 2 PATIENTS ON INSULIN: LATEST INSIGHTS AND NEW TOOLS ON THE HORIZON

Melanie Davies, MD (University of Leicester, Leicester, United Kingdom)

Dr. Melanie Davies took us on a whirlwind tour of guidelines and trials on self-monitoring of blood glucose for patients with type 2 diabetes. She concluded that patients using insulin seem clearly to benefit from SMBG, but the question is much more controversial in patients not using insulin. Without taking a dogmatic perspective either way, Dr. Davies encouraged her listeners to design studies and interventions to achieve the greatest benefits possible with SMBG (especially in cost-conscious environments like her home country, the United Kingdom). She is optimistic about the targeted use of SMBG in conjunction with new technologies like telemedicine and decision-support software, provided that the new interventions are developed with a focus on the factors most helpful to patients (e.g., education, motivation, flexibility, intuitiveness).

4. Insulin and Insulin Delivery

Session: ATTD Yearbook

INSULIN PENS AND THE NEW WAYS OF INSULIN DELIVERY

Lutz Heinemann, PhD (Science & Co., Dusseldorf, Germany)

Dr. Heinemann started his presentation with a strong statement "2011-2012 was not a good year for news of insulin delivery." Frustrated, he then noted this was his exact same takeaway last year! Dr. Heinemann focused on insulin pens to start, asserting that a "pen war" is going on between manufacturers (dosing accuracy, injection force, etc.). On oral insulin, there were 21 publications (71% from China and India), though none in humans (joked Dr. Heinemann, "All end in the same line – 'XXX is a promising candidate…'"). His last topic, insulin depot formation, was the most fascinating. One interesting study examined the shape of the insulin depot in subcutaneous depot. The short story is that insulin depots "by far" are not spherically shaped as most people think. Since different depots of the same dose or different doses have very different shapes, Dr. Heinemann strongly believes this could have an impact on insulin absorption problems. He fervently called for more research on this topic, potentially the creation of a working group.

- **Dr. Heinemann reviewed two interesting studies on insulin depot formation.** One was recently published by Leuenberger in *JDST* (2013). It tried to discover the shape of the insulin depot in the subcutaneous space. Dr. Heinemann noted that the shape of the insulin depot is not spherical like most people think. He showed pictures demonstrating a broad variance in depot shapes, and that insulin is most distributed in the channels of adipocytes. In his view, this might explain why insulin absorption is so variable (Mader et al., *Diabetes Care* 2012). Dr. Heinemann did note a few shortcomings of such studies: insulin was infused (not injected) and it was not applied to living human tissue.
- **"There is a lack of knowledge and interest about the details of the absorption of insulin from the subcutaneous insulin depot into the blood stream."** Dr. Heinemann noted that most of the studies in this area are decades old and probably not all the data reports are valid. He called for a systematic evaluation of insulin absorption, which would hopefully provide a better understanding of the determining factors. He slide posed the bullet, "Working group?" We completely agree with his sentiments – this certainly seems like an under-researched area with important potential to improve patient outcomes.

NEW INSULINS AND INSULIN THERAPY

Jan Bolinder, MD, PhD (Karolinska University, Stockholm, Sweden)

In his "appetizer" on insulin and insulin therapy, Dr. Bolinder briefly reviewed the ORIGIN trial and Dr. Geremia Bolli and colleagues' study investigating glargine and its metabolites (Bolli et al., Diabetes Care 2012) in his high level discussion on the relationship between insulin and cancer. He summarized the takeaway with a quote from Dr. David Owens (Cardiff University, Wales, UK) "…the chapter on whether insulin glargine per se is an independent risk factor for cancer should now be closed." Next, Dr. Bolinder turned his attention to Novo Nordisk's phase 3 study of insulin degludec in type 1 diabetes

(BEGIN Basal-Bolus Type 1 trial). As you know, he said, degludec is approved in Europe, while more cardiovascular data is required in the US – Dr. Bolinder did not offer his personal view on degludec's regulatory delay in the US. (For our report on FDA's Complete Response Letter for degludec, please see https://closeconcerns.box.com/s/xmf8u5te9oupnrmt3682.) He noted the major findings: near-identical improvements between degludec and glargine on A1c, similar effects on weight gain, non-significant difference in over-all confirmed hypoglycemia, and significant reduction in nocturnal confirmed hypoglycemia with degludec. Those were the appetizers, he concluded, "for the rest I would like to leave that for your own contemplation."

INSULIN PUMPS

John Pickup, MD (King's College London School of Medicine, London, UK)

Dr. John Pickup discussed pump themes of great practical interest – low glucose suspend (LGS), and reducing post-prandial hyperglycemia via bolus calculators or extended boluses with fat/protein counting. There is remarkable agreement that LGS is both safe and effective – it reduces hypoglycemia compared to regular pump therapy, most suspends are short, and even after two hour suspends (the maximum), blood glucose is typically around 150 mg/dl. Finally, he noted that randomized controlled trials show that bolus calculators do work better, and that fat/protein counting together with an extended bolus can help reduce post-prandial glucose excursions, although this approach could be complex for patients.

- **In his summary of his insulin pump chapter, Dr. Pickup discussed three themes of interest** – low glucose suspend (LGS), and reducing post-prandial hyperglycemia with bolus calculators and extended bolus/fat/protein counting.
- **There have been many papers on LGS, but there is remarkable agreement among them all regarding the good safety and efficacy of the technology, which Dr. Pickup characterized as "all very reassuring."** Specifically, they show that LGS reduces hypoglycemia versus conventional pump therapy, most suspensions during the day are less than ten minutes, and the majority of two hour suspends are at night. The average blood glucose after two hour suspends is around 150 mg/dl. Neither additional severe hypoglycemia nor diabetic ketoacidosis seem to occur. Dr. Pickup also quoted results from a study on the use of LGS for six months in type 1 patients with hypoglycemia unawareness (Jones et al., *Diabetes Care* 2012).
- **It's well known that post-prandial blood glucose is inadequately controlled on the pump and some papers have found positive evidence for the use of bolus calculators and fat/protein counting. However, Dr. Pickup wondered aloud whether this was going to be too complex for patients.** This year there have been a few randomized controlled trials studying the effectiveness of bolus calculators. In a twelve month study, 40 type 1 children had 55% time in target after a meal using the bolus calculator, versus ~30% in the control groups (Enander et al., *Pediatric Diabetes* 2012). Dr. Ewa Pankowska and colleagues studied 24 type 1 patients who ate mixed meals, causing the expected post-prandial glucose excursion after four to six hours (Pankowska et al., *Diabetes Technol Thera* 2012). The group with a six-hour dual wave extended bolus with carb, fat, and protein counting were much better controlled than the control groups (normal bolus or carb counting). Of course, it's hard to estimate fat/protein with reasonable accuracy, and it's not clear how to incorporate these into bolus calculators. However, the authors helpfully included a formula on adding fat in their paper; this is an area on which we hope that Dr. Howard Wolpert of the Joslin Clinic is consulted since he is such an expert on the topic as we found in his day #1 ATTD talk this year (Abbott symposium).

Session: Long Acting Insulins – Is Longer Always Better?

DID WE COME A LONG WAY?

J. Hans DeVries, MD (Academic Medical Center, Amsterdam, The Netherlands)

Dr. Hans DeVries kicked off the long-acting insulin session with a presentation comparing insulin glargine and insulin detemir. Most notable was his summary of a very recently published head-to-head comparison of once-daily detemir to once-daily glargine (Meneghini et al., Diabetes Obesity Metabolism *2013) in 457 insulin-naive type 2 patients. The "amazing" result was a 0.3% significant difference in A1c in favor of glargine (-0.74% for glargine vs. -0.48% for detemir from a baseline of 7.9%). Glargine brought more patients to an A1c <7% (53% vs. 38% for detemir; p=0.03) – detemir had an advantage on hypoglycemia (rate ratio: 0.73) and on weight (+1 kg for glargine vs. -0.5 kg for detemir). Dr. DeVries noted that all results were compatible with a longer duration of action for glargine. He also discussed a number of myths in this presentation, concluding that glargine is NOT a peakless insulin, it's not a 24-hour insulin for everyone, detemir has a weight sparing effect, and clamp study results need verification in clinical trials.*

- **In a recently published head-to-head comparison (Meneghini et al., *Diabetes Obesity Metabolism* 2013), once-daily glargine was compared to once-daily detemir.** The 26-week, multinational, randomized, treat-to-target trial involved 457 insulin-naïve adults with type 2 diabetes (mean A1c 7.9%, mean age: 57 years). Detemir or glargine was added to metformin, and any second oral therapy was discontinued.
    - **Mean A1c decreased by 0.74% with glargine and 0.48% with detemir** (baseline: ~7.9%; estimated between-treatment difference, 0.30% [95% CI: 0.14-0.46]). Dr. DeVries characterized this as an "amazing result," also because it destroys the notion that treat-to-target trials would never show a difference in A1c (i.e., they aim at the same fasting glucose target when comparing insulins). Glargine brought more patients to an A1c <7% (53% vs. 38% for detemir; p=0.03). Nine-point SMBG profiles confirmed that patients on glargine had a lower blood glucose than detemir patients over the course of the day. Hypoglycemia, which occurred infrequently, was observed less with detemir than glargine (rate ratio 0.73 [95% CI 0.54-0.98]). Dr. DeVries said these results were consistent with glargine's longer duration of action. In terms of body weight, detemir had an advantage: weight declined by 0.49 kg for detemir vs. a 1 kg gain in the glargine group.
- **Glargine is NOT a peakless insulin.** The idea that insulin glargine has no peak comes from one particular clamp study showing a very flat profile; however, other clamp studies have showed a more peaked profile. In scrutinizing the data, Dr. DeVries showed that the glucose infusion rate (GIR) protocol was very problematic. GIR was stopped if glucose >7.5 mmol/l ("reasonable"). However, between hours 16 and 24 of the clamp, the mean glucose was 7.8 mmol/l, suggesting more than 50% of patients had GIR stopped. This explains why later studies have indeed found some peak action with glargine. Studies show that the peak incidence of hypoglycemia occurs around 12 hours after injection of glargine.
- **Glargine is not a 24-hour insulin for everyone.** Dr. DeVries noted that the best study was done by Ashwell et al. *Diabet Med* 2006. The study concluded that once-daily glargine suits most type 1 diabetes patients. However, it also noted that around 15-30% of people with type 1 diabetes benefit from twice-daily glargine.

- **Detemir has a weight sparing effect.** Many studies have shown a slight weight advantage of detemir relative to glargine and NPH. Dr. DeVries showed an unpublished meta-analysis comparing NPH to glargine on body weight. Detemir had a weight advantage of about 1 kg.
- **"Clamp studies are not the absolute truth"** – they need verification in clinical trials and clinical experience. Dr. DeVries showed a graph of three clamp studies performed in Italy, Austria, and Germany. The groups clamped the same insulin and used almost the same doses, but results were almost 50% different (Heise et al., *Diabetes Obesity Metab* 2007; Swinnen et al., *Diabetologia* 2008).

Questions and Answers

Q: Was anything mentioned about the side effects with Lantus?

A: We did that in a meta-analysis. Detemir gives you a little bit more skin problems than glargine. These are differently formulated insulins. If someone develops a skin problem on one insulin, they could just switch to another.

Dr. Satish Garg (Barbara Davis Center, Denver, CO): We would have expected that with glargine with the difference in pH. Could you perhaps explain?

Dr. DeVries: I didn't search for explanations in the meta-analysis; we just counted skin problems.

Comment: You said in the beginning that we need to verify the clamp results in clinical practice. There's an important difference between clinical trials and practice. We randomize people in trials. We do not even try to use the best insulin. There is no rule about how to do that. It's the gut feel of the diabetologist in terms of which insulin may fit best with lifestyle, meal sizes, life conditions, etc. One should add that even the results of clinical trials need to be verified for the patients in clinical practice.

A: I fully agree.

Q: In the discussion of clamps, there was no mention of confirmatory results with PK. Is that not part of the equation?

A: If you have to rank them, I would say that PD is more important than PK. And you could even say PK needs confirmation from PD.

Dr. Lutz Heinemann (Science & Co Dusseldorf, Germany): At the Amsterdam meeting, Dr. DeVries bring the clamp centers together. We discussed how different details in clamp procedures and the issues with different assays for different insulins. This discussion is already five years old, and I thought the walls had settled.

Q: On this 0.3% difference in A1c – if you compare that to old UKPDS data, a 1% reduction is the same as 3 kg of body weight. So 0.3% should roughly be 1 kg of body weight.

Dr. Garg: In other words, the difference in A1c in the head-to-head study could justify the weight loss vs. the weight gain.

Dr. DeVries: The once daily head to head trial magnifies body weight differences. I fully agree.

INNOVATIVE LONG-ACTING INSULIN ANALOGUES

Azhar Rana, MD (Global Medical Director, Novo Nordisk, Denmark)

Dr. Azhar Rana gave a rapid overview of insulin degludec. We've covered these results elsewhere in a lot more detail, but here are the headlines. Insulin degludec was designed to attain the "wish-list" of the properties of an ideal insulin – in particular, a flat profile, low risk of hypoglycemia, and a long duration of action. A massive program of clinical trials demonstrated non-inferiority of A1c with respect to insulin glargine and some improvements in fasting plasma glucose and hypoglycemia, particularly at night. In questions, Dr. Rana didn't have much to say about the FDA's request for cardiovascular outcomes trials, except to note that the regulatory bodies in Europe and Japan had no such concerns.

- **The ideal insulin has many properties. In particular it has a flat profile, a low risk of hypoglycemia, and a long duration of action.** Other properties on the wish list might include: once daily dosing, flexible dose timing, low variability, appropriateness for both type 1 and type 2 patients, safety, effectiveness and tolerability in combination with mealtime insulin and GLP-1.
- **This wish list was the genesis for insulin degludec, which was developed by Novo Nordisk and has been approved in Europe and Japan.** Insulin degludec exists as a stable di-hexamer in solution and very long, soluble multi-hexamer chains in the subcutaneous tissue. Monomers release gradually from the ends of the long multi-hexamer chains, giving slow and stable kinetics.
- **Degludec exhibits a flat, peakless profile with low variability compared to insulin glargine.** The coefficient of variation is about 30% and is highly consistent over a 24-hour period with daily dosing. According to Dr. Rana it exhibits four times less variability compared to insulin glargine. The half life of degludec is over 24 hours, explaining the low variability in serum concentration, and it reaches a steady state within two to three days.
- **The degludec global clinical development program is very extensive. Dr. Rana described six trials for type 2 diabetes and three trials for type 1 patients.** The trials were mostly head to head with insulin glargine, on top of various oral agents (for type 2 patients) in the various populations. For regulatory reasons, all the studies investigated the same endpoints, had a treat-to-target study design, the same titration algorithm, and the same definition of hypoglycemia.
- **The degludec studies showed non-inferiority for A1c with respect to glargine and some improvements in fasting plasma glucose and hypoglycemia, particularly at night.** Nocturnal hypoglycemia showed a 36% reduction in insulin-naïve patients, 32% in all type 2s and 17% in type 1. For all hypoglycemia (both day and night), there was a non-significant worsening for type 1 patients, although there was a strong, significant reduction in type 2 patients. Dr. Rana suggested that Novo Nordisk was going to spend more time understanding this result. Finally, in an "extreme dosing" situation (flexing the time of day), insulin degludec still worked well.

Questions and Answers

Q: Do you have a comment on the FDA's requirement for further cardiovascular data?

A: The FDA has its own risk assessment criteria. I can't comment on what the FDA thinks, of course. But we have provided the same evidence to the EU and Japan regulators and they have stated that the risk is acceptable. We look forward to working more closely with the FDA to address their concerns.

Q: Did you use CGM in the clinical studies?
A: We did use CGM in 25% of the patients. But we didn't do it properly – there was too much variability between centers. We are going to get it right in future trials.

Q: Is there any weight gain improvement with degludec?

A: There is no difference in weight gain compared to glargine.

BRAVE NEW WORLD

Scott Jacober, DO (Eli Lilly and Company, Indianapolis, IN)

Dr. Scott Jacober reviewed Eli Lilly's novel basal insulin analog, LY2605541 (PEGylated insulin lispro, hereafter LY). He focused mostly on the data presented at ADA 2012 and EASD 2012 and highlighted the phase 2 study results recently published in Diabetes Care *(Rosenstock et al. 2013 and Bergenstal et al. 2012). Dr. Jacober's presentation had a major focus on LY's preferential hepatic action, which has been demonstrated through a number of preclinical experiments. Compared to glargine, the phase 2 data for both type 1 and type 2 diabetes suggested a lower risk of nocturnal hypoglycemia and less within-day glycemic variability with LY. However, a few safety signals did emerge in phase 2, and we expect the cardiovascular-focused FDA will pay especially close attention to the phase 3 data on LDL and HDL cholesterol and triglycerides. Lilly expects initial phase 3 trials for PEGylated insulin lispro to complete in 2013, and a possible regulatory submission could occur as early as 2014,*

- **Dr. Jacober summarized six key takeaways from the existing data on LY:** 1) In type 1 diabetes, LY improves glycemic control in tandem with weight loss, less nocturnal hypoglycemia, less day-to-day and within-day glycemic variability, and less prandial insulin than glargine; 2) in type 2 diabetes, LY improved glycemic control similar to glargine but with weight loss, less nocturnal hypoglycemia, and less within-day glycemic variability; 3) in type 1 and type 2 diabetes, ALT/AST levels were elevated with LY, although the means were within the normal range; 4) in type 1 diabetes, LY was associated with higher mean LDL cholesterol and triglycerides and lower mean HDL cholesterol compared with insulin glargine and baseline; 5) in type 2 diabetes, triglycerides were increased with LY compared to insulin glargine; and 6) the observed weight loss and modest increase in serum triglycerides suggest that LY may have a novel mechanism of action.
- **For more information on Lilly's LY2605541**, please see our ADA 2012 and EASD 2012 reports at https://closeconcerns.box.com/s/85f08fc8abe3c3bc10d7 and https://closeconcerns.box.com/s/kt7rf3v6uy09x6t9ldke and our Lilly 4Q12 report at https://closeconcerns.box.com/s/uibg653lp78ums0rapr1.

Questions and Answers

Dr. Satish Garg (Barbara Davis Center, Denver, CO): Knowing what's happened with degludec, what about issues of cardiovascular risk that clinicians might see in the trials?

A: Triglycerides are not a very well established cardiovascular risk factor – not like other lipid markers. There still needs to be some concern, however. In the VA implantable pump study, a pump was implanted into the peritoneum and insulin was infused there. They did look at triglycerides. They did not present stats on triglycerides in that manuscript, but they increased in the first four months of therapy. Then, they started coming down by eight months and normalized to baseline at the end of 12 months. One question we have is whether this is a transient phenomenon. You've previously had extensive stimulation of the adipose tissue to store lipids. Now, you're altering that balance. Maybe there is a transient release of triglycerides from stored adipose tissue. The consequence is that we don't know. We're looking extensively at a large number of lipid parameters throughout our phase 3 trial.

Dr. Jay Skyler (University of Miami, FL): This weekend, PEGylated erythropoietin was taken off the market. Are you scared this could happen with your PEGylated lispro?

A: These products have been available for 30 years. There is a protein portion of the molecule that is not native. The real issue is perhaps PEGylation is facilitating recognition by the immune system of non-native protein. Lispro has had a large number of patients using it for a long period of time – it has a track record of safety. As far as PEGylation, I can tell you that the most significant toxic effect that FDA is looking at is vacuolization in animal models. We have done studies in dogs and year long rat studies and have not seen any vacuolization in any tissue in the body. In rats that very resistant, we used five units per kilogram – at these very high doses, we did not see vacuolization.

WILL LANTUS CONTINUE FOREVER?

