Closer Look

European Association for the Study of Diabetes (EASD) 51st Annual Meeting

September 14-18, 2015; Stockholm, Sweden; Day #2 Highlights - Draft

Executive Highlights

Greetings from beautiful Stockholm, where we bring you coverage from day two of EASD 2015 while snacking on traditional Swedish meatballs (definitely better here than at the IKEA back in Oakland). We loved catching up with old friends and meeting new ones, both during the conference and at "The diaTribe Foundation's Solvable Problems in Diabetes" event tonight - below, we share a few of the many, many highlights below (you have to come live next year to get them all!) Thank you so much again to our sponsors for helping our nascent diaTribe Foundation, especially our largest sponsors who have been extraordinarily committed to our nonprofit - they are AstraZeneca, Abbott Diabetes Care, Intarcia, Novo Nordisk, and Sanofi - we are so proud to know you and to have your incredible help at our Foundation. There are incredibly few resources for patient education and advocacy around - incredibly few! - and it means so much to me personally to have your encouragement and support and help in improving life for people with diabetes and pre-diabetes and advocating for action. All of my work for the foundation (hundreds of hours per year) is gratis as is John's and we give so many thanks to all of you who have supported us as well as to the renowned Helmsley Charitable Trust, without whom diabetes would be far, far less vibrant and smart and able. .

Onward! Throughout the day, we saw ease-of-use human factors data for Locemia's intranasal glucagon powder and full phase 2 results for Isis' novel insulin sensitizer ISIS-PTP1BRx. We also heard the incredibly enlightening Claude Bernard Lecture given by Dr. Hans-Ulrich Haring (University of Tubingen, Germany) on the phenotypes of prediabetes. This is a very prestigious named talk and two of our three panelists this evening - Professors Holman and Ferrannini - said it was their biggest highlight of EASD thus far. In our "free time" (we love working for you), we explored the extravagant exhibit hall - our coverage brings that experience to you. See below for our top five highlights - and an honorable mention - from the day and see our EASD 2015 preview for a look forward at the rest of the meeting in this forward-thinking city (fun fact - Stockholm is one of the most environmentally friendly cities in the world).

1. The diaTribe Foundation's second annual EASD event, "Solvable Problems in Diabetes," featured valuable realism on the many challenges in diabetes care - the lack of preventative thinking, the incredible complexity of the disease - played against a background of optimism for the future of diabetes.

2. A brilliantly designed human factors study provided highly convincing ease-of-use data for Locemia's intranasal glucagon powder for severe hypoglycemia (and conversely, extremely grim usability data for injected glucagon kits).

3. We saw full phase 2 results for Isis' novel insulin sensitizer ISIS-PTP1BRx that looked quite promising.

4. In this EASD's prestigious Claude Bernard Lecture, Dr. Hans-Ulrich Haring (University of Tubingen, Germany) presented on the phenotypes of prediabetes, discussing the roles of brain insulin resistance, fatty liver, fatty pancreas, and genetics.

5. Our report shares exhibit hall coverage of 16 companies, including several unexpected technology findings in new pumps and under-the-radar CGM.

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Exhibit Hall

Abbott
Bayer
Dexcom
Diamesco (POCTech)
J&J/Animas
J&J/LifeScan
Kaleido
Lilly/BI
Lilly
Medtronic
Medtrum
MSD
Novartis
Roche
Sanofi
Ypsomed

Top Five Highlights

1. The diaTribe Foundation's second annual EASD event, "Solvable Problems in Diabetes," featured valuable realism on the many challenges in diabetes care - the lack of preventative thinking, the incredible complexity of the disease - played against a background of optimism for the *future* of diabetes. Moderated by our own Ms. Kelly Close (The diaTribe Foundation, San Francisco, CA), the wide-ranging conversation brought together Dr. James Gavin (Emory University, Atlanta, GA), Prof. Ele Ferrannini (University of Pisa School of Medicine, Pisa, Italy), and Prof. Rury Holman (University of Oxford, UK) to share their thoughts on a host of key issues, including how to maximize the benefits of existing tools, how to measure success in diabetes, and how they would invest $500 million. In response to the latter, prevention was the *answer du jour* though both Profs. Ferrannini and Holman introduced nuance by suggesting that systems that pull together information and generate actionable insights might have the biggest impact on current patients, payers, and physicians. Indeed, Dr. Gavin built on this "systems thinking" [our wording], stressing that neither drugs nor technology alone hold the solution to diabetes. Yessir! Though the task of integrating care is a tall one, all three panelists shared striking optimism that we are closer to the holistic models of care (needed to tackle the multifaceted nature of diabetes) than ever before. Indeed, it is interesting to think that for the many challenges in the diabetes ecosystem, we currently understand what does NOT work better than ever before. In the speakers' view, we are positioned

for success despite how daunting the task at hand appears. Perhaps it was unrealistic optimism brought on by the scholars of the stage (none of whom we'd ever bet against), but it was VERY inspiring nonetheless. For more on the above, see our selection of the most notable quotes from the evening below. As you can imagine, we mightily appreciate *all* of our sponsors and attendees for making this event a success - you have no idea how encouraged we feel at our Foundation when we can think about your support. Please look for our full report in the upcoming weeks for in-depth coverage of the event.

- *"Right now, the status of guidelines is like cookery with ingredients but with no recipes. We don't have the evidence to make the best choice for the patient in front of you at the right time."* - Dr. Rury Holman
- *"I don't invest too much hope in any one drug to save us. That won't happen. And that's fine, because the complexity of diabetes will defy us ... A complementarity of treatments will be required to address the pathophysiological complexity of diabetes. It's a great hope. We should grow the classes, show that approaches can marry and co-habitat. We'll get GREAT outcomes and glory and - I don't know - a polygamy [of approaches]!"* - Dr. James Gavin
- *"We heard from Dr. [Andrew] Boulton earlier today that diabetes is no longer the primary cause of blindness; we've seen in the NEJM recently that complications have fallen to 50% of what they were; and clearly, the survival and the quality of life for patients have improved. However, we just cannot cope with the number of new cases. For that, we can only use prevention."* - Prof. Ele Ferrannini
- *"A lack of money is a very real problem. There is limited cake and different countries cut it differently ... There is never enough money for everybody, but this is about getting the playing field level. For people with diabetes, it has not been as favorable as it should be."* - Prof. Rury Holman

