Executive Highlights

Discussion of insulin therapies during ADA 2013 ran the gamut from late-stage candidates (from Sanofi and Lilly in particular) to concentrated and alternative insulin formulations (including those of Novo Nordisk, Sanofi, Biodel, and Biocon) to methods for initiating insulin therapy - it's a given today that taking insulin is challenging, that doctors aren't helping so much, and that insulin therapy must become easier in order to compete with the tolerable, simple-to-dose oral drugs that are here to stay. Notably, on the basal insulin front, Sanofi presented new data on its insulin glargine U300 formulation in an oral presentation, a poster, and a press release, as well as during its Diabetes Update webcast. The poster, first-authored by the renowned Dr. Matthew Riddle (Oregon Health and Science University, Portland, OR) discussed the six-month phase 3a EDITION I study that compared U300 glargine to standard U100 glargine in ~800 type 2 patients already on a basal/bolus regimen - U300 provided non-inferior A1c reductions compared to U100 glargine, with statistically significantly lower rates of hypoglycemia (36% vs. 46% with U100; 43-LB). We were impressed by the reduction and also moved by how prevalent hypoglycemia continues to be, even with current and next-gen analog insulins. Sanofi's press release did not provide numerical data for EDITION II (which compared glargine U300 to glargine U100 in ~800 type 2 patients on basal insulin plus oral agent[s]), though it noted the EDITION II results confirmed those from EDITION I. Additionally, an oral presentation compared U300 and U100 glargine with respect to PK and PD. Following a euglycemic clamp (given after the last injection of each day during the eight days of therapy), euglycemia was maintained for longer with U300 glargine than with U100 glargine (113-OR). We give Sanofi a lot of credit for skipping mid-phase trials and moving its next-gen insulin through the pipeline so quickly - we remember hearing only in late 2011 that Sanofi even had a next-gen basal insulin in the works (for details, see our Sanofi 3Q11 report at http://www.closeconcerns.com/knowledgebase/r/f276d4ed).

Lilly also presented new data on its novel insulin analog LY2605541 (PEGylated insulin lispro) in a poster first-authored by Dr. Julio Rosenstock (University of Texas Southwestern, Dallas, TX; 915-P). Further analysis of a phase 2 open label trial in type 1 diabetes showed that patients required lower mealtime insulin doses on LY compared to glargine because LY provided a greater reduction in daily mean blood glucose levels. We've been especially keen to learn more about this candidate since Lilly and Boehringer Ingelheim announced in January that Lilly will reassume sole worldwide development and commercialization rights. While BI attributed the decision to "independent strategic portfolio decisions," we're curious whether BI's exit reflects any concerns regarding the candidate's safety or efficacy profile. As a reminder, the phase 3 IMAGINE program for LY is ongoing and will examine the potential for flexible dosing.

ADA 2013 also included an oral presentation on the relationship between insulin exposure and cardiovascular (CV) mortality in ACCORD (386-OR). The univariate analysis looked at data from roughly 10,000 trial participants (mean follow-up time of five years) and found a 1.8-3.4-fold increase in the risk of CV death for each additional unit of insulin per kilogram body weight. However, this relationship disappeared after investigators adjusted for 14 baseline covariates. Dr. Elias Siraj (Temple University School of Medicine, Philadelphia, PA) concluded that based on these data, it does not appear that insulin dose was an independent risk factor for CV mortality in ACCORD, though he hesitated to generalize the results to the broader context of insulin therapy use.

A symposium on new insulin preparations covered the clinical use of concentrated insulin formulations, new insulin formulations, and alternative insulin delivery systems. Dr. Mary Korytkowski (University of Pittsburgh, Pittsburgh, PA) discussed the use of U500 insulin before briefly commenting on two up- and-

coming concentrated insulins - Novo Nordisk's U200 insulin degludec and Sanofi's U300 insulin glargine. Dr. Thomas Donner (Johns Hopkins University, Baltimore, MD) noted that ultra-long-acting and ultra-rapid-acting insulins could provide advantages over current formulations and gave a sweeping review of new insulin candidates, covering insulin degludec, LY2605541, BIOD-123, and FIAsp. While we agree with the potential benefits of new formulations, we believe the current debate regarding new vs. old insulins centers on whether the newer formulations provide enough incremental benefit to justify their higher prices; for details on this debate, in particular on an article by Dr. David Nathan, please see our report at http://www.closeconcerns.com/knowledgebase/r/7aaf1b85. In his review of alternative insulin delivery systems (transdermal, nasal, sublingual, buccal, oral, inhaled, and intraperitoneal), Dr. William Cefalu (Pennington Biomedical Research Center, Baton Rouge, LA) focused on oral insulins, noting the potential of Biocon's IN-105, Oramed's ORMD-0801, Diabetology's Capsulin, Novo Nordisk's oral insulin candidate, and Diasome's hepatic-direct vesicles. We continue to be cautious in interpreting progress on the oral insulin front.

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Sanofi Diabetes Update

SANOFI DIABETES UPDATE

Insulin Therapies

Oral Sessions: Novel Therapeutics

NEW INSULIN GLARGINE U300 FORMULATION EVENS AND PROLONGS STEADY STATE PK AND PD PROFILES DURING EUGLYCEMIC CLAMP IN PATIENTS WITH TYPE 1 DIABETES (T1DM) (113-OR)

Thomas Jax, PhD (Profil, Neuss, Germany)

Dr. Thomas Jax presented steady state pharmacokinetics and pharmacodynamics results with a novel 300 U/ml formulation of insulin glargine (GlarU300) as compared to the current 100 U/ml formulation. Though single subcutaneous injections of GlarU300 have demonstrated prolonged duration of action and a flatter profile versus standard glargine in previous studies, this trial aimed to examine if these effects persist once patients are in the steady state. In the trial, patients with type 1 diabetes were randomized to receive either an eight-day regimen of 0.4 U/kg daily (n=18) or 0.6 U/kg daily (n=12) GlarU300, with crossover to an eight-day regimen of 0.4 U/kg daily dose of standard U100 glargine. When patients were monitored with a euglycemic clamp after the last injection at the end of each eight-day regimen, euglycemia was maintained for longer with the 0.4 U/kg U300 formulation (~32 hours) and 0.6 U/kg U300 dose (~34 hours) versus standard U100 glargine (~29 hours); these results were supported by a flatter and more constant profile of serum insulin glargine concentrations with GlarU300 at both doses versus standard U100 glargine as well. Dr. Jax suggested these changes could improve control while reducing the risk of hypoglycemia, though we await clinical outcomes data from the EDITION-I study, to be presented later in this meeting.

