Closer Look

**American Diabetes Association 74th Scientific Sessions**

**June 13-17, 2014; San Francisco, CA - Posters - Draft**

## Executive Highlights

*In this report, we bring you full details on the 19 standard posters and the additional 13 late-breaking posters we covered at this year's ADA. It was a packed and bustling poster hall this year, with over 2,000 total poster presentations in over 50 categories. Some of the new data that we were most excited to see arrived in the form of posters, including the first ever full phase 3 results on SGLT-2 inhibitor/DPP-4 inhibitor fixed-dose combinations (FDCs). Poster 127-LB on AZ's saxagliptin/dapagliflozin and posters 129-LB and 130-LB on Lilly/BI's empagliflozin/linagliptin both demonstrated very impressive A1c reductions (solidly above 1%, and close to 1.5% with saxagliptin/dapagliflozin, although patients in that trial had a high mean baseline of 8.9%), although neither FDCs' efficacy was truly additive or synergistic.*

*Some of the biggest GLP-1 agonist data of the conference were also presented as posters, including the much-awaited full results from the AWARD-6 head-to-head study of Lilly's once-weekly newcomer dulaglutide and Novo Nordisk's once-daily market leader Victoza (liraglutide). Those results showed that dulaglutide was non-inferior to liraglutide with respect to A1c lowering, although Victoza maintained a slight weight loss advantage in the face of dulaglutide's convenience advantage (110-LB). We saw full results from the FREEDOM-1HBL study of Intarcia's potentially game-changing implantable exenatide mini-pump (114-LB), in which patients saw a fairly A1c reduction of 3.2%, from a high baseline of 10.9%.*

*There were additionally with high-caliber presentations on SMBG, CGM, and insulin pumps. We got to see the results of Medtronic's Opt2mise study on the safety and efficacy of insulin pumps relative to MDI (102-LB). From a mean baseline of 9.0%, patients on insulin pumps saw a mean A1c reduction of 1.1% relative to a reduction of 0.4% with MDI, a statistically significant difference (p<0.001).*

*Details on the Close Concerns' poster on the skyrocketing costs of diabetes in the US (projected to be nearly half a trillion by 2030, not including indirect costs) are included below, as well as coverage of a poster from our sister market research company dQ&A on the stigma of diabetes and diabetes treatment. Titles of the most notable posters we covered are highlighted below in yellow, while the posters that were not included in our day-of coverage are highlighted in blue.*

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## Posters

### CGM

**CGM IS NOT A LIMITING FACTOR IN ARTIFICIAL PANCREAS SYSTEMS (75-LB)**

**T Bailey, K Nakamura, A Chang, M Christiansen, D Price, A Balo**

*This exciting poster shared in-clinic data from 51 patients that wore a version of the G4 Platinum with an improved algorithm (called "G4AP" in previous Dexcom presentations). The device's accuracy was compared to YSI and fingerstick values (Bayer Contour USB) on days one, four, and seven. The poster also compared the accuracy of Bayer Contour USB values to YSI - a clear move from Dexcom to demonstrate that its next-gen CGM accuracy is approaching fingersticks. Overall G4AP MARD vs. YSI was an impressive 9.0%, compared to a fingerstick MARD of 5.6% vs. YSI. Notably, G4AP and fingersticks had a similar mean absolute difference (MAD) in hypoglycemia vs. YSI: 6.4 mg/dl and 4.2 mg/dl, respectively. In addition, the Clarke Error Grid data vs. YSI suggested G4 AP is really approaching the clinical accuracy of fingersticks- A+B Zone data was nearly identical (99.5% with G4AP vs. 99.6% with the Contour USB) and A-Zone accuracy was quite similar (92% vs. 99%). Overall, we thought the data were very, very strong and showed highly impressive accuracy using Dexcom's existing G4 Platinum sensor and an improved algorithm - this hits the "holy grail" bar of a sub-10% MARD for CGM, a level of accuracy that some have called for to safely run tight closed loop control. This poster also underscored how much inherent inaccuracy there is in SMBG, and it makes us even more encouraged about the possibility of an insulin-dosing claim and factory calibration. A presentation later in the day noted that the "Share AP receiver" with the G4AP algorithm will be available for artificial pancreas research use in December 2014 (US) and 1Q15 (EU). We're not sure if this would be rolled out to consumers, but are optimistic.*

- **The poster concludes, "The clinical performance of this CGM is approaching that of current SMBG systems, particularly after the first day of use and in hypoglycemia ranges.** The system could be adequate for use in diabetes management decisions without the need for SMBG tests, in particular for reducing hypoglycemia. Accordingly, the CGM accuracy should not limit AP development." Given how many patients already use their existing G4 Platinum CGMs to dose insulin (technically "off label"), we agree and believe that G4AP surpasses the bar for independent diabetes management decisions.
- **This clinical trial enrolled 51 patients at three US centers.** Patients inserted and wore one sensor for seven days and participated in three 12-hour clinic sessions (days one, four, and seven) with YSI every 15 minutes and SMBG capillary tests every 30 minutes. Glucose was manipulated to provide sufficient data in low and high glucose ranges during the clinic session. The CGM was removed at the end of the seven-day wear. The closest matched data point between CGM, SMBG, and YSI were used to assess CGM performance. The fingerstick meter used was a Bayer Contour USB. The CGM calibration scheme was twice daily fingersticks, prospectively calibrated.
- **The science behind the G4AP algorithm was described by Garcia et al., *JDST* 2013.** The G4AP employs the same sensor and transmitter as the G4 Platinum, but contains updated denoising and calibration algorithms for improved accuracy and reliability. The JDST study used a retrospective G4AP algorithm application to the G4 Platinum pivotal study data. This poster reports on the prospective, clinical use of the G4AP algorithm - as we understand it, the G4AP clinical data (overall MARD: 9.0%) is even better than the retrospective data (overall MARD: 11.7%) because the study execution was better.

| | G4AP vs. YSI | SMBG vs. YSI | G4AP vs. SMBG |
|---|---|---|---|
| **Matched pairs** | 2,263 | 994 | 2,992 |
| **Overall MARD**<br>*On Day 1* | 9.0%<br>*10.7%* | 5.6%<br>*5.3%* | 11.2%<br>*12.7%* |

| | | | |
|---|---|---|---|
| *On Day 4*<br>*On Day 7* | *8.0%*<br>*8.5%* | *4.9%*<br>*6.6%* | *10.9%*<br>*9.9%* |
| **MAD in Hypoglycemia(<70 mg/dl)** | 6.4 mg/dl | 4.2 mg/dl | 7.8 mg/dl |
| **Overall Clarke Error Grid** | A+B Zones: 99.5%<br>A Zone: 92.4% | A+B Zones: 99.6%<br>A Zone: 98.5% | A+B Zones: 99.6%<br>A Zone: 98.5% |
| **% within 20%/20 mg/dl** | 93% | 99% | 87% |

**RATE-OF-CHANGE DEPENDENCE OF THE PERFORMANCE OF TWO CGM SYSTEMS DURING INDUCED GLUCOSE EXCURSIONS (846-P)**

**S Pleus, C Haug, M Link, E Zschornack, G Freckmann, K Obermaier, M Schoemaker**

*The authors compared the accuracy of two CGM systems: the Dexcom G4 and a prototype CGM system developed by Roche. This Roche-funded study enrolled 10 patients with type 1 diabetes who each spent about a week wearing four sensors simultaneously (two G4, two prototype). In an interesting wrinkle, the authors compared the performance of the sensors during two induced glucose excursions, which occurred roughly 40 hours and 70 hours after sensor placement. Measurements were compared to reference blood glucose readings drawn every 15 minutes during the excursions. (According to the poster these blood glucose measurements were also used for calibration; we are not sure exactly what this means or how it affected the results.) Notably, the G4 had numerically higher MARD than the prototype in every category of glycemic rate of change assessed, suggesting that the Roche sensor could be more clinically useful while glucose levels are rising or falling. The mean seven-day MARD was 10.9% for the G4 and 8.6% for the prototype. More than 80% of the prototype sensors had overall MARD below 10%, as compared to 20% of the G4 sensors.*

| | Dexcom G4 | | | Roche Prototype | | |
|---|---|---|---|---|---|---|
| Rate of Change (mg/dl/min) | MARD (%) | SD (%) | n | MARD (%) | SD (%) | n |
| < -3 | 24.9 | 15.6 | 46 | 10.6 | 8.4 | 44 |
| ≥ -3 to < -2 | 19.2 | 13.0 | 75 | 10.9 | 9.4 | 73 |
| ≥ -2 to < -1 | 17.1 | 12.5 | 151 | 9.8 | 8.4 | 144 |
| ≥ -1 to < 0 | 12.6 | 10.1 | 227 | 8.2 | 6.3 | 217 |
| ≥ 0 to < 1 | 11.3 | 9.1 | 88 | 10.0 | 10.6 | 83 |
| ≥ 1 to < 2 | 19.5 | 12.2 | 44 | 10.2 | 9.7 | 39 |
| ≥ 2 to <3 | 21.1 | 14.0 | 28 | 12.2 | 7.4 | 28 |
| ≥ 3 | 29.6 | 11.9 | 44 | 16.3 | 12.4 | 44 |

**CLINICAL BENEFIT IN GLYCEMIC CONTROL USING A LONG-TERM, IMPLANTABLE, CONTINUOUS GLUCOSE MONITORING SYSTEM IN A 90-DAY FEASIBILITY STUDY (837-P)**

**C Mdingi, R Rastogi, A Dehennis**

*In this poster, Senseonics presented 90-day data (45 days blinded + 45 days unblinded) on its implantable CGM system (fluorescence-based sensor, body-worn transmitter with Bluetooth connectivity, and a mobile smartphone app). Twelve patients took part in the three-month study, and sensor accuracy was compared to YSI at in-clinic visits every ~14 days. Overall MARD vs. YSI was a strong 11%, ranging from a low of 7.7% to a high of 17.7%. The Clarke Error Grid showed 85% of points in Zone A and 14% in Zone B (n=1,890 paired CGM-YSI points). However, the poster did not divulge the calibration scheme, in-clinic glucose ranges, or specific study design details/protocols, so it's hard to know how real-world this accuracy is. [From the Clarke Error Grid, the vast majority of points appeared to fall in the 70-180 range.] There was also no mention of the percentage of sensors lasting 90 days or any details on explantation. Indeed, the poster was really focused on comparing the 45-day blinded period of sensor wear to the 45-day unblinded (i.e., real-time) sensor wear - average glucose significantly improved from 175 mg/dl (blinded) to 156 mg/dl (unblinded), which included a 7% reduction in hyperglycemia, a 1% reduction in hypoglycemia, and an 8% improvement in time in range (75-180 mg/dl). Overall, these feasibility results are encouraging, but we would like to see a longer, larger, and more real-world study, along with more details on the sensor's calibration scheme.*

### SMBG

**HYPOGLYCEMIA PREDICTION USING SMBG DATA AND PATIENT MEDICATION INFORMATION (397-P)**

**B Sudharsan, M Shomali**

*This poster presented the latest update to WellDoc's exciting type 2 diabetes hypoglycemia prediction model, which was first unveiled at DTM 2013. The original model accurately predicted hypoglycemia risk (90% of the time) on the following day based on seven prior days of infrequent SMBG data (e.g., ~1 test per day) - this poster explored the additional benefit of adding patient medication information (drug dosing and class: short-acting insulin, long-acting insulin, pre-mix insulin, orals). Notably, the enhanced model was also constructed to predict the hour of the occurrence of hypoglycemia on the following day, a big step over the previous model's aim to predict whether hypoglycemia would occur in the next 24 hours. Adding medication information significantly boosted the model's specificity for accurately predicting hypoglycemia - 92% in the enhanced model vs. 70% in the previous SMBG-only model. The model's sensitivity for predicting hypoglycemia remained high at 89%, comparable to the prior model's 92% sensitivity. The study concluded that real-world SMBG frequency (~1 test per day) and medication information can provide adequate data to predict hypoglycemia in type 2 diabetes. The plan is to eventually incorporate this prediction module into BlueStar, WellDoc's FDA-approved mobile prescription therapy for type 2 diabetes We continue to be impressed by the company's approach, which centers on using data, algorithms, and real-time feedback to help patients better manage diabetes with minimal provider burden.*

- **As we understand it, the WellDoc clinical and behavioral R&D team intends to optimize the patient education and coaching around predicted hypoglycemia, and then incorporate the hypoglycemia prediction model into BlueStar.** Once incorporated, BlueStar's automated, real-time coaching will educate patients about how to best manage and avoid hypoglycemia. From a patient perspective, this system would be an incredible asset to managing diabetes, particularly in those who don't test very often or are at high risk of severe hypoglycemia.
- **The researchers used de-identified self-monitored blood glucose (SMBG) data and medication information from a randomized controlled trial (Quinn et al., 2011) to train a probabilistic model.** For each data sample, 11 SMBG data points were used in the seven days prior to a hypoglycemic event (defined as SMBG <70 mg/dl). Control samples used for training contained no hypoglycemia on the eighth day. The model was constructed to predict the hour of the occurrence of hypoglycemia. In order to validate the model after training, 2,099 samples not used

for training the model were presented to the model without the SMBG data from the eighth day. Sensitivity and specificity for predicting the hour of hypoglycemia or no hypoglycemia on day eight were then calculated. Further validation was performed with another distinct data set of 524 samples.