2. A brilliantly designed human factors study compared use of Locemia's intranasal glucagon powder to a standard glucagon emergency injection kit in a simulated episode of severe hypoglycemia (a mannequin; details below). The study included two groups to mimic realistic scenarios: (i) people with diabetes that taught a caregiver how to use the glucagon device a week prior to the simulation; and (ii) untrained participants with no connection to diabetes, who were shown the device and then asked to use it on the spot. In the key analysis, 94% of caregivers (15/16) correctly gave a full dose of glucagon with the intranasal device, and it took just 16 seconds on average. Conversely, only 13% of the same caregivers (2/16) delivered a full dose with the injection kit and 38% gave a partial dose (6/16); the average time for these eight individuals was 1 minute and 53 seconds (seven times longer than intranasal delivery). Shockingly, 50% of diabetes caregivers (8/15) failed to deliver any glucagon at all with the injection kit vs. just 6% (1/16) with intranasal. Even more frighteningly, two caregivers in the injection group mistakenly used insulin for the hypoglycemia rescue (cleverly included in the diabetes supply bag alongside the glucagon, to simulate a realistic hypoglycemia rescue situation), as they were confused about which injection to use. Whew. The results were equally strong for Locemia in the untrained acquaintance group. Overall, the data seem like a slam-dunk for Locemia's needle-free device, especially as it seeks regulatory approval and future reimbursement relative to existing devices. We've always said that injected glucagon kits are burdensome for caregivers, but this is just dismal. The study also revealed an unexpected concern: is an injected route of glucagon delivery is easy to mix up with injected insulin? (Could that be a strong marketing advantage vs. glucagon competitors Xeris and Biodel, who both have pens?) As a reminder, Locemia has now reported phase 3 adult and pediatric data, showing equivalence to injected glucagon; we assume a submission could happen sometime early next year. More details below.

- **Dr. Jennifer Sherr presented phase 3 results in 48 pediatric patients (4-17 years old) for Locemia's intranasal glucagon, showing comparable glucose-raising ability vs. injected glucagon.** The results mirrored those shown at ATTD 2015 in 75 adults. The primary endpoint - an increase in glucose >25 mg/dl within 20 minutes - was observed with intranasal glucagon in 47/48 treatments vs. 24/24 treatments with intranasal glucagon. The one exception was a patient who blew his nose immediately after receiving the intranasal dose. Dr. Sherr noted that

this scenario would be unlikely during a severe hypoglycemia episode. There was lots of enthusiasm for this device in Q&A; see below.

3. We saw full phase 2 results for Isis' novel insulin sensitizer ISIS-PTP1BRx that looked quite promising. As reported in the topline results announcement in February, ISIS-PTP1BRx produced significantly greater mean A1c reductions at 36 weeks (0.7% vs. 0.2%; baseline = 8.6%; p = 0.03). These results prompted some controversy at the time of the announcement because of the discrepancy in timing between the original primary efficacy endpoint (A1c reduction at 27 weeks) and the reported data (A1c reduction at 36 weeks). However, full results showed a separation between the groups beginning at week 13 that was sustained throughout the trial, even after the cessation of dosing at 26 weeks. Fill-in presenter Ms. Erin Morgan suggested that the product's unique mechanism (it targets PTP-1B at the mRNA level rather than the protein level) could explain the relatively slow ramp-up in efficacy - long-time diabetes watchers remember the slow ramp-up as a major disadvantage with the TZD class. More positively, Ms. Morgan noted that the sustained efficacy after the end of the treatment period reflects a long half-life and suggests potential for longer-term dosing. We also saw the magnitude of the weight benefit with ISIS-PTP1BRx for the first time in this presentation: a 2.7 kg reduction with ISIS-PTP1BRx vs. 1.4 kg with placebo (baseline weight not given; baseline BMI = 34 kg/m^2). Both the A1c and weight benefits increased over the course of the trial, and we suspect that the drug's benefits will become increasingly apparent in longer-term studies, especially if its efficacy is more durable than that of existing drug classes. Ms. Morgan shared that the next step for ISIS-PTP1BRx will be a trial in combination with insulin in obese, highly insulin resistant patients that will involve a higher dose and have a longer duration than this study. See the appendix below for more details on the results and additional commentary on the drug's prospects.

4. In this morning's compelling Claude Bernard Lecture, Dr. Hans-Ulrich Haring (University of Tubingen, Germany) presented on the phenotypes of prediabetes, discussing the roles of brain insulin resistance, fatty liver, fatty pancreas, and genetics. In reviewing the wide variety of phenotypes presented by people with prediabetes and better understanding their mechanisms, his work was an exciting glimpse into how we can begin to individualize prevention efforts. Dr. Haring first reviewed eight-year follow-up data demonstrating that insulin resistance in people with prediabetes increases over time, although some are able to up-regulate insulin secretion and better prevent the progression to type 2 diabetes. Looking to genetics to identify who was and was not able to compensate, Dr. Haring noted that the gene variant TCF7L2 has appeared to be the strongest variant (with a small per-allele odds ratio of ~1.4), but stated that this genetics approach does not provide an adequate explanation for the differences. However, in examining obesity subphenotypes, he demonstrated MRI and MR-spectroscopy data showing the fat distribution differences in those who are metabolically healthy obesity (MHO) vs. metabolically unhealthy obesity (MUHO). He highlighted that those with MUHO are much more likely to have fatty livers as well as increased pancreatic fat, thus stressing the importance of treating fatty liver disease. In addition, Dr. Haring brought up the speculation that brain insulin resistance may be the cause rather than the consequence of obesity and may begin as early as in utero. In developing a model, Dr. Haring therefore hypothesized that early brain insulin resistance may be contributing to obesity, in which there is crosstalk between the fatty liver, pancreatic fat cells, and inflammation that is ultimately accentuating beta cell dysfunction. Moving forward, Dr. Haring emphasized the value in defining subphenotypes and in understanding the pharmacology behind these hypothesized mechanisms to develop new targets and personalize prevention efforts to learn who responds to what and how to effectively intervene as early as possible. We were glad to see such a renowned lecture focus on prediabetes (talk about the growing focus on the need for prevention); and with lifestyle intervention and metformin as really the only mainstream approaches for treating prediabetes, we concur that this research into the progression's physiological basis will be key to identifying and personalizing a wider array of prediabetes treatment options.