Christoph Heinemann (Vice President, Global Diabetes Division, Sanofi)

Will Lantus become a "classic" diabetes drug? It might be argued that it already is, although Mr. Christoph Heinemann was very modest in his presentation, concluding that "time will tell." Nonetheless, there are currently seven million patients on Lantus, it's a blockbuster drug, and there is clinical trial data on over 80,000 patients. It's been shown that Lantus is neutral to heart disease and cancer, can sustain long term glucose control with low levels of hypoglycemia, and can be easily titrated. Looking to the future, other companies may produce biosimilar glargine, but they will have a challenge proving they are similar enough; and Sanofi is developing a "new Lantus," which should have a very flat profile and a lower injection volume.

- **The drugs that are used abundantly and in first line therapy – the "classics" – are the drugs that have been studied most extensively for at least 15 to 20 years.** For example, metformin is a 50-year story – it was first described in 1922. It was made available in the UK in 1958, but took until 1994 to be approved by the FDA for type 2 diabetes.
- **Lantus (Sanofi's insulin glargine) has been studied in many trials with over 80,000 patients, together with post-market observation.** It currently has seven million patients worldwide.
- **The landmark ORIGIN study showed very good long term outcomes with insulin glargine – fasting plasma glucose was normalized and A1c reduction was significant and broadly sustained over seven years.** The population had a high degree of cardiovascular risk (n=12,537). Lantus was shown to be neutral on cardiovascular disease and cancer risk, exhibited targeted and sustainable long term glycemic control, had a low absolute rate of severe hypoglycemia, and reduced progression from pre-diabetes to diabetes.
- **In 2009, there was a strong debate regarding Lantus and the risk of cancer – this was based on inconclusive scientific findings, but quickly attracted the public eye.** The health authorities asked for further epidemiological studies, which have now been performed. Four tightly designed large-scale studies have shown no evidence that Lantus is linked to an increased risk of cancer.
- **Different titration algorithms for Lantus have been studied in trials.** Titration is manageable by patients as well as physicians. In fact, the data showed that patient-driven titration yielded a lower fasting glucose after 24 weeks compared to a physician-driven titration.

- **Sanofi is currently working on a new insulin glargine formulation.** This "new Lantus" is intended to have a unique flat PK/PD profile and a lower injection volume. Clinical trials, known as EDITION, are underway for both type 1 and type 2 patients.
- **Other companies may produce biosimilar insulin glargine in the future. But this will require quality, pre-clinical and clinical studies to demonstrate a similar nature.** There are 250 steps and 2,000 tests required to produce Lantus. Each can affect the properties and performance of the drug. So to some extent the production process is the product, making it harder to copy.

Sessions: New Insulins

ACCELERATING INSULIN DELIVERY

Howard Zisser, MD (Sansum Diabetes Research Institute, Santa Barbara, CA)

Dr. Howard Zisser gave a series of ultra-fast updates on ultra-fast insulins – therapies that he noted "won't guarantee perfect control," but will provide patients and clinicians with "better tools to have optimal control." He offered a rough rule of thumb for interpreting insulin PK/PD graphs – "anything that pushes [the curve] up and to the left is superior" – and reviewed several promising investigational methods. Notably, he mentioned a rumor that Medtronic is starting to manufacture approximately 20 implantable pumps for month; he shared data on infusion-site warming with InsuLine's InsuPatch, from the Yale group's latest clamp study showing significantly faster time to half-maximal and maximal infusion rate at 40 degrees Celsius (104 degrees Fahrenheit); and he described how Thermalin's insulin analogs include artificial amino acids that accelerate the dissociation from dimers to monomers.

- **A variety of companies are studying a variety of approaches to accelerating insulin delivery, Dr. Zisser noted.** During this talk he mentioned BD (developing "kink- and occlusion-free disposables" for subcutaneous insulin pumps, as well as intradermal microneedles), Halozyme (studying the "spreading agent" PH20 for injection at the time of infusion set change and separately for co-formulation with injected insulin), Roche (about to enact the European launch of its second-generation DiaPort, a transcutaneous port that enables the Spirit pump to deliver insulin intraperitoneally), MannKind (studying inhalable Technosphere insulin, aka Afrezza, in pivotal trials for both type 1 and type 2 diabetes), Medtronic (according to rumor, starting to make approximately 20 implantable pumps per month), InsuLine (developing products to heat the sites of insulin infusion or insulin injection, thereby improving absorption), Novo Nordisk (initiating phase 3 trials for its ultra-rapid version of insulin aspart, FIAsp, later this year), and Thermalin (conducting preclinical studies of ultra-rapid insulin analogs that use artificial amino acids. With naturally occurring amino acids, amino-acid substitutions can be made only at the periphery of the insulin-dimer interface. However, by using artificial amino acids that contain halogens, Thermalin's researchers have been able to perform substitutions closer to the dimeric interface. Ideally, these analogs will dissociate faster into the active monomeric form, without sacrificing safety and efficacy compared to current therapies).

Questions and Answers

Q: Are there local adverse effects of hyaluronidase administration?

A: We have not studied it at our center, and I don't have any direct data with that. It is an approved drug used with other compounds. I think the goal is to inject it only at the time of infusion set change – once every few days.

CAN VERY LONG ACTING INSULINS REDUCE HYPOGLYCEMIA? (SPONSORED BY NOVO NORDISK)

Simon Heller, MD (University of Sheffield, Sheffield, UK)

Dr. Simon Heller discussed the results of studies comparing insulin degludec (Novo Nordisk's Tresiba) and insulin glargine (Sanofi's Lantus). He remarked that both insulins yielded good, sustained control in a treat to target study. In both type 1 and type 2 diabetes degludec was also associated with a lower risk of nocturnal hypoglycemia, and a lower risk of all-day hypoglycemia in type 2 diabetes only. In a hypoglycemia clamp study, degludec yielded larger amounts of counter-regulatory hormones than glargine. In questions, it became clear that degludec was dosed at the same time each day (evenings) while Lantus was dosed (according to the label) at any time. This has the potential to confuse the overnight hypoglycemia results, but unfortunately, the data on the glargine timing is not available, so we can't untangle the results. Dr. Heller also suggested that the overnight results might be explained in terms of a flatter profile for degludec.

- **Hypoglycemia is even more common in clinical practice than in clinical trials.** We see up to 3.2 severe events per patient-year in people with type 1 diabetes of over 15 years duration. Nocturnal hypoglycemia is also very common, and severe episodes can be fatal.
- **A one-year treat to target study of basal/bolus therapy in type 2 diabetes showed equivalent good control for insulin degludec (Novo Nordisk's Tresiba) versus insulin glargine (Sanofi's Lantus), and an improved risk of hypoglycemia.** The study was conducted with n=1,006 participants using insulin aspart (Novo Nordisk's Novolog) as mealtime insulin, on top of metformin and with/without pioglitazone. A1c at baseline was around 8.3%, and patients were controlled to around 7%. Control was good, identical with both basal insulins, and sustained for the entire trial. Dr. Heller suggested that investigators were encouraged to be aggressive. Minor hypoglycemia was classified as <56 mg/dl on testing which could be self treated. At the end of the trial there was an 18% lower risk of overall hypoglycemia with degludec, and a 25% lower risk of nocturnal hypoglycemia.
- **An analogous study was completed in type 1 diabetes, which again showed no A1c difference, good control that was maintained, and a lower risk of nocturnal hypoglycemia with degludec – but in type 1 diabetes (unlike type 2), overall rates of hypoglycemia were no different between the two basals.** This phase 3 treat to target trial consisted of n=629 subjects. A prospectively planned meta-analysis of seven studies reinforced similar conclusions regarding hypoglycemia for both type 1 and type 2 diabetes.
- **A hypoglycemia clamp study provided evidence that counter-regulatory hormones are increased with insulin degludec versus insulin glargine.** The study of n=28 patients with type 1 diabetes consisted of a crossover design in which basal insulin was given for five days and a hypoglycemia clamp administered. Patients were washed out for 13-21 days and then the second treatment period begun. The clamp protocol was 30 minutes at 63 mg/dl, 15 minutes at 45 mg/dl, and 120 minutes at 70 mg/dl. Degludec showed statistically higher levels of growth hormone and cortisol and a trend to a higher epinephrine response. Investigation of glucose infusion rates was inconclusive.

Questions and Answers

Q: How do we deal with the differences in the type 1 and type 2 data in daytime hypoglycemia?

A: We think that we should be giving less bolus insulin in the morning for the type 1 patients, and we want to do some follow up work to investigate this.

Dr. Buckingham: Why does Lantus have more nocturnal hypoglycemia? Is it to do with timing or intramuscular injections?

A: What's important to note is that degludec was given at a fixed time in the evening, and Lantus was given (according to label) at any time. If people had been allowed to give Lantus at the same time then might have seen a clearer difference. But one might argue that Lantus patients are sophisticated to know when it's the best time of day to take their medicine. Unfortunately, we don't have the data on when Lantus patients took their shot.

Dr. Hirsch: I struggle to explain why we see a lower fasting glucose with degludec but also lower nocturnal hypoglycemia.

A: I don't see this as a problem. Probably, glargine patients have higher glucose levels through the night. With a more stable insulin (degludec) we can push the titration more safely, explaining the lower fasting glucose.

Dr. Hirsch: But if [Lantus patients] have more nocturnal hypoglycemia, then they should have lower fasting glucose.

A: Not if the insulin is wearing out, to a degree. For Lantus, there is a peak, albeit shallow.

Dr. Hirsch: I didn't realize that there was variability in the timing of glargine administration. That is probably key to all of this. I suggest that we explore this. It might be said that the entire program is a little bit biased because of timing.

A: Fair comment.

Q: Was there a difference in dose?

A: They took less insulin with degludec, which was a statistically significant result.

Q: How do you explain the difference in stress hormones?

A: We don't really know. It's maybe because of different penetration into the brain. After all, we know that these responses are mediated centrally.

Session: Challenges and Solutions

GLYCEMIC MANAGEMENT USING SIMPLE CONTINUOUS SUBCUTANEOUS INSULIN INFUSION IN PATIENTS WITH TYPE 2 DIABETES (SPONSORED BY CEQUR)

Thomas Pieber, MD (University Hospital of Graz, Graz, Austria)

Dr. Thomas Pieber focused mostly on CeQur's PaQ insulin delivery device in this talk on insulin pumps for type 2 diabetes. He reviewed new results of a 20-patient, single-arm, six-week usability study of PaQ. Results were strong on various qualitative measures: all patients (100%) were able to assemble, fill, prime, and use PaQ, and all could correctly understand the signals emitted from the PaQ and

respond adequately. Overall, 83% of patients were "very satisfied" and 17% were "satisfied" with the time it took to learn and administer bolus doses with PaQ (training was limited to one hour). Patients did wear CGM in the study (Yes!), though CeQur is still analyzing the data; Dr. Pieber showed a promising CGM trace of one patient, who had greater time in range and less glycemic variability (no accompanying numerical statistics provided). We hope to see the full glycemic data at ADA 2013. Dr. Pieber seemed to do a great job of selling the merits of CeQur's PaQ – the company's small exhibit hall booth was completely mobbed at the coffee break following this presentation. His presentation also briefly touched on J&J/Calibra Medical's Finesse and Valeritas' V-Go, as well as the dearth of evidence supporting pumps in type 2 and issues of selection bias.

- **Dr. Pieber summarized results of a usability study of CeQur's PaQ in twenty patients with type 2 diabetes.** The single-center, single-arm study took place in Graz. It was not a dose optimization or treat to target trial, and A1c was not measured. Patients did receive CGM before starting on PaQ and after using it. The primary endpoint was patients' ability to use the device. The 20 enrolled patients were on MDI plus or minus orals and had a mean A1c of 9%. After screening, patients had a two-week period where their blood glucose on MDI was optimized. During a 24-hour visit to the CRC, they were transferred onto the PaQ device. A 6-15 day transition phase (e.g., patients were telephoned every day, insulin was adjusted) was followed by a treatment period of two weeks
    - **All patients (100%) were able to assemble, fill, prime, and use PaQ, and all could correctly understand the signals emitted from the PaQ and respond adequately.** Overall, 83% of patients were "very satisfied" and 17% were "satisfied" with the time it took to learn and administer bolus doses with PaQ.
    - **All patients transitioned to PaQ and 73% used the first basal rate chosen.** Patient training on the device was limited to one hour. We think both these points underscore the device's simplicity, which bodes well for uptake from an HCP and patient perspective. Total daily dose used on PaQ was the same as baseline (MDI) – we were surprised that total daily dose did not decline, though perhaps the study was too short. No severe hypoglycemic events occurred during baseline or on PaQ.
    - **A total of 149 PaQ devices were applied, with a PaQ changed every 2.6 days** (translating to ~7 PaQ devices per study participant and an average treatment period of ~19 days).
    - **The short study duration prevented researchers from measuring A1c, though they did use CGM.** The company is in the middle of analyzing all the CGM data, so Dr. Pieber only showed a CGM trace from a single patient. It compared his glycemic control while on MDI to that seen after using PaQ. Broadly, he had much better control on PaQ (same total daily dose) and "dramatically improved" time-in-range. On average, he also had reduced glycemic variability. Dr. Pieber did not provide any descriptive statistics to put numbers to these statements. He hypothesized that adherence to therapy is easier with PaQ, translating to fewer missed insulin doses. We're psyched to see the company using CGM data, and hope to see the full data set presented at ADA this June.
- **Dr. Pieber discussed J&J/Calibra Medical's Finesse, emphasizing that it is bolus-only and has "very, very limited data."** The one study comes from Dr. Nancy Bohannon et al., *DT&T* 2011. It included a total of 38 patients (type 1 and type 2). Glycemic outcomes were comparable between the Finesse and pen/syringes. However, patients scored better on six of seven subscales on the Diabetes Specific Quality of Life Scale (DSQOLS) and five of six subscales

on the Insulin Delivery System Rating Questionnaire (IDSRQ) while using the Finesse vs. pen/syringe. At study completion, 76% of subjects said they would choose to switch to the Finesse (p=0.001). As a reminder, Finesse delivers bolus insulin in one or two-unit increments, has a wear time up to three days, and a 200-unit reservoir. As of J&J's 4Q12 call in January, the company expects to begin clinical trials in 2013.

- **Dr. Pieber called Valeritas' V-Go "quite interesting."** He found just one trial of the device in six patients (Kapitza et al., *JDST* 2008). The once-daily V-Go was used for seven days, and overall glycemic control tended to improve on a number of parameters. As a reminder, the V-Go is currently available in the US, has predefined basal rates (20, 30, or 40 units per 24 hours) and allows bolusing in two-unit increments.
- **There is "weak" and "not very convincing" studies supporting use of pumps in type 2 diabetes.** In Monami's 2009 paper in *Exp Clin Endocrinol Diabetes*, four relevant trials were included in a meta-analysis. Trial sizes were generally small and ranged from 20-130 patients (two trials lasted one year). There was no significant difference in A1c or hypoglycemia when pumps were compared to MDI. Said Dr. Pieber, "Overall, the effect of pump treatment was somewhat disappointing." There was a borderline significant trend towards a lower insulin dose in those on pump therapy (10 units less; p=0.06). Dr. Bruce Bode subsequently analyzed 11 trials of pumps for type 2 diabetes in a 2010 paper in *DT&T*. Results were conflicting, though use of CSII was generally associated with a lower A1c, a tendency towards a lower insulin dose, and higher patient preference.
    - **As a reminder, Medtronic's OpT2mise trial is testing pumps in type 2 diabetes** (ClinicalTrials.gov Identifier: NCT01182493). The study has a primary completion date of December 2012 and an expected enrollment of 400 patients at 30 centers. It is still listed as recruiting participants and was last updated in March 2012.
- **Dr. Pieber repeatedly mentioned the issue of selection bias in type 2 pump studies** – by selecting highly motivated type 2 patients willing to go on a pump, trials may be biased. We completely agree with this, though note this is the case for most, if not all, trials of new technology and therapy.

Questions and Answers

Dr. David Harlan: At the University of Massachusetts, we have been using the V-Go pump you described. We've had a similar positive experience. Our patients really love them. Generally, we notice that we have to give much less insulin than what patients say they were taking.

A: That's an interesting point. With the patch pump, you cannot forget your pen. You can deliver insulin more easily. Patients definitely like that. But you have to look for patients that want to go into the study. Again, you preselect them in a way. One question we will have to answer is if this can be used in a broader population. But I have the same opinion as you. It's quite interesting to have an in-between simple injections and complex pumps.

Q: Why did it take one hour to train patients? When we talk about type 1 diabetes patients, we usually spend one hour with them, and that is for a pump with more features.

A: Well, patients had to learn to fill the reservoir with insulin, assemble the device, and put it on the body. We set this time to one hour. That was considered to be the maximum that we'd be able to offer in a large market. Some patients will definitely need less time. We wanted to make sure that when patients are at home, they are able to use it. This was all pen users who had never used a pump before.

NANOSCALE ENCAPSULATION TECHNOLOGY: ISLETS, GLUCOSE SENSORS AND INSULIN DELIVERY

John Pickup, MD, PhD (King's College London, London, UK)

Dr. John Pickup explored the design elements of layer-by-layer (LBL) nanoencapsulation of islet cells that make the technique a potential solution to the damaging inflammatory response associated with islet cell transplantation. Explained Dr. Pickup, LBL nanoencapsulation is designed to keep immune cells out while allowing the free exchange of glucose and insulin. The nanothickness film is comprised of a multilayer of alternating positively- and negatively-charged polymers, which allows for the fine-tuning of the film's permeability and biocompatibility because the number and composition of the layers can be adjusted. Essentially, said Dr. Pickup, the film is a "shrink wrapping" of the islets. In addition to its application in islet transplantation, he believes the LBL technique can be used to better formulate oral insulins and be used to make "smart tattoos" for non-invasive glucose sensing. Certainly, given the potential of oral insulins as a means to speed insulin delivery and act as an adjunct to closed-loop control, we are highly interested to see how the body would receive an oral insulin nanoformulation – Dr. Pickup suggested that a nanolayer coating could increase oral insulin's acid stability and prevent insulin denaturation in the stomach; however, LBL for oral insulin delivery seems to be furthest from clinical trials.

Questions and Answers

Q: Which of the three uses is closest with regard to clinical translation?

A: I think I would say both the implanted glucose sensor and the encapsulated islets are ready to move into clinical trials. That's different from saying they will come to clinical use, which as you know is completely unknown. But both of those have reached an exciting stage.

Session: Closing Session

CONTRIBUTIONS TO INSULIN INJECTION IN OBESE PATIENTS, AND NEW DEVELOPMENTS TO ENABLE THE ARTIFICIAL PANCREAS

Laurence Hirsch, MD (Worldwide VP of Medical Affairs, Becton Dickinson Diabetes Care)

Dr. Laurence Hirsch did not speak to Becton Dickinson's efforts to develop the artificial pancreas; rather, he focused on the "nuts and bolts" of how insulin is actually administered. In an compelling presentation, Dr. Hirsch tracked the development of insulin delivery through his own experience since being diagnosed with type 1 diabetes in 1957. His discussion went on to focus on the misconception that people with higher BMI need longer insulin syringe needles for subcutaneous insulin injections. Concluding his presentation with the BD tagline we've come to expect, said Dr. Hirsch: "Size matters. Smaller is a good thing…at least for insulin injections."

Oral Presentations

EVALUATION OF THE NEW ACCU-CHEK DIAPORT, A PORT SYSTEM FOR CONTINUOUS INTRAPERITONEAL INSULIN INFUSION, IN PATIENTS WITH TYPE 1 DIABETES: FIRST 3-MONTH RESULTS

Andreas Liebl, MD (Center For Diabetes and Metabolism, Fachklinik Bad Heilbrunn, Germany)

The Accu-Chek DiaPort (Roche) is a port that can deliver insulin directly to the peritoneal cavity via a flexible catheter. This has many advantages, notably a much faster insulin response, although it requires surgery to place the port. This study of twelve patients with type 1 diabetes who were failing pump therapy, was used to obtain the CE mark for the next generation of DiaPort, which will be marketed in Europe shortly (we learned from a sales representative at Roche's exhibit booth that this is expected to occur in April). Although the study wasn't powered for significance, the investigators saw a 1% increase in A1c, better glycemic variability, a lower daily dose of insulin, and no increase in hypoglycemia. The device was tolerated well. Problems with insulin crystallization were solved by switching to Insuman Infusat (Sanofi), which is designed to be more stable.