- **In the trial, patients with type 1 diabetes were randomized to receive either an eight-day regimen of 0.4 U/kg daily (n=18) or 0.6 U/kg daily (n=12) GlarU300, with crossover in 2x2 design to an eight-day regimen of 0.4 U/kg daily dose of standard U100 glargine.** Patients were monitored with a euglycemic clamp for 36 hours after the last injection at the end of each eight-day regimen.
- **Using the euglycemic clamp, euglycemia was maintained for longer with the 0.4 U/kg U300 formulation (~32 hours) versus standard U100 glargine (~29 hours), with a lower maximum glucose infusion rate as well (2.6 mg/kg/min vs. 3.4 mg/kg/min).** The 0.6 U/kg U300 patients demonstrated an even longer 34 hours of euglycemia, though a higher maximum glucose infusion rate (4.4 mg/kg/min).
- **These clamp results were supported by a flatter and more constant profile of serum insulin glargine concentrations with GlarU300 at both doses versus standard U100 glargine.** Similarly corroborative, glargine exposure was quantifiable with 0.4 U/kg GlarU300 for 32 hours and with 0.6 U/kg GlarU300 for 36 hours, with 28 hours of quantifiable exposure with 0.4

U/kg U100 glargine. The half-life for the 0.4 U/kg dose of GlarU300 was 14.4 hours, 13.8 hours for the 0.6 U/kg dose, and 11.2 hours for 0.4 U/kg standard U100 glargine.

Questions and Answers

Q: There is a lot of variability in the environments of patients, particularly with type 1 diabetes. How would you adjust for when patients need to change their dose on the fly?

A: The concept of the basal insulin is you want a steady state as much as possible. The theory is if you have a duration of action for a longer period you have a more stable glucose control. That said, this is clearly intended for once-daily subcutaneous injection, not necessarily for pump patients with rapid changes in dosing.

Q: I was a little surprised that the duration of action was not so different from standard glargine. Any comment on that?

A: Although there may only seem to be a small difference, it may make a large clinical difference. Those studies are on the way.

Comment: The duration of action is dose-dependent, so one should look at the basic insulin requirements of the people in this study beforehand.

Q: When comparing the two formulations, it looks like your data showed a peak with glargine standard when compared to the new formulation, but no peak with older studies versus NPH. Have you been able to identify populations that show more pronounced curves or others in whom it is truly flat?

A: To our knowledge, we don't know certain populations. But there are two things to remembers here. The data there was from two different studies; the graphs here also have a different scale, so the curves look a little more pronounced.

Oral Sessions: ADA President's Oral Session II

THE RELATIONSHIP BETWEEN INSULIN EXPOSURE AND CARDIOVASCULAR MORTALITY IN THE ACCORD TRIAL (386-OR)

Elias Siraj, MD (Temple University School of Medicine, Philadelphia, PA)

Dr. Elias Siraj presented an analysis of the relationship between cardiovascular (CV) mortality and insulin dose in the ACCORD randomized controlled trial. He reviewed that in ACCORD, all-cause and CV mortality were higher in patients randomized to intensive glycemic control (A1c goal of <6.0%; mean achieved A1c of 6.4%) rather than standard therapy (A1c goal of 7.0-7.9%; mean achieved A1c of 7.5%). Subsequent studies have shown that the intensively treated patients with greatest mortality were those whose A1c stayed high despite treatment; these patients also were given higher insulin doses. Therefore, the ACCORD researchers analyzed the CV hazard ratio associated with insulin exposure, as measured by updated total daily dose (units per kg body weight), in 10,163 subjects with a mean follow- up time of five years. Their univariate analysis showed a 1.8-to-3.4-fold increase in the risk of CV death, for each additional unit of insulin per body weight. However, after adjustment for 14 baseline covariates, the risk relationship disappeared. Dr. Siraj concluded that these results do not support the hypothesis that insulin dose is an independent risk factor for CV mortality in the population studied. However, he hesitated to make a "sweeping clinical recommendation" based on the study and called for additional research. During a lengthy Q&A session, several audience members disputed the study methodology (with one person even saying that he was now MORE convinced of insulin's CV risk). We expect to see much more work in the future, both to interpret ACCORD and to better understand the risks of intensive insulin therapy.

- **To analyze the effects of insulin exposure on cardiovascular mortality in ACCORD, Dr. Siraj and colleagues looked at data from 10,163 subjects with a mean follow-uptime of five years.** Insulin exposure was defined as updated average daily dosage, measured in units per

kilogram of body weight. Separate analyses were performed for all insulins, basal insulin, and prandial (aka bolus) insulin.

- **Cardiovascular risk was assessed using a and in a series of Cox proportional hazard models, including an unadjusted (univariate) analysis and four models that adjusted for increasing numbers of covariates.** The first model adjusted for 14 baseline characteristics, including age, baseline A1c, history of CV disease, QT index, amputation, presence of CDE on staff at randomization, presence of an integrated health plan, education status, use of ARBs, HDL, and measures of diabetic complications (e.g., amputation, urinary albumin:creatinine ratio). The second model adjusted for these baseline data as well as weight gain, severe hypoglycemia, and patients' assignments within the blood pressure or lipid substudies of ACCORD. The third model further adds patients' updated average A1c. Finally, atop all these other covariates, the fourth model adjusted for which glycemic treatment strategy patients were assigned. (Insulin doses were significantly higher in the intensive treatment group.)
- **Insulin exposure was associated with significantly higher cardiovascular mortality in the unadjusted analysis (1.8-to-3.4-fold increase in the risk of CV death, for each additional unit of insulin per body weight); however, an association was not seen in the adjusted models** (detailed results in the table below). The researchers concluded that these results do not support the hypothesis that insulin dose was an independent risk factor for cardiovascular mortality in the ACCORD population.