- **EASD President Dr. Andrew Boulton delivered a warm welcome and introduction prior to the lecture, providing his insights on how diabetes has evolved since EASD was founded in 1965.** After introducing 2015 as a "year of celebration" (ADA's 75th year, EDEG's 50th year, NEURODIAB's 25th year), Dr. Boulton illustrated that the "world has come a long way since 1965" when there was no blood glucose monitoring or glycated hemoglobin and with only

SFUs, metformin, and biguanides as the oral agents. Addressing the present state of diabetes, he pointed to the increasing prevalence of both type 1 and type 2 diabetes, the recent rapid escalation in the number of diabetes drugs, and greater attention toward public health policies such as the soda tax. As he summarized the future of the field, he expressed excitement about the closed-loop system, specifically citing the bionic pancreas work of Drs. Steven Russell and Ed Damiano, immunotherapy for type 1 diabetes, and new drugs for type 2 diabetes. Notably, he applauded the fact that this year is the first time in the UK that diabetes is no longer the leading cause of blindness for people of working age, as he strongly emphasized that "screening and prevention are the future" (a most fitting preamble for the Claude Bernard Lecture). In addition, he made a call to action to governments throughout the world to not ignore diabetes, as he referred to the enormous human and economic costs of the epidemic. We were so struck by Dr. Boulton's balance of optimism yet clear sense of urgency on the state of diabetes and were especially glad to hear him devote some attention to the bigger-picture public health needs of prevention and policy in diabetes at such a science-heavy meeting.

5. Our exhibit hall report covers 16 companies, including several unexpected findings in pumps and CGM. Startup Kaleido debuted a colorful new patch pump, while Ypsomed finally showed off its own durable touchscreen, prefilled YpsoPump, which we thought was very cool (much more than we expected) - the write-ups below have all the details. Meanwhile, relatively unknown Asian companies Diamesco (POCTech) and Medtrum had bold marketing for CGMs with reported MARDs of 10-12% (and in the case of Medtrum, plans to launch a predictive low glucose suspend system in Europe this year - no way!) - we are skeptical whether either is the real deal, and discuss both in more detail below. LifeScan came through with a new BGM 510(k) clearance (the OneTouch Verio Flex), while Roche announced plans to launch its Accu-Chek Connect (BGM + paired smartphone app) in Austria, Canada, Luxembourg, and France in the next six months. On the drug side, Novo Nordisk won the award for most forward-looking approach to the exhibit hall, with a booth devoted entirely to new arrivals Tresiba (insulin degludec) and Xultophy (insulin degludec/liraglutide) - the company is clearly going all in on products that it believes have transformative potential (so do all the experts here seem to - especially the latter). Lilly/BI's massive booth reeled attendees in with videos of baby animals accompanying the promotional materials for the newly launched Abasaglar (biosimilar insulin glargine). We were a bit surprised to see such heavy promotion for the biosimilar insulin, though this is consistent with Lilly's past statements that it intends to market Abasaglar as it would any new branded product. Sanofi's booth had a clear focus on Toujeo (insulin glargine U300), though it also reminded attendees that Lantus (insulin glargine) is still king with displays urging clinicians to "choose the one you know." In this season of CVOTs, cardiovascular safety was a theme of the day: Merck's booth was devoted almost entirely to the positive (aka neutral) TECOS results for Januvia (sitagliptin), and AZ's booth emphasized the reassuring primary results from SAVOR for Onglyza (saxagliptin) and the beneficial effects on CV risk factors with Farxiga (dapagliflozin).

Honorable Mention

- **Novo Nordisk presented three posters today, including new positive patient-reported outcomes data on Xultophy (insulin degludec/liraglutide) from DUAL V, safety and efficacy data favoring insulin degludec U200 over insulin glargine and a SCALE post-hoc analysis on Saxenda's (liraglutide 3.0 mg) weight loss predictors.** First, the company presented data from DUAL V (n=557) showing that Xultophy produced significantly better results on a number of patient-reported outcome measures compared to Sanofi's Lantus (insulin glargine), including treatment burden (p=0.017), diabetes management (p<0.001), physical functioning (p=0.045), bodily pain (p=0.012), and general health (p=0.008) -Dr. John Buse (University of North Carolina, Chapel Hill, NC) referred to these results during his ringing endorsement of Xultophy yesterday. The second poster - first shown at ADA 2015 - presented results from a randomized, open-label, crossover trial (n=145) demonstrating non-inferior A1c reductions with insulin degludec U200 vs. insulin glargine. In addition, insulin degludec U200 resulted in lower mean fasting plasma glucose (p<0.05) and lower rates of confirmed hypoglycemia (p<0.05). In terms of patient-reported outcomes, the delivery device for insulin degludec U200 was also rated

better for function (p<0.05) and less bother (p<0.05), and more patients stated that they preferred insulin degludec U200 treatment (55%) than insulin glargine treatment (20%). Lastly, the third poster of a post-hoc analysis from the SCALE Diabetes and SCALE Obesity and Prediabetes trials indicated that early responders to Saxenda (losing ≥5% weight loss at week 16) had greater observed mean weight loss (at week 56), had a greater proportion of individuals losing weight, and experienced greater improvements in cardiometabolic risk factors compared to early non-responders. These results also echo Dr. Donna Ryan's (Pennington Biomedical Research Center, Baton Rouge, LA) commentary yesterday on the importance of identifying predictors in obesity drugs to better individualize therapy.

Detailed Discussion and Commentary

Posters

NEEDLE-FREE NASAL DELIVERY OF GLUCAGON IS SUPERIOR TO INJECTABLE DELIVERY IN SIMULATED HYPOGLYCEMIA RESCUE (867-P)