- **The model is grounded in a key assumption: most type 2s are not CGM users or high frequency testers.** As a result, this model was designed to work based on a very real-world testing frequency observed in type 2 patients. Indeed, we think a model based on one test per day is pretty magical from a clinical and commercial relevancy standpoint. The hypoglycemia prediction is especially relevant in type 2s, where there are more patients on hypoglycemia-causing agents than there are type 1s in total.
- **We'd note that WellDoc has been pretty quiet following January's $20 million Series A round of financing** (led by Merck's prestigious Global Health Innovation Fund) - the investment was expected to fund a dedicated sales force to regionally rollout BlueStar.

### Insulin Delivery

**EFFICACY AND SAFETY OF INSULIN PUMP THERAPY IN TYPE 2 DIABETES: THE OPT2MISE STUDY (102-LB)**

**Y Reznik, O Cohen, I Conget, R Aronson, S Runzis, J Castaneda, S De Portu, SW Lee, Opt2mise Study Group**

*This poster presented the long-awaited results from the randomized, six-month Opt2mise trial, comparing insulin pump therapy (n=168) to MDI (n=163) in type 2 patients in poor control (mean A1c: 9.0%). Following a run-in phase, patients were 1:1 randomized to either use a pump or MDI. From a baseline of 9.0%, A1c declined by 1.1% in those on an insulin pump compared to 0.4% in the MDI group (p<0.001) after 27 weeks; 55% of the pump group achieved an A1c <8% vs. 28% of the MDI group. CGM data (baseline vs. six months) revealed no significant increase in hypoglycemia. Meanwhile, the group on pumps used 20% less insulin than those on MDI (p<0.001). HDL cholesterol improved by 8% in the pump group and declined by 7% in the MDI group (p=0.01). One episode of severe hypoglycemia occurred in the MDI group, while none occurred in the pump group. It was valuable to see this positive data from a randomized, controlled, multi-center study of pumps in type 2 diabetes - most importantly, we like that the investigators enrolled a population that could most use easier and more convenient approaches to insulin delivery. Given the high starting A1c of 9.0%, the magnitude of reduction (-1.1%) was perhaps not quite as high as some would have expected although patients may have been very hard to manage. We wonder if insulin titration could have been better, if a simpler device with on-body bolusing (e.g., Valeritas' V-Go or CeQur's PaQ) could have helped drive patients even lower, or if this simply underscores what a challenging population this is to manage.*

- **Following a three-visit run-in phase to optimize MDI therapy, 331 patients were randomized to six months of either pump therapy (n=168) or MDI (n=163).** The objective of the run-in phase was to optimize MDI therapy. All oral medications were replaced by metformin, and insulin therapy was intensified to >0.7 units/kg/day. During the study phase, the pump group initially used the same total daily insulin dose as before; patients randomized to MDI continued titration to target range. After six months, the MDI arm crossed over and switched to the pump. Both groups then spent months six through 12 on the pump during the study's continuation phase.
- **Patients had a mean age of 56 years, a mean 15 year duration of diabetes, a mean A1c of 9.0%,** a mean BMI of 33 kg/m$^2$, a mean total daily dose of ~109 units per day. The study had a high completion rate - 90% in the pump group vs. 96% in the MDI group.
- **From a baseline of 9.0%, A1c declined by 1.1% in those on an insulin pump compared to 0.4% in the MDI group (p<0.001) after 27 weeks;** 55% of the pump group achieved an A1c <8% vs. 28% of the MDI group. As would be expected, patients in the highest tertile of baseline A1c realized the largest improvement in A1c after six months of pump use.

| Baseline A1c Tertile | 8-8.5% | 8.6-9.2% | 9.3-11.9% |
|---|---|---|---|
| Difference in A1c Change (MDI-Pump) | -0.3% | -0.5% (p=0.01) | -1.1% (p<0.001) |

- **Despite the improved A1c, the group on pumps used 20% less insulin vs. those on MDI (p<0.001) at the end of six months.** The MDI group saw total daily insulin dose steadily increase from 106 units per day to ~120 units per day. Meanwhile, the pump group saw total daily insulin dose decline from 112 units to ~100 units per day.
- **CGM data (baseline vs. six months) revealed a significant improvement in 24-hour mean glucose, a significant reduction in hyperglycemia, and no significant increase in hypoglycemia.** CGM data was collected over six days at baseline and at the end of the study. We assume the iPro2 was used, though it was not specified.

| | Pump | MDI |
|---|---|---|
| **Change in 24-hour Mean Glucose** | -23 mg/dl* | -6 mg/dl* |
| **Change in time spent >180 mg/dl** | -226 minutes per day** | -57 minutes per day |
| **Change in time spent <70 mg/dl** | +9 minutes per day | + 5 minutes per day |

*p<0.01; **p<0.001

- **One episode of severe hypoglycemia occurred in the MDI group, while none occurred in the pump group.** There no episodes of DKA in either group. Four device-related serious adverse events occurred in the MDI group: two hyperglycemic hospitalizations (not DKA), one episode cellulitis, and one abscess.

## Incretin-Based Therapies

### EFFICACY AND TOLERABILITY OF ITCA 650 (CONTINUOUS SUBCUTANEOUS EXENATIDE IN POORLY CONTROLLED TYPE 2 DIABETES WITH BASELINE A1C >10% (114-LB)

**RR Henry, J Rosenstock, and MA Baron**

*Dr. Robert Henry and colleagues report six-month data from an open-label trial of Intarcia Therapeutics' ITCA 650 (continuous subcutaneous exenatide infusion) in 60 type 2 patients with baseline A1c >10% (FREEDOM-1HBL). The participants first received the three-month, low dose (20 mcg/day) ITCA 650 mini-pump for 13 weeks followed by the six-month high dose (60 mcg/day) mini-pump for 26 weeks. Background anti-diabetic medications were maintained for the treatment period. This initial interim analysis included data from the patients who had completed treatment up to 13 weeks (n=50), 19 weeks (n=39), or 26 weeks (25). Increasing reductions in A1c were observed at each time point: -2.5% at 13 weeks, -2.9% at 19 weeks, and -3.2% at 26 weeks. Furthermore, an impressive proportion of these patients achieved A1c reductions of ≥2% (78%), ≥3% (50%), ≥4% (22%), and ≥5% (10%). Of the cohort, 30% achieved the A1c target of ≤7% and only two patients were classified as non-responders (i.e., A1c reduction <0.05% at the time of the interim analysis). Lastly, a mean weight loss of 2.4 lbs (1.1. kg) was observed at 26 weeks. Based on these data, the authors conclude that ITCA 650 has the potential to markedly improve glycemic control in patents with severe hyperglycemia and longstanding diabetes.*

- **This study enrolled 60 type 2 patients whose high A1c level (>10%) made them ineligible to participate in the main double-blind placebo-controlled trial (FREEDOM 1).** These patients met all of the other inclusion criteria for FREEDOM 1. At baseline, the

participants had a mean age of 52 years, BMI of 32 kg/m², A1c of 10.7%, fasting plasma glucose of 248 mg/dl, and duration of diabetes 9 years. Sixty-nine percent of the cohort also used oral anti-diabetic medications and 33% were male.

- **The figure below gives mean baseline A1c and mean A1c reduction for participants completing treatment periods of 13, 19, and 26 weeks:**

| | **13 weeks** (n=50) | **19 weeks** (n=39) | **26 weeks** (n=25) |
|---|---|---|---|
| **Mean baseline A1c** | 10.8% | 10.7% | 10.9% |
| **Mean A1c at time point** | 8.3% | 7.8% | 7.7% |
| **Mean change in A1c** | -2.5% | -2.9% | -3.2% |

- **The authors note that adverse events were consistent with previous trials with ITCA 650 (data not provided).**

**EFFICACY AND SAFETY OF ONCE WEEKLY DULAGLUTIDE VS. ONCE DAILY LIRAGLUTIDE IN TYPE 2 DIABETES (AWARD-6) (110-LB)**

**KM Dungan, ST Povedano, T Forst, JGG González, C Atisso, W Sealls, JL Fahrbach**

*This poster presented the results of the long-awaited AWARD-6 trial, which found that Lilly's once-weekly GLP-1 agonist dulaglutide provided non-inferior A1c lowering relative to Novo Nordisk's once-daily Victoza (liraglutide). The open-label study randomized 599 type 2 diabetes patients on metformin. Head-to-head studies can sometimes use fairly wide non-inferiority margins (we've seen as large as 0.4%), so even though the topline results announced that dulaglutide achieved non-inferiority, there were plenty of potential surprises in the full data. However, the two drugs had similar glycemic effects - dulaglutide led to a mean A1c reduction of 1.42%, while liraglutide 1.8 mg led to a mean reduction of 1.36% (p < 0.001, baseline A1c = 8.1%). Approximately 68% of both groups achieved a final A1c of less than 7%, and seven-point SMBG profiles were effectively superimposable. The slight differences between groups emerged in the weight and hypoglycemia categories. Patients in the liraglutide arm lost an average of 3.6 kg (~8 lbs), while patients in the dulaglutide arm lost an average of 2.9 kg (~6 lbs) (p = 0.01) - we wonder if a difference that small will be perceived as clinically meaningful by HCPs. The incidence of hypoglycemia was slightly higher in the liraglutide arm (0.52 events/patient/year) than the dulaglutide arm (0.34 events/patient/year), but the number of events was so small that the difference is likely not very clinically meaningful. On the whole, the results of the study demonstrate that dulaglutide has a comparable clinical profile to liraglutide, and sets the stage for the two to compete on other points like pricing, device design, and patient preferences on does frequency.*

- **The incidence of hypoglycemia in both groups was very low, but appeared very slightly higher in the liraglutide arm.** The incidence of hypoglycemia (defined as blood sugar at or below 70 mg/dl with or without symptoms) was 0.34 events/patient/year in the dulaglutide arm and 0.52 events/patient/year in the liraglutide arm. The incidence in both groups was so low that the difference may not be clinically meaningful, whether or not it is statistically significant (which was not mentioned).
- **Liraglutide came out ahead with regards to weight loss, but only slightly.** From a mean baseline of 94 kg (~210 lbs), patients in the dulaglutide arm lost 2.9 kg (~6 lbs), while patients in the liraglutide arm lost 3.6 kg (~8 lbs). The difference was statistically significant (p = 0.01), but given that both groups achieved weight loss of ~3kg, the difference may not be highly clinically significant. Novo Nordisk management has speculated that Victoza would come out ahead on weight during previous quarterly updates, primarily because liraglutide is a smaller molecule that is believed to cross the blood-brain barrier to a greater extent and act at neural appetite regulation centers.
- **The incidence of nausea was similar between arms** - we have heard in the past that longer-acting GLP-1 agonists have less of an effect on GI motility and, as a result, generally cause less

nausea. We might have therefore expected a slight advantage for dulaglutide, but of course other characteristics of the molecule beyond PK/PD could impact GI tolerability. Approximately 19% of patients in both arms experienced nausea, while ~7-8% experienced vomiting.