	All Insulin	**Basal Insulin**	**Bolus Insulin**
Unadjusted	1.83 (1.45, 2.31)	2.29 (1.62, 3.23)	3.36 (2, 5.66)
	p<0.0001	p<0.0001	p<0.0001
Model 1 (adjusts for baseline	1.21 (0.92, 1.6)	1.3 (0.87, 1.94)	1.65 (0.88, 3.11)
data)	p=0.1726	p=0.2073	p=0.1172
Model 2 (adds grouping in BP and	1.21 (0.91, 1.61)	1.29 (0.85, 1.95)	1.63 (0.85, 3.12)
lipid trials, severe hypo, wt change)	p=0.1912	p=0.2272	p=0.1399
Model 3 (adds updated average	1.12 (0.84, 1.49)	1.13 (0.74, 1.72)	1.48 (0.77, 2.84)
A1c)	p=0.4540	p=0.5636	p=0.2365
Model 4 (adds glycemic strategy	0.99 (0.74, 1.34)	0.94 (0.61, 1.46)	1.23 (0.63, 2.4)
assignment in trial)	p=0.9693	p=0.7955	p=0.5478

Hazard ratio (95% confidence interval) of cardiovascular mortality, per updated daily average insulin dose (units/kg)

Questions and Answers

Q: What were the findings on the relationship of insulin exposure with all-cause mortality?

A: We did not look at this.

Comment (from same questioner): It would have been obvious to do, and it seems like it could have been done with two extra hours of analysis. With model four, you are probably getting up to 30 or 40 degrees of freedom. I am actually more convinced now that there is an association. I think that you should report all-cause mortality as well.

Q: It was reassuring to see no association after adjustment. In general we shouldn't think that a high insulin dose should be dangerous in itself. We need high doses because people are very sick. It could be reverse causality. Highly insulinized patients are high in insulin resistance; maybe they die because they are very sick.

A: We wanted to do this study because of the reasons you say. Many of us see insulin-resistant patients and escalate their dosage, and we wonder if we are doing something bad. In the unadjusted model, there was a clear-cut correlation between insulin dose and CV mortality. The significance was wiped out after adjustment. We can't conclude that there is a correlation.

Q: The use of covariates could be misleading. Maybe being insulin resistant increased the risk of endpoints, but high insulin dosage increased this risk further. Insulin could be driving a problem in people who were already insulin resistant. I don't think it's disproven.

A: I don't think we said that it was disproven, just that our analysis didn't support the hypothesis.

Comment (from same questioner): There could still be a risk of giving insulin in large doses. I don't see that as disproven.

A: I think that we did a valid analysis. In model one, we took away the baseline covariates. What happened with treatment is different in different patients, so in the other models we adjusted for those factors as well.

Comment (from same questioner): The risk is masked within the covariates. Q: Would you be willing to release the data for others to analyze?

A: We will discuss this with the ACCORD group.

Q: Do you have any information on adherence to insulin administration within the study?

A: In general it was pretty good.

Comment (from same questioner): I would disagree. If A1c is elevated and you increase insulin dose, A1c will fall unless people aren't taking the insulin. If they were not taking it and their A1c stayed high, the protocol called for a progressive increase in therapies; there was a disconnect between what doctors said and what patients were doing. But every now and then people would actually take the insulin dose, which was now considerably more than what they needed. This hypothesis goes into reverse causality argument just raised, and I think the Matt Riddle paper addressed it as well.

A: But maybe patients aren't taking insulin at other levels of A1c, either. We haven't looked at noncompliance by A1c level. But if you look at the correlation by A1c and insulin level, I think that it will hold.

Q: Clearly more work is needed. What message should clinicians take from this, especially with regard to highly insulin-resistant patients?

A: I think that it is difficult to make sweeping clinical recommendation. Based on the population we have, we were not able to confirm that insulin was an independent risk factor for CV mortality. All of us continue to have this concern that we are driving the dose of insulin, because next time A1c is still above goal. I think it is still a healthy concern but that we need more data like this to confirm or refute, so we have a stronger basis for clinical decision-making.

Oral Sessions: Epidemiology of Diabetes Complications and Mortality

CANCER OUTCOMES IN PATIENTS WITH DYSGLYCEMIA ON BASAL INSULIN: RESULTS OF THE ORIGIN TRIAL (281-OR)

Louise Bordeleau, MD (McMaster University, Hamilton, ON)

Dr. Louise Bordeleau presented results from a sub-analysis of the ORIGIN trial that examined cancer outcomes. As a reminder, the ORIGIN trial was a multicenter, randomized 2x2 factorial trial that examined the effect of insulin glargine treatment vs. standard care and omega 3 fatty acid treatment vs. placebo on cardiovascular outcomes in patients at risk for CV disease who had either impaired fasting glucose,

impaired glucose tolerance, or early type 2 diabetes. Results from the trial presented at least year's ADA demonstrated no increased risk of cardiovascular outcomes or cancer with glargine treatment. This subanalysis further examined cancer outcomes in the ORIGIN trial. Data on cancer deaths and cancer-related hospitalizations was collected from the date of randomization at every visit, while cancers not requiring hospitalizations and any other cancer events since the date of randomization were ascertained starting in January 2010. 953 patients (7.6% of all patients) developed cancer during the trial, and cancer incidence was 1.32/ 100 person-years. There was no significant difference in cancer death rates or adjusted incidence of cancer between the study's glargine vs. standard care arms. There was also no significant difference in the incidence rate of common subtypes of cancer (lung, colorectal, breast, prostate) between the study's two arms. Finally, use of metformin and dose of metformin at baseline or post-randomization did not impact the risk of developing cancer. These results underscore the strong message delivered at last year's ADA about glargine's neutral effects on cancer - we continue to see this as a big win for the drug.