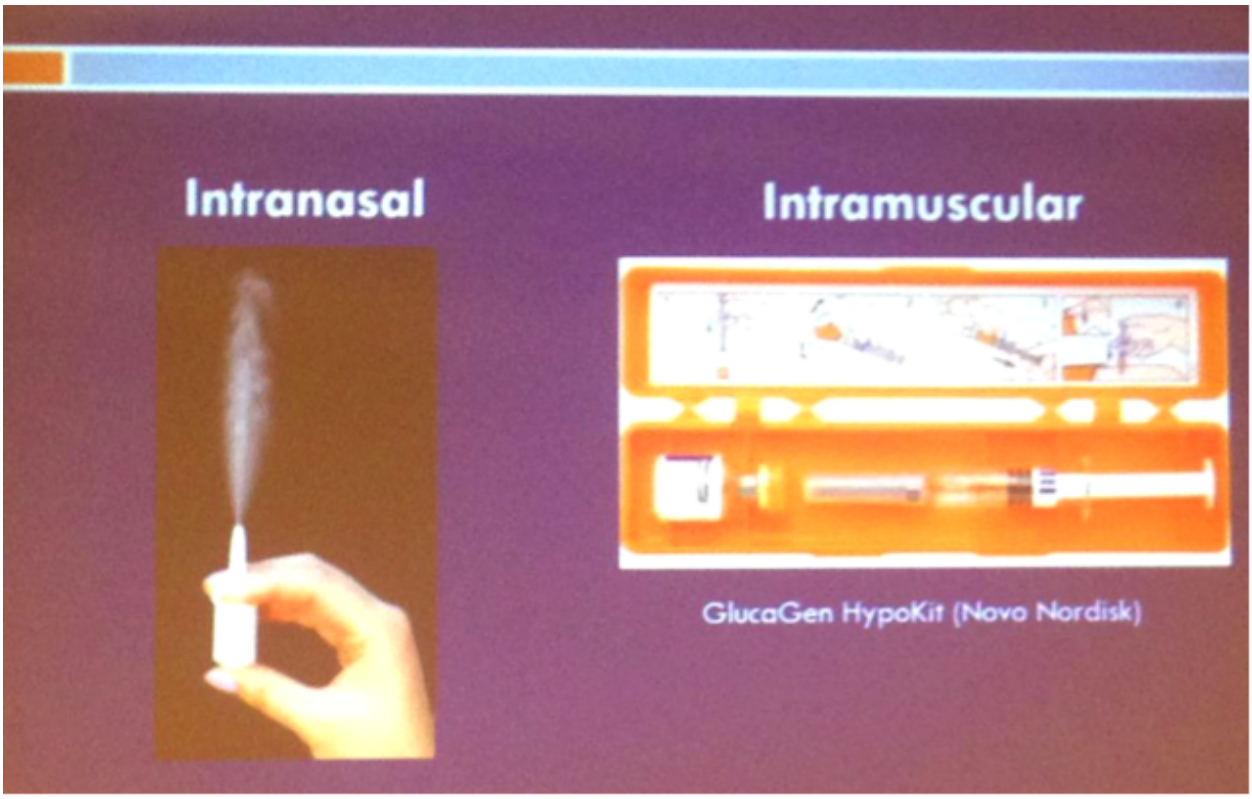
J Yale, C Piché, M Lafontaine, R Margolies, E Dissinger, A Shames, N Fink, M Egeth, H Dulude

This brilliantly designed human factors study compared use of Locemia's intranasal glucagon powder to a standard glucagon emergency injection kit in a simulated episode of severe hypoglycemia (a mannequin; details below). The study included two groups to mimic realistic scenarios: (i) people with diabetes that taught a caregiver how to use the glucagon device a week prior to the simulation; and (ii) untrained participants with no connection to diabetes, who were shown the device and then asked to use it on the spot. In the key analysis, 94% of caregivers (15/16) correctly gave a full dose of glucagon with the intranasal device, and it took just 16 seconds on average. Conversely, only 13% of the same caregivers (2/16) delivered a full dose with the injection kit and 38% gave a partial dose (6/16); the average time for these eight individuals was 1 minute and 53 seconds, or seven times longer than intranasal delivery. Shockingly, 50% of diabetes caregivers (8/15) failed to deliver any glucagon at all with the injection kit vs. 6% (1/16) with intranasal. Even more frighteningly, two caregivers in the injection group mistakenly used insulin for the hypoglycemia rescue (cleverly included in the diabetes supply bag alongside the glucagon, to simulate a realistic hypoglycemia rescue situation), as they were confused about which injection to use. Whew. The results were equally strong for Locemia in the untrained acquaintance group: 93% success (14/15) with intranasal in an average of 26 seconds vs. 0% success for a full-dose (0/15) and 20% success for a partial dose (3/15) with the injection kit in an average of 2 minutes and 24 seconds. Overall, the results are a slam-dunk for Locemia's needle-free device, especially as it seeks regulatory approval and future reimbursement relative to existing devices. We've always said that injected glucagon kits are burdensome for caregivers, but who knew it was this hard to use them correctly and quickly? The study also revealed an unexpected concern with an injected route of glucagon delivery that is easy to mix up with injected insulin - this could be a strong marketing advantage vs. competitors Xeris and Biodel. As a reminder, Locemia has now reported phase 3 adult and pediatric data, showing strong equivalence to injected glucagon; we assume a submission could happen sometime early next year.

- **The severe hypoglycemia simulation included a fully clothed adult mannequin representing a person with diabetes.** Participants were told that the mannequin was having an episode of severe hypoglycemia and that they had to administer the rescue glucagon as quickly as possible. The glucagon rescue device was located in the patient's backpack, which also contained a diabetes supply pouch (glucose meter and strips, alcohol swabs, lancing device, insulin vial, and syringe). Sound effects and distractions created a sense of urgency - a nice touch.
    - **The trained caregiver arm included 16 adult insulin-using people with diabetes and their caregivers.** Patients were taught how to use one of the glucagon devices (in random order) and then instructed their caregivers, replicating real-life transfer of information. One week later, caregivers were asked to treat a mannequin during a simulated episode of severe hypoglycemia. The procedure was repeated with the other device.

    - **The untrained acquaintance arm included 15 adults with no diabetes connection, but who said they were willing to assist someone in distress.** They were not trained on device use and only shown the device prior to the simulation. This group treated two episodes of severe hypoglycemia with the injection kit and intranasal powder in random order, with a delay of about ten minutes between each simulation.

- **Two caregivers in the injection group mistakenly used insulin for the hypoglycemia rescue attributed to "form factor confusion."** An additional two caregivers in the intranasal group and three caregivers in the injection group attempted to give insulin *in addition to glucagon* "due to misunderstanding of diabetes management" (i.e., "insulin helps the patient with their blood glucose, so I should give that too"). The data simply underscores the tremendous educational challenges related to glucagon, even amongst diabetes caregivers!
- **It was notable to see that untrained acquaintances were able to deliver intranasal glucagon successfully and at a similar rate as trained caregivers.** We agree with the poster's conclusion that it highlights the ease of use of Locemia's needle-free nasal glucagon delivery system.
- **"Glucagon delivery using a different route and device form than those used for insulin may reduce the risk of confusion and accidental delivery of insulin."** This was a fascinating point we had never thought of, but a realistic one since insulin might be co-located with a glucagon kit. Certainly, this gives Locemia some marketing advantage for injected rescue glucagon competitors Xeris and Biodel.



GLUCAGON NASAL POWDER: AN EFFECTIVE ALTERNATIVE TO INTRAMUSCULAR GLUCAGON IN YOUTH WITH TYPE 1 DIABETES

Jennifer Sherr, MD (Yale University, New Haven, CT)

Dr. Jennifer Sherr presented phase 3 results in 48 pediatric patients (4-17 years old) for Locemia's intranasal glucagon, showing comparable glucose-raising ability vs. injected glucagon. The results mirrored those shown at ATTD 2015 in 75 adults. The primary endpoint - an increase in glucose >25 mg/dl within 20 minutes - was observed with intranasal glucagon in 47/48 treatments vs. 24/24 treatments with intranasal glucagon. The one exception was a patient who blew his nose immediately after receiving the intranasal dose. Dr. Sherr rightly noted that this scenario would be unlikely during a severe hypoglycemia episode. The study also tested two doses of the intranasal glucagon, revealing that the same 3 mg adult dose can be used across the pediatric population. That's a manufacturing win for Locemia. The intranasal glucagon had a slightly higher rate of head/facial discomfort (17-24% vs. 13%), though a much lower rate of nausea (39-43% vs. 67%). Given the rescue indication, we don't see those events as truly impactful on the drug's chances.