- **The results of AWARD-6 make dulaglutide the only GLP-1 agonist to achieve non-inferiority to liraglutide in a phase 3 trial.**

## BETTER GLYCEMIC CONTROL AND LESS WEIGHT GAIN WITH ONCE WEEKLY DULAGLUTIDE VERSUS ONCE DAILY INSULIN GLARGINE, BOTH COMBINED WITH PRE-MEAL INSULIN LISPRO IN TYPE 2 DIABETES PATIENTS (AWARD-4) (962-P)

**J Jendle, J Rosenstock, L Blonde, V Woo, J Gross, H Jiang, Z Milicevic**

*This phase 3, open-label, 52-week study (n=884 with type 2 diabetes) compared Lilly's once-weekly GLP-1 agonist dulaglutide to the basal insulin Lantus (once-daily insulin glargine), both in combination with the mealtime insulin lispro (Lilly's Humalog). The idea that a GLP-1 agonist could actually* replace *a basal insulin is a pretty novel concept, and the authors of the poster note that AWARD-4 is the first study exploring use of a GLP-1 agonist with mealtime insulin. Impressively, results of this trial show that (as in AWARD-2) both the 0.75 mg and 1.5 mg doses of dulaglutide showed statistically greater A1c reductions at 26 and 52 weeks compared to insulin glargine (see table below). At 52 weeks, statistically more patients on dulaglutide 1.5 mg achieved an A1c goal of <7% (59%) compared to glargine (49%). The difference between dulaglutide 0.75 mg (56%) and glargine was not significant. At 52 weeks, there was no statistically significant difference between arms for achieving A1c ≤6.5%. Consistent with the other phase 3 results for dulaglutide presented at ADA, dulaglutide showed very modest weight changes (but still better than insulin glargine; see table below). Total hypoglycemia in events/patient/year was lower on dulaglutide 1.5 mg compared to glargine (44 vs. 63), but similar between dulaglutide 0.75 mg and glargine (53 vs. 63). Percentage of patients modest weight and hypoglycemia benefit of dulaglutide vs. glargine in this trial is likely explained by the background insulin lispro therapy. Patients at baseline were 59 years old, had mean A1c of 8.5%, mean BMI of 32.5 kg/m², mean insulin dose of 56 U/day, and mean diabetes duration of 12-13 years.*

| | **Dulaglutide 1.5 mg (n=295)** | **Dulaglutide 0.75 mg (n=293)** | **Insulin glargine (n=296)** |
|---|---|---|---|
| **Primary Endpoint: 26 weeks** | | | |
| A1c change | -1.64% | -1.59% | -1.41% |
| Patients with A1c <7% | 68% | 69% | 57% |
| Weight change | -0.9 kg (-1.9 lb) | -0.2 kg (-0.4 lb) | 2.3 kg (5.1 lb) |
| **Final Endpoint: 52 weeks** | | | |
| A1c change | -1.48% | -1.42% | -1.23% |
| Patients with A1c <7% | 59% | 56% | 49% |
| Weight change | -0.4 kg (-0.8 lb) | 0.9 kg (1.9 lb) | 2.9 kg (6.4 lb) |

## SAFE AND EFFECTIVE USE OF THE SINGLE-USE PEN FOR INJECTION OF ONCE WEEKLY DULAGLUTIDE IN INJECTION-NAÏVE PATIENTS WITH TYPE 2 DIABETES (122-LB)

**G Matfin, A Zimmermann, K Van Brunt, R Threlkeld, D Ignaut**

*This poster presented results from an open-label, four-week outpatient study investigating the usability of the single-use pen (SUP) designed to administer 0.5 ml of Eli Lilly's dulaglutide in injection-naïve individuals with type 2 diabetes, as assessed by the injection success rate during the final of four weekly*

*injections of placebo using the SUP. Study participants (n=211) were on average 61 years old, with diabetes duration of 7.7 years, and BMI of 31.7 kg/m² at baseline (36% of participants only had a high school education or less). All but two of the 211 participants successfully injected placebo using the SUP during their final (fourth) injection, for a success rate of over 99%. The injection success rate for the initial injection was 97.2%, suggesting ease of use without much practice. Participants reported experiencing very little injection pain, rating the pain an average across injections of 1.0 on a 0-10 scale. In addition, participants reported a significant reduction in fear of self-injecting, as assessed by the change in their average modified D-FISQ Fear of Injecting Subscale Score. The vast majority of participants found the pen easy to use, and said they would be willing to use the pen if it were available.*

**EFFECT OF SAXAGLIPTIN ON RENAL OUTCOMES (544-P)**

**O Mosenzon, D Bhatt, L Litwak, M Shestakova, G Liebowitz, B Hirshberg, A Parker, N Iqbal, B Scirica, R Ma, I Raz**

*This poster presented renal outcomes results from SAVOR-TIMI 53, the cardiovascular outcomes study for BMS/AZ's saxagliptin (Onglyza). As a reminder, SAVOR randomized 16,452 patients with type 2 diabetes and established cardiovascular disease or multiple risk factors to saxagliptin or placebo for a median follow-up of 2.1 years (presented initially at ESC 2013; stratification of results by baseline renal function presented at ACC 2014). As noted in the primary analysis, patients treated with saxagliptin demonstrated more improvement in albumin to creatinine ratio (ACR; 11% vs. 9%; p<0.01) and less worsening in ACR (13% vs. 16%; p <0.01) versus placebo-treated patients, with greatest benefit observed in patients with known baseline microalbuminuria (31.3% returned to normal albuminuria vs. 25.7%; p<0.0001). Interestingly, this effect appeared independent of glucose control, with improvement in ACR similar in patients with A1c decline of >0.5% at one year versus those without. However, this benefit to ACR did not translate to significant differences in predetermined renal outcomes with saxagliptin, including doubling of serum creatinine (HR 1.04; 95% CI 0.83-1.30), initiation of chronic dialysis, renal transplant, or serum creatinine >6.0 mg/dl (HR 0.90; 95% DI 0.61-1.32), or composite end point of death and all of the above (HR 1.08; 95% CI 0.96-1.22).*

**MEDICATION COMPLIANCE RATES OF WEEKLY ALBIGLUTIDE VS. DAILY ORAL COMPARATORS IN PHASE III TRIALS (994-P)**

**LA Leiter, RA Scott, J Ye, MC Carr**

*This study compared the rates of compliance between GSK's once-weekly GLP-1 agonist albiglutide (now Tanzeum following its recent US regulatory approval) and three once-daily oral comparators (glimepiride, pioglitazone, and sitagliptin) in HARMONY trials 3, 5, and 8. Overall compliance was consistently higher in both the albiglutide and albiglutide matching placebo groups than in any of the oral comparator groups. Low compliance was defined as ≤ 80% compliance - many providers would probably love to get long-term adherence of 80%. Low adherence was more frequent in the oral comparator groups (7.5% to 14.9%) than in the albiglutide groups (1.6% to 2.3%). Compliance was measured at each visit using pen and/or pill counts. While the results bode well for patient compliance on albiglutide, it will be important to conduct follow-up studies in real-world clinical settings. Device design has a major impact on adherence for GLP-1 agonists - see our GSK exhibit hall coverage (from today as well) for an overview of how the administration process works.*

**EFFECT OF LIXISENATIDE VS. LIRAGLUTIDE ON GLYCEMIC CONTROL, GASTRIC EMPTYING, AND SAFETY PARAMETERS IN OPTIMIZED INSULIN GLARGINE T2DM ± METFORMIN (1017-P)**

**JJ Meier, J Rosenstock, A Hincelin-Mery, C Roy-Duval, A Delfolie, HV Coester, T Forst, C Kapitza**

*This study compared the effect of Sanofi's Lyxumia (lixisenatide) and Novo Nordisk's Victoza (liraglutide) on postprandial glucose in patients with type 2 diabetes ± metformin after optimal insulin glargine titration. In an 8-week, open-label trial, patients were randomized to three treatment arms: lixisenatide 20*

*µg (n=46), low-dose Victoza (liraglutide 1.2 mg; n=44), and high-dose Victoza (liraglutide 1.8 mg; n=46). Lixisenatide showed a benefit over both liraglutide doses in lowering postprandial glucose and delaying gastric emptying. All arms benefited from decreased A1c and body weight, with liraglutide 1.8 mg arm seeing the greatest decrease in body weight. Symptomatic hypoglycemia was slightly more frequent in the lixisenatide arm (14 events vs. 9 and 10 events in the liraglutide arms), whereas more GI side effects were noted in the liraglutide treatment arms (17 in lixisenatide vs. 21 and 22 events in the liraglutide arms). One case of severe symptomatic hypoglycemia was noted in the lixisenatide arm. Overall, both lixisenatide and liraglutide provided improved glycemic control, with lixisenatide offering a greater effect on postprandial glucose and gastric emptying and liraglutide providing a slightly better safety profile. This finding is not surprising given our understanding of short-acting*

| AUC PPG (h)(mg)/dl | lixisenatide 20µg | liraglutide 1.2 mg | liraglutide 1.8mg |
|---|---|---|---|
| Baseline mean ± SD | 282.2 ± 120.9 | 280.1 ± 99.9 | 307.0 ± 103.2 |
| Week 8 mean ± SD | 63.6 ± 117.9 | 171.7 ± 95.2 | 156.7 ± 62.2 |
| LS mean change from baseline ± SD | -240.2 ± 20.0 | -131.8 ± 20.2 | -157.1 ± 21.0 |

## RELATIONSHIP BETWEEN CHANGES IN POSTPRANDIAL GLUCAGON, PATIENT CHARACTERISTICS, AND RESPONSE TO LIXISENATIDE AS ADD-ON TO ORAL ANTIDIABETICS (971-P)

**M Nauck, S Azar, L Blonde, D Dicker, MP Domingo, FG Eliaschewitz, E Nikonova, r Roussel, K Sakaguchi, L Sauque-Reyna, C Bailey**

*This poster presented an analysis of the predictors and consequences of glucagon changes in response to treatment with lixisenatide, Sanofi's once-daily "short-acting" GLP-1 agonist, as an add-on to oral therapy for type 2 diabetes. A total of 423 patients drawn from the GetGoal-M and -S trials were divided into two groups ("Greater Change" and "Smaller Change") based on the magnitude of their change in two-hour postprandial glucagon levels over the course of the 24-week study. The authors found that patients who experienced larger reductions in postprandial glucagon also displayed significantly greater improvements in a variety of efficacy and safety parameters (see table below), suggesting that lixisenatide's effects on glucagon suppression are an essential part of its overall therapeutic impact. The authors also determined that patients with newer-onset diabetes who had spent less time on their baseline oral medication regimen were more likely to end up in the Greater Change group, suggesting that lixisenatide treatment is most effective when begun early in the progression of type 2 diabetes.*

**Table: Differences in glycemic control and other parameters based on change in postprandial glucagon**

| | **Greater glucagon change** | **Smaller glucagon change** |
|---|---|---|
| **A1c reduction (average)** | 1.1% | 0.67% |
| **Fasting plasma glucose reduction (average)** | 25.2 mg/dl | 9.3 mg/dl |
| **Postprandial glucose reduction (average)** | 129.4 mg/dl | 78.22 mg/dl |
| **Weight loss (average)** | 2.3 kg | 1.2 kg |
| **Percent achieving A1c<7%** | 46.5% | 32.4% |

| | | |
|---|---|---|
| **Preprandial glucose reduction** | 31.9 mg/dl | 16 mg/dl |
| **Fasting glucagon reduction** | 17 mg/dl | 5.6 mg/dl |
| **Percent experiencing symptomatic hypoglycemia** | 6.1% | 12.9% |

*All differences listed in the table were statistically significant

- **The goals of this analysis were to determine: (i) which baseline characteristics best predicted the magnitude of postprandial glucagon reduction with lixisenatide; and (ii) whether patients who experienced greater postprandial glucagon reduction displayed differences in other efficacy and safety outcomes.** The outcomes assessed included (i) changes in A1c, fasting plasma glucose (FPG), postprandial glucose (PPG), and body weight; (ii) the percentage of patients who achieved glycemic targets; (iii) indicators of beta-cell function; and (iv) frequency of hypoglycemia.
- **The analysis involved 423 patients with type 2 diabetes on oral medications who were randomly assigned to receive once-daily injections of either lixisenatide or placebo.** The patients analyzed were participants in the GetGoal-M and GetGoal-S studies evaluating the effects of lixisenatide added to oral therapy in the treatment of type 2 diabetes. The patients in the GetGoal-M study were receiving metformin monotherapy and the patients in the GetGoal-S study were receiving either sulfonylurea monotherapy or sulfonylurea and metformin combination therapy. All patients had been diagnosed with type 2 diabetes for at least 1 year and had a baseline A1c of 7-10%.
- **Patients receiving lixisenatide were divided into two cohorts based on their change in 2-hour postprandial glucagon levels over the course of the 24-week study.** The Greater Change cohort (n=213) consisted of patients with a median change of >23.57 ng/l and the Smaller Change cohort (n=210) consisted of patients with a median change of £23.57 ng/l.
- **Short duration of diagnosed diabetes and less time on oral medications were associated with greater reductions in postprandial glucagon with lixisenatide.** Patients in the Greater Change cohort had an average diabetes duration of 7.3 years, compared to 9 years in the Smaller Change cohort. Patients in the Greater Change cohort had been treated with oral medications for an average of 4.5 years, compared to 5.7 years in the Smaller Change cohort. Multivariate regression analysis found that older patients and males were more likely to see a greater change in glucagon. In our minds, it was curious and somewhat contradictory that older age and shorter diabetes duration were both correlated with a greater change in glucagon.
- **Greater reductions in postprandial glucagon were associated with greater improvements in efficacy parameters over the course of the study.**
    - **The average A1c reduction was 1.10% for the Greater Change cohort compared to 0.67% for the Smaller Change cohort.** The average reduction in FPG was 25.2 mg/dl for the Greater Change cohort compared to 9.3 mg/dl for the Smaller Change cohort. The average PPG reduction was 129.4 mg/dl for the Greater Change cohort compared to 78.22 mg/dl for the Smaller Change cohort. All else being equal, it is not surprising that greater improvements in glucagon levels led to improved glycemic control.
    - **Patients in the Greater Change group lost an average of 2.3 kg (~5 lbs), while patients in the Smaller Change group lost an average of 1.2 kg (~3 lbs).**
    - **Approximately 47% of patients in the Greater Change cohort achieved an A1c <7% by the end of the trial compared to 32% of patients in the Smaller Change cohort.**

- **Beta-cell function:** Patients in the Greater Change cohort showed greater improvements in beta-cell function as demonstrated by a greater reduction in preprandial glucose (31.9 mg/dl compared to 16 mg/dl) and fasting glucagon levels (17 mg/dl compared to 5.6 mg/dl). The Greater Change cohort also experienced a significant increase in the HOMA-b index, while the Smaller Change cohort did not.