- **As a reminder, the ORIGIN trial was a multicenter, randomized 2x2 factorial trial that examined the effect of glargine treatment vs. standard care and omega 3 fatty acid treatment vs. placebo on cardiovascular outcomes.** It enrolled 12,537 people with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes mellitus who were at high risk of CV events; participants could not have active cancer. Participants were randomized to glargine or standard of care, and omega 3 or placebo. Patients were followed for a median of6.2 years (IQR 5.8 - 6.6 years). Data from the trial presented at least year's ADA showed that glargine treatment was not an increased risk of cardiovascular outcomes or cancer. For more details on the trial, see our ADA 2012 ORIGIN coverage at: http://www.closeconcerns.com/knowledgebase/r/10be2669
- **This subanalysis examined cancer outcomes in the ORIGIN trial.** Data on cancer deaths and cancer-related hospitalizations was collected from the date of randomization at every visit. Cancers not requiring hospitalization and any other cancer events since the date of randomization were also ascertained starting in January 2010. Cancers were classified by their primary anatomic site, status (new or recurrent), clinical consequence (death/hospitalization), certainty (definite probable or possible; definite or probable were included in analyses). 12,537 patients (35% female) with a median age of 63.5 years were included in the analysis. 82% had prior diabetes, with a mean diabetes duration of 5.4 years. Overall, 953 patients (7.6%) of patients developed cancer during the trial. Cancer incidence was 1.32/ 100 person years.
- **There was no significant difference in cancer death rate or adjusted incidence of cancer between the study's glargine vs. standard care arms.** There was also no significant difference in the incidence rate of common subtypes of cancer (lung, colorectal, breast, prostate, etc.) between the study's two arms. Analyses of baseline data suggested that those who developed cancer were older, had higher alcohol intakes, had higher rates of CV events, and were more likely to smoke. Additionally, patients with new diabetes were more likely to develop cancer. Metformin use was similar between those who did and did not develop a cancer event.
- **Use of metformin and dose of metformin at baseline and post-randomization did not impact the risk of developing cancer.** It also didn't impact the hazard ratio of cancer due to glargine. Similarly, use of metformin in combination with an SFU, A1c, and weight had neutral effects. Use of metformin and metformin dose also did not have an effect on development of breast cancer in women participants. Use of metformin with a sulfonylurea, A1c, and weight post-randomization similarly had no effect on this outcome.

Questions and Answers

Q: Why didn't you look at the effect of insulin dose on cancer outcomes the way you looked at metformin dose?

A: The insulin dose was fairly low. We did not set the trial up to do an analysis with insulin doses, so it's not something that could be done down the road.

Q: On one of the slides you showed that there were more people with no cancers among those taking SFUs. The difference was statistically significant. Yet afterwards, you analyzed SFU use along with metformin. Are SFUs protective for cancer?

A: We haven't looked at SFU use alone, but when you add metformin, it doesn't have an effect.

Q: But SFU use seems to be overrepresented in the ones without cancer.

A: These are baseline characteristics at the time of randomization. It is hard to make a causal relationship from the baseline characteristics. What is important is exposure during the trial. When we included this variable in the model, it didn't make a difference.

Q: Can you comment on the cases of pancreatic cancer?

A: This is a rare cancer. We didn't see a significant difference between the treatment arms.

Oral Sessions: Hypoglycemia-Mechanisms and Clinical Aspects

TACKLING INTRACTABLE PROBLEMATIC HYPOGLYCEMIA IN TYPE 1 DIABETES: THE DAFNE-HART PILOT STUDY (255-OR)

Stephanie Amiel, MD (King's College London, London, UK)

Dr. Stephanie Amiel presented results of the DAFNE-HART pilot study, which aimed to develop an intervention to address motivational and psychosocial factors underlying persistent impaired hypoglycemia awareness. This pilot study enrolled 24 adults with type 1 diabetes that had a median 16 episodes of moderate hypoglycemia in the six weeks prior to study start and mean patient-reported severe hypoglycemia of 3.5 events over the last year (mean baseline A1c was 7.8%). The intervention delivered included motivational interviewing and cognitive behavioral therapy to educate and alter patients' thoughts and behaviors around hypoglycemia. The program identified and addressed three "thinking traps:" 1) that one can "soldier on" through hypoglycemia; 2) there are no adverse outcomes to impaired hypoglycemia awareness; and 3) overestimation of the risks associated with hyperglycemia. Three months after engaging in the six-week course, patients' average A1c remained the same, and annualized severe hypoglycemia event rate fell from 3.5 to zero. In addition, the median number of moderate hypoglycemia events in the last six weeks fell to one. Patients wore a CGM for five days before and after the intervention, which revealed that the change in hypoglycemia was driven by a reduction in duration of daytime hypoglycemia. Measures of psychological distress improved - there was a significant change in worrying about hypoglycemia avoidance and a significant change in behaviors around low blood glucose. Audience members seemed very impressed with Dr. Amiel's results during Q&A; notably, Kaiser Permanente's Dr. Jim Dudl asked if the curriculum would be available for Kaiser or others to engage with.

Questions and Answers

Q: My question is about using CGM. To what extent do you think the technology made available to these people with alarms and whistles played a role in helping them avoid severe hypoglycemia?

A: The data I showed you were from blinded CGMs they couldn't see. A very small number of patients were already using real time CGM. We didn't give patients any new technology. What was interesting in subsequent follow-ups that will confound follow-up for this study is that - several patients have now engaged with new technology, including patients who had previously not expressed interest in doing so. So we're not just changing their hypoglycemia experience, but we're also changing their understanding of the severity of the problem.

Q: How did you ascertain these patients that are so refractory to treatment? Did these patients' families insist? Where did their readiness for change come from?

A: That has been looked at quite closely. We found these patients through educators. People were referred to our program for refractory hypoglycemia. These people don't not engage with services, they just don't engage with avoiding hypoglycemia.

Dr. Jim Dudl (Kaiser Permanente): We've published similar results with a behavioral approach for people with A1cs over 9%. It's very attractive. I wonder if your curriculum is propriety or could it be reviewed for us or others to build the same sort of model for hypoglycemia?

A: The curriculum is being modified according to input from patients and educators. There's still some tinkering to do, and we believe we'll have to do an RCT for it. We'll have to prove for our payers that it works with more sustained benefit than three months. We'd be delighted, particularly, to look at collaborating over an early roll out. We think the publication of this curriculum is one of the outcomes that we will be telling the National Institute of Health Research (NIHR), our funders in the UK, we can provide.

Q: Do you think recurrent hypoglycemia determines personality phenotype or the other way around?

A: Relatives often say to me that the person with hypoglycemia unawareness is prone to recurrent behaviors they know to be unhealthy, even outside of diabetes, and can't stop. There are data suggesting may be a genetic predisposition to hypoglycemia unawareness. We need to see if we can reverse it fully as this would make an inherited risk less likely.