- **Bringing insulin into the peritoneal cavity has many advantages over subcutaneous insulin, notably a much faster absorption.** Not having a subcutaneous depot has real advantages – fast delivery, no variability due to temperature, massage, or movements, and no inter- and intra-patient variability of insulin kinetics. The inter-peritoneal approach has low variability, low hypoglycemia, and near normal blood glucose regulation.
- **The Accu-Chek DiaPort (Roche) has been upgraded and will shortly be relaunched.** The DiaPort is a port that delivers insulin directly to the peritoneal cavity. It can be linked to a pump. The body of the port sits in the subcutaneous tissue and a catheter leads to the peritoneal cavity. The new upgrades include a polyester felt around the body for better biocompatibility, and a flexible catheter.
- **In an open-label 12 month trial of n=12 patients with type 1 diabetes, we saw an improvement in A1c, a lower daily dose of insulin, and lower glycemic variability with no increase in hypoglycemia.** Patients were selected to be those unsuccessfully controlled on a pump (high severe hypoglycemia, high A1c, or severe problems at the infusion site). A1c improved from 9.0% to 8.0% after 12 months; mean daily insulin dose decreased from 49 units to 45 units.
- **The device itself was well tolerated, with only minor healing problems, and no adhesions, inflammatory reactions, or major pain. But all patients had problems because of insulin crystallization that were solved by changing the insulin formulation from Humalog (Eli Lilly's insulin lispro) to Insuman Infusat (Sanofi).** Although some patients reported some initial pain, after the first 12 weeks it was resolved in all cases. One patient had to have the DiaPort removed because of infection and non-compliance. In weeks four to eight, almost all patients had problems with catheter occlusions, which turned out to be insulin crystals. Changing insulin from Humalog to Insuman Infusat solved this problem.

Questions and Answers

Q: Who places the catheters?

A: Unfortunately, we need a surgeon because we are opening the peritoneum. It takes 15 to 20 minutes under general anesthetic.

Q: How long do you want to leave it in?

A: In theory it can stay forever, but we know that with the old catheter we saw adhesions and encapsulations, so we don't think it's unlimited. With the new catheter, all looks good so far, but eventually we will have to change them.

Q: So when is the right time to change?

A: When we get problems that we can't resolve, such as blockage that can't be fixed with a wire.

Q: When will it be available?

A: It will be on market in the next few months. They have CE mark now. I expect that they will market it worldwide.

PAQ, A SIMPLE 3-DAY BASAL/BOLUS INSULIN DELIVERY DEVICE, IN PATIENTS WITH TYPE 2 DIABETES

Julia Mader, MD (Medical University of Graz, Austria)

In a single-center, single-arm study designed to assess patient's ability to use CeQur's PaQ, a basal bolus insulin delivery device for people with type 2 diabetes, 20 patients with type 2 diabetes were transitioned from multiple daily injections (MDI) to PaQ therapy. On average, patients were taking five injections per day, 60 units of insulin per day, and had A1c of 7.7% at baseline (≤9% inclusion requirement). Patients received one hour of training on PaQ at the onset of therapy and basal rates were adjusted as needed. All patients transitioned to PaQ with 73% using the first basal rate given; no adverse device effects were observed due to use errors. Eighty-three percent of patients were "very satisfied" with the time it took to learn to use the device and 17% were "satisfied." Dr. Mader interpreted the survey and study results to mean that the patients were able to safely use the device, that the one hour training session was appropriate, and that patients were satisfied with the transition from MDI to PaQ.

Questions and Answers:

Q: On satisfaction with learning, can you explanation why only 17% were satisfied?

A: No one was not satisfied.

Dr. Lutz Heinemann (Science & Co., Dusseldorf, Germany): Were you satisfied?

A: Yes, it was easy to use and easy to train. It is very easy for older patients.

THE MINIATURIZED JEWEL INSULIN PATCH PUMP (DEBIOTECH) IS MORE PRECISE, MORE SENSITIVE TO OCCLUSION AND BETTER ACCEPTED THAN CONVENTIONAL CATHETER PUMPS

Sophie Borot, MD (Jean Minjoz Hospital, Besancon, France)

Dr. Sophie Borot presented in vitro data assessing the precision and occlusion sensitivity of Debiotech's Jewel insulin patch pump and in vivo data assessing patient comfort with the pump. The in vitro precision study compared the JewelPump to Insulet's OmniPod and Medtronic MiniMed's Paradigm over 24 hours of continuous micro-weighing at one insulin unit per hour. Dr. Borot and her team found that the insulin quantity delivered over 24 hours was similar, but that the JewelPump's dispersion of errors over 60 minutes had less spread, suggesting greater pump precision. The in vitro occlusion study

compared the JewelPump to Insulet's OmniPod, Roche Accu-Chek's pump, J&J Animas' pump, and Medtronic MiniMed's Paradigm (we assume the Accu-Chek Spirit and Animas OneTouch Ping were used). After full occlusion, the number of non-injected insulin units prior to the occlusion alarm was assessed: the Debiotech pump tallied 0.1 units vs. Medtronic's 1.3 units, Animas' 1.5 units, Accu-Chek's 3.0 units, and Insulet's 4.7 units. We would be interested to see whether these in vitro results are representative of what would happen in the clinic and whether results would differ with companies' next- or newest-generation devices as it was unclear whether the latest-gen pumps were used (e.g., the first- or second-generation OmniPod). In vivo, thirteen patients with type 1 diabetes wore their usual pump and a JewelPump over 28 24-hour periods. The usual pump continued to deliver insulin aspart, while the JewelPump delivered a non-significantly different quantity of saline. Patient satisfaction with the pumps were scored according to a visual analogue scale (VAS) that ranked pump comfort on a scale of 0 to 10, with 0 being uncomfortable to wear and 10 being comfortable to wear. We note that the comparison was not a perfectly fair one given the potential of the insulin itself to contribute to patients' comfort assessment. According to the VAS, the JewelPump scored 8.1 and patients' usual pumps scored 5.5 ($p < 0.01$). We would be interested for greater clarity as to how specific pump types that made up the "usual pump" category performed.

5. Type 2 Diabetes, Obesity, and Bariatric Surgery

Session: ATTD Yearbook

BARIATRIC SURGERY AND DIABETES: ACCESS DENIED

Walter Pories, MD (East Carolina University, Greenville, NC)

"Medical treatment of type 2 diabetes has not been as successful as we had hoped," said Dr. Pories. In spite of the broad armamentarium and recent advancements in drugs, type 2 diabetes remains a primary or major cause of myriad comorbidities and a major cost to healthcare systems. He explained that bariatric surgery can induce full and durable remission of type 2 diabetes in 80-95% and results in a reduction of mortality from type 2 diabetes of 82%; however, the use of bariatric surgery has plateaued in the US (Livingston, Am J Surg *2010). Dr. Pories attributed the failure to use this therapy to three factors: 1) excessive requirements by insurance carriers; 2) failure to educate the public; and 3) a lack of communication between endocrinologists and "metabolic" surgeons. He believes the latter is the primary culprit and called for greater collaboration. Addressing the endocrinologists in the audience, he concluded, "We need your help. We need your help now."*

- **"Imagine if someone had invented a pill that induced full and durable remission of type 2 diabetes in 80-95% of cases."** Bariatric surgery can provide this benefit, explained Dr. Pories. The procedure has safety comparable to a routine cholecystectomy (90-day mortality of 0.3%) and costs ~$18,000, an amount which is recovered in medication alone in two years time according to Dr. Pories. He did not specify bariatric surgery type during his presentation; however, we assume his discussion was focused on Roux-en-Y Gastric Bypass.
- **Excessive requirement by insurance carriers exclude many patients from bariatric surgery.** First, carriers require medical documentation of five years of obesity. Second, qualification requires documentation of six months of professional dietary supervision. Third, qualification is based on weight requirements that "make no sense." Dr. Pories believes strongly

that BMI is not an appropriate metric to deny access to bariatric surgery as it discriminates by age, gender, race, and fitness. To drive his point home, he described a 5' 8" male with a BMI of 47 kg/m^2, which would qualify the individual for bariatric surgery. You could never catch him though, said Dr. Pories, as the individual is also Eastern Carolina University's fastest running back. Dr. Pories argued that the indication for metabolic surgery should be the same as the indication for other surgical procedures: when the disease can no longer be managed well by medical measures.

- **Most people have never heard of the bariatric field.** Said Dr. Pories, the failure to educate the public about bariatric surgery and the benefits of bariatric surgery for patients with diabetes is a major barrier to patient use.
- **"It's time for an endocrinology and metabolic surgery partnership."** Cardiologists collaborate with cardiac surgeons and neurologists with neurosurgeons, said Dr. Pories. Metabolic surgeons need the help of endocrinologists. Especially because of the substantial changes that patients go through following bariatric surgery, endocrinologist involvement becomes very important.
- **For more reading on bariatric surgery**, see our interview with Dr. David Cummings (University of Washington, Seattle, WA) at https://closeconcerns.box.com/s/t5h3909fvlk6kh5coi2c.

DIABETES TECHNOLOGY AND THE HUMAN FACTOR

Bruce Buckingham, MD (Stanford University, Stanford, CA)

The charismatic Dr. Bruce Buckingham rounded out this year's ATTD yearbook session with a presentation on the impact of patient attitude on type 2 diabetes treatment success. He described the "vicious circle" by which negative attitudes result in treatment neglect, and thus, more diabetes care failures. These failures only further perpetuate the patients' negative attitudes, which recharge the circle. In a study of newly diagnosed patients with type 2 diabetes following short-term continuous subcutaneous insulin infusion treatment, patients who experienced remission (defined as being drug free for one year with fasting glucose <126 mg/dl and two hour glucose tolerance test <180 mg/dl) tended to have lower "negative attitude" scores and higher care ability scores (Chen et al., Diabetes Care *2012). Dr. Buckingham believes that an absent psychosocial support system for patients with type 2 diabetes could be contributing to these negative attitudes and poorer health outcomes. He concluded, "it is important to invest in the psychosocial support of patient with type 2 diabetes." We are so glad to hear increasing focus in this area.*

Session: Medical Treatment of Type 2 Diabetes – Are There Regional Differences?

MEDICAL TREATMENT OF T2D IN CHINA

Linong Ji, MD (Peking University Diabetes Center, Beijing, China)

Dr. Linong Ji ably demonstrated that the burden of diabetes in China is huge. Currently about 10% of Chinese people have diabetes, control of type 2 is poor, and the pattern of medical treatment is glucose centric. Guidelines are similar to IDF, with metformin as first line therapy. The only notable difference

is the greater use of acarbose (27% of patients). Current hypoglycemic medications have the same effect in Asians and Caucasians, so it seems that China does not need a population specific drug for diabetes.

- **In a 2007 study, it became clear that the diabetes prevalence in China is 9.7% for type 2 diabetes.** Over 70% of people with type 2 diabetes also have other cardiovascular risk factors and as expected, their complications scale with the duration of diabetes. Forty-five percent of Chinese people with type 2 diabetes have an A1c less than 7%, and 31% have an A1c less than 6.5%. However, only 5% have A1c <6.5% and blood pressure and lipids at target. This data is taken from the China cardiometabolic registry from a set of n=25,460 type 2 patients.
- **In China, 5% of type 2 patients are on diet/exercise, 50% are oral agents only, 15% insulin only, and 30% insulin + oral agents.** Thirty eight percent take metformin, 29% take sulfonylureas, 27% take acarbose (different from Western countries). Almost no patients use incretins since they have only just launched and are not (yet) reimbursed.
- **The current (2010) Chinese guidelines are similar to the current IDF treatment algorithm.** Metformin is first line therapy, second line is an insulin secretagogue or acarbose. Third line is basal/premix insulin or a secretagogue/TZD/DPP-4/GLP-1. Fourth line is basal/bolus insulin therapy (or a move to basal/premix insulin).
- **Although Chinese BMI at diagnosis is lower than Caucasians, the differences in drug effects between Asians and Caucasians at any BMI are much smaller than many people believe.** In a study of n=33 newly diagnosed patients with type 2 diabetes, metformin had no difference in effectiveness across BMI groups. Acarbose reduced A1c by the same amount (~0.7%) in both Asians and Caucasians. The same finding holds for TZDs. Sitagliptin (Merck's Januvia) appeared to reduce A1c by 1.0% in monotherapy with an Asian population, and exenatide twice daily (Amylin's Byetta) and once weekly (Amylin's Bydureon) appeared similar across the races (A1c -0.85% for twice daily, and a further -0.3% for once weekly). Dr. Ji commented that to date they have not found any relationship between BMI and the treatment efficacy of a drug.

Questions and Answers

Q: What is the value of traditional Chinese medicine (TCM) in diabetes?

A: We have compared a combination of fixed dose TCM plus glyburide versus glyburide alone. We found no hypoglycemic effect with TCM, but the risk of hypoglycemia did decline. There is also no evidence that Chinese herbs can be used as a weight loss agent.

MEDICAL TREATMENT OF T2D IN EUROPE

Cees Tack, MD, PhD (Radboud University Nijmegen, Nijmegen, The Netherlands)

Europe is very diverse and heterogeneous. There are large regional differences in healthcare delivery and results across the countries. There has been a rapid increase in diabetes prevalence in Europe over the past few decades, but this is partly because we are catching patients earlier. In fact, Europe's population, while still growing, is likely past the point of peak growth, according to Dr. Cees Tack. Although there has been a gradual improvement in average A1c across Europe, the big problem is rising cost as a percentage of GDP. Costs are set to rise as the population ages in the absence of strong economic growth. Dr. Tack suggested that the solution is to enforce performance at the primary care level, particularly by the use of specialist nurses, who are more cost effective and have been shown to improve standards.

- **There has been a rapid increase in diabetes prevalence in Europe over the past few decades, but Europe's healthcare system is catching patients earlier.** The evidence for this is that at diagnosis, hardly anyone has retinopathy any more. But, Dr. Tack is confident that there will be more patients in future – that's because the population is ageing, there is likely to be an increase in obesity, there are still undiagnosed cases, and because people with diabetes will likely live longer. But Europe's prevalence, although still growing, is likely past the point of peak growth rate, unlike Asia (for example).
- **There has been a gradual improvement in average A1c in Europe, most likely because of guidelines and increased focus on optimizing therapy. There might also be an effect of earlier diagnosis.** The UKPDS suggested that diabetes is a progressive disease; however, in the more recent ADVANCE trial, the control arm stayed stable for six years. This is probably because of a progressive improvement in optimizing glucose control at physician practices. The PANORAMA study showed a variety of control in EU countries, but the average is good (around 7%) and is improving because reimbursement is increasingly based on following guidelines. Dr. Tack also noted that practices that are nurse led obtain lower A1c levels.
- **The cost figures for healthcare are staggering, yet they are set to go up as a percentage of GDP, meaning that cost will become more and more of an important issue.** The UK spends 9.4% of its GDP on healthcare and Germany 11.6%, compared with 17.6% in the US and 11.4% in Canada. Since there is an ageing population in Europe with no strong economic growth, healthcare costs are expected to increase. In diabetes, drugs are getting more expensive and long-term complications are costly.
- **The key to good cost effective diabetes care is strict treatment protocols, enforcing the performance of primary care with quality indices, and utilizing specialist nurses wherever possible.**

MEDICAL TREATMENT OF TYPE 2 DIABETES IN INDIA: THERAPIES AND TECHNOLOGIES 2013

Shashank Joshi, MD (Lilavati and Bhatia Hospital, Mumbai, India)

Dr. Shashank Joshi gave a high-speed, data-driven presentation on the Asian Indian phenotype and its implications for diabetes treatment. The burden of diabetes is especially sobering is India – approximately 62.4 million have diabetes and 77 million have prediabetes. Dr. Joshi posited that the "thin-fat" (i.e., higher truncal and abdominal adiposity) sarcopenic phenotype of Asian Indians make this ethnic group particularly susceptible to type 2 diabetes. To demonstrate this phenotypic discrepancy, Dr. Joshi showed a comparative body composition study in which Asian Indian males had body fat/BMI ratio of 1.34 vs. 1.02 for African Americans and 1.01 for Caucasians (Banerjee et al., J Clin Endocrinol Metab *1999). Myriad factors contribute to this phenotype (nutritional imbalance, physical inactivity, genetic predisposition, early-life adverse events), which in turn contribute to higher rates of insulin resistance in this population, a lower age at onset of type 2 diabetes, and a lower BMI threshold for diabetes. Taking this phenotype and higher carbohydrate loads into consideration, Dr. Joshi suggested that Asian Indians may require lower doses of DPP-4 inhibitors, GLP-1 analogs, and TZDs (with the caveat that more studies are needed). With a carbohydrate-rich diet, alpha glucosidase inhibitors also have a more potent effect. You need the right treatment for the right patient at the right time, said Dr. Joshi, but it also has to be affordable. The proposed Indian diabetes treatment algorithm is designed to take the latter into consideration as well.*

- **The proposed treatment algorithm** starts with lifestyle and metformin. After which if A1c is greater than 7% and the patient can afford it and is obese, liraglutide is added to the therapy. If the patient can afford it and is non-obese, DPP-4 inhibitor is added. If the patient cannot afford liraglutide/DPP-4 inhibitor, a low dose SFU is added. If the patient remains uncontrolled on these therapy combinations, insulin is considered next.

Questions and Answers

Q: There is a difference in the type of grain consumption in Northern versus Southern India. Is there a difference in incidence of diabetes?

A: No, wheat is as bad as rice and both our cereals are refined.

Q: My question is in a high glycemic stress situation, would an SFU be appropriate or would it accelerate beta cell damage? And what are your thoughts on early introduction of insulin?

A: We have used insulin pumps even in patients with type 2 diabetes. The first part of your question is logical. If you use secretagogues, you could get beta cell burnout, but we need prospective data. In India secretagogues are still used because of the cost, though if patients can use gliptins that is a good choice.

MEDICAL TREATMENT FOR TYPE 2 DIABETES IN THE UNITED STATES: GOOD, BAD, OR UGLY?

Irl Hirsch, MD (University of Washington, Seattle, WA)

"Treatment for type 2 diabetes in the US is sometimes good, often bad, and invariably ugly," said Dr. Irl Hirsch in his review of US' healthcare system and type 2 diabetes care. His presentation began with broad discussion on healthcare costs for diabetes – in 2007, 20% of US healthcare dollars was spent caring for patients with diabetes and 10% was spent directly on diabetes and its complications (ADA, Diabetes Care *2008). The challenge in treating diabetes is compounded by fragmented and inconsistent healthcare structures. Dr. Hirsch explained that there is no "one system" for diabetes management; rather, different payers have different costs for drugs and services and different providers have different care approaches. For Americans with insurance, the cost of managing type 2 diabetes can be challenging or prohibitive. For Americans without insurance (53 million; 17.6% of the population), the cost is even more so. Necessarily, on both the state and federal level, discussion is ongoing as to the best approach to curb costs whilst improving care – Dr. Hirsch believes that accountable care organizations have the potential to incentivize value in healthcare systems. Certainly, creative approaches to address both cost and quality need to be considered and Dr. Hirsch predicts that in the type 2 diabetes arena, healthcare system innovation (more so than drug innovation) will be the focus of the next decade.*

Questions and Answers

Q: In the US we're unique in being an extremely litigious society and I think that needs to change.

A: Tort reform and concerns about malpractice – it is very different depending on the state you live in. In Florida it's extremely litigious. Where I live now, not so much so. Medicare keeps track not just of physicians, but regions. Where I live in the Pacific Northwest, we are spending less on healthcare than other parts of the county and I think it is because of that.

Q: You predicted that healthcare innovation will be focused on system changes. I make the argument that behavior changes are even more important. Is the healthcare system going to help people self manage their diabetes?

A: I think that's true. But there are caveats to that discussion and that has to do with the huge number of patients living in poverty where they don't have access to all the technologies and tools. In the end, from a system's point of view, they cost more. But your point is well served and I do agree with it.