- **Greater reductions in postprandial glucagon were also associated with lower rates of hypoglycemia.** No patients in either group experienced severe hypoglycemia, but only 6.1% of the patients in the Greater Change cohort experienced symptomatic hypoglycemia, while 12.9% of the patients in the Smaller Change group did. This was a somewhat counterintuitive finding, as a greater change in glucagon (i.e.: less glucagon secretion) could be seen as a predictor of more hypoglycemia, not less. This phenomenon suggests that the differences in the changes in glucagon might be a manifestation of more sweeping changes in metabolic health occurring as a result of lixisenatide treatment.

### SGLT-2 Inhibitors and SGLT-1 Inhibitors

**DUAL ADD-ON THERAPY IN POORLY CONTROLLED TYPE 2 DIABETES ON METFORMIN: RANDOMIZED, DOUBLE-BLIND TRIAL OF SAXAGLIPTIN + DAPAGLIFLOZIN VS. SAXAGLIPTIN AND DAPAGLIFLOZIN ALONE (127-LB)**

**J Rosenstock, L Hansen, P Zee, Y Li, W Cook, B Hirshberg, N Iqbal**

*This poster featured the first detailed phase 3 results of AZ's SGLT-2 inhibitor/DPP-4 inhibitor fixed dose combination (FDC), saxagliptin/dapagliflozin (n=534). This 24-week study compared the FDC to each of its individual components: the SGLT-2 inhibitor Forxiga (known as Farxiga in the US; dapagliflozin) and the DPP-4 inhibitor Onglyza (saxagliptin). All patients were on background metformin. AZ released topline results from this trial in May, announcing A1c reductions of 1.5% on the saxa/dapa arm compared to 1.2% in the dapagliflozin arm and 0.9% in the saxagliptin arm (not quite additive, and definitely not synergistic, as had been hoped). From the poster, we learned that the baseline A1c in the trial was quite high: 8.9% in the saxa/dapa and dapagliflozin arms and 9.0% in the saxagliptin arm. See the table below for A1c reductions stratified by baseline A1c - across these subgroups, saxa/dapa consistently had greater A1c reductions than the other two groups, but as would be expected, the A1c-lowering effect was smaller in people with lower starting A1cs. Changes in body weight, as would be expected, seemed driven by the dapagliflozin component. The saxa/dapa group lost 2.1 kg (4.6 lb), the saxagliptin group had zero weight change, and the dapagliflozin group lost 2.4 kg (5.3 lb) from a baseline BMI of 32 kg/m² (baseline weight not specified). No adverse events of interest (including major or minor hypoglycemia, urinary tract infections, or genital infections) were any higher on saxa/dapa compared to dapagliflozin or saxagliptin. Notably, urinary tract infections on saxa/dapa (1%) were actually numerically lower than on either saxagliptin (5%) or dapagliflozin (5%) (p-value not specified), and genital infections in the saxa/dapa arm (0.6%) were the same as the saxagliptin arm (0.6%) and lower than the dapagliflozin arm (6%) (p-value not specified). Overall, it appears that the saxa/dapa combination has an excellent glycemic, weight, and safety profile compared to other oral agents (e.g., metformin, DPP-4 inhibitors, SFUs, TZDs), but is perhaps not quite as different from SGLT-2 inhibitors as had been hoped at this stage - we look forward to seeing longer term data to assess duration, etc.*

- **As reported in the topline release, both fasting plasma glucose (FPG) and two-hour postprandial glucose (PPG)** were significantly better on saxa/dapa vs. saxagliptin, but not significantly different from dapagliflozin. Mean change in FPG was -38 mg/dl on saxa/dapa from a baseline of 180 mg/dl, -14 mg/dl on saxagliptin from a baseline of 192 mg/dl, and -32 mg/dl on dapagliflozin from a baseline of 185 mg/dl. Mean change in two-hour PPG was -80 mg/dl from a baseline of 242 mg/dl on saxa/dapa compared -36 mg/dl from a baseline of 256 mg/dl on saxagliptin and -70 mg/dl from a baseline of 246 mg/dl on dapagliflozin.
- **As reported in the topline release, more people on saxa/dapa achieved an A1c goal of <7% compared to saxagliptin or dapagliflozin.** On saxa/dapa, 41% of patients got to goal,

compared to 18% on saxagliptin and 22% on dapagliflozin. Given that patients had a relatively high starting baseline A1c, this is a pretty strong finding.

| | Saxa/dapa + met | Saxagliptin + met | Dapagliflozin + met |
|---|---|---|---|
| **Baseline A1c <8% subgroup** | | | |
| Mean baseline A1c | 7.5% | 7.6% | 7.4% |
| N | 37 | 29 | 37 |
| Adjusted mean change from baseline | -0.8% | -0.7% | -0.5% |
| **Baseline A1c ≥8% to <9% subgroup** | | | |
| Mean baseline A1c | 8.4% | 8.5% | 8.5% |
| N | 56 | 51 | 52 |
| Adjusted mean change from baseline | -1.2% | -0.5% | -0.8% |
| **Baseline A1c ≥9% subgroup** | | | |
| Mean baseline A1c | 10.0% | 9.9% | 10.0% |
| N | 65 | 63 | 62 |
| Adjusted mean change from baseline | -2.0% | -1.3% | -1.9% |

## FIXED DOSE COMBINATIONS OF EMPAGLIFLOZIN/LINAGLIPTIN FOR 24 WEEKS IN DRUG-NAÏVE PATIENTS WITH TYPE 2 DIABETES (T2DM) (129-LB)

**A Lewin, R DeFronzo, S Patel, D Liu, R Kaste, HJ Woerle, UC Broedl**

*The first of two phase 3 posters on Lilly/BI's Jardiance/Trajenta (empagliflozin/linagliptin; "empa/lina") presented the results of a study in 667 drug-naïve type 2 diabetes patients. There has been a great deal of excitement about the combination of DPP-4 inhibitors and SGLT-2 inhibitors, as the combination of an insulin-dependent and insulin-independent mechanism of action were thought to potentially yield additive or synergistic efficacy. While the efficacy seen with the high-dose FDC (empagliflozin 25 mg/linagliptin 5mg) was certainly strong for an oral compound, it fell well short of additive efficacy - in fact, it did not achieve a statistically significantly greater A1c reduction than dapagliflozin monotherapy. Empa/lina 25 mg/5 mg yielded a mean A1c reduction of 1.08% after 24 weeks, compared to -0.67% with linagliptin 5mg (p<0.001) and -0.95% with empagliflozin 25 mg (p = 0.179), from a baseline of ~8%. From what we could tell, the results may have been dampened by a weaker-than-expected performance from the high-dose FDC group, as the lower-dose FDC (empa 10 mg/lina 5 mg) had a greater mean A1c reduction (-1.24%) and achieved statistically significantly better efficacy than its component monotherapy doses. A sub-analysis in patients with a baseline A1c at or above 8.5% yielded slightly more logical results: although the high-dose FDC once again did not achieve significantly greater A1c reduction than empagliflozin 25 mg monotherapy, it was not less effective than the lower-dose FDC. Although the results were not altogether negative (A1c reductions of over 1% for an oral are impressive), it was somewhat disappointing to not see truly additive efficacy with the combination.*

- **The phase 3 study randomized 677 drug-naïve type 2 diabetes patients** - 667 completed the trial. Patients were randomized to one of five treatments: empagliflozin 25 mg/linagliptin 5 mg,

empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg. The poster presented 24-week data, but the study will go on for a total of 52 weeks.

- **Empa/lina demonstrated solid efficacy and non-glycemic effects, but the high-dose combination performance was weaker than we might have expected.** The high-dose combination fell short of the low-dose combination across categories, from A1c reduction (1.08% vs. 1.24%, respectively), the number of patients reaching an A1c goal of below 7.0% (55% and 62%, respectively), and weight loss (-2.0 kg [~4 lbs] and -2.7 kg [6 lbs]). While the A1c reductions seen with the low-dose combination were statistically significantly greater than those seen with its component monotherapies, the high-dose combination did not achieve statistical superiority over high-dose empagliflozin monotherapy, although it did over linagliptin monotherapy. The percentage of patients achieving a final A1c below 7.0% provided a more positive framing of the data than did the raw mean A1c reductions.
- **As opposed to the metformin add-on trial (see 130-LB below), empa/lina did not demonstrate significant reductions in fasting plasma glucose relative to empagliflozin monotherapy.** The combinations did achieve reductions in FPG over linagliptin monotherapy, on the order of ~23 mg/dl.
- **Interestingly, in this study, there was no clear increase in genital infections with empagliflozin, either as monotherapy or in combination with linagliptin**. However, the number of overall events was quite small. Other adverse events were more or less balanced between groups.

## FIXED-DOSE COMBINATIONS OF EMPAGLIFLOZIN/LINAGLIPTIN FOR 24 WEEKS AS ADD-ON TO METFORMIN IN PATIENTS WITH TYPE 2 DIABETES (T2DM) (130-LB)

**R DeFronzo, A Lewin, S Patel, D Liu, R Kaste, HJ Woerle, UC Broedl**

*The second of two phase 3 posters on Lilly/BI's Jardiance/Trajenta (empagliflozin/linagliptin; "empa/lina") presented the results of a study in 674 type 2 diabetes patients on background metformin. As opposed to the other empa/lina poster, the efficacy results here were more logical and consistently statistically significant. From a baseline of ~8%, the high-dose combination (empa 25 mg/lina 5 mg) arm achieved a mean A1c reduction of 1.19%, which beat out the 0.62% reduction with empagliflozin 25 mg and 0.70% reduction with linagliptin 5 mg - we found it interesting that linagliptin had numerically greater efficacy than empagliflozin in this trial. The lower-dose combination (empa 10 mg/lina 5 mg) achieved a mean A1c reduction of 1.08%, while the empagliflozin 10 mg arm achieved a mean reduction of 0.66%. Over 60% of patients on the high-dose combination achieved a final A1c below 7%, while only 33% of empagliflozin 25 mg patients and 36% of linagliptin patients achieved that goal. Weight loss appeared to be tied to the empagliflozin dose - empagliflozin 25 mg (with or without linagliptin) led to a mean weight reduction of ~3 kg (~7 lbs), while empagliflozin 10 mg (with or without linagliptin) led to about a pound less weight loss. Genital infections were more common with empagliflozin, but the relationship did not appear to be dose-dependent. Overall, the combination (and each of the component monotherapies) was well tolerated. Although the A1c reduction for the combination was not additive, the percentage of patients who achieved a goal of < 7.0% was fairly close to additive.*

- **The study enrolled 686 type 2 diabetes patients on background metformin** - 674 patients completed the study. Patients were randomized to one of five treatments: empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg. The poster presented 24-week data, but the study will go on for a total of 52 weeks.
- **Both empa/lina arms achieved a mean A1c reduction over 1%**. From a mean baseline of ~8%, the empa 25 mg/lina 5 mg arm achieved a mean A1c reduction of 1.19%, which was significantly greater than the 0.62% reduction in the empagliflozin 25 mg arm and 0.70% reduction in the linagliptin arm. We found it interesting that linagliptin beat out empagliflozin - it seemed like the high-dose empagliflozin arm performed worse than might have been expected. The empa 10 mg/

lina 5 mg arm achieved a mean A1c reduction of 1.08%, relative to a 0.66% reduction in the empagliflozin 10 mg arm. All comparisons between the combination arms and component monotherapies were highly statistically significant.