INTENSIFICATION OF BASAL INSULIN THERAPY WITH STEP-WISE ADDITION OF INSULIN ASPART BOLUSES VS. BASAL-BOLUS THERAPY: THE FULLSTEPTM STUDY (256-OR)

Helena Rodbard, MD (Endocrine and Metabolic Consultants, Rockville, MD)

Dr. Helena Rodbard presented the fairly intuitive findings that step-wise initiation of basal-bolus therapy provided non-inferior glycemic control compared to immediate initiation of a full basal-bolus regimen; meanwhile, the step-wise regimen was associated with a lower risk of hypoglycemia and better patient satisfaction. In addition, ~half of completers on the step-wise protocol required only one or two bolus injections/day at the end of the study, whereas all patients in the basal-bolus arm were on three bolus injections/day. Notably, about twice as many patients on the basal-bolus protocol dropped out of the study compared to the step-wise protocol.

- **The FullSTEP study aimed to compare the efficacy and safety of incremental addition of bolus insulin aspart to basal insulin therapy against complete basal- bolus insulin therapy (three boluses/day).** People with type 2 diabetes (n=401) with mean baseline A1c of 7.9% participated in an eight-week run-in period with insulin detemir. They were then randomized to add step-wise insulin aspart (starting with one daily bolus injection and intensifying to two and three if A1c ≤7% was not achieved at 11 and 22 weeks, respectively) or full basal-bolus (insulin aspart three times/day). Treatment duration was 32 weeks.
- **Mean A1c change from baseline to week 32 was similar between the two arms (0.9% vs. 1.1% reduction [n.s.] on step-wise vs. basal-bolus, respectively).** Basal-bolus therapy initially provided superior A1c reductions at weeks 11 and 22, as might be expected, though by the end of the trial (week 32) the differences had abated. Mean fasting plasma glucose was similar between the two groups throughout the trial.
- **Overall hypoglycemia was almost twice as frequent in the basal-bolus group compared to the step-wise group.** When treatment-emergent hypoglycemic episodes were plotted by week, the step-wise group experienced fewer episodes of hypoglycemia every week.
- **Only ~half of participants in the step-wise group who completed the trial required three bolus injections at the end of the trial.** In the stepwise group, 17% required only one bolus injection/day; 27% required two bolus injections/day, and 40% required three after 32 weeks (14% dropped out). In contrast, 73% in the basal-bolus group were on three bolus injections (26% dropped out). Notably, nearly twice as many participants dropped out of the basal-bolus arm than the step-wise arm.

- **The DiabMedSat patient satisfaction scale revealed that patients in the step-wise arm experienced greater treatment satisfaction.** They scored more favorably on the burden, efficacy, and overall scores of this scale.

Questions and Answers:

Q: At initiation, did you stop all OADs or maintain them?

A: They maintained background OADs at the same dose with no changes. There were about the same number of oral agents in both groups. The predominant oral agents were metformin or sulfonylurea. A few patients were on pioglitazone, and a few patients were on DPP-4 inhibitors.

Q: How did you monitor hypoglycemia?

A: It was depending on patient symptoms or using measurements. They were not on CGM. That would have been ideal, of course.

Q: How often did you see each patient to advise about dose adjustment? Was there any difference in weight gain between the groups?

A: There was no effect on weight gain. Both gained about 2 kg [4.4 lbs] at the end of the 32 weeks, but there was no difference between the groups. In terms of adjusting insulin doses, the basal insulin dose was adjusted weekly by the patients, depending on what the blood glucose levels had been over three consecutive days, using the 3-0-3 algorithm. Regarding the bolus insulin doses, they were adjusted on a daily basis by one unit. Patients were adjusting themselves going up or down one unit at a time.

Q: To clarify, you said step-wise had lesser hypoglycemia but more nocturnal hypoglycemia?

A: No, the step-wise group had fewer hypoglycemia episodes across the board, including less nocturnal hypoglycemia.

Posters

IMPROVED GLYCEMIC CONTROL DESPITE REDUCTIONS IN BOLUS INSULIN DOSES WITH BASAL INSULIN LY2605541 COMPARED WITH BASAL INSULIN GLARGINE IN PATIENTS WITH TYPE 1 DIABETES (915-P)

Julio Rosenstock, Richard Bergenstal, Thomas Blevins, Linda Morrow, Yongming Qu, and Scott Jacober

LY2605541 (LY) is a long-acting novel basal insulin analog designed to have a large hydrodynamic size that may contribute to slower insulin absorption and reduced clearance. A phase 2, randomized, open- label, 2x2 crossover study found a greater improvement in glycemic control and reduction in prandial insulin requirements with LY compared to insulin glargine (GL) in patients with type 1 diabetes (n=108). The present analysis sought to further interrogate these initial results in order to explain the need for lower mealtime insulin doses. In the trial, LY-treated patients had significantly reduced daily mean blood glucose levels vs. patients receiving insulin glargine (143.0 mg/dl vs. 151.7 mg/dl compared to baseline of 161.8 mg/dl; p<0.001) at eight weeks. LY use was also associated with numerically more total hypoglycemia, but nocturnal hypoglycemia rates were significantly lower. Patients in both treatment arms required comparable doses of basal insulin, whereas the decreased need for bolus insulin use was consistent for every meal. Researchers concluded that these findings are perhaps related to LY's prolonged duration of basal insulin action and/or greater suppression of hepatic glucose production related to a preferential hepatic effect.

- **Participants with type 1 diabetes (n=108) received a once-daily basal insulin (either LY [n=56] or GL [n=52]) plus prandial insulin for eight weeks, followed by crossover treatment for an additional eight weeks.** Patients were comparable in terms of baseline demographics. Overall, 64.8% were men and 94.4% were Caucasian. Mean baseline age was 38.5 years, and mean duration of diabetes was 17.9 years. For both treatment groups, the mean BMI was 27.4 kg/m2, weight was 84 kg (185 lbs), and baseline A1c level was 7.6%.