Session: Treatment or Cure T2D

INTERVENTIONAL APPROACHES TO TYPE 2 DIABETES

Dimitri Pournaras, PhD (Imperial College London, London, United Kingdom)

Dr. Dimitri Pournaras discussed many aspects of bariatric surgery, but focused on endoscopic alternatives to traditional metabolic surgery. He presented unpublished, encouraging one-year data on GI Dynamics' EndoBarrier; he also conveyed enthusiasm for Aspire Bariatrics' AspireAssist and for endoscopic vertical gastroplasty. To conclude he encouraged greater cooperation between surgeons and diabetologists; he also called for wider use of regimens that combine both surgery and medication.

- **Dr. Pournaras briefly mentioned several studies of metabolic surgery's efficacy and safety.** For example, the Swedish Obesity Study has shown that metabolic surgery is effective at forestalling diabetes onset in high-risk patients (Carlsson et al., NEJM 2012) and preventing heart attacks (Romeo et al., Diabetes Care 2012), among other benefits. Surgery's effects seem to involve the path of nutrients down the gut (rather than just caloric restriction), as seen in a small study of roux-en-Y gastric bypass surgery patients who were temporarily fed via gastrotomy (Pournaras et al., Surg Obes Relat Dis 2012).
- **Endoscopic procedures tend to be less effective than roux-en-Y gastric bypass, but Dr. Pournaras suggested a few situations in which they can be particularly useful.** He noted that many patients might want traditional metabolic surgery but have too low a BMI to receive it. (For such patients, Dr. Pournaras said, "I am sure that we can do more than say 'come back when you are heavier.' ") Another indication is "bridge treatment" for patients who are too *heavy* for highly invasive procedures; endoscopic interventions might reduce these patients' weight enough so that major surgery can be safely performed. He also suggested endoscopic therapy as a form of palliative care in homebound, terminally ill patients with extreme obesity (e.g., BMI ~70 kg/m^2).
- **The intragastric balloon is probably the most widely accepted endoscopic intervention for obesity, Dr. Pournaras said.** As a reminder, the balloon is placed inside the stomach and filled with air and liquid up to a volume that patients feel fuller while eating less food. Dr. Pournaras showed unpublished data on 33 patients who, with the balloon, reduced mean BMI from 65 to 56 kg/m^2. He said that balloons were "very good" for patients trying to lose weight in preparation for true bariatric surgery, but that they can cause complications. (He mentioned that sometimes patients feel too sick to drink anything.)
- **Endoscopic vertical gastroplasty has yielded "promising results" – weight loss of roughly 10 kg.** Dr. Pournaras noted that this technique involves using sutures to reduce the size of the stomach. It has been advanced by Massachusetts General Hospital and the Cleveland Clinic.

- **Dr. Pournaras briefly mentioned Aspire Bariatrics' AspireAssist Aspiration Therapy System, which he called "an excellent idea."** As a reminder, patients using the system wear a percutaneous endoscopic gastrotomy (PEG) tube, through which they aspirate (drain) roughly 30% of their caloric intake after meals. (For details on the AspireAssist, see our coverage of Dr. Katherine Crothall's presentation at ATTD 2013.) Dr. Pournaras noted that one might expect "biochemical disturbances" from periodic draining of the stomach, but he said that these seem not to have occurred in clinical studies to date.
- **Dr. Pournaras presented unpublished, one-year data from a pilot study of the EndoBarrier – GI Dynamics' duodenal-jejunal liner, which prevents nutrients from contacting the foregut.** The study was carried out in Brazil under the leadership of Dr. Ricardo Cohen (Oswaldo Cruz Hospital, Sao Paolo, Brazil), in collaboration with Imperial College London. It enrolled 16 patients with type 2 diabetes duration of two-to-10 years and A1c between 7.5% and 10.2%. All of the participants were taking metformin, and none were taking insulin or incretins.
    - **Mean baseline A1c was slightly over 30 kg/m²; small (but statistically significant) reductions in mean BMI were observed at both 12 and 52 weeks.**
    - **More striking was the decline in mean A1c from 8.6% at baseline to 7.5% at 52 weeks.** Also of note, 62.5% of participants had A1c below 7.0% at 52 weeks. When the EndoBarrier was explanted, patients' A1c rose, but not at a very sharp rate. Dr. Pournaras portrayed the slow rise as a relatively encouraging sign, and he attributed it to a legacy effect of good control while the EndoBarrier was implanted.
    - **Insulin secretion did not change with the EndoBarrier, as it does with roux-en-Y gastric bypass; however, insulin sensitivity improved during the first week after implantation – before any significant weight loss had occurred.** Dr. Pournaras noted that food intake did not change; he reminded the audience that the study participants were already eating fairly low-calorie diets before implantation. During the panel discussion, Dr. Pournaras emphasized that these data are still quite new and that researchers are still figuring out why the EndoBarrier has its particular profile of metabolic effects.
- **"At the moment we are treating metabolic surgery as a shotgun; we need to make it a laser beam."** Dr. Pournaras called for a redoubling of efforts to understand metabolic surgery's effects, to advance the development of therapies that have less risk, with similar or greater efficacy. He also hopes that clinicians will become better at predicting which patients are likely to benefit from an intervention. In the interim, Dr. Pournaras advised his surgical colleagues to remain vigilant of safety concerns and to cooperate with diabetologists for multi-disciplinary interventions. He encouraged listeners to tell their funders that traditional surgery, endoscopy, and medications should all be offered to people with diabetes – after all, as he remarked, "We don't ask cancer patients to choose between endoscopy and chemotherapy."

MOVING BEYOND A1C – ROLE OF INCRETIN THERAPY IN IMPROVING A1C WITHOUT HYPOGLYCEMIA OR WEIGHT GAIN

Richard Bergenstal, MD (International Diabetes Center at Park Nicollet, Minneapolis, MN)

In the view of Dr. Richard Bergenstal, "moving beyond A1c" is a theme that runs throughout ATTD, with its emphasis on myriad new ways to characterize, measure, and improve diabetes control. He said that in today's world, a glucose control therapy is expected not only to optimize A1c but also to minimize

hypoglycemia and glycemic variability, to avoid weight gain (and ideally cause weight loss), and to improve quality of life. On that note, he said that GLP-1 receptor agonists consistently outperform other agents in aggregate metrics such as percentage of patients who achieve A1c of 7.0% without weight gain or hypoglycemia (Zinman et al., Diabetes Obes Metab 2011; Bergenstal et al., Diabetes Obes Metab 2013). (Dr. Bergenstal acknowledged that many of his colleagues oppose such composite endpoints, but he also noted that they seem to be the way of the future. According to proposed quality performance standards for diabetes management, accountable care organizations would be evaluated based on the percentage of patients who meet the target for all five of: A1c, blood pressure, LDL cholesterol, not smoking, and taking aspirin.) Of course, much remains unknown about the long-term safety of incretin agents, as highlighted just days before in a much-publicized database study suggesting that the drugs double patients' odds of pancreatitis (Singh et al., JAMA Intern Med). Dr. Bergenstal seemed to agree with the joint ADA/AACE response to the paper, which cautioned patients and providers not to quit their drugs because of observational findings, limited as such studies inherently are – especially with large, long-term randomized controlled trials set to report in the relatively near term.

A PUBLIC HEALTH PERSPECTIVE ON THE COST/BENEFIT OF SURGERY FOR DIABETES

David Flum, MD, MPH (University of Washington, Seattle, WA)

Dr. David Flum invited each member of the audience to imagine that they were the nation's "health czar" and to address two key questions about metabolic surgery: "Is it worth it?" and "Can we afford it?" Many modeling studies have indicated that metabolic surgery should be cost-effective or even cost-saving, given its myriad health benefits. However, real-world data have not shown great cost differences with surgery, suggesting that the models are flawed (Zingmond et al., JAMA *2005; Maciejewski et al.,* Arch Surg *2012; Weiner et al.,* JAMA Surg *2013). Dr. Flum suggested that future research should involve reconciling these discrepancies, understanding the impact of metabolic surgery within various health systems, modeling ramp-up costs (e.g., training enough surgeons to meet a large increase in demand), and weighing the tradeoffs of metabolic surgery and other healthcare expenditures.*

PANEL DISCUSSION

Bruce Bode, MD (Emory University, Atlanta, GA); Dimitri D. Pournaras (Imperial College London, London, United Kingdom); Richard Bergenstal, MD (International Diabetes Center at Park Nicollet, Minneapolis, MN); David Flum, MD, MPH (University of Washington, Seattle, WA); Dr. Walter Pories (East Carolina University, Greenville, NC)

Q: Is it just absence of food that causes quick remission of diabetes in the first couple weeks after surgery?

Dr. Flum: Animal studies are looking at three main hypotheses about why surgery affects diabetes so quickly: exclusion of food in foregut, accelerated delivery of food to hindgut, and partial vagotomy. There are theories about bile salts, as you heard, but I think these fall into the gut-location categories. To your question, I would mention Dr. le Roux's group's study in which gastrotomy effectively turned diabetes on and off. It is a very exciting time to be in this field.

Dr. Pournaras: Bile acids seem to combine the proximal and distal gut hypotheses. The way I see it, bile salts may be a message from the proximal to the distal gut. It improves your insulin sensitivity but also your GLP-1 production.

Dr. Pories: We now think that the gut is a very carefully synchronized organ. If you interrupt that in any way, it seems to interrupt diabetes. You can move part of the distal jejunum up and have diabetes taken away.

Q: I run an adolescent obesity clinic. One of my patients is 15 years old and has BMI 45. She's black and has insulin resistance. What would you recommend to such a patient?

Dr. Flum: LABS is a Framingham-like study of 5,000 patients with bariatric surgery to see the effect of risk factors on their lives. Dr. Pories and I are co-investigators. Tom Inge in Cincinnati is running a teen version of LABS to guide people like the patient you describe, but right now there is a paucity of data. Gastric bypass is typically thought of as an irreversible procedure … this may be a place where adjustable gastric banding has a real role to play. In some sub-cohorts, it is more effective than in the adult population.

There is also a Swedish study, similar in design to the SOS, that reported outcomes in obesity last year. Mainly these patients received bypasses; so far it is still in its early days, but it has shown that younger patients respond to surgery in a very similar way to adults. But one important question that you mentioned is, "what do you have to lose?" Her risk at the moment is extremely high. She probably won't make it to 65 years old.

Dr. Pories: Teenagers who receive bariatric surgery tend to see remarkably better in terms of socioeconomics, performance in school, etc.

Comment: I worry more about my type 2 patients than my type 1s.

Dr. Bergenstal: We diabetologists have to rethink our algorithms maybe. I didn't see surgery on there, but maybe that will change.

Dr. Flum: [Regarding the large hall's sparse attendance] If this session had been on a drug with this profile, I think that there would be a lot of interest in the diabetological and endocrinological community.

Dr. Pories: It is also striking to me that we talk so much about the cost-effectiveness of this operation. We do not ask that question of hip replacement or cancer surgeries.

Dr. Flum: Or GLP-1 receptor agonists.

Q: Dr. Bergenstal, I have been studying the positive effects of GLP-1 receptor agonists on cognitive dysfunction in type 2 diabetes. Do you have anything to share from your personal studies?

Dr. Bergenstal: I am not sure whether this would reflect a direct effect of incretins or avoidance of hypoglycemia, which might be aggravating to cognitive dysfunction. I have no other specific insights. Do you have any, Dr. Bode?

Dr. Bode: Not that I'm aware of. Memory loss will be an adverse event in the ongoing cardiovascular outcomes trials, so hopefully a signal would be picked up, but maybe not.

Dr. Bode: How would you explain that the sleeve is almost as good as bypass from a weight-loss and diabetes perspective?

Dr. Flum: It is unclear if the time-course is as quick with the sleeve as with bypass. This is why Dr. Phil Schauer's study is especially important. It did not look as good as bypass in that study, and is probably not as good as bypass. Its effects may be related to ghrelin, which is dramatically altered.

Dr. Pournaras: I think that the sleeve does exactly the opposite of what it was 'supposed' to do [i.e., make the stomach smaller so you eat less at a time]. You have quicker delivery of nutrients down your gut. If you have nutrients hitting faster, you are more likely to produce GLP-1. If you change the dynamics of nutrients and bile, do you get bile or food hitting the gut first, or is it a combination of the two? I definitely don't think that it is because you have a smaller stomach.

Dr. Bode: A 50-year-old patient comes in with diabetes and a BMI of 45 kg/m², and says "tell me doc, what do you think is best treatment for me?" They are 50 years old. What will you tell them?

Dr. Flum: We are surgeons. We would have a conversation about their goals. If they are trying to cure their diabetes, that to me is perfect case for surgery.

Dr. Pories: [Commenting on the session's small audience] The overall attendance at this meeting is 2300 people. Yet when you talk about this technique that literally reverse disease at a diabetes session, it's interesting to how little we talk to each other.

Dr. Bergenstal: We [diabetologists] are talking a lot more surgery now than we used to. It's not a slam-dunk that it's automatic, but we will have a discussion with patients and probably give them more time to think about it while they are still on their medications.

Dr. Flum: I think it's on the ADA/EASD algorithm for patients with BMI at or above 40 kg/m².

Dr. Bode: Yes, but patients who actually get surgery also tend to be 'failing everything else.' They've tried everything. My question is, do any of you use banding?

Dr. Flum: It varies by country. I don't really see anyone putting in bands in the states anymore.

Dr. Pournaras: In the UK, we ask first, "do you want to have surgery," then "what do you want to do." There is level-one evidence that laparoscopic adjustable gastric banding is very good for diabetes.

Dr. Pories: Dr. Flum, it was interesting that in the example you gave us, the beginnings of cardiac surgery, the mentality was "if it's really bad, then we'll send it to the surgeon."

Dr. Flum: As you play with it, the patient gets to be older and have inulin resistance, and it gets to be a more complex situation.

Dr. Pournaras: For patients with BMI 50 kg/m², guidelines say that surgery is the primary model of care. We don't actually do that on the whole, but that's what the guidelines say.

Dr. Bode: When would you recommend sleeve gastrectomy instead of gastric bypass?

Dr. Flum: There is a risk profile that is in some ways better with the sleeve than with bypass. Some feel that post-surgical recovery is quicker. There is no clear advantage of the sleeve over bypass. Certainly we have more information about bypass.

Dr. Flum: And some insurance agents don't feel that there is enough evidence for the sleeve.

Dr. Pournaras: With the sleeve, the long-term evidence is very limited. With bypass, you know that we have 40-year data.

Dr. Flum: The datasets on gastric bypass are more like 10-to-15 years old.

Dr. Pournaras: For the large studies, yes, but there are people alive who had gastric bypass 40 years ago. There are *no* data on beyond ten years with gastrectomy. You would not meet someone who had a gastrectomy more than 40 years ago.

Dr. Bode: This is a very important treatment, and I am sorry that there isn't a bigger crowd here.

International Fair of New Technologies in Diabetes

ASPIRE BARIATRICS: ASPIRATION THERAPY – A NOVEL APPROACH TO WEIGHT LOSS

Katherine Crothall, PhD (CEO, Aspire Bariatrics, King of Prussia, PA)

Dr. Katherine Crothall gave a quick summary of Aspire Bariatrics' Aspiration therapy, emphasizing its safety, efficacy, and favorable comparison to bariatric surgery. With Aspiration Therapy, patients "aspirate" (drain) a portion of their stomach contents into the toilet after each meal through an endoscopically-implanted percutaneous tube – the process drains ~30% of calories consumed and takes about 5-10 minutes. To date, 54 patients have had tubes implanted (20-minute outpatient procedure), and the safety profile has been positive: 100% implantation success, only 1/54 patients had difficulty tolerating the tube, no serious adverse events, and all that on top of a long history with PEG tubes (used for over 30 years). Weight loss with Aspire's product is similar to conventional sleeve gastrectomy/banding: ~22% body weight loss at 52 weeks (50% excess weight loss) and comparable data at 104 weeks. The device has a CE Mark and approval in New Zealand, Saudi Arabia, and Israel (filed in Australia and Canada). Sales have begun in several countries. A 10-center, 175-patient US pivotal study is currently recruiting participants (ClinicalTrials.gov Identifier: NCT01766037) and expected to complete in July 2014. The safety and efficacy data to date looks encouraging – for us, one key question is patient perceptions of the device. Dr. Crothall addressed this quite well in her presentation, and we look forward to learning more once a greater number of individuals use the device.

- **With Aspiration Therapy, patients "aspirate" (drain) a portion of their stomach contents into the toilet after each meal through an endoscopically implanted tube**. Aspiration performed about twenty minutes after a meal will remove about a third of the calories consumed. The tube is implanted in the stomach, and leads to a "low-profile" port at the surface of the skin.
- **Weight loss with Aspire's product ~22% body weight loss at 52 weeks (50% excess weight loss) and comparable data at 104 weeks.** In the feasibility study, there were no non-responders to Aspiration therapy:

Feasibility Study Data		
Excess Weight Loss of at least…	**52 weeks (n=10)**	**104 weeks (n=7)**
20%	100% of patients	100% of patients
25%	100%	86%
35%	50%	71%
50%	40%	57%
75%	10%	29%

- **In clinical studies, the most common complications were abdominal discomfort and constipation/diarrhea.** Dr. Crothall notes other less commonly reported risks (infection, anemia, and buried bumper syndrome) were generally resolved with medical care or tube replacement. As with PEG tubes, the body "heals" around the implanted tube, reducing susceptibility to infection. Two concerns are a reduction in serum iron (typically seen with weight loss) and hypokalemia – Aspire is recommending prophylactic use of potassium, proton pump inhibitors, and iron supplements (the latter only for patients with low iron). However, in Sweden, a lack of supplementation has not been a problem.
- **Dr. Crothall highlighted that unlike many other weight loss procedures, Aspiration therapy is minimally invasive and completely reversible at any time.** The AspireAssist can be removed at any time though a simple 15-minute non-invasive outpatient procedure. Removal is similar to the placement procedure, and is performed under conscious sedation (general anesthesia is not required). The A-Tube site usually closes naturally on its own afterwards.
- **In preliminary type 2 diabetes data (n=6), A1c declined from 7.1% to 6.2% at 10 weeks.** This is an impressive reduction in a fairly short time period – we wonder if Aspire could pursue a type 2 diabetes-specific indication like GI Dynamics. Given the challenges of obesity reimbursement (this is certainly changing, but it's still early days), pursuing the diabetes route could be a promising approach for the company. We'd suspect hypoglycemia could be concern for insulin users, though certainly oral users could stand to benefit; from a payer perspective, the potential for diabetes remission would certainly make reimbursement attractive.
- **Dr. Crothall remarked that patient acceptance of the device has been quite good.** While the therapy may sound unusual, she emphasized taking the viewpoint of someone considering bariatric surgery (i.e., complications, irreversible, high cost, etc.). Dr. Crothall also mentioned that AspireAssist enables behavior change – it forces patients to eat slowly, to chew carefully, and drink water. Also, lifestyle modification program will be an integral part of the education process with aspiration therapy.
- **While many patients say they'll only use the device for one year, the majority end up continuing therapy.** Dr. Crothall highlighted that this is entirely patient dependent. However, most patients recognize that obesity is a chronic problem, and certainly success with the device would encourage continued use beyond one year.
- **There are a few patient populations that Aspiration therapy does not seem to work well for:** those with highly chaotic lives, those who are unwilling to do what is recommended, and those with major family issues.

6. Hospital Diabetes Care

Session: Diabetes Care in the Hospital

INTRAVASCULAR BLOOD GLUCOSE MONITORING SYSTEMS FOR THE OR, SICU, AND MICU

Jeffrey Joseph, DO (Thomas Jefferson University, Philadelphia, PA)

Dr. Jeffrey Joseph updated the audience on progress toward developing safe and easy-to-use CGM for intensively managed patients in the hospital. Among his many practical tips and insights, Dr. Joseph emphasized the prevalence of pre-analytical error in inpatient blood glucose monitoring: accuracy can be compromised by contamination, dilution, and other factors even before a measurement is taken. (The key for optimizing performance, said Dr. Joseph, is methodological consistency – e.g., taking the same type of measurement from the same type of blood vessel throughout a study.)