Questions and Answers

Q: You have an attractive device. My issue here is you have administered in conscious patients that are able to inhale powder. How about unconscious patients?

A: In actuality, the glucagon powder is passively absorbed through the nasal mucosa. Patients do not inhale; that does not help in terms of the absorption of medication.

Q: It's so rare that we have a new innovations in this area. This may really be important. Could it be a useful tool in emergency cars? When will it be on the market?

A: I can't speak to when it will be on the market. The company has been having discussions with the regulatory bodies. I suggest inquiring with them.

It will absolutely be useful for emergency settings.

Q: What is the stability? Can you store it at room temperature?

A: It is stored at room temperature. I believe it has a two-year shelf life.

Q: From an adult clinician view, this is great. So often glucagon is not given. What do you think is driving the differences in nausea?

A: I cannot say I know. The glucagon concentrations with injected seem to get a little bit higher than intranasal in some cohorts. I don't know the mechanism behind it.

Q: Have you studied variability of absorption? What about stuffy noise due to a common cold?

A: Actually, the company did conduct a study doing that. They brought in patients with colds and tested it with and without nasal decongestant. In both situations, the powder was well-absorbed.

Q: The insulin infusion was stopped when you reached lower glucose concentrations. How would this affect the response to glucagon, because in a clinical situation, insulin will remain on board?

A: We resumed normal basal delivery. We stopped the higher rates to induce hypoglycemia. If someone was on injections, they had their previous basal injection from the prior day.

ISIS PTP-1BRX, A NOVEL PTP-1B ANTISENSE INHIBITOR, IMPROVES HBA1C AND BODY WEIGHT IN PATIENTS WITH TYPE 2 DIABETES ON METFORMIN ± SULPHONYLUREA

Erin Morgan (Isis Pharmaceuticals, Carlsbad, CA)

Filling in for Dr. Andres Digenio, Ms. Erin Morgan presented full phase 2 results for Isis' novel insulin sensitizer ISIS-PTP1BRx. As reported in the topline results announcement in February, ISIS-PTP1BRx produced significantly greater mean A1c reductions (-0.7% from a baseline of 8.8%) vs. placebo (-0.2% from a baseline of 8.4%) at 36 weeks (p=0.03). These results attracted some controversy at the time of the announcement because of the discrepancy in timing between the original primary efficacy endpoint (A1c reduction at 27 weeks) and the reported data (A1c reduction at 36 weeks). However, full results showed a separation between the groups beginning at week 13 that was sustained throughout the trial, even after the cessation of dosing at 26 weeks. Ms. Morgan suggested that the product's unique mechanism (it targets PTP-1B at the mRNA level rather than the protein level) could explain the relatively slow ramp-up in efficacy. More positively, she noted that the sustained efficacy after the end of the treatment period reflects a long half-life and suggests potential for longer-term dosing. ISIS-PTP1BRx also produced significant improvements in short-term glycemic parameters (fructosamine and glycated albumin). We also sa the magnitude of the improvement for the first time in this presentation: a 2.7 kg reduction vs. 1.4 kg with placebo (baseline weight not given; baseline BMI = 34 kg/m²). The drug also led to improvements in leptin and adiponectin levels; Dr. Morgan noted that adiponectin levels rose before weight loss began, suggesting it was a direct result of reduced PTP1B activity in adipocytes. ISIS-PTP1BRx was safe and well tolerated with no serious adverse events or abnormalities in laboratory parameters.

- **We suspect that ISIS-PTP1BRx could produce even more impressive effects in longer-term trials.** Both the A1c and weight benefits seemed to increase over the course of this study, suggesting that the longer-term effects could be even greater. Even efficacy of this magnitude could become more clinically meaningful if it proves more durable than that of existing drug classes. This would be consistent with the product's insulin-sensitizing mechanism: for example, head-to-head studies have shown that TZDs initially appear less efficacious than sulfonylureas but ultimately produce much more durable A1c reductions.
- **The next step for ISIS-PTP1BRx will be a study in combination with insulin in obese, highly insulin resistant patients.** It will involve a higher dose and have a longer duration than this trial, though Dr. Morgan did not disclose any additional details. Isis has stated in the past that it plans to seek a partner before initiating phase 3 trials for this candidate, and this upcoming trial could be an attempt to increase interest from industry by better defining an initial target population and demonstrating durable efficacy.
- **Isis has expressed hope that ISIS-PTP1BRx could help "refresh" the insulin sensitizer class after the baggage associated with the TZDs.** A successful insulin sensitizer would be a significant advancement in the type 2 diabetes drug arena, as it would address the underlying pathophysiology of the disease to a greater extent than existing drug classes. Other companies developing PTP1B inhibitors include TransTech Pharma (TTP814; phase 2) and OHR Pharmaceutical (trodusquemine; phase 1). Other companies developing novel insulin sensitizers include J&J (JNJ-41443532; phase 2), Metabolic Solutions (MSDC-0160 and MSD-0602; phase 2), Shionogi (S-707106; phase 2), and XOMA (XMetS; preclinical).

IMPROVED POSTPRANDIAL GLYCAEMIC CONTROL WITH FASTER-ACTING INSULIN ASPART IN INDIVIDUALS WITH TYPE 1 DIABETES USING CSII

Marek Demissie (Novo Nordisk, Soborg, Denmark)

Novo Nordisk presented a randomized, crossover, phase 1 study comparing 14-days of faster-acting insulin aspart to insulin aspart in 43 adults on Medtronic insulin pumps. The primary endpoint was two-hour postprandial glucose following a meal test, though patients also wore blinded CGM throughout the two weeks. Faster aspart showed an ~18 mg/dl postprandial advantage at two hours following the meal test (+55 mg/dl vs. +72 mg/dl; p=0.04), a clinically meaningful improvement in our view. The advantage at one hour was a bit lower at 9 mg/dl (+34 mg/dl vs. +43 mg/dl; p=0.08), a bit odd considering prior PK/PD studies showing a solid advantage for fast aspart in the first 30 minutes post-injection. Using blinded CGM over the 14 day treatment period, faster aspart was significantly better at both one at two hours after all meals, particularly after breakfast - the postprandial increase was ~10-12 mg/dl lower with fast aspart for

all meals (p <0.005), and ~16-20 mg/dl lower with fast aspart following breakfast (p<0.02). Breakfast is where faster insulin will really shine in our view, setting up patients for more time-in-zone through the morning and middle of the day. On hypoglycemia (measured by CGM), faster aspart demonstrated encouraging results, reducing time below 70 mg/dl by 25 minutes per day (2.5 hours vs. 2 hours; p=0.008); overall event rates were not significantly different. There were slightly higher adverse events (99% vs. 79%) in the faster aspart arm, though the cause was not specified. Novo Nordisk reported topline phase 3a results for fast aspart in March, and in 1Q15, announced plans to submit in the US and EU around the end of 2015. We assume this would include a pump indication, but aren't sure.