- **At eight weeks, LY met statistical criteria for superiority vs. GL in lowering daily mean blood glucose levels (143.0 mg/dl vs. 151.7 mg/dl compared to baseline of161.8 mg/dl; p<0.001).** The improvements in glycemic control during LY treatment were notfound to be due to over-dosing, because fasting plasma glucose levels were comparable between the two treatment groups.
- **Following eight weeks of treatment, basal insulin doses were comparable between the two treatment groups, but bolus insulin doses were significantly lower in LY- treated patients compared with GL.** In the first treatment period (2-6 weeks afterrandomization), patients receiving LY used significantly less basal insulin than those on GL; however, this difference dissipated during the second treatment period (after crossover). LY- treated patients needed significantly less bolus insulin compared with GL. This reduced use occurred primarily during the second treatment period (when basal doses for both groups was comparable) and was consistent for all meals (least-squares mean differences between LY and GL): breakfast (-0.9 IU; p=0.021), lunch (-1.4 IU; p<0.001), dinner (-2.0 IU; p<0.001), and total daily bolus dose (-4.3 IU; p=0.005).
- **LY treatment was associated with significantly fewer nocturnal hypoglycemia events (0.9 vs. 1.2 events/30 days; p=0.007) and a numerically higher total hypoglycemia rate (9.2 vs. 8.1 events/30 days; p=0.074) than GL.** Even though the incidence of total hypoglycemia (BG ≤70 mg/dl) was higher in LY than GL (RR= 1.20), the rate of early morning hypoglycemia was lower (RR=0.73). This trend was consistent throughout the eight-week treatment period.

NEW INSULIN GLARGINE FORMULATION: GLUCOSE CONTROL AND HYPOGLYCEMIA IN PEOPLE WITH TYPE 2 DIABETES USING BASAL AND MEALTIME INSULIN (EDITION I) (43-LB)

Matthew Riddle, Geremia Bolli, Monika Ziemen, Isabel Muehlen-Bartmer, Florence Bizet, and Philip Home

This six-month phase 3a study compared the efficacy and safety of a new long-acting 300 U/ml (U-300) insulin glargine formulation to insulin glargine 100 U/mL (U-100) in patients with type 2 diabetes previously using both basal and mealtime insulin. U-300 has a longer and flatter pharmacokinetic profile than U-100, suggesting a possible advantage in diabetes treatment. Study subjects (n=807) were randomized to once-daily evening U-300 (n=404) or U-100 (n=403), while continuing their mealtime regimen. At baseline, subjects had a mean age of 60 years, BMI of 36.6 kg/m², duration of type 2 diabetes of 15.8 years, and A1c of 8.15%. Following six months of treatment, U-300 was non-inferior to U-100 in A1c-lowering efficacy (both groups lowered A1c an average 0.83% from baseline). Patients receiving U-300 showed a significant 21% reduction in severe or nocturnal confirmed hypoglycemia from month three to month six (36.1% with U-300 vs. 46.0% with U-100; p=0.0045). Furthermore, the occurrence of any hypoglycemic event was numerically lower, but not statistically significant, in patients receiving U-300 vs. U-100. Given the comparable glycemic efficacy of U-300 and U-100, the potential of U-300 to reduce the risk of hypoglycemia indicates that it is an improved basal insulin that should be considered, especially for people with high insulin requirements.

Symposium: Update on New Insulin Preparations for the Management of Diabetes

CLINICAL USE OF CONCENTRATED INSULIN FORMULATIONS - WHEN AND HOW TO USE THEM (U-200, U-300, U-500)

Mary Korytkowski, MD (University of Pittsburgh, Pittsburgh, PA)

After providing background information on U-500 insulin, Dr. Mary Korytkowski reviewed the current guidelines for its use and discussed its use in clinical practice, then briefly touched on concentrated insulins on the horizon (U-200 insulin degludec and U-300 insulin glargine) and how they will be incorporated into clinical practice. Dr. Korytkowski explained that U-500 is currently used alone, or in combination with long-acting, intermediate-acting, or rapid-acting analogs. Given the 12-16 hour duration of action of U-500,

the introduction of truly long-acting concentrated insulin formulations such as U-200 or U-300 may restrict U-500 to use as a pre-meal insulin in the future. Dr. Korytkowski noted that because concentrated insulin formulations have different pharmacokinetics and pharmacodynamics versus U-100 insulin, adjustments in insulin doses are required when changing patients from U-100 to concentrated insulin. Dr. Korytkowski commented that the use of concentrated insulin formulations is likely to continue to increase in the future, given the increasing prevalence and severity of obesity and insulin resistance.

- **Dr. Korytkowski briefly discussed U-200 insulin degludec and U-300 insulin glargine, noting that they provide similar glycemic control as U-100 insulin glargine, and have low risk of hypoglycemia.** In the BEGIN LOW VOLUME trial in insulin- naïve patients with type 2 diabetes, U-200 insulin degludec improved glycemic control similar to insulin glargine, with a low risk of hypoglycemia (Gough et al., *Diabetes Care* 2013). In a PK/PD study of U-300 insulin glargine versus U-100 insulin glargine in patients with type 1 diabetes, the profile of U-300 was much flatter than U-100 (Tillner et al., ADA 2012). In the EDITION I trial,U-300 insulin glargine brought about similar changes in A1c compared to U-100 insulin glargine,but with a slightly lower incidence of hypoglycemia (Riddle et al., ADA 2013).

Questions and Answers

Q: The U-200 formulation of insulin degludec has the exact same PK profile as the U-100 formulation of insulin glargine, so this is the exception to the rule. Otherwise, I fully agree that highly concentrated insulin [has different PK compared to U-100].

A: That's a good point, thank you. In the study in *Diabetes Care*, in the supplemental materials, the dosing of U-100 insulin glargine and U-200 insulin degludec were essentially identical.

Q: I presented a poster here of U-500 insulin in 15 patients who had their glucose tracked using continuous glucose monitoring before starting and six months later. In the CGM tracings, U-500 was clearly much better as a basal insulin, and not much for reducing postprandial glucose. Are there any studies utilizing GLP-1 analogs in combination with U-500?

A: I'm sorry to have missed your poster, I'll have to come by and see it. There is one case report on using U-500 in combination with liraglutide. In this case, U-500 was used more as the basal insulin, and liraglutide was used to control postprandial glucose. There were significant reductions in A1c in this one case report, but it's a proof-of-concept idea. This person lost weight, and the dose of insulin actually decreased. There could be some promise there using the two together.

NEW INSULIN FORMULATIONS - ARE THEY BETTER THAN CURRENTLY AVAILABLE HUMAN INSULINS?