    - **The poster also broke out mean A1c reductions for patients with a baseline A1c at or above 8.5%.** From a mean baseline of ~9.1%-9.3%, the high-dose combination group experienced a mean reduction of 1.84%, the low-dose combination group experienced a mean reduction of 1.61%, the high-dose empagliflozin group experienced a mean reduction of 1.22%, the low-dose empagliflozin group experienced a mean reduction of 1.29%, and the linagliptin arm achieved a mean reduction of 0.99%. All comparisons between the combination arms and the component monotherapies were highly statistically significant.
    - **Empa/lina helped more patients achieve an A1c goal of less than 7%.** Approximately 62% of the high-dose combination group and 58% of the low-dose combination group achieved that goal, compared to 33% of the high-dose empagliflozin group, 28% of the low-dose empagliflozin group, and 36% of the linagliptin group.
    - **Both empa/lina combinations achieved significantly greater fasting plasma glucose reductions than the component monotherapies.** The difference between the high-dose combination and high-dose empagliflozin was 16 mg/dl, while the difference between the high-dose combination and linagliptin was 22 mg/dl.

- **The reduction in weight from baseline appeared to largely be a function of the empagliflozin dose, independent of combination with linagliptin.** The high-dose combination arm and high-dose empagliflozin arm lost 3 kg (~7 lbs), while the low-dose combination and low-dose empagliflozin groups lost 2.5 kg (~6 lbs). The linagliptin group lost less than 1 kg (~2 lbs).
- **Adverse events were generally balanced between groups.**

**SODIUM GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITION WITH EMPLAGLIFLOZIN REDUCES MICROALBUMINURIA IN PATIENTS WITH TYPE 2 DIABETES (1125-P)**

**D Cherney, M von Eynatten, S Lund, S Kaspers, S Crowe, H Woerle, T Hach**

*This study pooled data from four phase 3 randomized, controlled trials to examine the effect of empagliflozin on urine albumin to creatinine ratio (UACR) in type 2 diabetes patients with microalbuminuria. Of the 2,477 patients who were randomized to placebo or empagliflozin in the 24 week trials, 458 patients on placebo (n=157), empagliflozin 10 mg (n=146), and empagliflozin 25 mg (n=155) started with microalbuminuria (UACR 30-300 mg/g). At week 24, patients on empagliflozin had significantly lower UACR for both the 10 mg (30% reduction; p <0.001) and 25 mg (25% reduction; p=0.004) dose. Finally, the treatment group did not have more adverse events than the control. These findings suggest that SGLT-2 inhibitors like empagliflozin could be renal-protective. Only one SGLT-2 inhibitor is being studied in a renal outcomes trial, J&J's Invokana in CREDENCE.*

- **The three groups of patients with microalbuminuria had similar baseline characteristics in terms of mean A1c, blood pressure, BMI, UACR, eGFR, age, and time since diagnosis of diabetes.** Mean A1c levels for the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups were 8.13%, 8.26%, and 8.18%. Average blood pressure was 132.0, 132.8, and 133.6 mmHg, and average UACR was 61.9, 57.5, and 60.1 mg/g, respectively. Mean BMI was ~28-29 kg/m$^2$ and mean age was ~55-57 years.
- **Patients with microalbuminuria treated with empagliflozin displayed a significant reduction in A1c and blood pressure.** At week 24, patients on empagliflozin 10 mg and 25 mg showed significant placebo-adjusted reductions in A1c of 0.56% from a baseline of 8.26% (p <0.001) and 0.62% from a baseline of 8.18% (p <0.001). After accounting for placebo effects, blood pressure for these groups also decreased by 3.6 mmHg (p=0.011) and 3.5 mmHg (p=0.012), respectively.

- **Of all the patients in the four clinical trials, patients with microalbuminuria experienced a greater relative reduction in UACR.** For the overall pooled population (n=2349), the percentage decrease in geometric mean UACR at week 24 for the empagliflozin 10 mg and 25 mg groups were only 10%, compared to 30% and 25% for the patients with microalbuminuria.

**LX4211, A DUAL INHIBITOR OF SGLT1/SGLT2, REDUCES POSTPRANDIAL GLUCOSE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND MODERATE TO SEVERE RENAL IMPAIRMENT (132-LB)**

**P Lapuerta, A Sands, I Ogbaa, P Strumph, D Powell, P Banks, B Zambrowicz**

*Dr. Pablo Lapuerta and colleagues present the results of a double-blind randomized, seven-day trial of Lexicon Pharmaceuticals' LX4211 in 31 type 2 patients with moderate to severe renal impairment (mean baseline eGFR of 43 ml/min/1.73m²; other baseline characteristics detailed below). The participants were randomized to LX4211 400 mg once daily (n=16) or to placebo (n=15) in additional to their insulin therapy or oral anti-diabetic medication, with a treatment period of seven days. A standard breakfast meal was administered on days -1, 1, and 7, and data on glucose and GLP-1 were measured 15 minutes before the breakfast, as well as 1, 2, 2.5, 3, and 4 hours post-breakfast. LX4211 treatment resulted in statistically significant reductions in post-prandial glucose vs. placebo (which were evidence in patients with eGFR <45 ml/min/1.73m²), as well as reductions in fasting plasma glucose (average of -20 mg/dl; p=0.056). Participants on LX4211 also experienced statistically significant increases in post-meal total and active GLP-1 levels vs. those on placebo, which reflected the drug's inhibition of gastrointestinal SGLT-1. The authors highlight that urinary glucose excretion was only slightly elevated in the LX4211 group (37 g/24 hours) compared a minor decrease in those on placebo (-1.4 g/24 hours; p<0.001). They also note that the PK results support the use of LX4211 400 in renally impaired patients, as there was no increase in LX4211 exposure for patients with eGFR <45 ml/min/1.73m² relative to those with eGFR ≥45 ml/min/1.73m². Based on these results, the authors conclude that LX4211 improves glycemic control in type 2 patients with renal impairment and call for longer-term clinical studies in this patient population.*

- **At baseline, the participants had a mean age of 66 years, BMI of 34 kg/m², duration of diabetes of 17 years, and eGFR of 43 ml/min/1.73m².** Seventeen percent of the patients were male, and 21% were Caucasian. The participants reported recent or concomitant use of insulin (61%), SFU (39%), metformin (29%), TZD (10%), and DPP-4 inhibitors (10%). As expected, the rates of common co-morbidities were high: hypertension (90%), hyperlipidemia (90%), neuropathy (42%), and cardiovascular disease (39%).
- **The tables below detail the change in fasting plasma glucose and urinary glucose excretion, stratified by eGFR level:**

**Table 1: Fasting Plasma Glucose**

| | LX4211 vs. Placebo | p-value |
|---|---|---|
| **eGFR 45-59 ml/min/1.73m²** | -17 | 0.29 |
| **eGFR <45 ml/min/1.73m²** | -27 | 0.08 |
| **Mean for all patients** | -20 | 0.056 |

**Table 2: Urinary Glucose Excretion**

| | LX4211 | Placebo | p-value |
|---|---|---|---|
| **eGFR ≥45 ml/min/1.73m²** | 51.6 | -1.9 | <0.001 |
| **eGFR <45 ml/min/1.73m²** | 19.4 | -1.0 | 0.032 |

| | | | |
|---|---|---|---|
| **Mean for all patients** | 37.3 | -1.4 | <0.001 |

- **All adverse events were of mild to moderate intensity, and the frequency of adverse events was comparable between the LX4211 and placebo group:**

| | **LX4211** (n=16) | **Placebo** (n=15) |
|---|---|---|
| **Number of patients (%) with ≥1 treatment-emergent adverse event (TEAE)** | 7 (44%) | 5 (33%) |
| **Number of patients (%) with ≥1 drug-related TEAE** | 1 (6%) | 3 (20%) |

## EFFICACY AND SAFETY OF TWICE-DAILY REMOGLIFLOZIN FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS (1103-P)

**WO Wilkison, AP Sykes, L Kler, J Lorimer, R O'Connor-Semmes, R Dobbins, S Walker**

*This poster was one of three that Islet Sciences presented on their novel SGLT-2 inhibitor remogliflozin etabonate. This poster featured results from a 12-week dose-ranging phase 2 trial testing twice-daily remogliflozin etabonate (n=336) at five doses (50 mg, 100 mg, 250 mg, 500 mg, and 1000 mg, each twice daily). The top dose tested, 1000 mg twice-daily, achieved an impressive 1.1% placebo-adjusted A1c reduction from baseline (~8.1%) - while it is challenging to compare trials, this is the highest A1c reduction achieved by an SGLT-2 inhibitor in a 12-week phase 2 dose ranging trial, and an Islet press release referred to the results as "best-in-class efficacy". Weight loss was approximately 3 kg (~7 lbs) for both groups, and there were slight increases in LDL cholesterol and genital mycotic infections (11% in the 1000 mg dose group). Another poster (1102-P) presented efficacy and safety data on a once-daily formulation of remogliflozin etabonate - it found A1c and weight reductions that were statistically significant but less pronounced than those seen with twice-daily dosing, but a relatively low incidence of genital infections and no apparent increase in LDL (perhaps as a result of reduced nocturnal exposure). Based on these phase 2b results, Islet has developed a "biphasic" combination of immediate-release and delayed-release remogliflozin that it theorizes should preserve the efficacy of twice-daily dosing with the safety profile of once-daily dosing. The company also presented results at this ADA from a PK/PD study (1101-P) showing that the biphasic formulation achieved relatively high daytime exposure and low nighttime exposure, but only further testing will show if this characteristic results in the "best-in-class" safety and efficacy profile the company believes is possible.*

- **In the phase 2b study investigating twice-daily dosing of the original formulation:** weight loss was somewhat dose dependent, with both the 500 mg and 1000 mg doses providing about 3 kg [6.6 lb] weight loss from baseline (baseline weights for these two groups were 87 kg [191 lbs] and 89 kg [196 lbs], respectively).
    - **As with other SGLT-2 inhibitors, remogliflozin etabonate was associated in this trial with LDL cholesterol increases,** although the LDL changes did not appear to have a dose-dependent relationship with the drug (patients experienced up to a mean 13.4 mg/dl increase on the middle [250 mg] dose, but only a 9.4 mg/dl increase on the highest [1000 mg] dose).
    - **Rates of genital mycotic infections were somewhat dose dependent, with the highest rate (11%) seen in the highest, 1000 mg, dose.**
- **Read our report on the topline phase 2b results for thoughts from Islet CEO James Green on the biphasic formulation.**

## SODIUM GLUCOSE CO-TRANSPORTER-2 (SGLT2) INHIBITOR EMPAGLIFLOZIN (EMPA) IN TYPE 1 DIABETES (T1D): IMPACT ON DIURNAL GLYCEMIC PATTERNS (1051-P)

**B Perkins, D Cherney, H Partridge, N Soleymanlou, H Tschirhart, B Zinman, R Mazze, N Fagan, S Kaspers, H Woerle, U Broedl, O Johansen**

*To further analyze the effects of Lilly/BI's SGLT-2 inhibitor empagliflozin in type 1 diabetes patients, this research group used CGM to explore diurnal glycemic patterns in 40 type 1 diabetes patients on empagliflozin in a single-arm open-label pilot study lasting eight weeks. It was exciting to see measures like glucose variability as major endpoints in a trial, although the study's findings on time in zone were surprising and we've asked for follow up on this. There were some reductions in overall glucose exposure (AUC) and improvements in glucose variability, but these were not statistically significant in many cases, which was surprising. Moreover, the initiation of empagliflozin therapy caused a reduction in basal insulin dose, but a slight and not statistically significant reduction in bolus insulin dose. We were surprised that the improvements in variability and stability were as modest as they appeared to be in this trial, although the small sample size (n = 40) and lack of a comparator group likely played a role. When empagliflozin therapy was withdrawn, patients saw a rebound in glucose AUC and variability to levels that were actually above baseline, demonstrating proof-of-effect.*

- **The study compared AGP profiles at baseline, "mid-treatment," at the end of treatment, and following cessation of treatment.** The AGP profiles combined the two weeks of data into a 24-hour profile.
- **For all CGM parameters, the study revealed a general trend of improvement from baseline to mid-treatment and end-of-treatment.** However, most of these were not statistically significant. Parameters measured included glucose exposure measured as glucose AUC, glucose variability through blood glucose inter-quartile range, and glucose stability expressed as the mean hourly rate of change of glucose levels. In addition, the parameters also included time spent in hyperglycemia (>180 or >140 mg/dl), normoglycemia (70-140 mg/dl), and hypoglycemia (<70 mg/dl or <60 mg/dl).
- **Interestingly, after beginning treatment with empagliflozin, patients saw a statistically significant reduction in basal insulin (25.7 to 19.5 units, p<0.0001) but not bolus insulin (29.0 to 27.0 units, p = 0.19).** SGLT-2 inhibitors are known primarily for their effect on postprandial glucose, so one would expect to see a reduction in bolus insulin. It is possible that the modest reductions in glucose variability were enough to allow patients to better titrate their basal insulin.
- **The positive trends in glucose control were seen both during the day and during the night.** This finding does not support the theory that SGLT-2 inhibition during the day plays a disproportionate role in improving glycemia.
- **Demonstrating proof-of-effect, following cessation of treatment, glucose AUC rebounded to levels that were significantly higher than those seen at baseline despite a rebound in daily insulin dose.** Glucose stability and glucose variability demonstrated patterns following the cessation of treatment. A rebound would be expected, and is a positive sign that empagliflozin treatment had some effect while it was being administered, but the fact that final glucose exposure was higher than at baseline could indicate the lasting presence of a counterregulatory response (possibly via the glucagon axis), although there is room for it to have been a chance finding.
- **This trial suggests avenues for future study.** If empagliflozin acts in a more balanced fashion on both fasting and postprandial glucose in type 1 diabetes patients, then it would affect the titration of insulin when patients begin empagliflozin therapy. The relatively small size of the study of course limits the interpretability of its findings, but interest continues to grow in the use of SGLT-2 inhibitors in type 1 diabetes, and we expect to receive data from larger trials in coming years - AZ

recently announced plans to begin phase 3 testing of dapagliflozin in type 1 diabetes patients in 2014.