- **If approved, how will the label for faster-acting aspart compare to Afrezza?** As a reminder, Afrezza's label does not currently include a faster-acting claim or a hypoglycemia advantage. Will Novo Nordisk be able to obtain either?
- **Mr. Demissie suggested that the advantage of faster aspart vs. aspart may be of similar magnitude to the advantage of insulin analogs over human insulin.** A study published this year (Heise et al., Diabetes Obes Metab 2015) showed fast aspart increases insulin action by at least 48% within 30 minutes of subcutaneous injection. The same comparison between aspart and human insulin yielded a similar advantage of 38%.

Exhibit Hall

ABBOTT

Abbott's distinctive yellow booth was packed with attendees' enthusiasm for FreeStyle Libre, now one year out on the EU market. We did not glean any new insights, though tried our very best to learn about the US timeline for a consumer version - no dice (and not really any surprise). Much like last year, promotional videos and posters advertised the simplicity and convenience of the factory-calibrated technology: "You can do it during a movie"; "You can do it in a meeting"; "You can do it in public"; "You can do it on the dance floor"; "You can do it without lancets"; "You can do it anytime, anywhere". Clever with a twist of innuendo - this company has really nailed the marketed on this product. A smaller component of the booth promoted the Ambulatory Glucose Profile software, which clinicians and patients both praised in Abbott's symposium yesterday and which has impressed us quite a lot - boy has Dr. Rich Bergenstal worked hard on this and we'd LOVE to see this taken up by more so we can get more standardization going on. This lounge-like area featured a large-screen video presentation of the product and generated a surprising amount of interest in its own right. Yeah. They've got it going on. We also heard by the way that reimbursement in Germany (!!) was going quite well - that's from our German blogger friends.

BAYER

Bayer was conspicuously absent from the Exhibit Hall floor, the only one of the Big Four BGM companies that did not invest in a booth at EASD 2015. The absence was not particularly surprising considering the company's absence at ADA 2015 and the divestment of the Diabetes Care business to Panasonic Healthcare for ~€1.0 billion (~$1.2 billion) in June 2015. But we hope KKR will get with the program and invest some very needed R&D dollars into the next-generation technology. Although valuable Medtronic customers make up a lot of their users now, Medtronic wants to pull all of them toward CGM.

DEXCOM

Dexcom's booth in the far back of the hall advertised the newly CE-Marked G5 mobile system ("First fully mobile CGM"), which was announced yesterday in the company's symposium (launching in the coming weeks in Europe). Signage highlighted the EU approval down to age 2 and the newly acquired replacement claim. Though G5 was under glass and not on formal hands-on display, a Dexcom rep let us play with a demo version of the new app. We're very psyched for this. Our trial suggested a simple menu structure (Home, Trends, Alerts, Setup Wizard, CGM Scenarios) and reinforced the great use of color for glanceability, valuable lock screen notifications (like a text message), and the highly customizable alarms (22 different sounds, with lots of timing options). The demo version did not let us enter a calibration or see any data analytics, so we'll have to wait until we try G5 in the US (also slated to launch in the coming

weeks). Dexcom has done some subtle but meaningful things with the G5 app user interface - for example, the trend graph screen background dynamically changes color based on whether the current value is in-range (gray) or out-of-range (bright red or yellow). On the previous G4 receiver, the background remains black while only the individual glucose points change color. It's another small but meaningful reminder of how much more is possible on a mobile app! Dexcom is highly highly valued but in stirring shape from what we can see - lots of things need to go right to sustain the valuation and so far so good.

DIAMESCO (POCTECH)

POCTech advertised a new seven-day CGM requiring just one calibration at startup. A handout boasted a 10.8% MARD vs. fingersticks in an unconvincing 15-patient study (10 had type 2 diabetes, only 250 paired points vs. fingersticks). The rep told us a larger 110-patient study was just completed, showing a 10-12% MARD. There was no handout on the new study, and the rep was unable (or didn't want) to answer our questions. Diamesco expects a CE Mark in early 2016 and Chinese FDA approval by the end of 2016. The company hopes to return to EASD 2016 announcing a launch. We are skeptical at this stage, particularly because the CGM flyer made several shifty data mistakes - for example, showing a graph with only one patient's (!)data; using type 2s, who have lower glycemic variability and don't provide a true test of the system; not using YSI as the comparator.

J&J/ANIMAS

Animas was positioned in the middle of the J&J booth. The area was packed despite occupying a small sliver of the expansive J&J layout. Attendees crowded around an educational display on the features of the Animas Vibe integrated with Dexcom G4 Platinum CGM. Reps expressed big-time enthusiasm for the product, talking at length about how positive the patient response has been - indeed, it saw 32% operational growth in the US per J&J's most recently quarter update. We did not see any reference to the recently announced partnership with Tidepool. We were dreaming and hoping to see a next-gen artificial pancreas offering on demo, but that was wishful thinking ... for now!

J&J/LIFESCAN

LifeScan's portion of the J&J exhibit captured a significant portion (~25%) of the booth's real estate, one of the larger investments we can recall seeing in some time. The company brought a pair of BGM announcements to EASD: (i) LifeScan has updated its data downloading software (the "Reveal" app that pairs with the VerioSync); and (ii) the company recently received FDA 510(k) clearance for its Bluetooth-enabled OneTouch Verio Flex meter.

- **LifeScan debuted its new Reveal mobile app and web portal.** The company has given a facelift to the software (which, as a reminder, pairs to LifeScan's VerioSync meter and now the Flex meter) while retaining many of the positive features of the original software: a colorful time-in-range chart (blue for hypoglycemia, green for in-range, red for hyperglycemia); pattern recognition for any high or low glucose patterns; easy sharing of results via email or text message. We wonder if the data will now post to HealthKit on the iPhone, a complaint in reviews of the app. We are fans of more seamless and automatic blood glucose data upload, though hope the results can also flow freely to other platforms.
- **We learned today that LifeScan recently received FDA 510(k) clearance for its Bluetooth-enabled OneTouch Verio Flex meter.** The device has been available in the EU "for some time," though we cannot recall having seen it previously. The meter is sends blood glucose data wirelessly to the Reveal mobile app on an iPhone, iPad, or iPod touch. See pictures here. Reps did not provide a timeline for a US launch or pricing. It's good to see movement from LifeScan on the BGM pipeline front (especially considering the very challenging US BGM market), and the company has trickled out a few new meters over the past year. The compelling advantage of the Flex over the VerioSync seems to be the addition of a color range indicator and a few buttons (the VerioSync is very slim and stripped down). This meter marks the third smartphone-connected BGM commercialized by a Big Four company, following LifeScan's OneTouch VerioSync and Roche's Accu-Chek Connect. We like that they are moving faster of late.