Thomas Donner, MD (Johns Hopkins University, Baltimore, MD)

Dr. Thomas Donner expressed optimism that ultra-long-acting and ultra-rapid-acting insulins in development could improve upon current insulin formulations. Specifically, he noted that there is evidence that ultra-long-acting basal insulins reduce nocturnal hypoglycemia and have less weight gain (or even can cause weight loss) compared to insulin glargine. Meanwhile, ultra-rapid-acting insulins could be more effective in reducing postprandial hyperglycemia than current rapid-acting analogs. Nonetheless, Dr. Donner noted that long-term studies are needed to confirm the efficacy and safety of these new candidates. During his presentation, he covered several specific ultra-long-acting insulins (insulin degludec, LY2605541) and ultra-rapid-acting insulins (BIOD-123, rapid-acting analogs plus hyaluronidase, and FIAsp).

- **Insulin degludec:** Insulin degludec forms soluble multihexamers after subcutaneous injection, allowing for the gradual release of insulin monomers into circulation. It has a 25-hour half life, a duration of action of over 42 hours, and similar A1c-lowering efficacy when dosed either at a fixed time of day, or at intervals of 8-40 hours apart (Meneghini et al., *Diabetes Care* 2013). Insulin degludec's profile appears flatter than current basal insulins. In a one-year, randomized, treat-to-

target study in insulin-naïve patients with type 2 diabetes comparing insulin degludec with insulin glargine (BEGIN Once Long), the two insulins provided nearly identical glycemic control, but insulin degludec had a 36% lower incidence of nocturnal hypoglycemia (p=0.04) (Zinman et al., *Diabetes Care* 2012). Two-year data from the BEGIN Basal-Bolus trial for patients with type 1 diabetes showed a 25% lower incidence of nocturnal hypoglycemia with insulin degludec versus insulin glargine (n<0.05), with insulin degludec bringing about similar glycemic control to insulin glargine, but with reduced insulin requirements (Bode et al., *Diabetic Med* 2013). Dr. Donner reviewed insulin degludec's regulatory status in the US, noting that the FDA requested additional cardiovascular data from a dedicated cardiovascular outcomes trial prior to approval.

- **LY2605541:** LY2605541 is insulin lispro, modified with a 20-kDA polyethylene glycol moiety. Its larger size delays absorption and slows clearance. In a dog model, LY2605541 displayed preferential hepatic uptake and greater lipolysis, suggesting potential for less lipogenesis, increased oxidation, and weight loss as opposed to gain. In a 12-week study in patients with type 2 diabetes, LY2605541 brought about similar effects on fasting glucose and A1c versus insulin glargine, but with less daytime glucose variability, significantly less nocturnal hypoglycemia (48% less), and weight loss as opposed to weight gain (Bergenstal et al., *Diabetes Care* 2012). LY2605541 increased triglycerides relative to insulin glargine, and was also associated with small increases in ALT and AST. In an eight-week crossover study in patients with type 1 diabetes of LY2605541 versus insulin glargine, LY2605541 decreased daytime glucose levels by approximately 10 mg/dl, reduced mealtime insulin dosing by 17%, had less daytime glucose variability, and conferred weight loss (Rosenstock et al., *Diabetes Care* 2013). Dr. Donner noted that both studies had two subjects with three-fold elevations in liver enzymes occurring four weeks after study end. In addition, Dr. Donner commented LY2605541 needs to be explored longer with regards to cardiovascular safety.
- **BIOD-123:** BIOD-123 consists of insulin lispro with citrate and calcium EDTA; the chelating effects of the calcium EDTA leads to rapid dissociation of insulin hexamers, and inhibition of insulin monomer/dimer re-association. Compared to insulin lispro alone, BIOD-123 has a much earlier peak action, and clears out more rapidly. A phase 2 study comparing BIOD-123 versus insulin lispro is expected to complete in 3Q13.
- **Hyaluronidase (PH20):** Hyaluronidase has been shown to increase the dispersion and absorption of subcutaneously administered drugs, with no increased injection site pain. In a study in patients with type 1 diabetes, insulin pharmacokinetics were accelerated with co- administration of PH20 and prandial insulin versus prandial insulin alone (Hompesch et al., *Diabetes Care* 2011). In another study, co-administration of PH20 with rapid-acting analogs decreased time to 50% exposure from about two hours to 75 minutes, doubled early first-hour exposure, and halved exposure beyond two hours for all three rapid-acting analogs (Morrow et al., *Diabetes Care* 2013).
- **FIAsp:** FIAsp is aspart insulin combined with the excipients nicotinamide (to help speed absorption) and arginine (to stabilize the insulin). Dr. Donner noted that there is no published human data of FIAsp. In pigs, subcutaneous injections of FIAsp were shown to reduce postprandial glucose. Phase 3 trials for FIAsp are planned to start in 2013 and 2014 in both patients with type 1 diabetes and patients with type 2 diabetes.

Questions and Answers

Q: In studies comparing insulin glargine and insulin degludec, dosing was quite different - glargine was dosed any time, and degludec dosing was fixed around the evening meal. Could you comment on whether you think that contributed to the differences observed in nocturnal hypoglycemia?

A: I don't know how they made the decision to dose at different times, but you would expect to have less nocturnal hypoglycemia with glargine if it's dosed in the morning.

Q: Do you really think we need a liver-specific insulin? I know it's important in normal physiology, but we've already seen some side effects, and [a large proportion] of our patients have fatty liver disease.

A: Ideally you'd have a liver-specific insulin to help suppress hepatic gluconeogenesis. If you have insulin preferentially taken up in the liver, it would lower systemic insulin levels - there are some suggestions that systemic insulin levels may influence cardiovascular risk. You're right though in that any insulin that has preferred hepatic action needs hepatic safety.

Q: Do you know anything about the status of smart or glucose-sensitive insulin?

A: That's really our holy grail, isn't it? Glucose-dependent insulin would only be activated when glucose is elevated. I know of at least two companies who are working on it. These insulins would typically have a moiety attached to the insulin that would dissociate when glucose becomes elevated, and become activated.