- **Presenting 72-hour data on Edwards/Dexcom's GlucoClear CGM (n=100 patients in the clinical research center), Dr. Joseph emphasized that the device is even more accurate than suggested by its MARD of 8.2% and its ISO 15197 score of 93.2%:** he said that many of the reference/sensor discrepancies were likely due to pre-analytical error. Arterial blood is ideal for reference measurements, explained Dr. Joseph, but arterial sampling became difficult on days two and three of the 72-hour study. Thus the researchers began making YSI reference measurements with central venous blood. Dr. Joseph noted that these venous blood measurements were used in 51% of the outlier reference/CGM data pairs, suggesting that the errors in these cases may have been due to the reference measurement rather than the CGM measurement. A detailed paper on the study by Bochicchio et al. is in press with an unspecified journal.
- **Dr. Joseph presented a table comparing nine companies' products for continuous, inpatient monitoring of blood glucose.** (For the sake of formatting, we have split the information into two separate tables.)

Inpatient continuous blood glucose monitors:

Manufacturer, regulatory status, and sampling frequency

Product Name	Company Name	Regulatory Status – Hospital Use	Time between Measurements
GlucoClear	Edwards Lifesciences	CE Mark	5 minutes
GlucoScout	International Biomedical	FDA-approved	5 minutes
Optiscanner	OptiScan	CE Mark	15 minutes
GluCath	GluMetrics	Pending	1 minute
Glysure System	GlySure	Pending	1 minute
Diramo System	Flowsion	Pending	5 to 10 minutes
Eirus System	Dipylon	CE Mark	5 to 10 minutes
MicroEye	Probe Scientific	Pending	5 to 10 minutes
GlucoDay	A. Menarini Diagnostics	CE Mark	5 to 10 minutes

Inpatient continuous blood glucose monitors:

Technological approaches

Product Name	Sample Location	Glucose Source	Sensor Location	Measurement Method
GlucoClear	Catheter in peripheral or central vein	Venous blood	Sensor in catheter lumen	Electrochemical / Enzymatic
GlucoScout	Catheter in peripheral or central vein, or radial artery	Venous or arterial blood	External sensor with tubing	Electrochemical / Enzymatic
Optiscanner	Catheter in central vein	Venous blood transformed into plasma	External sensor with tubing	Absorption spectroscopy
GluCath	Optical fiber in peripheral or central vein, or radial artery	Venous or arterial blood	Sensor in artery or vein lumen	Quenched fluorescence
Glysure System	Optical fiber in peripheral or central vein, or radial artery	Venous or arterial blood	Sensor in artery or vein lumen	Quenched fluorescence
Diramo System	Micro-dialysis catheter in peripheral or central vein, or radial artery	Dialysate from venous or arterial blood	External sensor with tubing	Quenched fluorescence
Eirus System	Micro-dialysis catheter in peripheral or central vein, or radial artery	Dialysate from venous or arterial blood	External sensor with tubing	Electrochemical / Enzymatic
MicroEye	Micro-dialysis catheter in peripheral or central vein, or radial artery	Dialysate from venous or arterial blood	External sensor with tubing	Electrochemical / Enzymatic
GlucoDay	Micro-dialysis catheter in peripheral or central vein, radial artery, or subcutaneous tissue	Dialysate from venous/arterial blood, or interstitial fluid	External sensor with tubing	Electrochemical / Enzymatic

Questions and Answers

Dr. Irl Hirsch (University of Washington, Seattle, WA): You said something about using IV insulin for meals. You can certainly see real-time excursions if you are on top of it with CGM. But if you are using IV insulin at mealtimes for sick patients, that really concerns me. When we are putting patients back onto their regular diets, I favor using subcutaneous insulin since it allows more time.

A: We are not using IV insulin for meals yet. We are collecting data to assess the feasibility of a closed-loop system using IV insulin. We are looking at the PK and PD of IV insulin around meals.

Q: In my hospital in London, 18-20% of patients at a time have diabetes. It's a vast, underserved population in many ways. You are comparing the data from these new CGM systems with Hemocue, YSI, or Accu-Chek meters. Often the variation is with these systems – our gold standards tend to be bronze at best.

Dr. Joseph: This is a key question, especially for regulators. When allowed, the best thing is to take blood draws five minutes apart to avoid sampling error. We measure blood at the bedside to minimize time delay, and we use all three of Hemocue, YSI, and glucose meters. They give you numbers that are close, but different. The key is to be consistent with your methods.

Comment: Getting quality assurance on our extra-corporeal methods was important but difficult to achieve, when we studied this.

USING COMPREHENSIVE ELECTRONIC SUBCUTANEOUS (SC) INSULIN ORDER SETS TO IMPROVE GLYCEMIC CONTROL AND REDUCE CLINICAL INERTIA IN THE HOSPITAL SETTING

Jane Jeffrie Seley, DNP, MPH, BC-ADM, CDE (New York-Presbyterian/Weill Cornell, New York, NY)

Dr. Jane Seley described her experience implementing an electronic order set for subcutaneous insulin dosage, sharing practical advice to guide improved intern behavior in hospitals. She has tried to make the order set comprehensive and intuitive – the order set includes everything from insulin sensitivity profiling to hypoglycemia treatment to pre-discharge education. Dr. Seley indicated that the computerized order set has reduced problems such as miscalculated boluses, mis-timed blood glucose tests, omission of basal insulin in people with type 1 diabetes, and last-minute referrals for discharge education. Initial data analysis of glycemic control comparing pre-launch and post-launch glycemic control has shown a significant reduction in the rates of hypoglycemia; however, less patients are in their target range and more patients are in hyperglycemia. This led Dr. Seley to conclude that the insulin doses were not aggressive enough and the next iteration of the order set will address this.

Questions and Answers

Q: You saw a decrease in hypoglycemia and an increase in hyperglycemia. Did you look at mortality?

A: No, we haven't. We're starting to drill down with the data and look at the second year as well. In the first year, there was issue with adoption and not going with higher dose order sets, so I'm hoping it has improved.

Dr. Irl Hirsch (University of Washington, Seattle, WA): First, congratulations. What you've done is herculean. The biggest issue is the ultimate outcome, but the other issue is what happens when patients go home on insulin regimens. My concern is that you are putting in all this effort but after that it falls away.

A: Transition of care could be a whole other lecture. There has to be things done before the patient leaves the door to make sure certain things happen. We have follow up phone calls in two to three days and we also make sure that they are keeping the appointments made for them. Additionally, patients cannot leave the hospital until that appointment has been made. The appointment has to be made and the patient has to agree with the appointment time.

Q: What about previous medications? I have the impression that interns are not interested in diabetes. What about a nurse-driven scheme?

A: We take patients off orals when they come in. We might transition them back to orals on the day of discharge. You can't rely on giving them oral medication in the hospital, what if they can't tolerate po [by mouth] intake?...TZDs have the drama of edema. Possibly DPP-4s could be useful in the hospital, but I would not advise orals in the hospital. I think it's dangerous.

Q: Can you let the nurse prescribe insulin?

A: It's not permitted in the US.

Dr. Bode: You can have nurse-mandated orders for titration.

A: For a drip you can have it. Maybe it's different in Georgia. In New York, nurses cannot prescribe insulin.

Dr. George Alberti (Imperial College, London, UK): The reason this is being done is the notion that controlling blood glucose improves outcomes and that's been a very controversial issue where some studies have corroborated it, others have not. When you show a greater mortality with glucose complexity or hyperglycemia, do you think controlling glucose is the answer to better outcomes or is it the severity of the illness? Is it a reflection of the stress the body is under? Is the essential illness of the patient driving glucose or is glucose driving the illness? I'd like to open this for comments.

Dr. Holzinger: I think glucose control will improve outcomes because lots of these studies are corrected for severity of illness. I have to say the glucose control itself has an effect. So, yes, because severity of illness can be ruled out in most of the studies.

Dr. Bode: When you go to computerized systems that target different glucose ranges, you minimize variability in both groups. So being at 120 mg/dl vs. 160 mg/dl, with all else equal, might not make a difference – we don't know. I think controlling variability is important, though.

Dr. Joseph: The great majority of studies that have been done to date have not been standardized with respect to how they drew, handled, or measured blood and there is great difference if you do not standardize those methods.

Dr. Alberti: The contention is that most of the epidemiological studies including NHANES have given totally inaccurate results because of the lack of standardization of glucose methodology and failure to preserve blood samples properly. Methodological aspects are very, very important

Dr. Seley: There is a group of endocrinologists, intensivists, and others forming a consortium to do this sort of research. I am hopeful that we will soon learn more.

Dr. Hirsch: I've been talking about glycemic variability for over a decade. There is a study by Dr. Guillermo Umpierrez showing that patients without diabetes who are not treated actually had higher mortality and what we showed is that patients without diabetes not treated have higher adverse outcomes. It's more than the glucose. The insulin has a huge impact of how our patients do. It's a signal coming up over and over again in the literature.

Session: Nothing New Under the CGM-Sky?

GLUCATH INTRAVASCULAR CONTINUOUS GLUCOSE MONITORING SYSTEM

Paul Strasma, MBA (Glumetrics, Irvine, CA)

Mr. Paul Strasma presented on Glumetrics' optical CGM for use in critical care, discussing the science behind its design and clinical results. The sensor is inserted into a standard arterial catheter, uses single point calibration and daily recalibration, displays data on a small, battery-powered handheld device, does not interfere with routine ICU and operating room procedures, and has low interference. Mr. Strasma reviewed a three-center ICU study of the system in 15 patients post-cardiac surgery. A solid 83% of paired YSI-CGM points (202/243) met ISO 15197 criteria. The data collected was prospectively calibrated without any filtering or dropped points – it's great to see a focus on quality representation of data, something we're increasingly noticing over the past year. A study of twenty patients was completed last spring and presented at an ICU meeting in Australia. The system demonstrated a 12.6% MARD and 82% of points meeting ISO 15197. The company has since developed a new algorithm to account for temperature and pH. More recent clinical experience has been quite strong: a very solid MARD of 5.5% in five patients with data thus far; 15 of 30 have now been completed and the study will be presented at ISICEM 2013 in Brussels. Glumetrics will focus on Europe, and the company is actively seeking European investigators for a proposed pivotal study.

Oral Presentations

OPTIMISING THE GLUCOSE SAMPLING PERFORMANCE OF AN INTRAVASCULAR MICRODIALYSIS-BASED CONTINUOUS GLUCOSE MONITORING DEVICE FOR USE IN HOSPITAL SETTINGS

Fausto Lucarelli, PhD (A. Menarini Diagnostics, Florence, Italy)

After describing an investigational microdialysis-based CGM in development by A. Menarini and Probe Scientific, Dr. Fausto Lucarelli presented interim data from an evaluation in patients with type 1 diabetes. So far 8 patients have completed the 72-hour study (n=1491 data pairs), and the device has performed with mean absolute relative difference (MARD) of 11.0% compared to YSI reference values. Dr. Lucarelli noted that the CGM data could be considered "raw," since no filters or compensation algorithms had been applied. Given the encouraging results and the room for software-based improvement, we look forward to hearing about the group's research in ICU patients (the eventual target population).

BLOOD GLUCOSE CONTROL IN THE INTENSIVE CARE UNIT: LOGIC-INSULIN VS LEUVEN NURSE

Tom Van Herpe, PhD (Katholieke Universiteit Leuven, Leuven, Belgium)

Summarizing a recent publication by his group (Van Herpe et al., Diabetes Care *2012), Dr. Tom Van Herpe discussed a randomized, controlled trial of tight glycemic control in the ICU (n=300). Control was guided by either 1) a computerized algorithm called LOGIC-Insulin or 2) nurses with paper-based protocol – specifically, nurses from Leuven, where glucose control in the ICU was pioneered (Van den Berghe et al., NEJM 2001). Relative to the paper-based protocol, LOGIC-Insulin led to statistically significant improvements in time-in-target (60.1% vs. 68.6%), number of patients experiencing hypoglycemia below 70 mg/dl, number of hypoglycemic readings (whether the cutoff was <70, <60, or <40 mg/dl), and glucose penalty index (a measure of effective glycemic control that was the study's primary endpoint). These results came at the cost of higher nurse workload: on average, LOGIC-Insulin*

called for blood samples more often than the paper-based protocol did (every 2.2 hours vs. every 2.5 hours). Dr. Van Herpe seemed to find this tradeoff favorable, and he looked forward to validation of the results in an upcoming multicenter randomized controlled trial.

7. Pharmacotherapy, Telemedicine, Software, and Other

Session: ATTD Yearbook

NEW MEDICATIONS FOR THE TREATMENT OF DIABETES

Satish Garg, MD (University of Colorado, Denver, CO)

Dr. Satish Garg gave a whirlwind review of emerging therapies for the treatment of diabetes. He noted the plethora of interest in SGLT-1 and -2 inhibitors, DPP-4 inhibitors, and GLP-1 analogs. Zeroing in on SGLT-2s, the FDA has not yet approved any SGLT-2 candidate; however, one is pending approval (editors note: J&J's canagliflozin). He commented that there seems to be concern in the FDA's mind as the long-term safety of these drugs is unknown, especially with respect to dapagliflozin (BMS/AZ). Dr. Garg also posed the question of whether these emerging therapies could be used in patients with type 1 diabetes and directed conference attendees to the fresh-off-the-press article in Endocrine Practice discussing their limited role in type 1 diabetes (Garg et al., Endocrine Practice *2013). Dr. Garg then transitioned his discussion to alternative ways to deliver insulins with focus on buccal insulin spray. Buccal spray is built on the idea that patients don't like to inject insulin, but Dr. Garg seemed unsure of the approach. He remarked that most of the studies on buccal spray have been difficult to replicate and felt that a proper phase 2 or 3 study in the US or Europe has yet to be done. Rounding out his presentation, Dr. Garg commented briefly on insulins in development. There's a huge amount of interest in basals he said, which is driven in part by the dollars. Lantus, remarked Dr. Garg, is an $8 billion dollar per year insulin. (Editor's note – Lantus global sales in 2012 reached $6.4 billion, while global sales of Lantus, Apidra, Amaryl, and iBGStar were approximately $7.2 billion.) He also mentioned Lilly's investigation of PEGylated lispro (which is intended to be more liver specific and thereby reduce weight gain), Sanofi's phase 3 work on U-300 glargine, insulin delivery through microneedles, and emerging interest in smart insulin. The latter, he said, could overcome both the basal and prandial parts to the equation. Looking at closed-loop development, he stressed that if the field is ever going to close the loop "we need an ultra-fast-acting insulin." Those available today, he emphasized, are not all that rapid. We remember a decade ago when AP development faced three major barriers – sensor accuracy and reliability (and wearability), algorithm quality, and speed of insulin. While both sensors and algorithms have improved enormously during that period, most AP studies still use the same insulin analogs that were available 10 years ago. An ultra-fast-acting insulin would certainly place researchers a large step closer to a control-to-range system.*

TYPE 1 DIABETES MELLITUS: IMMUNE INTERVENTION

Jay Skyler, MD (University of Miami, Miami, FL)

Dr. Jay Skyler's presentation highlighted four studies in type 1 diabetes immune intervention: 1) FINDIA (reduced development of insulin autoantibodies after removing bovine insulin from milk); 2) a Polish study on infusing polyclonal regulatory Tcells (an early pilot study, but "safe and may have

benefit"); 3) Dr. Denise Faustman's BCG study (it needs a full scale trial and let's "not jump that this is the cure for diabetes"); and 4) TrialNet data examining C-peptide levels two years post-diagnosis (93% of patients had some detectable C-peptide at two years, and 66% exceeded the key threshold for preventing complications).

- **The FINDIA study (Vaarala et al., Archives of Pediatric and Adolescent Medicine 2012) builds on the TRIGR cow's milk study by specifically looking at bovine insulin.** Participants were randomized to three groups: control, whey-based hydrolyzed formula, or whey-based FINDIA formula essentially free of bovine insulin. The group assigned to the FINDIA formula had a reduced risk of development of β-cell autoimmunity.
- **A pilot study from Poland looked at infusion of polyclonal regulatory Tcells (Marek-Trzonkowska et al., *Diabetes Care* 2012).** There was an increase in the percentage of circulating FoxP3+ Tregs. This was accompanied by a decrease in A1c, insulin dose, and glucose level. C-peptide levels were also sustained to a greater degree in the subjects treated with Tregs. Dr. Skyler concluded it was "safe and may have benefit," though he cautioned that it was "the first dipping of the toe in the water with this approach."
- **Dr. Skyler expressed skepticism of Dr. Denise Faustman's study of BCG vaccine (Faustman et al., *PLoS ONE* 2012).** He first noted the study's small size: three patients treated with BCG vaccine vs. three patients in placebo (arguably only two placebo patients, since the authors wanted to exclude one patient who got EBV). Dr. Faustman et al. claimed that fasting C-peptide was better in the treated group, though Dr. Skyler highlighted the use of an ultra-sensitive measure of C-peptide. He was fairly critical of all the publicity the trial received and believes BCG vaccine needs a full scale trial – for now, it's too early to jump to the author's conclusions that this is the cure for diabetes.
- **To conclude, Dr. Skyler reviewed interesting TrialNet data on C-peptide levels following diagnosis of type 1 diabetes** (Greenbaum et al., *Diabetes* 2012). The study looked at the percent of individuals with detectable C-peptide and C-peptide $\geq$0.2 pmol/ml over time (a threshold established in the DCCT that was linked with a reduced risk for severe hypoglycemia, progression of retinopathy, and kidney disease). A substantial 93% of patients had some detectable C-peptide at two years – this was encouraging to hear in our view, and we wonder if this has changed over time as technologies and insulins have improved. A solid 66% of individuals exceeded the $\geq$0.2 pmol/ml C-peptide threshold. Over time, older individuals tended to have a slower decline in C-peptide levels. Interestingly, younger individuals typically started with a lower level of C-peptide, and thus, their ending level at two years was much lower relative to adults. Over the two-year period, C-peptide declined much faster in the first year following diagnosis. In Dr. Skyler's view, the key implication is that we must be cautious when deciding when to start studies in this area.

USING HEALTH INFORMATION TECHNOLOGY TO PREVENT AND TREAT DIABETES

Neal Kaufman, MD (UCLA Schools of Medicine and Public Health, Los Angeles, CA)

Lower cost access to technology is revolutionizing diabetes education and support for the self-management of diabetes. There are a number of cellphone apps, although they are not all made equal. Computer assisted self-management support (CASM) showed only a small improvement compared to usual care in a recent trial, but Dr. Neal Kaufman was supportive, suggesting that the control group performed better than likely in the real world. Their version of CASM included such elements as

psychosocial support, goal setting and tracking, feedback, rewards, and relapse prevention. In another paper, it was made clear that elderly and low income patients improved A1c and adherence over five years of interacting with healthcare providers via telemedicine.

- **There has been a revolution in diabetes education and support because of the use of technology.** These technologically enabled self-management support interventions include such features as just in time delivery, personalization, goal setting, behavior tracking, feedback, links to clinicians, family, friends, and others. Often these approaches have a very low cost to go to scale, making for a very exciting future, although Dr. Kaufman implied that not all are high quality. The implication of this is a new role for clinical educators. Clinicians can increase levels of support, and they empower patients to do more things for themselves.
- **In a paper by Dr. Russell Glasgow and colleagues, computer assisted self-management support (CASM) for diabetes showed only a small health improvement compared to usual care, although Dr. Kaufman believes that they had "the curse of an effective diabetes system" in the control group, which minimized the impact.** The 12-month program studied n=463 people with diabetes who were randomized to usual care, or CASM at high or low intensity (Glasgow et al., *Patient Education and Counseling* 2012). High intensity CASM included such aspects as feedback, rewards, and relapse prevention. Regular CASM included things like psychosocial support, goal setting, and tracking. Although it was a year-long trial, most patients stopped using the tools after six months. Use of the tools did improve health, but the 12 month impact was small, although enough to have a meaningful public health impact. The keys to success were tailored education, integration to primary care, and links to community resources. Dr. Kaufman commented that the authors could have also upgraded their educational curriculum, added small steps to success and additional key elements of diet and physical activity.
- **In a five-year study of telemedicine, increased self care in elderly and low income patients improved A1c and adherence** (Trief et al., *Ethn Health* 2012). The study included n=1,665 elderly patients (not typical technology early adopters). The telemedicine was based around video conferencing between the healthcare providers and the patient. Success in self-management increased with duration of diabetes and high levels of education. Dr. Kaufman suggested that to be really successful the program must be carefully targeted at the population.