KALEIDO

In the rear of the hall, we unexpectedly found Kaleido, a new patch pump company that debuted here at EASD (website). The pump and paired handheld are currently in the CE Mark process, and the UK and Netherlands are the first planned launch markets "soon." The approach resembles Cellnovo, giving patients two reusable pump units, a wireless controller handheld, and an insulin cartridge that connects to a short on-body infusion set (5 cm or 30 cm). Unlike Cellnovo or the OmniPod, the handheld doesn't have a built-in blood glucose meter. The body-worn pump and iPod-like handheld are both quite slim (measurements here), and the company has put a major emphasis on customizable color offerings. The pump cartridge holds 200 units, and the pump body is rechargeable, waterproof, and lasts for two years (the rep wasn't positive on the latter). The handheld doesn't have cloud/app connectivity, a downside vs. Cellnovo's handheld and the upcoming next-gen OmniPod PDM. We asked the rep what separates Kaleido from OmniPod, and he emphasized the personalized colors and the ability to remove the pump (though it is waterproof, so this is not required). The rep had not heard of Cellnovo and was unable to compare the devices - this was odd and not confidence inspiring. We like the focus on making pumps cooler, though the key differentiator seems to be color - is that enough to distinguish Kaleido from everything else out there and coming along? The company making Kaleido is ViCentra, co-founded by Dr. Joesph Cefai, a principle founder of Cellnovo. We're not sure about the IP and trade secret implications of that history.

LILLY/BI

Lilly/BI's massive booth commanded attention with its placement in the center of the exhibit hall - this booth combined with Lilly's adjacent display easily claimed the largest amount of floor space of any company in attendance. Approaching attendees were immediately greeted by an attention-grabbing display (complete with videos of baby animals interspersed with the phase "do we have your attention?") for Abasaglar, Lilly/BI's newly-launched (though only in ex-US markets) biosimilar version of Sanofi's Lantus (insulin glargine). The marketing surrounding Abasaglar acknowledged that "first times can be awkward" and emphasized easing the initiation phase for Abasaglar. Walking further into the booth, attendees entered a rustic-yet-modern refreshment area that exuded warmth with its wood-paneled walls and coordinating wood floors. On the other side of the refreshment area, attendees found a variety of interactive trivia games based on Lilly/BI's impressively broad portfolio of products (the broadest around). One game focused on Jardiance (empagliflozin) and Synjardy (empagliflozin/metformin) had participants tossing beanbags into different holes to answer multiple-choice questions about their dosing, mechanism of action, and more. For Tradjenta (linagliptin) and Jentadueto (linagliptin/metformin), visitors to the booth could try their hand at a Mario Kart-style video game in which questions about the products were peppered into the driving experience. Not to brag, but we placed 5th on the leaderboard during our visit.

LILLY

Lilly's booth came across almost as an extension of the massive Lilly/BI booth next door, with a prominently-displayed reprise of the baby animal videos and photos for Abasaglar. We were a bit surprised to see such heavy promotion for the biosimilar insulin, though this is consistent with Lilly's past statements that it intends to market Abasaglar as it would any new branded product. Biosimilar insulin glargine has been highly anticipated, largely due to hopes that it could represent a reprieve from skyrocketing insulin prices. So far Abasaglar has only been priced at a 15-20% discount relative to Lantus [insulin glargine]), though we expect that the discount could be steeper in the US (where full approval is on hold pending the outcome of a Sanofi lawsuit). New arrivals Trulicity (dulaglutide) and Humalog U200 KwikPen were also on display, though Trulicity's exhibit hall presence continues to be relatively subdued for what is arguably a best-in-class product. The booth also included a corner devoted to Lilly initiatives including diabetes books for kids and the company's NCD [non-communicable diseases] Partnership in developing countries.

MEDTRONIC

Medtronic's booth was mostly devoted to the new MiniMed 640G with predictive low glucose management. The pump launched at ATTD 2015 in Europe, and a demo today reminded us of the design improvements over the MiniMed 530G - e.g., a larger color screen, four way arrow navigation, more customizability for

alarms, insulin-on-board right on the home screen with sensor information, the ability to stop a bolus mid-delivery, etc. We had two new learnings from our ATTD test drive: (i) the pump indicates boluses on the trend graph screen with a blue dot (helpful to quickly understand when a last bolus was given and how it affected the glucose trend); and (ii) the history menu includes more robust analysis, such as CGM pie charts showing time-in-zone. The rep told us that patients love the system at night, especially because the alarms can be turned off (allowing the system to work in the background with disturbing sleep).

MEDTRUM

Our red flag alarms went wild in Medtrum's booth, who advertised a predictive low glucose suspend artificial pancreas complete with its own CGM (9% MARD, Bluetooth-enabled) and patch pump. What! The company plans to launch in Europe later this year. The reps freaked out when we started asking hard questions about the CGM data (comparator, in-clinic days, paired points, type of patient), and the vague posters around the booth were of little (read: no) help. We have low confidence this is the real deal.

MSD

MSD (Merck's international equivalent) was very clearly all about the recent results from its CVOT TECOS for Januvia (sitagliptin), which demonstrated resounding neutrality. The booth's posters exclaimed, "now even more reason to choose Januvia first as a partner to metformin," with summaries of the TECOS safety evidence. MSD has even scheduled Meet-the-Expert sessions (three times a day!) focused on the CVOT's data. A "Wall of Discovery and Development" in the back of the booth walked attendees through the history of DPP-4 inhibitors and highlighted the date of the release of the full TECOS results at ADA as the most recent milestone in the class' journey. While the majority of the booth focused on TECOS, the booth also had a few standard posters on Janumet (sitagliptin and metformin HCl), a corner on the company's LDL-lowering drug Atozet (ezetimibe/atorvastatin), along with iPads that gave attendees the chance to experience hypoglycemia virtually. Overall, we are not surprised at all that the company is making the most out of TECOS' positive results, as management suggested it would do so in its last company update - these data will very likely maintain, if not bolster, Januvia's dominant position within the DPP-4 inhibitor class, due to provider familiarity with the drug as well as the slightly more questionable results from SAVOR (for AZ's Onglyza [saxagliptin]) and EXAMINE (for Takeda's Nesina [alogliptin]).