## Insulin Therapies

### RATE RATIOS FOR NOCTURNAL CONFIRMED HYPOGLYCEMIA WITH INSULIN DEGLUDEC VS. INSULIN GLARGINE USING DIFFERENT DEFINITIONS (402-P)

**S Heller, C Mathieu, R Kapur, ML Wolden, B Zinman**

*This poster presents the results of a post-hoc analysis by Novo Nordisk to determine the robustness of their previous finding that treatment with ultra-long acting insulin degludec (trade name Tresiba) led to significantly lower rates of nocturnal hypoglycemia than treatment with insulin glargine (Sanofi's Lantus) in patients with type 2 diabetes and numerically lower rates in patients with type 1 diabetes. This analysis was likely fueled by FDA criticism of the methods used in the original meta-analysis in degludec's registration packet. This new study conducts several analyses using different definitions of nocturnal hypoglycemia including i) only confirmed episodes with symptoms; ii) the ADA definition; and iii) a different time frame for the nocturnal period to show that the original findings remain robust no matter which definition of "nocturnal" or "hypoglycemia" is used. The results of these analyses confirmed the findings from the original meta-analysis under nearly all of these conditions. The one exception was when the nocturnal period was extended to 0:01-7:59, in which case hypoglycemia was reduced only in the population of patients with type 2 diabetes treated with basal-bolus therapy (and not in type 1 diabetes or in insulin-naïve type 2 diabetes). Under all other conditions, treatment with insulin degludec led to significantly lower rates in all patients with type 2 diabetes and to numerically but not significantly lower rates in patients with type 1 diabetes. The table below summarizes the rate ratio and 95% confidence intervals for all conditions (rate ratio of 1 indicates an equal rate of hypoglycemia, <1 indicates a lower rate with insulin degludec, >1 indicates a lower rate with insulin glargine). Overall, the data seems to indicate that treatment with insulin degludec may lead to significantly lower rates of nocturnal hypoglycemia in patients with type 2 diabetes compared to treatment with insulin glargine, though the less impressive results with the time period 0:01-7:59 do provide some reason for cautious skepticism.*

**Table: Rate ratio for nocturnal confirmed hypoglycemia, insulin degludec/insulin glargine**

| | **Type 2 insulin-naïve**<br>**IDeg N=1279**<br>**IGlar N=631** | **Type 2 basal-bolus**<br>**IDeg N=742**<br>**IGlar N=248** | **Type 1**<br>**IDeg N=637**<br>**IGlar N=316** |
|---|---|---|---|
| **Nocturnal confirmed hypo, original definition (0:01-5:59)** | 0.64 [0.48, 0.86] | 0.75 [0.58, 0.99] | 0.83 [0.69, 1.00] |
| **Nocturnal confirmed symptomatic hypo (0:01-5:59)** | 0.56 [0.39, 0.80] | 0.68 [0.51, 0.91] | 0.88 [0.72, 1.08] |
| **Nocturnal ADA documented symptomatic hypo (0:01-5:59)** | 0.73 [0.56, 0.97] | 0.72 [0.55, 0.93] | 0.91 [0.74, 1.11] |
| **Nocturnal confirmed hypo,** | 0.60 [0.45, 0.80] | 0.73 [0.59, 0.91] | 0.88 [0.76, 1.03] |

| | | | |
|---|---|---|---|
| **original definition (21:59-5:59)** | | | |
| **Nocturnal confirmed hypo, original definition (0:01-7:59)** | 0.93 [0.75, 1.15] | 0.77 [0.60, 0.97] | 1.00 [0.86, 1.17] |

- **This was a post-hoc meta-analysis of six 24- or 52-week randomized, controlled, open-label phase 3a trials involving patients with type 1 and type 2 diabetes and using several definitions of nocturnal hypoglycemia.** Definitions included i) confirmed symptomatic episodes; ii) symptomatic episodes with plasma glucose £70 mg/dl (the ADA definition); and iii) the original definition with a different time frame for the nocturnal period (21:59-5:59).
- **Insulin-naïve patients with type 2 diabetes treated with basal-only insulin had significantly lower rates of nocturnal hypoglycemia when treated with insulin degludec (N=1279) than with insulin glargine (N=631), using those three definitions.** The rate ratios and 95% confidence intervals with the three definitions listed above were i) 0.56 [0.39, 0.80]; ii) 0.73 [0.56, 0.97]; and iii) 0.60 [0.45, 0.80], compared to 0.64 [0.48, 0.86] in the original meta-analysis. A rate ratio of 1 indicates equal rates of hypoglycemia, a ratio <1 indicates a lower rate with insulin degludec, and a ratio >1 indicates a lower rate with insulin glargine.
- **Patients with type 2 diabetes on basal-bolus therapy had significantly lower rates of nocturnal hypoglycemia when treated with insulin degludec (N=742) than with insulin glargine (N=248), using those three definitions.** The rate ratios and confidence intervals with the three definitions were i) 0.68 [0.51, 0.91]; ii) 0.72 [0.55, 0.93]; and iii) 0.73 [0.59, 0.91], compared to 0.75 [0.58, 0.99] in the original meta-analysis.
- **Patients with type 1 diabetes had numerically but not significantly lower rates of nocturnal hypoglycemia when treated with insulin degludec (N=637) than with insulin glargine (N=316), using those three definitions.** The rate ratios and confidence intervals with the three definitions were i) 0.88 [0.72, 1.08]; ii) 0.91 [0.74, 1.11]; and iii) 0.88 [0.76, 1.03], compared to 0.83 [0.69, 1.00] in the original meta-analysis.
- **Additional analysis using 0:01-7:59 as the nocturnal period demonstrated an advantage of insulin degludec over insulin glargine only for patients with type 2 diabetes on basal-bolus therapy.** The rate ratios and confidence intervals were 0.93 [0.75, 1.15] for insulin-naïve patients with type 2 diabetes, 0.77 [0.60, 0.97] for patients with type 2 diabetes on basal-bolus therapy, and 1.00 [0.86, 1.17] for patients with type 1 diabetes.
- **Additional analysis of the maintenance period only (after the initial 16-week titration period in each trial) showed that all patients with type 2 diabetes had significantly lower rates of hypoglycemia with insulin degludec than with insulin glargine using all definitions and that patients with type 1 diabetes had significantly lower rates with insulin degludec only with the original definition.**

**GLYCEMIC CONTROL AND HYPOGLYCEMIA WITH NEW INSULIN GLARGINE 300 U/ML IN PEOPLE WITH T1DM (EDITION IV) (80-LB)**

**PD Home, RM Bergenstal, MC Riddle, M Ziemen, M Rojeski, M Espinasse, GB Bolli**

*This study presented the primary results from the EDITION IV phase 3a trial of Sanofi's new U300 insulin glargine. In the trial, patients with type 1 diabetes on background basal-bolus therapy (n=549) were randomized 1:1:1:1 to once-daily U300 or standard insulin glargine in either the morning or evening while continuing mealtime insulin. As noted in the topline results, U300 was non-inferior to standard insulin glargine in reducing A1c levels (mean change -0.40% with U300 vs. -0.44% with standard insulin glargine;*

*baseline 8.1%) at the end of six months of treatment. Rates of any time confirmed or severe hypoglycemia (<70 mg/dl) were not different between the two groups, although U300 users had reduced nocturnal hypoglycemia in the first eight weeks of treatment (HR 0.69; 95% CI 0.53-0.91). These results are similar to* EDITION III*, in which benefit to nocturnal hypoglycemia was weighted to the initial weeks of treatment - while different from* EDITION I *and* II*, it remains unclear if this will represent a meaningful benefit overall. We are curious if the inclusion of morning administration was able to reduce the risk of nocturnal hypoglycemia overall. Notably, we do note that rates of nocturnal hypoglycemia from week eight to six months of treatment was not a pre-specified main secondary endpoint for this study.*

- **This global, multi-center, open-label study, patients with type 1 diabetes (n=549) were randomized 1:1:1:1 to either U300 insulin glargine or standard insulin glargine in either the morning or evening.** Average baseline A1c was 8.1%, average BMI was 27.6 kg/m$^2$, and average diabetes duration was 21 years for both U300 (n=274) and insulin glargine (n=275) groups. Patients were followed over a six-month period. As noted across the EDITION studies, the total insulin dose at the end of the treatment period was slightly higher for U300 users (+0.19 units/kg/day from baseline) compared to standard glargine users (0.10 units/kg/day from baseline).
- **U300 demonstrated non-inferior A1c reductions compared to standard insulin glargine (mean change -0.40% with U300 vs. -0.44% with standard insulin glargine; baseline 8.1%).** There were no significant differences between the morning and evening groups.
- **Rates of any time confirmed or severe hypoglycemia (<70 mg/dl) were not different between the two groups, although U300 users had reduced nocturnal hypoglycemia in the first eight weeks of treatment (HR 0.69; 95% CI 0.53-0.91).** Rates of hypoglycemia were equal between the morning and evening groups. Overall, severe hypoglycemia was seen in 6.6% of the U300 users versus 9.5% of the standard glargine users.
- **Notably, similar to EDITION II, patients taking U300 gained significantly less weight versus standard glargine users (difference -0.56 kg [1.2 lbs]; p=0.037).** U300 users gained an average of 0.5 kg (1.1 lbs), while insulin glargine users gained an average of 1.0 kg (2.2 lbs).

**NEW INSULIN GLARGINE 300 U/ML: EFFICACY AND SAFETY OF ADAPTABLE VS. FIXED DOSING INTERVALS IN PEOPLE WITH T2DM (919-P)**

**MC Riddle, GB Bolli, PD Home, R Bergenstal, M Ziemen, I Muehlen-Bartmer, M Wardecki, L Vinet, H Yki-Jarvinen**

*Dr. Matthew Riddle and colleagues conducted two sub-studies of Sanofi's insulin glargine (Lantus) 300 U/ml comparing the effects of fixed dosing (FD) vs. adaptable dosing (AD) in 198 type 2 patients. The sub-studies were part of two larger, six-month open label studies comparing glargine 300 U/ml to glargine 100 U/ml: EDITION 1 (basal insulin plus mealtime insulin; n=53 for FD and n=56 for AD) and EDITION 2 (basal insulin plus oral anti-diabetic medications; n=44 for FD and n=45 for AD). To generate the sub-studies, participants who completed the glargine 300 U/ml on-treatment during the main trials were re-randomized to either FD (injections at 24 hour intervals) or AD (injections at 24 ± 3 hr intervals; participants were asked to use an injection interval of exactly 21 hours or 27 hours at least twice a week). Endpoint measurements were taken at month nine (three months after the re-randomization) and the intent-to-treat analysis included data from 194 patients. In both sub-studies, the primary endpoint - change in A1c - was comparable between the FD and AD groups. Similarly, the FD and AD groups had comparable rates of adverse events, overall hypoglycemia, and nocturnal hypoglycemia. Based on this data, the authors conclude that type 2 patients who occasionally adapted the timing of their glargine 300 U/ml injections did not compromise the safety or efficacy of the drug.*

- **Baseline characteristics were comparable between the FD and AD groups within each sub-study, and between the two sub-studies:** average age of 57-61 years, A1c of 7.2-7.5%, and percent male of 43-50%.