ADVANCES IN EXERCISE, PHYSICAL ACTIVITY AND DIABETES MELLITUS

Michael Riddell, PhD (York University, Toronto, Canada)

Dr. Michael Riddell hosted a fascinating talk on a very important issue. He focused entirely on HIT – high intensity interval training. In a small study with older, more obese people with type 2 diabetes, HIT lowered post-prandial glucose by ~30 mg/dl after only two weeks, and seemed to have made some major changes to metabolic processes. Furthermore, the participants did only 20% of the ADA recommended exercise duration, and loved it!

- **In the chapter on exercise, Dr. Riddell considered over 900 abstracts and selected 81.** They covered topics such as high intensity exercise, resistance versus aerobic exercise, interaction with medications, and exercise effects on blood flow.
- **There is a current craze on high intensity interval training (HIT), which consists of bursts of intense activity with small rest periods in between.** Typically HIT is interval training of one to two minutes with 30 second rests, for a 10-15 minutes total duration.

- **In a remarkable study of people with type 2 diabetes, after only two weeks of HIT post-prandial glucose was ~30 mg/dl lower than the control group (!). Average glucose was also lower and a muscle biopsy showed that markers of mitochondrial biogenesis were greatly increased** (Little et al., *J Appl Physiol* 2011)**.** The eight participants were on average 63 years old with high BMI. They completed 10 repetitions of cycling at 100% of power intensity three times a week for two weeks. Heart rate rises to 90% of maximum during the exercise program. This is a total of only sixty minutes exercise in two weeks – the ADA recommends five hours. Participants ranked the quality of the exercise as 9 on a 10-point scale. CGM data showed a reduction in average blood glucose after 2 weeks and the reduction in post-prandial glucose.

Session: Challenges in Diabetes

APPROACHES TO IMPROVING TYPE 1 DIABETES WITH BENCHMARKING: SWEET (EUROPE) VS. TYPE 1 DIABETES EXCHANGE (US)

Thomas Danne, MD (Kinderkrankenhaus auf der Bult, Hannover, Germany)

Dr. Thomas Danne explored the appropriateness of adjusting A1c goals in the pediatric population. For background, he explained that some contention exists between the ADA and ISPAD: whereas ADA advocates for lower A1c targets in the pediatric population due to the higher risk of hypoglycemia in young children, ISPAD and the German Pediatric Working Group recommend an age-independent A1c target. Dr. Danne reviewed data from the Type 1 Diabetes Exchange to demonstrate that "we are not reaching our goals." The outlook is, of course, better when using ADA's <8.5% target vs. ISPAD's <7.5%; however, Dr. Danne feels strongly that changing targets is not a solution for not reaching targets. He suggested that benchmarking between centers can encourage discussion of best practices and help centers achieve better glucose control in their patient population. SWEET Pediatric Diabetes has implemented a process for becoming a Center of Reference for Pediatric Diabetes and as part of this accreditation, centers join an anonymized data exchange. This is intended to provide benchmarking analysis such that centers can compare their performance to participating centers', continually assess quality of care, and learn best practices from centers of higher performance. Currently, there are 14 Centers of Reference and Dr. Danne encouraged audience members to make a difference in their own center and go about the process to join this group.

Questions and Answers

Dr. John Pickup (King's College London School of Medicine, London, England): Have you looked at hypoglycemia in your benchmarking analysis?

A: Hypoglycemia is a different issue and we are still discussing the best ways to assess that. In the past we have just counted severe hypoglycemic events with convulsions and we try to assess data for the past three months. As you would imagine, there is no clear correlation between A1c and hypoglycemic rates. Hypoglycemia has a lot to do with education and raising the level of A1c of course has some influence, but its not all of it. It's a mix of A1c, technology, and education.

Dr. Pickup: Do you have plans to expand SWEET to the adult population?

A: We are happy to do it. Technology-wise it is very easy. We are already doing that in Germany. It can be done, it's just a matter of hooking them to the various electronic health records.

Dr. Pickup: I like idea of Centers of Reference, but how will you prove their effectiveness?

A: I think that from the German experience simply having people together in quality control circles is already helping to ensure quality. We also need health economic data to prove which approaches are cost effective. But you're quite right, at end of day we'd like an RCT of centers participating vs. not participating.

Q: Are there differences in staffing levels of education?

A: It varies, I wish to refer to you the publication in Pediatric Diabetes [Danne et al., *Pediatric Diabetes* 2012]; there are a lot of pointers in there.

BETA-CELL REPLACEMENT

Jay Skyler, MD (University of Miami Miller School of Medicine, Miami, FL)

"If we are really going to change this disease," said Dr. Jay Skyler, "we need to stop the immune destruction, preserve beta cell mass, then have beta cell replacement or regeneration." Dr. Skyler's discussion zeroed in on the latter and his presentation considered two important factors to beta cell replacement: the source of islet cells and the delivery of islet cells. As to the former, he explained that using cadaveric human pancreas will never provide a sizeable enough source of cells. He highlighted a slew of potential alternatives, including: 1) xenotransplantation via pig islets; 2) reprogrammed cells, which use transcription factors to induce insulin cell development; 3) transdifferentiated cells, whereby liver cells biopsied from a patient with diabetes are manipulated into surrogate beta cells then given back to the same individual; and 4) islets derived from human embryonic stem cells. The next step after finding an appropriate source of islet cells, explained Dr. Skyler, is to optimize the delivery of the cells. This requires modulating the environment during islet implantation. He suggested that biomaterial scaffolds can provide mechanical protection, three-dimensional distribution of islets, retrievability and monitoring, and the necessary platform for environmental modulation.

Questions and Answers

Dr. Pickup: What is the site of implantation you are using?

A: We're putting them in the omentum in a number of animal models. Most go portal-y, but not 100%.

Dr. Pickup: Can you stick your neck out on which of these cell technologies is likely to be successful in man in next five years?

A: You said successful and I don't like to project timeframes. I used to show a slide with a series of newspaper headlines about the artificial pancreas and transplantation and the problem is that slide was first made in 1974. Trying to make a timeframe for success is difficult. But there are three or four technologies that I expect to be in human clinical trials. I don't know whether any will work, but I think we will get them into trials and begin to get answers.

IMPROVING HBA1C LEVELS IN SUBJECTS WITH TYPE 1 DIABETES

H. Peter Chase, MD (Barbara Davis Center, Aurora, CO)

In this retrospective sub-analysis of data from the sensor-augmented pump arm of the STAR 3 trial, Dr. Peter Chase explored whether glycemic improvement at a particular time of day were more strongly associated with A1c reductions. So far, this ongoing investigation suggests that A1c benefits are more strongly related to mean CGM readings in the five-hour post-breakfast period than any of the other periods studied (five-hour post-lunch, five-hour post-dinner, or six-hour overnight). Dr. Chase

emphasized that these results are limited by the dataset chosen and by the preliminary stage of the statistical analysis (e.g., the "postprandial" periods were defined by the same range of times for every patient, rather than personalized according to the time of each individual's bolus; area-under-the-curve has not yet been studied). Nonetheless, the data suggest that breakfast time (and the preceding nighttime hours when the "dawn phenomenon" can strike) may be an especially powerful target for glycemic interventions. This supports our anecdotal understanding that all-day glycemia is much better on days that begin with good control; we look forward to more analyses of STAR 3 and other datasets to characterize the relationship between overnight control, the dawn phenomenon, and post-breakfast glucose values.

- **Improvements in A1c were significantly associated with reductions in both daytime and nighttime CGM values, but A1c benefits were most strongly linked to mean CGM value in the "post-breakfast" period (6 am to 11 am).** To assess the relationship of A1c to mean CGM from the entire day (6 am to midnight) and entire night (midnight to 6 am), Dr. Chase and his colleagues conducted a single-variable linear regression. They found that mean CGM declines of ≥29 mg/dl from both the day- and nighttime periods were significantly associated with A1c declines of 0.73% and 0.57%, respectively. (The researchers found similar results when they used 15 mg/dl or 45 mg/dl as their threshold for a decline in mean CGM, Dr. Chase noted.) The researchers drilled down further with a multivariate linear regression of A1c decline with mean CGM declines from four different time ranges: "post-breakfast" (6 am to 11 am), "post-lunch" (11 am to 4 pm), "post-dinner" (5 pm to 10 pm), and overnight (12 am to 6 am). Notably, in this analysis, only mean CGM values from the post-breakfast period were significantly associated with A1c reductions.

Questions and Answers

Dr. Pickup: It's very interesting, the power of breakfast for affecting A1c. Where you able to tease out the relationship between the breakfast values and the dawn phenomenon?

A: I think that they probably are related. As everyone knows, all the counterregulatory hormones are high during this period, so control can be quite important. If we can't better control nighttime, we've seen that 29 mg/dl can be achieved by rapid-acting insulin use 20 minutes before breakfast. Nighttime control and breakfast might be good places to start in type 1 diabetes.

Session: Hypoglycemia – The Barrier to Good Control

HYPOGLYCEMIA AWARENESS AND UNAWARENESS

Stephanie Amiel, MD (King's College London, London, United Kingdom)

One of the world's leading authority on hypoglycemia, Dr. Amiel gave an excellent talk on hypoglycemic awareness and its treatment. Compared to people with awareness of hypoglycemia, hypo-unaware patients tend to have not only a reduced counterregulatory response, but also less displeasure associated with low glucose. Because hypoglycemia is no longer experienced as an unpleasant sensation, many people with hypoglycemia unawareness have little motivation for the strict hypoglycemia avoidance that is necessary to restore hypoglycemia awareness. To address such subjective issues, Dr. Amiel is piloting a "psycho-educational" program within the UK's DAFNE diabetes education initiative. The program, called DAFNE HART (Hypoglycemia Awareness Restoration and Training), has enrolled 24 patients for three months, during which time these patients experienced

significant declines in both severe and moderate hypoglycemia (DeZoysa et al., 2013). We thus share Dr. Amiel's optimism that well-designed interventions can help patients and their families to overcome the great challenges of hypoglycemia unawareness, even when modern technologies and therapies are not yet enough by themselves.

Questions and Answers

Dr. Satish Garg (University of Colorado Denver, Aurora, CO): We have seen that sometimes there is a delay not only in patients' recognition of hypoglycemia, but also in their decision to take corrective action.

A: You are absolutely right. Many patients do often know that they are hypoglycemic but delay taking action. The data suggest that if you slightly prolong your exposure, you significantly increase your risk for a subsequent hypoglycemic episode. This is something that we address in our program.

THE POTENTIAL OF TECHNOLOGY TO REDUCE HYPOGLYCEMIA

Simon Heller, MD (University of Sheffield, Sheffield, UK)

Dr. Simon Heller discussed major technological advancements and their respective impact on severe hypoglycemia. His review of seminal SMBG, CSII, CGM, and sensor augmented insulin pump therapy trials showed that technology to date has been relatively disappointing in reducing severe hypoglycemia; however, underlying his review was the notion that perhaps, RCTs are not the most appropriate way to access technologies for this impact. He explained that in RCTs to date, severe hypoglycemia has been confined to a few individuals, leading to non-significant p-values despite marked reduction in hypoglycemic events (as was the case in the JDRF study of CGM [Tamborlane et al., NEJM 2008]). Further, differing definitions of hypoglycemia have complicated meta-analyses. This is a major challenge for RCTs and diabetes care broadly given that reimbursement authorities make decisions based on the highest quality of evidence (i.e., meta-analyses). Further reflecting on past RCTs, Dr. Heller remarked that trials have generally failed to integrate technology with other aspects of self care. Looking forward, he awaits the outcomes of Hypo COMPaSS trial (set to read out in a matter of weeks) and REPOSE Trial (of which he is a researcher), both of which will assess the effect of diabetes technology combined with education intervention on hypoglycemia. "Technology is only one component of care," said Dr. Heller. "…Patients must integrate technology more effectively into self management if the full potential of reducing hypoglycemia is to be realized."

Questions and Answers

Dr. Skyler: One of the conclusions of the CGM paper [Tamborlane et al., NEJM 2008] was that it is useless unless patients were motivated. How do you motivate them?

A: That's an interesting question. In our own adolescent clinic we use pumps a lot and patients who engage get the benefits. I think it is a question of working with young people and individualizing approaches. With time and encouragement it may be that we can engage them in way that makes a difference. The people who do well with technology are people who do well with very conventional tools. Maybe as technology develops it will engage patients at a higher level.

Dr. Skyler: Should we include self-management training with everyone?

A: Absolutely.

Session: Reaction Project – EU-Funded Project on Diabetes Management

INTRODUCTION TO THE REACTION PROJECT

Lydia Montandon (Atos Origin, Madrid, Spain)

Ms. Lydia Montandon described the Reaction Project, a EU-funded initiative of which she is the project coordinator. The overarching goal is to develop an intelligent web-based platform to improve management of diabetes – especially type 1 diabetes. Now entering its fourth and final year, the €12-million program includes 16 partners working on a variety of disparate projects. As described in the session, these projects range from telemedicine to inpatient glucose control to the ambulatory artificial pancreas.

APPLYING THE IEEE 11073 DEVICE STANDARDS TO RESEARCH PROJECTS

Malcolm Clarke, PhD (Brunel University, Uxbridge, UK)

Dr. Malcolm Clarke discussed the Reaction project's important efforts to apply IEEE 11073 device standards to diabetes. Notably, the project has built an interoperable system that works across several domains, uses universal standards, is inexpensive, and simple to use. It supports protocols such as USB, Bluetooth Low Energy, Bluetooth, 2.4 GHz, and others. The researchers took commercial devices (blood glucose meters, insulin pumps, CGMs, blood pressure monitors, weight scales, etc.) and added new wireless boards to make them compliant with the universal standards. The devices all communicate with a simple to use home gateway, which plugs into a wall outlet. Data then goes to clinician and patient portals. Notably, the project is working on bringing pump and CGM manufacturers together to adopt single communication standards – in the past, Dr. Clarke noted that it sometimes takes two years (!) to sign an NDA and get access to a pump manufacturer's communication standards. Wow. We had no idea things were as slow as this. We're very excited to hear about these efforts, however, since they have potential to really help patients (integrating their devices, making downloading less of a hassle) and providers (more complete, integrated data gives a more holistic picture of patient's control and glycemic influences; ideally, that would translate into easier therapy changes).

REACTION ALGORITHM AS AN IMPROVED PROTOCOL FOR IN-HOSPITAL MANAGEMENT OF TYPE 2 DIABETES

Thomas Pieber, MD (University Hospital of Graz, Graz, Austria)

Dr. Thomas Pieber described his group's pilot study of a paper-based insulin-dosing protocol for managing blood glucose in the hospital (n=37). As seen when similar algorithms have been introduced elsewhere (e.g., Umpierrez et al., 2013), Dr. Pieber's REACTION protocol led to better glycemic control and was generally well-received by nurses. The next step is to transition the paper protocol to a "tablet-based workflow support system." He noted that such a system could facilitate data storage and visualization, integrate with electronic medical records, and prevent errors associated with manual data entry.

DEVELOPMENT AND APPLICATION OF A PHYSIOLOGY-BASED PREDICTION MODEL FOR CLOSED LOOP GLYCAEMIC CONTROL

Stephan Schaller (RWTH Aachen University, Aachen, Germany)

With an eye toward closed-loop control, Mr. Stephan Schaller described an unconventional strategy to modeling insulin and glucose interactions. The traditional approach in closed-loop glucose control has been to start with simplified models based on a few bodily compartments – and then to build that model up over time, as necessary to improve system performance. By contrast, Mr. Schaller and Bayer's Systems Biology group are using physiological models that include the entire body in granular detail – the approach that has been used for decades by drug companies in pharmacokinetics research. These researchers' current model is individualized based on 8 time-invariant parameters, and it has been refined based on clinical data from bihormonal closed-loop research (el-Khatib et al., Sci Transl Med *2010). The team recently began validating the model in prospective feasibility studies, where they have already learned some key lessons (e.g., the model requires more than 300 minutes of observational data before it can make accurate predictions). Mr. Schaller said that he and his colleagues have adjusted the model based on this first round of tests; he is "looking forward to next week" when the research will resume.*

Oral Presentations

UTILIZATION OF SELF-GATHERED PATIENT DATA IN A MOBILE-PHONE-BASED FEEDBACK SYSTEM FOR PATIENTS WITH TYPE 1 DIABETES

Stein Skrøvseth, PhD (University Hospital of North Norway, Trømso, Norway

The Few Touch Application (FTA) is a data-driven feedback system for people with type 1 diabetes, designed to increase their awareness and motivation. The system provides three data analysis and feedback tools: periodicity, trends, and situation matching. The idea is to help patients learn from the past and make better quality decisions moving forward. However, the application doesn't give any explicit advice.

- **The Few Touch Application (FTA) is a data-driven feedback system for people with type 1 diabetes, designed to increase their awareness and motivation.** It's a mobile application, running on an Android phone (formerly Windows Mobile) that stores diabetes data and uses various data analysis techniques to drive insight and awareness. However, the application doesn't give any explicit advice.
- **The system provides three data analysis and feedback tools: periodicity, trends, and situation matching.** There are daily and weekly patterns of blood glucose for nearly all patients. They can be displayed to reveal things like regular lows at dinnertime, or regular highs on Friday and Sunday evenings. The application also uncovers blood glucose trends that are going on and multiple simultaneous trends can be displayed. Finally, the system uses case-based reasoning to perform situation matching. When deciding how much insulin to administer, patients can get a list of similar situations and how they worked previously. The idea is to help them learn from the past and make better quality decisions moving forward. This isn't a bolus calculator though, just a replay of prior data.

Questions and Answers

Q: How patient intensive is it?

A: The blood glucose data is collected automatically, but patients have to register insulin, carbs, and physical activity by entering them manually.

Q: How secure is it?

A: We don't have any security beyond the users locking their phones.

EFFECT OF GLUCOSE MONITORING WITH SMARTPHONE INTEGRATION ON METABOLIC CONTROL AND COMPLIANCE IN TYPE 1 DIABETES (INEW TREND): STUDY DESIGN

Valentino Cherubini, MD (Universitia Politecnica delle Marche, Ancona, Italy)

Adolescents and young adults with type 1 diabetes often test their blood sugar less frequently and have higher A1c levels than older patients, but Dr. Valentino Cherubini believes that telemedicine interventions can encourage compliance and improve outcomes. With this in mind he described the design of the iNew Trend Study, which will compare the use of Sanofi's iPhone-integrated iBGStar to self-monitoring of blood glucose (SMBG) with a traditional meter. The trial will enroll type 1 diabetes patients aged 14-to-24 who have A1c above 8.0% and "poor compliance with SMBG." The primary endpoint is whether the iBGStar is superior at promoting six-month A1c reduction – quite an ambitious target in our view but one that will clearly be great from a cost-effectiveness perspective if it can be shown. The co-primary endpoint is whether the iBGStar can increase the percentage of patients who perform at least 30% of recommended SMBG tests during the same six-month period.

Questions and Answers

Q: Do you have an estimate as to how much additional healthcare professional time this will involve?

A: We will check for that.

REMOTE PATIENT REPORTING AND AUTOMATED MOBILE TELEPHONE FEEDBACK REDUCE HBA1C AND WEIGHT IN INDIVIDUALS WITH TYPE 2 DIABETES: RESULTS OF PILOT RESEACH

William Fisher, PhD (University of Western Ontario, Ontario, Canada)

Since patients see healthcare providers so infrequently, a better job needs to be done assisting with diabetes self-management. Any automated system has to incorporate well-researched motivational and behavior management. The Sipoo Finland study implemented a system for reporting and immediate feedback via a mobile phone. The feedback was either motivational or coaching (behavioral). After nine months, A1c and weight had improved from baseline in the intervention group.