NOVARTIS

Novartis' booth had an impressively large amount of real estate that promoted Galvus (vildagliptin) and Lucentis (intravitreal ranibizumab), with less attention focused on Eucreas (vildagliptin/metformin fixed-dose combination). On one side of the booth, tall touch screens featured images of various patient profiles, promoting the idea that Galvus is appropriate for a wide range of patients, specifically focusing on its renal safety and low hypoglycemia risk. On the other side, Lucentis was the star of the booth's more interactive activities, branded as "designed to save sight" and as the "most prescribed licensed anti-VEGF therapy to help improve vision for diabetic macular edema patients." Touch screens featured interactive quizzes that included questions regarding patients' most feared complication (which was unsurprisingly problems with vision) and Lucentis' mechanism of action. The booth featured other activities surrounding Lucentis including a retinopathy screening station (which used a telemedicine approach by sending your retina images to a remote ophthalmologist, perhaps hinting towards Novartis' greater attention towards digital health) as well as a virtual reality simulation of diabetic macular edema. In addition, the booth promoted a strong sense of urgency around the diabetes epidemic, with the text "It's time to do more about diabetes" on its overarching floating ring (alongside the logos of Galvus, Lucentis, and Eucreas). Several touch screens and videos were devoted to a theme of "Time2DoMore" with statistics from the IDF Atlas and calls to action, as well as ellipticals coupled with screens that attendees could use to learn more about the movement while getting their daily dose of exercise. With Galvus' declining revenues and Novartis having even explicitly stated its reallocation away from Galvus, we were very surprised to see the larger size of the company's booth, although we would guess that the larger European demographic (Galvus is only marketed ex-US) and the losses from the German market are strong motives to more aggressively market the drug.

ROCHE

Roche's booth was decked out in its classic navy colorway and located toward the right side of the hall, advertising a host of Accu-Chek products from the Mobile (one of its older BGMs) to the Insight (its insulin pump with prefilled cartridges) to the Connect (its newest BGM). Roche launched the Connect BGM and paired smartphone app (with a bolus calculator!) in the US in early August, and we learned today that 2015 launches have also included Australia, Turkey, and Brazil. The system hit the market in the EU in September 2014 with availability in South Africa, Italy, and Germany. Roche hopes to launch the Connect in four additional territories in the upcoming six months: Austria, Canada, Luxemburg, and France. Whether the company can establish reimbursement (especially in the tough French market) will be a key to accessibility, though regardless, the fuller scale launch is an important move toward reducing the hassle of downloading and insulin dose calculation for patients and providers. See diaTribe's test drive here.

SANOFI

Toujeo (insulin glargine U300) was the clear focal point of Sanofi's exhibit hall booth, with half of its outer perimeter taken up by the product's distinctive green and purple logos. The materials on Toujeo heavily emphasized its flat action profile, with the slogan "the insulin of today for a steady tomorrow." We liked that - it is what it is! Sanofi also reminded attendees that Lantus (insulin glargine) is still king with displays urging clinicians to "choose the one you know" despite the prominent displays for the new biosimilar version (Lilly/BI's Abasaglar) and Novo Nordisk's next-generation Tresiba (insulin degludec) a few steps away. Lyxumia (lixisenatide) was also allocated some booth space (its "award-winning" pen was emphasized), as was Amaryl (glimepiride). Aside from drug products, Sanofi also showcased its blood glucose meters, its "Every 1 Matters" initiative,, and a quiz game that donated up to €15,000 to the Swedish Diabetes Association. We think the GLP-1 combo with Lantus will be extremely successful - they may need another ratio eventually - and we will be excited to see this become an offering.

YPSOMED

The bright green booth debuted the company's in-house developed, touchscreen, durable, prefilled insulin pump, YpsoPump. Launch is slated for Germany and the Netherlands in 1Q16, with a broader EU launch to follow. We had a chance to demo the device, which felt slightly smaller than a MiniMed 530G with an iPhone-like, black-and-white, fully icon-driven touchscreen. We LOVED the prefilled cartridge and thought all this was very easy. The pump will launch with prefilled insulin cartridges (160 units), and we can't wait to hear who its insulin partner is. We might guess it is Novo Nordisk, who has a non-exclusive partnership with Roche for 160-unit prefilled NovoRapid cartridges for the Accu-Chek Insight pump. Overall, the combination of touchscreen, prefilled, and icon-driven could differentiate YpsoPump from other pump offerings in Europe. From our view, it's more about expanding the market and all the companies should be getting far better data on this fron than pumps have had in the past. There's lots of competition vs. the MiniMed 640G, Insulet's OmniPod, Animas' Vibe, and Roche's Accu-Chek pumps - but the brand here has reined supreme. More details following our demo are below.

- **Notably, the YpsoPump user interface is entirely icon driven and navigated by swiping left to right - there are no words to distinguish anything in the menus,** a bold design choice that walks a fine line between simple and potentially confusing but we liked it. At points it may err towards the latter, making it hard to know what different buttons do without some training (e.g., we kept entering the history and priming and rewind menus, which have non-obvious icons). Of course, once someone learns what the icons mean, it would probably be quite liberating to navigate a pump in this way. In a major positive, the icon-driven interface makes the pump language neutral, a brilliant choice for a European product that clearly drove the design.
- **The pump does not have a bolus calculator,** though Ypsomed will give patients a companion smartphone app with this feature. YpsoPump has Bluetooth built-in, but in talking to the rep, it will not communicate with the smartphone app, so the calculator-to-pump transfer will be manual.

- **Ypsomed also plans to launch a self-filling reservoir after the prefilled version.** The rep would not disclose any timing. We assume the prefilled version will be the focus, given the marketing advantages to patients and HCPs.
- **The Orbit infusion set** will be marketed alongside the pump. The set offers 360 degree rotation and both steel and Teflon cannulas.
- **As far as cannibalizing the OmniPod, a banner above the booth proclaimed "Freedom of choice in pump therapy," flanked by icons of the YpsoPump and OmniPod.** Both Insulet and Ypsomed have maintained that the pumps will not compete against each other, and there are certainly some points of differentiation. Still, much of the YpsoPump marketing sounds like the OmniPod - "Enjoy simplicity," "Easy to learn," "Easy to operate," "simply discrete" - so it will be interesting to see what happens once both are available side-by-side next year.

-- by Melissa An, Adam Brown, Helen Gao, Varun Iyengar, Emily Regier, and Kelly Close