- **Variability in the timing of injections between the FD and AD groups were measured** by recording the time between two consecutive injections during the last seven days before the two endpoint assessments, which occurred one-and-a half and three months following the re-randomization. In the FD group, a low percentage of patients administered injections outside of a 24 ± 1 hr interval (13% for the EDITION 1 sub-study and 11% for the EDITION 2 sub-study). As would be expected, larger percentages were recorded for the AD group (37% and 48%, respectively). Notably, a fraction of patients in the AD group injected their insulin more than three hours above or below the standard 24-hour interval (14% for EDITION 1 and 19% for EDITION 2).
- **In both sub-studies, the FD and AD groups experienced similar changes in A1c, fasting plasma glucose, and eight-point SMPG profiles after three months** (see table below; note: A1c increased slightly in EDITION 1 sub-study). Furthermore, the participants made only small changes to their mean daily basal insulin dose, and these changes were similar across the FD and AD groups in both sub-studies.

| | **EDITION 1** | | **EDITION 2** | |
|---|---|---|---|---|
| | FD | AD | FD | AD |
| **Change in A1c** | | | | |
| Baseline A1c | 7.21% | 7.17% | 7.41% | 7.47% |
| Change | 0.21% | 0.15% | -0.12% | -0.25% |
| Mean difference between groups | 0.05% | | 0.13% | |
| **Change in Fasting Plasma Glucose** | | | | |
| Baseline FPG | 132 mg/dl | 121 mg/dl | 128 mg/dl | 129 mg/dl |
| Change | 26 mg/dl | 21 mg/dl | -8 mg/dl | -5 mg/dl |
| Mean difference between groups | 4.9 mg/dl | | -3.8 mg/dl | |

- **In both sub-studies, the FD and AD groups had similar rates of overall and nocturnal (midnight to 6 am) hypoglycemia** (see table below). Only one event of severe hypoglycemia was reported in the sub-studies (in the FD group of Edition 1).

| | **EDITION 1** | | **EDITION 2** | |
|---|---|---|---|---|
| | FD | AD | FD | AD |
| Percent experiencing any hypoglycemia* | 65% | 57% | 42% | 37% |
| Percent experiencing nocturnal hypoglycemia* | 24% | 25% | 23% | 17% |

* numbers estimated from graph

**BASAL INSULIN PEGLISPRO DEMONSTRATES PREFERENTIAL HEPATIC VS. PERIPHERAL ACTION RELATIVE TO INSULIN GLARGINE IN HEALTHY SUBJECTS (886-P)**

**RR Henry, S Mudaliar, SL Choi, TP Ciaraldi, DA Armstrong, J Pettus, P Garhyan, MP Knadler, SJ Jacober, ECQ Lam, H Linnebjerg, N Porksen, MJ Prince, and VP Sinha**

*Dr. Robert Henry et al. conducted a single-center, randomized, open-label trial comparing the sites of action of Lilly's basal insulin peglispro (referred to as LY2605541) vs. Sanofi's insulin glargine (Lantus) in eight healthy male participants (mean baseline age of 26 years and BMI of 24 kg/m²; all had fasting plasma glucose <108 mg/dl ). The study measured the drugs' abilities to suppress endogenous glucose production (EGP, which reflects their actions on the liver), as well as their abilities to stimulate the glucose disposal rate (GDR, which reflects their actions outside the liver - i.e., peripheral action). The participants underwent four eight-hour euglycemic clamp studies (maintained at 90 mg/dl): the first three with primed, continuous infusions of LY2605541 (five doses ranging from 5.1 to 74.1 mU/min), and the fourth with insulin glargine (either 20 or 30 mU/m²/min). The investigators used D-[3-³H]-glucose infusion to assess EGP and GDR. Suppression of EGP and stimulation of GDR were observed with increasing concentrations of both insulins. Notably, the LY2605541 dose needed for 100% EGP suppression had little effect on GDR. In contrast, the glargine dose required for a comparable suppression of EGP led to an increase in GDR. These results indicate that in healthy males, LY2605541 exhibits greater hepato-preferential action compared to insulin glargine.*

**INSULIN THERAPY: EXPLORING PROVIDER PERSPECTIVES ON NEEDLE PHOBIA AND NONADHERENCE (685-P)**

**J Krall, K Williams, R Gabbay, L Siminerio**

*In a BD-supported study, 23 primary care providers and three pharmacists were interviewed to assess their familiarity with and use of smaller and shorter needles as a solution for addressing problems with insulin therapy adherence. A full 70% of the physicians (n=16) reported that needle phobia is the primary challenge to initiating insulin therapy, and a striking 87% of physicians (n=20) stated that the availability of smaller needles would be an important factor in persuading patients to start injections. However, few physicians were familiar with the smallest needle available (BD's 32-gauge, 4 mm Nano needle) or the fact that shorter needles can be used in any patient regardless of weight. Only 39% (n=9) reported prescribing a specific needle - most physicians instead deferred to default options in prescribing systems or assumed that a pharmacist would choose the best needle. To add insult to injury, the pharmacists in the survey reported referring decisions to PCPs. The authors argue, and we agree, that provider education will need to be revisited in order to increase awareness of these options and ultimately improve patient adherence to insulin therapy.*

## Novel Drugs

**THE NOVEL GLUCAGON ANALOGUE ZP-GA-1 HAS SUPERIOR PHYSICOCHEMICAL PROPERTIES WHILE MAINTAINING THE PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE OF NATIVE GLUCAGON (390-P)**

**P Noerregaard, M Svendgaard, A Valeur, L Giehm, F Macchi, K Fosgerau, D Riber**

*Dr. Pia Noerregaard et al. provide in vitro and animal data indicating that Zealand Pharma's glucagon analogue ZP-GA-1 has greater solubility and stability compared to native glucagon while exhibiting a similar PK/PD profile. Specifically, ZP-GA-1 was found to have a solubility of >25 mg/ml at physiologic pH compared to native glucagon (~0.2 mg/ml). Chemical stability studies showed that after seven days at 40°C, ZP-GA-1 (1 mg/ml tested at a pH of 6.5-7) showed a lower rate of degradation (1.8%) compared to native glucagon (51%; 1 mg/ml tested at a pH of 4). In addition, a 360-day study of ZP-GA-1 at 5°C showed a degradation of 3.3% (no glucagon comparison was performed). Regarding PK/PD parameters, a crossover study in four male beagles showed that ZP-GA-1 and glucagon had similar PD profiles (based on glucose plasma concentrations) and PK profiles (based on Tmax, Cmax, and half-life) when compared as single injections or as IV infusions. The PK results were also confirmed in rats. Similarly, rat models of*

*hypoglycemia indicated that both ZP-GA-1 and native glucagon injections provided dose-dependent increases in blood glucose levels, which were restored to baseline levels or above. In concluding, the authors note that based on these data, ZP-GA-1 is suited as a liquid formulation for the treatment and/or prevention of severe hypoglycemia either as a rescue kit and/or as part of an artificial pancreas.*

**ISIS-GCGR$_{RX}$, AN ANTISENSE GLUCAGON RECEPTOR ANTAGONIST, CAUSED RAPID, ROBUST, AND SUSTAINED IMPROVEMENTS IN GLYCEMIC CONTROL WITHOUT CHANGES IN BW, BP, LIPIDS, OR HYPOGLYCEMIA IN T2DM PATIENTS ON STABLE METFORMIN THERAPY (109-LB)**

**E Morgan, A Smith, L Watts, S Xia, W Cheng, R Geary, S Bhanot**

*Dr. Erin Morgan report the results of a double-blind 13-week trial that randomized type 2 patients on stable metformin therapy to placebo (n=26) or ISIS Pharmaceutical's ISIS-GCGR$_{Rx}$ (n=23 for 100 mg dose, n=10 for 200 mg dose with load, n=16 for 200 mg dose without load). As background, ISIS-GCGR$_{Rx}$ is an antisense drug that targets the mRNA of the glucagon receptor (GCGR). Baseline characteristics were similar across the four groups (mean age of 50-57 years, BMI of 31-38 kg/m², baseline A1c of 8.6-9.1%, and fasting plasma glucose of 168-224 mg/dl). As calculated in the intent-to-treat analysis, ISIS-GCGR$_{Rx}$ provided statistically significant A1c reductions (ranging from -1.3% to -2.0%) vs. placebo (0.16%). Similar statistically significant improvements were observed for fructosamine and GLP-1 levels (data provided below). Furthermore, a higher percentage of patients in the ISIS-GCGR groups achieved an A1c of ≤ 7% (ranging from 48-75%) vs. those in the placebo group (13%). In addition, ISIS-GCGR$_{Rx}$ resulted in higher C-peptide levels during a 2-hour oral glucose tolerance test compared to placebo. The authors highlight that ISIS-GCGR$_{Rx}$ is well tolerated and did not trigger the off-target effects seen with small molecules - i.e., the investigators observed no changes in LDL-cholesterol, triglycerides, blood pressure, or body weight. The authors conclude that because ISIS-GCGR$_{Rx}$ directly reduces the production of the glucagon receptor, it may provide greater glycemic control vs. small molecule drugs, with fewer non-specific effects.*

- **A subset of participants (the 200 mg "with load" group) first received a loading dose of ISIS-GCGR$_{Rx}$ (four injections over 14 days) followed by the standard once-weekly dosing for 11 weeks.** Other participants (the 200 mg "without load" group) received the standard dosing for the entire treatment period.
- **ISIS-GCGR$_{Rx}$ provided statistically significant A1c reductions, as well as a four-fold increase in GLP-1 levels:**

| | Placebo (n=26) | 100 mg (n=23) | 200 mg (load; n=10) | 200 mg (no load; n=16) |
|---|---|---|---|---|
| Baseline A1c | 8.61% | 8.62% | 9.13% | 8.83% |
| A1c reduction at week 14* | -0.16% | -1.33% | -1.95% | -1.56% |
| Baseline GLP-1 level (pmol/l) | 5.35 | 6.83 | 8.16 | 4.76 |
| Change in GLP-1 level at week 14* (pmol/l) | -0.31 | 9.86 | 16.20 | 20.01 |

* measurements were taken one week after the last drug dose.

- **A greater proportion of the ISIS-GCGR$_{Rx}$ group achieved an A1c ≤7% compared to the placebo group.**

| | Placebo (n=26) | 100 mg (n=23) | 200 mg (load; n=10) | 200 mg (no load; n=16) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Percentage achieving an A1c ≤7% at week 14* | 13% | 48% | 75% | 56% |

* measurements were taken one week after the last drug dose.

- **ISIS-GCGR$_{Rx}$ was well tolerated:** the investigators observed no cases of symptomatic hypoglycemia and only infrequent, predominantly mild injection site reactions that resolved rapidly. The authors note that while ISIS-GCGR$_{Rx}$ did increased liver enzyme levels, these target-related ALT elevations were "consistent with the pharmacology of glucagon receptor inhibition and similar to those observed with small molecule glucagon inhibitors" (mean ALT elevation was 1.6x ULN for the 100 mg group and 2.7x ULN for the 200 mg group). The liver enzyme elevations declined after drug discontinuation, and ISIS-GCGR$_{Rx}$ had no effect on liver function or bilirubin.

## LEUCINE AMPLIFIES THE EFFECTS OF METFORMIN ON INSULIN SENSITIVITY AND GLYCEMIC CONTROL IN DIET-INDUCED OBESE MICE (1108-P)

**B Xue, L Fu, F Li, A Bruckbauer, Q Cao, X Cui, R Wu, MB Zemel, H Shi**

*In this intriguing collaboration between NuSirt Biopharma and Georgia State University, the investigators show synergistic glycemic effects between metformin and the amino acid leucine in mouse studies. Given that metformin is associated with GI side effects that make it intolerable for a substantial proportion of patients (we've heard up to 20%), NuSirt hopes that this approach of adding leucine to metformin may enable patients to achieve similar efficacy to full-dose metformin at a lower metformin dose, thereby reducing side effects. In this study, mice fed a high fat diet for six weeks to induce hyperglycemia and hyperinsulinemia were treated with sub-therapeutic levels of metformin (the human equivalent of 150-500 mg/day) combined with the human dose equivalent of leucine 2.2 g/day. While leucine alone had no effect, the Leu+Met combination produced dose-dependent improvements on glucose tolerance within four weeks, insulin tolerance by five weeks, fasting glucose by five weeks, and HOMA-IR. Specifically, the Leu+Met 500 mg dose (the highest dose tested) produced similar effects compared to full-dose 1,500 mg/day metformin on insulin tolerance area under the curve and fasting glucose. Leu+Met 500 mg produced even statistically significantly greater improvements in area under the glucose tolerance curve and greater improvements in HOMA-IR compared to full-dose 1,500 mg/day metformin. The lower Leu+Met 250 mg dose produced statistically comparable effects to full-dose metformin with regards to all four measures of glucose tolerance, insulin tolerance, fasting glucose, and HOMA-IR. Leu+Met 150 mg only showed an effect similar to full-dose metformin for glucose tolerance, fasting glucose, and HOMA-IR, but not insulin tolerance.*

- **For background, this group has previously found leucine to activate the sirtuin/AMPK pathway, and metformin is also thought to act on this pathway.** NuSirt had previously been focused on resveratrol as a sirtuin/AMPK activator, but found that leucine, sans resveratrol, was sufficient for the effects in this study. Management remarked to us, "Although resveratrol is where we started, it is no longer a part of the NuSirt equation."
- **We would be curious to see data comparing the Leu+Met combinations to metformin 2,000 mg/day, as that is the maximum dose prescribed for many patients.** Even 500 mg/day metformin dose can produce GI side effects, so we are also curious to see which Leu+Met dose the company plans to pursue.
- **Dr. Zemel is now leading NuSirt; the company's previous approach was an over the counter one and we are glad to see this directional shift.** Joe Cook, the former CEO of Amylin, is a primary investor and we were glad to see the company's philosophical shift since there is so much "noise" on the OTC front. To be sure, this small company has very impressive leadership and is enormously mission-driven (it understands patient constraints very well) and we look forward to seeing more data.