- **We have to help patients do a better job of diabetes self-management and provide better access to healthcare professionals in a cost-effective way.** But it's difficult in today's world. In 28 studies of mobile communication devices in diabetes focused only on type 1 diabetes, most actually increased physician time.
- **Success requires well researched motivational and behavior management.** The Information Motivation Behavioral Skills Model suggests that patients need to: 1) be informed with correct data to get right outcomes; 2) find the motivation to act on what they know are the critical aspects; and 3) possess the behavioral skills to get the result.
- **People with diabetes "jump through flaming hoops on a daily basis." They perform a complex series of often novel behaviors that they have to do consistently over time.**

- **The Sipoo Finland study investigated remote reporting and feedback and found that the provision of immediate information, coaching and motivation improved A1c and weight from baseline.** The study comprised n=48 people with type 2 diabetes aged 30-70 who were randomized to remote reporting and feedback versus usual care. Blood pressure and weight were measured weekly, activity was tracked with a pedometer, and paired SMBG was recorded three times a week. Participants were given rich automated feedback using a mobile phone based system. This feedback could be a motivational message or specific coaching. After nine months, A1c had reduced in the intervention group by 0.4% and weight was down 1.7 kg (~3.7 lbs) from baseline.

International Fair of New Technologies in Diabetes

XERIS PHARMACEUTICALS, INC: STABILIZED LIQUID GLUCAGON FOR TREATMENT OF HYPOGLYCEMIA

Brett Newswanger (Xeris Pharmaceuticals, Austin TX)

Mr. Brett Newswanger of Xeris Pharmaceuticals gave a snapshot overview of the company's efforts to make a stabilized liquid glucagon. Near the end of his presentation, Mr. Newswanger also divulged Xeris' plans to develop an ultra-rapid-acting insulin and an insulin/pramlintide coformulation. He shared new and promising real-time six-month stability data on the company's glucagon formulation at five degrees Celsius (no degradation at six months), 25 degrees Celsius (2% degradation), and 40 degrees Celsius (20% degradation). These data translate to an estimated two-year stability at 25 degrees Celsius. Interestingly, Xeris' formulation has also shown potential for enhanced pharmacology in preclinical studies – compared to Lilly's glucagon, Xeris' formulation has shown a greater Cmax, a faster Tmax, and comparable bioavailability at half the dose. Said Mr. Newswanger, "The FDA always loves when smaller amounts of a drug have similar efficacy." Xeris is developing its stabilized glucagon for use in an emergency pen for severe hypoglycemia (G-Pen), a mini-dose pen for mild/moderate hypoglycemia (G-Pen Mini), and a formulation for a bi-hormonal pump (G-Pump). The presentation's final slide noted that FDA approval of the G-Pen could come by 2015 [505(b)(2) pathway], approval of the G-Pen Mini by 2016 [505(b)(2) pathway], and approval of the G-Pump by 2017-2018 (IDE) – the 2015 timing on the G-Pen is one year behind the best-case scenario timeline given at DTM 2012 last fall. At that time, Xeris had planned to start a phase 2 clinical trial in 1Q13 under PI Dr. Ralph DeFronzo – it sounded like this had not started yet. We are cautiously optimistic about Xeris' glucagon approach, though look forward to seeing the clinical data to confirm our early take. Our confidence is certainly bolstered by the list of KOLs working with the company: Drs. Ralph DeFronzo, Ed Damiano, Steven Russell, and Ken Ward.

- **In new news, Xeris is planning to apply its technology to develop an ultra-rapid-acting insulin and an insulin/pramlintide coformulation.** The early glucagon results suggest a potentially enhanced physiological response and greater bioavailability, and Xeris is hoping these benefits will transfer over to create an insulin formulation in its preferred, monomeric state. Regarding the insulin/pramlintide coformulation, the product would not be water based. The idea is to set the pH of the two different APIs, and maintain the pH in the co-formulated product.
- **Xeris is mixing glucagon powder with an FDA approved, biocompatible, non-aqueous solvents (e.g., DSMO).** Notably, it allows for an 80% volume reduction, meaning 1

ml of normal liquid glucagon is just 0.2 ml of Xeris' glucagon. As we understand it, the FDA-approved diluent is fairly commonly used and approved at volumes ~200 times greater than what Xeris is using. It's also approved for chronic use, whereas the rescue indication would involve acute use. This seems encouraging from a regulatory perspective, though it's always tough to accurately gauge FDA's view.. The company has three products in development:

  - **The G-Pen is intended for severe hypoglycemia.** Mr. Newswanger characterized it as an EpiPen for diabetics, as users will simply need to remove the cap and inject it subcutaneously. He held up the pen, which indeed looked identical to the EpiPen. Xeris surveyed 500 diabetes patients at UCSD to get a sense of interest in the G-Pen. Over 80% of patients said they want a product that's portable and does not require refrigeration, and 93% were definitely likely to purchase over the existing Lilly or Novo Nordisk kit.
  - **Xeris is leveraging the same glucagon formulation for the G-Pen Mini, a multiuse, titratable pen for mild/moderate hypoglycemia**. Patients will be able to change the size of the dose based on their body weight and blood glucose levels. Mr. Newswanger held it up, and it looked very similar to a standard insulin pens. Xeris believes it is a "strong market opportunity" and clinicians are "really excited" about it, especially for adolescents. The company is working with Dr. Morey Haymond (Baylor College of Medicine, Houston, TX), who will lead the Phase 1 mini-dose-ranging clinical study.
  - **In work with Dr. Ed Damiano, early preclinical studies of Xeris' glucagon for a bi-hormonal pump are "very promising."** Mr. Newswanger showed PK/PD data from a diabetic pig model. The pigs were on basal insulin and given a bolus of insulin at time zero. A graph showed glucagon doses boosting blood sugar levels quite quickly; a second dose again raised sugar levels, but with greater effect. The results came after glucagon had been incubated in the pump chamber for seven days (in excess of minimum pump requirements, since sets are changed every three days).

- **The company has raised about $5 million in non-dilutive grant funding in addition to equity and convertible note funding.** Xeris plans to partner with large pharma, but is considering taking its glucagon through NDA before doing a licensing deal.
- **Mr. Newswanger briefly addressed other glucagon competition (Biodel, Arecor, Latitude, PhySci), noting some of their key limitations**: all are aqueous based formulations, however, none have shown stability similar to Xeris' glucagon, and none are offering both mini dose and pump delivery. Said Mr. Newswanger, "We're ahead of the game" and our formulation is "a gamechanger."

Questions and Answers

Q: How much will you charge for the G-Pen?

A: Probably a slight premium to the current products, but it will be very close. We are evaluating this and will likely work with our commercial partner to determine optimal pricing and patient access.

Q: Do you need more funding?

A: Right now, we're funded through a phase 2 G-Pen clinical study and phase 1 mini-dose and pumped glucagon studies. We are considering taking the G-Pen through NDA, but we definitely want to partner with larger pharma for sales and marketing.

Corporate Symposium: AGP (Ambulatory Glucose Profile): The Diabetes ECG? (Sponsored by Abbott Diabetes Care)

AGP ORIGINS AND DEVELOPMENT

Roger Mazze, PhD (International Diabetes Center at Park Nicollet, Minneapolis, MN)

Dr. Roger Mazze proposed that in the evolution of both SMBG and CGM, the "what" has come before the "why" – in other words, glucose monitoring technology has developed faster than clinicians and patients fully understand how to use all the new data that can be generated. He argued that this uncertainty has constrained uptake of both SMBG and CGM, and he outlined some of the "why" factors for CGM in particular. Notably, CGM devices collect data for 24 hours rather than only when someone is awake and at the precise moments they choose to test. However, the patterns identified by CGM can vary from day to day, suggesting the need for a long-term summary report that can be readily interpreted around the world – just as electrocardiograms (ECGs) are universal regardless of nation or manufacturer. To address this need, Dr. Mazze and his colleagues adapted a graphic called the ambulatory glucose profile (AGP), which they had originally developed in the 1980s to summarize SMBG data. The AGP was described in detail in Dr. Bergenstal's talk during the same session, but Dr. Mazze made a few brief points about the metric. He noted that the AGP "gold standard" report uses 30 days of data at a time, since the pattern may not be consistent from one week to the next (though 14-day periods are also quite good, as they can be used to predict 30-day results with 95% certainty). Also, Dr. Mazze reviewed a month-long study of 32 normoglycemic individuals, showing that their AGPs are flat. (He smiled that though the AGP is like an ECG in many respects, a flat AGP is desirable – quite the opposite of a flat ECG).

AGP TODAY: DETAILS OF THE COMMON REPORT

Richard Bergenstal, MD (International Diabetes Center at Park Nicollet, Minneapolis, MN)

In a valuable and wide-ranging talk, Dr. Richard Bergenstal discussed CGM's low uptake thus far and pointed out his view that this is due to, in addition other patient-specific factors, to the hurdles of incorporating CGM data into clinical practice – e.g., non-standardized data collection, non-standardized data visualization, and difficulties uploading data to electronic medical records. To address these issues, in March 2012 he led a panel of experts in discussing what should be contained in a standardized CGM "title page." (The panel's final report will be published on March 1, 2013 concurrently in Diabetes Technology and Therapeutics *and the* Journal of Diabetes Science and Technology*; for our coverage of the meeting at the time, see https://closeconcerns.box.com/s/a4a4b3baccd6915ab731). As a reminder, the central graphic is the AGP itself – a 24-hour image with five non-intersecting lines (median, 25th and 75th percentiles, and 10th and 90th percentiles) to summarize 14 days' worth of data. Also included in the first page are several numerical statistics on time in- and outside of range, variability, etc., as well as thumbnail images of each individual day (arranged in a calendar format for comparison by day of week). Dr. Bergenstal and his colleagues are developing a software, capturAGP, that could be included in any (and ideally every) CGM manufacturer's software; they have also linked capturAGP to the Park Nicollet electronic medical records system as a proof of concept for wider EMR integration. Having watched Dr. Bergenstal's presentations on AGP last March and again at November's Second Global Diabetes Summit (https://closeconcerns.box.com/s/i18xxkrfdtldafh2r2uz), we were excited to see Abbott Diabetes Care show support for the idea. (Unsurprisingly, since*

companies typically do not give commentary at corporate symposia, we did not hear any comments from the company per se, beyond their sponsorship of the symposium.)

THE NEXT LEVEL OF AGP: INTERPRETING CGM

Howard Wolpert, MD (Joslin Diabetes Center, Boston, MA)

Renowned clinician Dr. Howard Wolpert looked toward the future of AGP – both how the current system could be used in clinical practice, and how he hopes that the software will evolve. He emphasized that a big benefit of AGP will be to identify "glycemic trouble spots" so that clinicians and patients can make focused, informed decisions about adjusting treatment and modifying behavior. For example, if at a particular time of day a patient tends to have a great deal of variability that extends into the hypoglycemic range, they probably should not increase their insulin dose even if their median glucose is high. Dr. Wolpert believes that AGP can also be useful in matching insulin dosage with postprandial hyperglycemic excursions, the timing of which can vary based on the macronutrient content of the meal (e.g., sharper excursion for high-glycemic-index carbohydrates, slower excursion for fatty foods). Another key concern in managing postprandial hyperglycemia is not to over-treat, which Dr. Wolpert said is especially a concern for patients using CGM, since glucose reductions in the subcutaneous fluid have been shown to lag behind those in arterial blood. In the panel discussion that followed, Dr. Wolpert and his fellow presenters shared their hopes that future versions of the AGP would expand beyond retrospective analysis to give patients real-time, prospective, personalized decision support; such software would ideally make use of non-glycemic data such as insulin dose. The Q&A that followed was most valuable and we'll be including this in our full ATTD report to follow in March!

Corporate Symposium: SMBG T2D Advisor (Sponsored by Bayer)

DIABETES SOFTWARE FOR DOWNLOADING: PRACTICAL ADVICE FOR THE CLINICIAN

Irl Hirsch, MD (University of Washington, Seattle, WA)

Dr. Irl Hirsch reminded the audience that manual logging was the only option for urine-glucose data and in the early days of SMBG, but these handwritten records were cast into doubt when compared to automatically recorded data (Hoskins et al., Diabetes Care *1988). Today automatic downloading is the standard (at least among brand-name devices), and in some cases it is necessary (e.g., for patients that want more strips than are typically reimbursed). He observed that glycemic data downloads are especially useful when they include information on insulin dosage, as occurs automatically for patients using Medtronic sensor-augmented pumps. On that note, Dr. Hirsch said that he would like MDI patients in the US to have more options for automatic logging of insulin data (e.g., insulin pens with memory functions). He also noted just how time-consuming the download process can be (Budica et al., Diabetes 2012; 61 (suppl 1): A130), and he made a general call for better automatic-download systems, perhaps ones using smart phones and cloud-based data storage. His hope – as he poetically put it – is that "the flow of information is facile and no one is bothered by painfully slow technology."*

Questions and Answers

Dr. David Harlan (University of Massachusetts, Worcester, MA): I do not have a financial stake in this but wanted to say that we have developed a system that can upload 45 meters, and we have integrated it with AllScripts. We never have to print any download; it goes directly into electronic medical records.

A: You are ahead of the curve.

Dr. Satish Garg (University of Colorado Denver, Aurora, CO): That is amazing. Can such technology be integrated with other centers?

Dr. Harlan: you should accept my invitation to come and visit.

Q: I am from Mendor, a Finnish company developing a cloud-based system like the one you describe. Has there been study of the factors that motivate some patients to upload data and others not to do so?

A: Everyone is motivated differently; people have wondered about why some patients are more motivated than others since the discovery of insulin. Frequently severe hypoglycemia and unawareness motivates adults more than it does 15-year-olds.

Dr. Jane Seley (New York Presbyterian-Weill Cornell Medical Center, New York, NY): Ideally in the near future at my center, patients will be able to register their meters in a way that allows downloading as soon as they walk in the center. I would want to have the data in front of me already when patients come in, so that I can look face-to-face at the patient rather than stare at a computer during the actual visit.

EXPERIENCES OF SMBG ADVISORS IN TYPE 2 DIABETES

Sylvia Franc, MD (Sud-Francilien Hospital, Corbeil-Essonnes, France)

In this overview of advising software in type 2 diabetes, Dr. Franc defined four "levels" of technology. The first level consists of systems to facilitate data uploading and display (e.g., iBGStar, Glooko); these allow transmission of data to healthcare providers but do not provide immediate advice to patients. The second level includes bolus calculators (e.g., Accu-Chek Aviva Expert, FreeStyle InsuLinx); these give direct auto-regulatory feedback to patients but do not transmit frequent feedback to healthcare providers. At the third level are systems like WellDoc's DiabetesManager that have two "loops" of feedback – real-time coaching for patients and real-time data availability to healthcare providers. Such systems have been shown powerful (Quinn et al., Diabetes Care 2011), but Dr. Franc noted that they offer no explicit advice to patients about treatment adjustment. Thus at the highest level are systems designed for decision support and treatment adjustment. In this vein Dr. Franc mentioned Hygieia's DIGS decision support software (Bergenstal et al., Diab Technol Ther 2012). She also noted that she and her colleagues are studying one system for patients using oral medications and/or basal insulin (the Telediab 2 study in partnership with Novo Nordisk; results potentially presented at ATTD 2014) and another, Diabeo, for titration of basal/bolus therapy (the Telesage study in partnership with Sanofi). All in all Dr. Franc is quite optimistic about the role of data management systems for type 2 diabetes: "far from keeping the caregiver and patient apart," she concluded, "new technology in fact brings them closer together."

Efficient Solutions for Challenging Cases in Diabetes Management (Sponsored by Medtronic)

CARELINK PRO 3

Ohad Cohen, MD (Sheba Medical Center, Tel Hashomer City, Israel)

Perennial ATTD presenter Dr. Ohad Cohen provided an overview of Medtronic's CareLink Pro 3 software. Though he spoke on Day #1 of last year's ATTD in a workshop on the very same topic, this year's presentation differed in that it was entirely based on case studies. He emphasized that Medtronic's CareLink Pro 3 is a fully integrated system incorporating insulin pump data, CGM data, and blood glucose meter data into one package – for Dr. Cohen, synergistic combination makes problem identification and data interpretation much easier. He also pointed out that patients' use of technology is not enough – providers must go beyond that and integrate all the data into a feedback loop. We thought his talk could have done a better job of showcasing CareLink Pro's very powerful data analysis capabilities. Dr. Cohen did not once refer to what we think are two of the best features of the software program: hyper- and hypoglycemia pattern recognition and the episode summary. Happily, attendees were given an excellent booklet, "CareLink Pro 3: The Practical Guide," although unfortunately, this was not used during the workshop.

- **We were impressed with the succinct and informative CareLink Pro 3 Practical Guide provided to attendees.** The 27-page guide has four main sections: setting up CareLink, patient behavior, therapy outcomes (identify issues and determine the cause), and optimizing therapy (define an action plan). It was developed in cooperation with a board of HCPs experienced in using CareLink. We think it does a good job of showcasing how CareLink Pro 3 can help HCPs optimize pump therapy – it really holds the reader's hand and demonstrates how to systematically interpret a download report. It does a good job of including pictures and examples (e.g., "hypoglycemia caused by incorrect nocturnal basal rate" or "wide glucose swings when not using the BolusWizard for correction"), as well as what to do once a problem is identified,
- **Case #1: Use of technology without downloads.** In this case, a 73-year-old with type 2 diabetes was using a non-Medtronic pump, so CareLink could only obtain his blood glucose meter data. The patient was complaining of hypoglycemia, but without the pump data, it was impossible to determine the cause. After getting him on a Medtronic pump, the pump data on CareLink revealed that he had tripled his basal rate, which had preceded the hypoglycemia. Dr. Cohen emphasized that even in "simple cases of type 2 diabetes," data downloading is very important.
- **Case #2: Use of poorly integrated downloads.** This 33 year-old type 1 patient had an A1c of 7.2%, but a high level of glycemic variability (196 ± 80 mg/dl). Similar to the last case, he was using a non-Medtronic pump, so only blood glucose downloads could be loaded into CareLink. After switching him to a Paradigm Veo, the integrated blood glucose meter and pump data revealed a very high level of adherence (11 SMBGs and six boluses per day on average. Despite what seemed like a very motivated patient, Dr. Cohen revealed (using the day-by-day summary) that the patient was inputting made up blood glucose numbers into the wizard. Besides the fact that these were not "linked" blood glucose values, this behavior was not very evident to us from the CareLink report.
- **Case #3: Use of integrated downloads with inertia to change.** In this case, a 27-year old with type 1 diabetes had an A1c of 9.2% and fear of hypoglycemia. The recommendations were clear – a she was going high after meals (presumably not counting all her carbs) and needed a nocturnal increase in her basal rate. A report three months later showed very little difference, and Dr. Cohen cited clinical inertia as the main problem ("If you're not intervening with the patient…all the technology does not make a difference").
- **Cases #4-5: Integrated system for patients' glycemic control.** Both of these cases involved pregnancy. IN the first case, the patient was had gained weight in the prior weeks. That fact, combined with her high after-meal highs, suggested she was eating too much. In the second

case, the patient was going high after meals – the culprit was late prandial bolusing, revealed on the daily detail reports.