**COSTS OF DIABETES IN THE U.S.: 1996-2030 (142-LB)**

**H Chen, MV Venkat, L Rotenstein, JP Dong, N Ran, M Yarchoan, R Kahn, K Close**

*This study (our very own!) looked at costs directly attributable to diabetes in the US from 1996 to 2010, adapting the methodology used in the ADA's five-year cost-of-illness studies, and projected costs up through 2030. Total costs rose from $64 billion in 1996 to $167 billion in 2010 - those numbers may sound low, but only because the analysis did not count the sizable indirect costs of diabetes (lost productivity, premature death, etc.). Astoundingly, annual diabetes costs were projected to rise to $494 billion by 2030 based on the historical trajectory. The primary driver for costs was increasing prevalence of diabetes. If annual diabetes incidence were reduced by 5% from the years 2010 through 2030, the US could save a cumulative total of $427 billion; a 10% reduction would lead to cumulative savings of $798 billion. A breakdown of costs encouragingly found that inpatient hospitalization costs went from a 58% share of total costs in 1996 to 46% in 2010, and were forecast to account for 36% of total diabetes costs in 2030. On the other hand, non-insulin medication costs increased the most, from 7% of total costs in 1996 to a forecasted 26% in 2030 - the authors suggest that better glycemic control could have contributed to the reduction in hospitalizations, although a cost-of-illness study cannot be used to support causation. Overall, these numbers present a compelling argument for primary prevention, as the magnitude of the costs attributable to diabetes is proportional to the size of the affected population.*

- **Investigators of this study found that the total costs directly attributable to diabetes in the US rose from $64 billion in 1996 to $167 billion in 2010, and are predicted to rise further to $494 billion in 2030.** The nearly half-trillion 2030 figure would be a whopping 196% increase from 2010, and is higher than estimates in past scientific literature.
- **Relatively modest reductions in annual diabetes incidence could save the US hundreds of billions of dollars through 2030.** A 1% reduction in annual incidence between 2010 and 2030 was projected to save a total of $87 billion, a 5% reduction was projected to save $427 billion, and a 10% reduction was projected to save $798 billion. The majority of savings would occur towards the end of the 2010-2030 time period as prevalence curves diverge from the unaffected estimate
- **In an analysis of the components of total diabetes costs, the investigators found that inpatient hospitalization costs decreased the most in terms of percentage of total diabetes costs, while non-insulin prescription medications and diabetes supplies gained the greatest share.** Care categories studied included hospital inpatient, hospital outpatient, emergency department, physician's office, nursing home, home health, prescription medications excluding insulin, insulin, and diabetes supplies. Inpatient hospitalization represented 58% of total costs in 1996, 46% in 2010, and a projected 36% in 2030. Non-insulin medications represented only 7% of total costs in 1996, 16% in 2010, and a projected 26% in 2030. The costs of diabetes supplies also increased proportionally, from a mere 3% in 1996 to 10% in 2010, and a projected 12% in 2030. The authors hypothesized that usage of medications and supplies might be contributing to reduced hospitalizations, but this is an area that needs to be explored further.
- **In a segmentation of costs by complication/primary diagnosis, the investigators found that costs associated with renal and endocrine complications are rising rapidly.** Treating nephropathy remains an area of unmet need in diabetes care, and additionally the type 2 diabetes patient population with existing renal impairment has fewer treatment options for hyperglycemia.
- **Future studies may look at demographically segmented data, quality-of-life costs, and differences between the various types of diabetes**.

## Obesity

### SUSTAINED-RELEASE NALTREXONE/BUPROPION IMPROVES GLUCOSE CONTROL IN INDIVIDUALS WITH PREDIABETES (1046-P)

**P Hollander, B Walsh, K Gilder, A Halseth**

*This poster highlighted the greater weight and glycemic benefits of treatment with naltrexone/bupropion (NB; Orexigen's Contrave) vs. placebo in overweight and obese subjects who had impaired fasting glucose, and not type 2 diabetes. The study analyzed data for a subset of participants from the Contrave Obesity Research (COR) program, which consisted of four multicenter, 56-week, Phase 3 studies in overweight and obese individuals. All subjects received either 32 mg naltrexone sustained-release/360 mg bupropion SR or placebo. At the end of 56 weeks, people taking NB lost significantly (p <0.001) more weight than the control group (9% vs. 5%). Regarding NB's glycemic effects, the NB ended the study with a greater fasting plasma glucose reduction of 11 mg/dl compared to PBO's 7 mg/dl (p <0.013). The mean fasting insulin level dropped 30.4% in the NB arm. In contrast, in the control group, it only decreased 12.9% (p <0.002). We are encouraged by these results, and hope to soon see data on whether or not these improvements in glycemic measures in people with prediabetes on Contrave conferred a reduced risk of progressing to type 2 diabetes.*

- **The analysis included 284 overweight or obese participants with impaired fasting glucose but not overt diabetes.** Results from three out of four COR program phase 3 studies were used - COR-I, COR-II, and COR-BMOD - but the COR-DM study was omitted as it included only individuals with diabetes. From these trials, only individuals with baseline fasting plasma glucose between 100 and 126 mg/dl were included in the analysis. As a result of these criteria, the analysis only examined a small subset of the COR program's initial enrollees, 284/4031 or 7%.
- **Baseline characteristics were similar between the NB and placebo groups.** At baseline, both groups had a mean age of 51 years and a mean BMI of 37 kg/m². In the placebo group, 68% of participants had dyslipidemia and 29% had hypertension, compared to 69% and 39%, respectively, for NB.
- **Participants in the NB group demonstrated greater weight loss along with better improvements in glycemic indices.** The NB group had a mean weight loss of 9% from a baseline of 104 kg (229 lbs.), compared to 5% from 102 kg (225 lbs) baseline for the placebo group. In the NB group, FG decreased from 111.1 to 100 (-11.1 mg/dl) compared to a decrease from 109.4 to 104 mg/dl (-5.4 mg/dl) in the placebo group. Fasting insulin levels decreased by 30.4% in the NB group compared to 12.9% in the control, with similar baselines of 15.5 and 15.3 micro IU/ml, respectively. Insulin resistance (as measured by HOMA-IR) improved by 37.4% in the NB arm compared to -18.6% in the placebo arm; the baseline HOMA-IR was similar between groups, 4.2 and 4.1, respectively.

## Type 1 Diabetes Therapies (Cure Related)

### PATIENTS WITH T1DM SHOW REDUCED BUT CLINICALLY SIGNIFICANT ELEVATIONS IN GLUCOSE IN RESPONSE TO GLUCAGON INJECTION IN THE PRESENCE OF LY2409021 (1038-P)

**CM Kazda, P Garhyan, Y Ding, RP Kelly, TA Hardy, C Kapitza**

*Lilly presented a study showing that type 1 diabetes patients (n=20 males) receiving a glucagon receptor antagonist (LY2409021 100 mg or 300 mg) were still responsive to exogenously administered glucagon. For background, glucagon receptor antagonists are under investigation as a potential treatment for type 1 or type 2 diabetes. One safety concern about the class is that it may hinder a patient's ability to recover from hypoglycemia, and this study aimed to test whether glucagon would still be an effective treatment for hypoglycemia in the presence of a glucagon receptor antagonist. The study found that one day after a single dose of LY2409021, intramuscular administration of 1 mg of glucagon in a fasting state resulted in a blunted but clinically significant elevation in blood glucose. As would be expected, the glucose rise in the placebo group was greatest (peaking at 202 mg/dl) followed by the 100 mg group (155 mg/dl) and the 300*

*mg group (141 mg/dl) from a baseline of ~85 mg/dl. The study did not examine the role of* endogenous *glucagon response, nor did it test the response during hypoglycemia. We hope to see those studies conducted as well.*

### Additional Topics

**INVESTIGATION OF THE PRESENCE AND IMPACT OF SOCIAL STIGMA ON PATIENTS WITH DIABETES IN THE USA (59-LB)**

**A Folias, A Brown, J Carvalho, V Wu, K Close, R Wood**

*Understanding what the social perceptions of diabetes are, and how they impact patient health are the first steps in developing intervention strategies that can reduce diabetes-related stigma and improve patient experience. Folias and colleagues surveyed 5,410 diabetes patients, including both type 1 (29%) and type 2 (71%) diabetes patients to determine whether patients felt there was a social stigma attached to diabetes [note: the patients studied are part of a larger patient panel (n=12,000) managed by dQ&A, a diabetes market research company that is a sister company of Close Concerns]. The clear majority of type 1 diabetes patients (76%) affirmed that there was a stigma attached to diabetes. Interestingly, a smaller percentage of type 2 diabetes patients (52%) reported that diabetes and its care came with a stigma - although the percentage increased further (61%) amongst type 2 diabetes patients on intensive insulin therapy (multiple daily insulin injection or insulin pump). Out of those who believed that diabetes was associated with stigma, 72% stated that the stigma was based on a perception that diabetes represents a failure of personal responsibility. Over 50% of participants strongly felt that this stigma affected them socially, and over 25% reported that social stigma impacted their ability to manage their treatment. Notably, the perception of stigma did not vary significantly by annual household income, region, education, or duration of diabetes. However, perception of stigma was found to increase with intensity of therapy, poor self-reported glycemic control, and higher BMI. Of course, this survey measured perception of stigma rather than stigma itself, but the perception of stigma is an important barrier to adherence.*

- **The 5,422 survey participants represented a wide variety of type 1 and type 2 diabetes patients, differing by age, glycemic control, treatment type, and geographic region.** Type 1 diabetes participants made up 29% of the survey pool and varied by age (13% children and 87% adults) as well as A1c (49% ≤ 7% and 51% > 7%). Type 2 diabetes participants, 71% of the respondents, included insulin users (45%) as well as non-insulin users (55%), and also varied by A1c (61% ≤ 7% and 39% > 7%). The panel also included participants who were on GLP-1 analogs (11%), multiple daily insulin injections, (MDI) (12%) ; used an insulin pump (24%); used continuous glucose monitoring (14%); and/or tested their blood glucose three or more times a day (54%). Participants were distributed through the West (21%), Midwest (25%), South (33%), and Northeast (20%) regions. Parents of children (<18 yrs) with type 1 diabetes (13%) took the survey on behalf of their children.
- **A majority of respondents with type 1 diabetes (76%), and a smaller majority of those with type 2 diabetes (52%), believed that diabetes comes with social stigma.** Within type 2 diabetes patients, perception of stigma was greater among those on intensive insulin therapy (61%).
- **Out of the respondents who perceived a stigma, a significant proportion (27% - 42%) strongly stated that it impacted their diabetes management.** Of course stigma has massive intangible impact on quality-of-life, but the way it impacts disease management is how it can most directly affect patient outcomes.
- **The majority of patients believed that people with diabetes face the perception of a failure of personal responsibility (72%), being a burden on the healthcare system (65%), and having a character flaw (52%).** These negative views may also impact how the public approaches diabetes treatment and prevention.
- **Patients with more intensive diabetes therapies, worse measured and self-reported glycemic control, or higher BMI were more likely to feel guilt, shame, or isolation due**

**to diabetes.** Just as notably, the perception of diabetes stigma did *not* appear to vary by annual household income, region, education, or duration of diabetes.

- **Broken down by categories: More parents of children with type 1 diabetes** reported experiences of guilt, shame, embarrassment, isolation, or blame due to diabetes (39%), than did adults with type 1 diabetes (38%). Next came type 2 patients on MDI or a pump (35%), while 21% of type 2 diabetes patients on oral therapies alone reported negative emotional impact of stigma.

*-- by Melissa An, Adam Brown, Eric Chang, Hannah Deming, Jessica Dong, Katherine Sanders, Manu Venkat, Nina Ran, Michelle Xie, Rebecca Xu, and Kelly Close*