8. Exhibit Hall Report

- **Abbott**: Bright yellow arches adorned with orange butterflies drew the boundary of Abbott's exhibit hall booth, and one couldn't help but envision a sunny Sunday afternoon. Complementing the butterflies above, vases of orange and yellow flowers stood topped four white stands beneath the arches. Each stand displayed one of Abbott's blood glucose meter offerings (FreeStyle InsuLinx, FreeStyle Precision, FreeStyle Freedom Lite, and FreeStyle Lite). While no sales representative manned the booth when we made our visit, Abbott's exhibit seemed to have three focuses. Large digital displays drew attention to the FreeStyle Navigator II continuous glucose monitor, about which we've heard a lot of good things, Ambulatory Glucose Profile (AGP) analysis system, and FreeStyle InsuLinx insulin bolus calculator.
    - **FreeStyle Navigator II**: Abbott's display emphasized the "security" provided by the early-warning alarm system of the Navigator II and its small transmitter with extended range (30 meters, according to the display). The Navigator II receiver looked quite sleek in silver and black and bore a rough resemblance in form to a blackberry phone (though this was difficult to discern from a picture-only display). It was exciting to see the CGM front and center at the booth after its low-key launch just prior to the European Association for the Study of Diabetes (EASD) conference and notable absence from the EASD booth. We wonder, of course, whether Abbott has any intentions to pursue FDA clearance – the company already has a third-generation CGM slated for EU entrance by year-end 2014. For background, the company's pivotal trial of the Navigator II showed 97.7% of readings in the Clark Error Grid A- and B-Zones (83% and 14.7%, respectively). For more details on the study, please see our Abbott 3Q12 report at https://closeconcerns.box.com/s/o2qyq8d5inpnpm6ss72l.
    - **AGP**: Abbott positioned AGP as the diabetes ECG and the means to which data could become actionable. Abbott's corporate symposium on the topic dives into this topic in greater detail (see above).
    - **FreeStyle InsuLinx**: Abbott advertised that the meter's dose calculator could help alleviate the challenges associated with manual insulin dose calculations ("In a study, 63% of insulin calculations done manually were incorrect," read the sign. "With FreeStyle InsuLinx there were 10x fewer errors.") As a reminder, the built-in bolus calculator is only available in the EU and no timeline or intention for FDA submission has been disclosed. We suspect that the FDA harbors concern for dose calculators that depend on patients correctly inputting their insulin data; though, there are certainly patients who could benefit from this feature.
- **Animas**: "Hello. We're Animas," read the blue sign at the top of the company's exhibit booth. "Meet CGM-enabled Animas Vibe." The display's blue, green, and white color scheme inspired an aquatic feel that spoke to the waterproof quality of the Vibe – two pumps were submerged completely in vertical water cylinders. The sales representative present explained that this characteristic is especially good for small children or those times when you sit down on the toilet

and your pump falls out. The representative explained that the high-contrast color screen, intuitive design, and CGM were patients' three favorite features of system. Interestingly, she explained that where CGM reimbursement is poor or lacking (she pointed to Germany as an example), the company will market the Vibe for its pump-specific benefits, as many patients may not be willing to pay out-of-pocket for the CGM. Indeed, during Dr. Joroen Hermanides' afternoon talk, he showed just how challenging the CGM reimbursement environment in Europe is (see above).

- **CeQur:** The CeQur booth was small in size but grand in excitement, as many visitors (including us!) got their first hands-on experience with the company's PaQ insulin delivery device for people with type 2 diabetes, which received CE Mark in November 2012 (see our report at https://closeconcerns.box.com/s/qktpdznx4v5rw6tss896). The booth's handouts included two ATTD abstracts about PaQ, one of which highlights patient satisfaction scores from CeQur's feasibility study. (Of 20 patients with type 2 diabetes in the six-week trial, 83% were "very satisfied" and 17% were "satisfied" with PaQ). Additional data from the study, including glycemic efficacy and patient-reported outcomes, will be presented at ATTD 2013. Meanwhile management continues to raise Series B funding, scale up manufacturing in anticipation of a "focused" European launch in 2013 or 2014, and prepare a 510(k) submission for US regulatory clearance. The company is targeting a large-scale launch for 2015, when it would debut a new version of the PaQ (optimized for large-scale manufacturability). As for pricing, we understand that CeQur intends the PaQ to be competitive with pens and cheaper than traditional pumps. Management mentioned that they are closely watching Valeritas, whose already-marketed V-Go delivery device is PaQ's most similar competitor. (Notable differences include the V-Go's one-day wear time vs. PaQ's three days, as well as the absence of electronics in the V-Go). Management would not comment on partnership talks but said that they remain "fully prepared to go solo."
    - **As a reminder, the PaQ (pronounced "pack") holds a reservoir of 330 usable units and is designed for three days of use.** It will be available in seven different versions, each with a different pre-set basal rate (16, 20, 24, 32, 40, 50, or 60 units per day); every version will also allow bolus dosing with the push of a button. The round, white device is roughly the length and width of a business card and roughly the thickness of a smartphone (we left our tape measurer stateside!). It has two components that fit together along an S-shaped intersection. The bigger, disposable piece contains the reservoir (an elastomeric bladder), the cannula, a window to indicate visually whether the cannula has successfully been inserted, and a button for bolus dosage. A smaller, reusable part sits atop the disposable piece. This reusable part contains the PaQ's only electronics and features a button that patients can press for an audible indication of how much longer their insulin supply will last. (A "happy tone" plays for the first 48 hours of reservoir use; one vibration indicates that between six and 24 hours are left; three vibrations occur during the last six hours; four vibrations indicate an empty reservoir.) The battery for this electronic messenger lasts roughly six-to-12 months.
    - **Only one button must be pressed to deliver insulin; to prevent unintentional dosing this button is indented into the curvature on the lower side of the PaQ and counterweighted so that a firm press is needed.** The button's click is barely audible, but CeQur's engineers designed the button to give very clear tactile feedback when a bolus is delivered.
    - **We learned that CeQur's name is an acronym:** the Ce stands for CE Mark (gained in November), the Q stands for quality, and the ur stands for "user requirements"

(specifically, the user requirements for a simplified insulin delivery device in type 2 diabetes). CeQur lists these user requirements as follows: simple, effective, comfortable & discreet, freedom from daily injections.

- **The CeQur booth featured pictures of three elderly, heavy people, each smiling and holding PaQ –** real patients from the device's feasibility study who were also featured in a video that played continuously on a TV screen. Though this is only a superficial indication, we certainly liked that the company featured the images and experiences of real people with diabetes rather than models or actors. The booth was mostly white, with CeQur written in dark blue, PaQ written in violet, and a column of text that consisted of the word "freedom" written in multiple different languages. Blue, purple, and white M&Ms were available for booth visitors seeking glycemic excursions, and most excitingly – as noted above – the PaQ and its user guide were on hand for close inspection.

- **Debiotech:** In a prominently located booth as large as any in the exhibit hall, Debiotech reps showcased their company's Jewel patch pump. The specifications of the 500-unit semi-disposable device and its accompanying handheld, a custom-designed Android smartphone with an integrated blood glucose meter, remain largely unchanged – and still quite impressive – since our EASD 2012 exhibit hall report (see https://closeconcerns.box.com/s/eu7m3zn7sdg7lm8qkrgx). However, we did hear some updates on the company's business plan. Debiotech's main goals are to gain CE mark and 510(k) clearance and to license the Jewel Pump to a large partner that could bring the technology to market. (No timelines for these events have been announced externally.) The license agreement would also include access to the closed-loop algorithm developed by Debiotech and studied by a consortium of seven French endocrinologists using the Jewel pump and a Dexcom CGM sensor. (We understand that data from these "Diabeloop" experiments will be published soon.) Buzz also surrounded a recently completed study with 35 patients; the company has characterized the results as successful but is waiting to release results (we hope at ADA or sooner).

  - **Debiotech recently finished lining up all the partners necessary to manufacture Jewel pumps on a large scale.** In the week prior to ATTD, Debiotech announced that its fellow Switzerland-based company Valtronic will manufacture the electronics in the patch pump's controller unit, which is designed to last for roughly two years. Longtime partner ST Microelectronics will provide the microfluidics for the pump's disposable unit. Other confirmed partners include companies that will make the disposable unit's cannula, produce the phone's glucose meter and its strips, and create the "Jewel Card" that is placed in each phone to enable secure communication with a single unique patch pump. Management noted that as part of the clearance and regulatory process before they ultimately out-license the Jewel Pump, they will perform clinical studies in France and the US.

- **Dexcom:** From across the exhibit hall, we couldn't miss the four young children gracing a billboard on the back of Dexcom's booth – the sparkling, and quite compelling (lots of people stopped to say so including typically hard-to-impress US diabetes advocates) new ad announced the very recent CE Mark of the G4 Platinum in children as young as two years old (previously, it was ≥18 years). A brochure displayed the clinical accuracy results comparing the G4 Platinum accuracy in adults and pediatrics; results were largely similar, with an overall MARD (40-400 mg/dl) of 13% in adults, rising slightly to 15% in pediatrics. Hypoglycemia accuracy (MARD 40-80 mg/dl) was also a tad better in adults at 19%, compared to 23% for pediatrics. A-Zone accuracy

reflected these small differences (80% in adults, 76% in pediatrics). Sensor life was the most noticeable metric that declined in pediatrics, with 81% of sensors lasting up to seven days vs. 94% in adults. We think many factors make pediatrics a tougher population for sensor accuracy, so these fairly comparable results are a testament to the G4 Platinum's strong innovation. A brochure noted that the G4 Platinum is only approved for use on the abdomen in adults, while pediatrics can use the abdomen or the upper buttocks. As a reminder, Dexcom has submitted the PMA supplement to the FDA for a pediatric indication, and approval is expected in 2H13. Elsewhere in the booth, a concise eight-page handout succinctly summarized Dexcom's new Studio software, with the tagline, "Help take the guesswork out of glucose pattern management." Arrows and directions in the handout did a good job of highlighting what different things mean and how to interpret them, especially the new pattern recognition feature on the Portrait report. On the international front, a sign in the back of the booth displayed Dexcom's geographic spread – we certainly took note of "Coming Soon" captions for India, Saudi Arabia, Canada, and Slovenia. On our way out, we were surprised not to see any signage for the Animas Vibe; according to the representative we talked to, this is Animas' product, so Dexcom is only supplying sensors.

- **Diasend:** In its ongoing quest to create a total system for diabetes management, Diasend had good news to report and is expecting more on the way. As a reminder, the company's products include a multi-cabled box for downloading of multiple different devices in diabetes clinics, as well as a web-based software for patients to transmit data from home. We were told that the latest list of compatible devices, which includes dozens of glucose meters and most pumps besides Medtronic's, now includes the two newest CGM systems – Abbott's FreeStyle Navigator II and Dexcom's G4 – as well as the "intelligent" insulin pen Pendiq. (A Diasend rep lamented that, despite the clinical demand, insulin pens with memory do not seem to be a big development priority among the major insulin manufacturers – we share this lament.) The company is also expanding its integration into electronic medical records (especially in US clinics) and its overall presence worldwide (roughly 2,000 clinics in 16 countries use Diasend's boxes, all of which can be wirelessly updated whenever the company changes its software or becomes compatible with a new device). Perhaps most excitingly to us, Diasend plans to launch a mobile app later in 2013 – one more step toward a future world where healthcare are stored primarily in the cloud and accessed largely through handheld devices.
- **Medtronic:** Medtronic's spacious booth was one of the biggest headlines in the exhibit hall, showcasing three products we had never before seen in person: an integrated CGM sensor/insulin infusion set, a mobile hub that wirelessly sends pump and sensor data to CareLink and smartphone apps ("Connected Care"), and the recently CE Marked Sentrino critical care CGM. A video playing on the side of the booth also displayed the future improvements for the Enlite sensor (we presume this is the next-gen Enlite referred to in Medtronic's pipeline) and the company's closed-loop research system. Details on each are below.
    - **"The world's first integrated sensor and infusion set":** We saw a poster on Medtronic's Combo-set at ADA 2012 in Berlin, though this was the first time we had ever seen it in person. It incorporates an insulin infusion catheter and a CGM sensor separated by a short distance (i.e., two skin punctures under a single adhesive patch). The set uses a single insertion device that is similar in look and feel to the Enlite inserter. From a top view of the integrated set, it looks like a Mio infusion set fused with the clamshell-shaped Guardian/Enlite transmitter. A video advertised a "small footprint" and "improved comfort, convenience, and patient acceptance." The Medtronic rep showed us the set behind a glass case and let us handle the inserter, despite a small label on the bottom of

the case noting that it is "non CE-marked." According to the rep, the combined set is beginning early trials now.

- **As a reminder from our Medtronic F3Q13 report, the company plans to begin a 50-patient study in March of the integrated sensor and infusion set** (ClinicalTrials.gov Identifier: NCT01775059). Each subject will wear five sets for three days each, and completion is slated for July 2013. While we do think the convenience of an integrated set will be appreciated by many patients, a key challenge in our view is matching disparate lengths of wear – a three-day integrated set would require a CGM sensor with a fast startup and good accuracy for the first 72 hours, an R&D barrier to date (i.e., sensors typically get more accurate over time, with the worst accuracy on day one). Our Medtronic F3Q13 report is at https://closeconcerns.box.com/s/i7sh0gcsdmxfy0zx0srv.

- **"Connected Care"** is a mobile hub that wirelessly and automatically sends insulin pump and sensor data to CareLink Personal and a smartphone app (the booth had an iPhone). The hub itself is a bit larger than a hockey puck, though the rep assured us that it was a prototype and the final commercial product will be smaller. As we understand it, the device's battery is rechargeable and the hub would not have to be plugged into a wall (i.e., it could be carried in a backpack and pump/CGM data would be wirelessly sent to CareLink). We did not confirm whether the device operates on a cellphone or Wi-Fi – based on the symbol on the outside of the device, we assume it sends data over Wi-Fi. The smartphone app itself displayed a standard CGM screen: a large sensor glucose value, a trend arrow, trend graphs (three, six, 12, and 24-hours), and a red bar with details on a hypoglycemia alarm. The system seems to make good use of alerts, as "care partners [are] alerted to glucose highs or lows" on their cell phones. A poster displayed a woman on her cellphone and a caption stating, "Message from CareLink about Gary: LOW SG 65 mg/dl at 13:18 30-July 2012." The device is currently in two early trials in the EU, so it also displayed the "non-CE Marked" label. It was developed in partnership with eDevice (http://www.edevice.com). We're glad to see Medtronic improving on its mySentry system – though that device was certainly an excellent foray into the nascent remote monitoring space, we believe pump/CGM data wirelessly and automatically sent to smartphones is the way of the future (certainly, that's where Dexcom is going with its new Share product and Gen 5).

- **Sentrino critical care CGM:** Freshly CE Marked in December 2012, Medtronic had its new in-hospital CGM on display. We got to play with the device's bedside monitor, and liked the touchscreen interface and color alerts. The screen readability was quite good, though the alarms did not strike us as particularly loud. The rep gave no details beyond those in our initial Closer Look – as a reminder, the Sentrino was launched in the UK and Germany following CE Marking (no reimbursement yet, though Medtronic is pursuing studies). The device incorporates redundant sensing (two novel subcutaneous sensors, not Enlite nor Sof-Sensor), a wired cable, and a bedside monitor. (EHR integration could come down the road, but is not supported in this version.) Medtronic is working with the FDA to support US commercialization, though there is no timeline yet. Patients can wear the Sentrino for up to 72 hours before the sensors need to be replaced. It is accurate within 10-15% of reference glucose and is approved for adjunctive use. The device is calibrated using the hospital's standard of care blood glucose measurement. Warm-up time is 30 minutes (pretty fast!) and a blood glucose calibration is required upon insertion, at one hour, two hours, eight hours, and then every eight hours thereafter. One

hundred patients were studied prior to CE Mark submission, and 50 of them were critically ill patients. We look forward to understanding how hospitals like using the device, whether they feel it improves outcomes, and ultimately, whether it is cost-effective technology. For more on Sentrino, see our report on the CE Mark at https://closeconcerns.box.com/s/34ybjff0bfr6pyid6emi.

- **Next-gen Enlite:** A TV screen played a video cycling through Medtronic's various pipeline initiatives, including improvements in the Enlite sensor. Future Enlite improvements include: 1) an 80% size reduction from the current sensor; 2) a new electrode design; and 3) removed tubing. NO further details were given. In Medtronic's pipeline as of the 2011 Analyst Day, a next-gen Enlite launch was slated for May 2014-April 2016.
- **Closed-Loop Research System:** The same video showcased Medtronic's closed-loop research system, which seems to have one change from the portable glucose control system we've previously seen in conference presentations: what looks like an iPhone controller (the picture seemed to show an iPhone, though the caption vaguely called it a "smartphone"; in the original portable glucose control system we saw at DTM 2011, this was a Blackberry smartphone). As a reminder, the system also includes the MiniMed Veo sensor-augmented pump system, "a translator" (a square one inch by one inch piece of hardware), and a tablet PC for physician monitoring. We've always anticipated that a commercialized closed-loop device from Medtronic would put the algorithm in the pump, alleviating the smartphone and translator.

- **Roche**: The company's exhibit booth touted a pastel pallet of maroon, yellow, blue, and orange. Five standing screen displays, each manned by a sales representative, presented Roche's Accu-Chek products. The DiaPort (intraperitoneal insulin infusion device; available in EU only), Combo (Aviva meter and Spirit insulin pump), Aviva Expert (blood glucose meter with built-in bolus calculator; available in EU only), Accu-Chek Mobile (strip-free glucose meter; available in EU only), and 360° diabetes management system were on display. Roche's "scientific center" was located towards the center of the booth and featured an array of scientific publications, including the results of its Automated Bolus Advisor Control and Usability study (ABACUS), which tested the effect on the Aviva Expert's insulin bolus advisor on glycemic control in patients on MDI. (For previous coverage of the first results from this study, see page 94 of our Diabetes Technology Society Meeting 2012 full report at https://closeconcerns.box.com/s/3b1bj4dx1e7wu8kgrixa.) The Aviva Expert is currently available in eight countries, and according to the sales representative, seven more country launches and FDA submission are slated for this year. From another sales representative we learned that Roche is also in the process of exploring the US regulatory process for its Accu-Chek Mobile System. Meanwhile, Roche is readying for a small April launch of the second-generation DiaPort in Centers of Excellence in France, Germany, Australia, and the UK. One of the biggest improvements of the second-generation, explained the sales representative, is the polyester felt band that surrounds the flower-shaped plate (the piece inserted under the skin). The felt is designed to reduce irritation with the DiaPort by minimizing movement of the plate. (For additional detail on the technical improvements of the second-generation DiaPort, see page 67 of our Diabetes Technology Meeting 2012 full report at https://closeconcerns.box.com/s/3b1bj4dx1e7wu8kgrixa.)
- **Sanofi Diabetes:** Here on its home French soil, Sanofi used the ATTD 2013 exhibit hall to launch a new branding initiative: MyStar Diabetes Care. We understand that the MyStar name will eventually be associated with all of Sanofi's insulin delivery devices (e.g., ClikStar and

SoloStar) and glucose meters (e.g., iBGStar and BGStar), as well as decision-support algorithms and all customer service for diabetes patients. (Given that a chief purpose of the MyStar label is to shore up Sanofi Diabetes' worldwide brand identity, the name "MyStar" will apparently be used even in non-English-speaking countries.) In light of Sanofi's eclectic range of diabetes products, we think that the company is smart to try to unify its image – especially with the friendly-looking MyStar logo (which includes the outline of a 5-pointed star, playfully askew and with a single missing line, which the company says is the open star inviting consumers). The MyStar umbrella will eventually cover the company's entire plethora of region- and nation-specific "patient services and solutions" – from patient education programs, call centers, and digital tools; to a recently launched Italian diabetes management software called MyStar Connect, which can integrate glucose data with lab results, comorbidity data, and other health records. We were told that the MyStar family would welcome a few other notable additions in 2013, but we were left to wonder about the specifics. Sanofi also presented some of its collaborations with diabetes societies and academia, such as the E-Diabetes telemedicine training project for 1,000 physicians in 18 African countries, and the basal-bolus titration software Diabeo, which is being studied with some success in 700 type 1 and type 2 diabetes patients in France (Charpentier et al., Diabetes Care 2011).

- **Ypsomed:** Ypsomed's small booth had a clear focus on the second-generation mylife OmniPod and the compact mylife Unio blood glucose meter. The little pod was getting rave reviews from management and a promotional video emphasized both products' simplicity, discretion, and design with taglines such as "making diabetes a smaller part of life," "simple to use when out and about," "simple and private," and many others. We also saw Ypsomed's ServoPen on display, and a rep emphasized that it's a business-to-business (B2B) product for Ypsomed – despite the company's growing number of business-to-consumer products, B2B still represents the majority of the company's revenues. A glass case and demonstration table also showcased mylife Clickfine pen needles and Roto infusion sets.

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