ALTERNATIVE INSULIN DELIVERY SYSTEMS--INHALED, ORAL, PATCHES, AND MICRONEEDLES

William Cefalu, MD (Pennington Biomedical Research Center, Baton Rouge, LA)

Dr. William Cefalu provided an excellent review of alternative insulin delivery systems, aptly commenting that 25 minutes was not enough to cover the entire field. To begin, he remarked that alternative delivery systems - transdermal, nasal, sublingual, buccal, oral, inhaled, and intraperitoneal - have a "huge hurdle to jump" since they must address the many significant barriers to insulin use. Turning first to transdermal delivery, he detailed the types of microneedles available (solid, coated, dissolving, hollow) and commented that the U-Strip Transdermal insulin is currently in phase 3 (developed by Transdermal Specialties). Dr. Cefalu's subsequent discussion on buccal insulins centered on Oral-yn (phase 3), which he believes requires a better formulation to reduce the number of puffs per meal. Dr. Cefalu focused the largest portion of his talk on oral insulins and swiftly reviewed several candidates: Biocon's IN-105, Oramed's ORMD-0801 (with new data in poster 1054-P), Diabetology's Capsulin, Novo Nordisk's oral insulin candidate, and Diasome's hepatic-direct vesicles (we recently published a review of oral insulins, available at http://www.closeconcerns.com/knowledgebase/r/5439ad6a). Dr. Cefalu concluded his talk with a brief mention of inhaled insulin, noting that the only company still pursuing this approach is Mannkind (phase 1 data on Afrezza is being presented in poster 982-P).

Questions and Answers

Q: Regarding inhaled insulin, we're all very hopeful. One of the limiting factors is the question about whether it has pulmonary effects and what happens in the long term. What is your take on this?

A: We'll wait for the information from studies. We saw a small pulmonary effect that appeared to be maintained across time, and which stopped after drug discontinuation. I think that long term studies will be needed.

Q: I'm wondering about the viability of using insulin preparations or delivery systems that only have an efficiency of 5-10%, because this means that if you increase absorption through some physical change in the patient, then you could triple the dose. Is that going to be a limiting factor?

A: I don't know. At this point, you're talking about a buccal or oral insulin. For the buccal delivery, it's going to take more insulin. For the oral insulin, you have to think about the liver effects. We don't really know, and we don't have enough data. We know that some oral insulin products work, but we need more studies on their efficacy and their systemic levels.

Comment: I want to advise that in the intradermal space, BD has been working in this area using a 150 micron steel microneedle and has published a number of studies showing reproducible accelerated kinetics of insulin by about 40%. I just wanted to mention that.

Q: Oral insulin is facing a number of obstacles. Do you think we'll get by all the obstacles and really have a preparation?

A: I can't predict the future; I don't know. There are some tremendous hurdles. I've shown you the proof of concept but there are obviously a lot of hurdles. These are small studies in a limited number of patients. If we can get past those and prove proof of concept in larger studies, perhaps we'll see. Time will tell and studies will tell.

INSULIN STRATEGIES IN PREGNANCY

Celeste Durnwald, MD (University of Pennsylvania, Philadelphia, PA)

Dr. Celeste Durnwald reviewed a series of small studies investigating the safety and efficacy of new insulin analogs in pregnant women with type 1 diabetes, emphasizing that this field is highly understudied and requires greater attention because of the increased risk of complications during pregnancy. She reminded the audience that tight glycemic control is essential during pregnancy to decrease the risk of congenital malformations, miscarriage, fetal overgrowth, and diabetic ketoacidosis, though she warned that tighter control could increase the risk of hypoglycemia. Small studies comparing insulin lispro (Lilly's Humalog) to regular insulin have shown similar rates of retinopathy progression, antibodies in the cord blood, and frequency of specific and cross-reactive antibodies. Importantly, the investigators did not observe any placental transfer of insulin lispro or abnormal rates of fetal overgrowth. Studies comparing insulin aspart (Novo Nordisk's NovoLog) to regular insulin in pregnant women showed that insulin aspart was associated with significantly less major hypoglycemic episodes, higher quality of life, and no difference in A1c levels. Based on these data, Dr. Durnwald suggested that insulin lispro and insulin aspart could be adopted into clinical use due to their lack of major safety concerns and their similar efficacy compared to regular insulin. She noted that because data on insulin glargine (Sanofi's Lantus) is limited, she could not recommend its use in pregnant patients, although early studies have not shown increases in complications compared to NPH. Finally, Dr. Durnwald instructed that HCPs should consider insulin detemir (Novo Nordisk's Levemir) on an individual basis, as results from a single randomized controlled trial suggested comparable efficacy and neonatal outcomes relative to NPH; however, concerns still remain over the significant maternal hypoglycemia observed in the study.

Sanofi Diabetes Update

SANOFI DIABETES UPDATE

Sanofi held a conference call this morning to review results presented at ADA for its new U300 insulin glargine formulation and to provide an update on the Lyxumia/Lantus combination product. Management guided for phase 3 to begin in 1H14 for "lixi/lan;" disappointingly, management did not provide any detail on the functionality of the fixed-ratio device or details on the technical difficulties encountered with the fix-flex device, as was expected. Results of the U300 insulin glargine's EDITION I and EDITION II studies were very impressive - EDITION I showed a 21% reduction in nocturnal hypoglycemia compared to Lantus. Topline EDITION II results confirmed this finding.

- **Management highlighted that these two studies enrolled very difficult type 2 patients** (in both studies, all participants required >42 u/day of insulin at baseline). In both studies, U300 provided non-inferior glycemic control to Lantus while significantly reducing hypoglycemia: specifically in EDITION I both Lantus and U300 provided a 0.8% A1c reduction while U300 provided a 21% relative reduction in number of patients experiencing nocturnal hypoglycemia (severe and/or confirmed) from month three to six.
- **Management emphasized that measuring the number of people experiencing hypoglycemia rather than simply hypoglycemic events was a more stringent measure for hypoglycemia superiority.**
- **Notably, management confirmed during Q&A that the EDITION I extension study examining a flexible dosing schedule will report results later this year.**

- **Lastly, management provided a financial update showing that Lyxumia reached 8% of the GLP-1 market share by volume in Germany in its first 11 weeks.** This was almost on par with BMS/AZ's Bydureon. In Q&A management commented that Lyxumia is priced roughly at parity with Byetta across markets.
- **While Sanofi continues to aim for becoming a comprehensive diabetes care company, the company remained very Lantus-centric on today's call** - the presentation closed out with a slide on multiple growth drivers to sustain Lantus growth, one of which was the opportunity for combination therapy with Lyxumia.

Questions and Answers

Q: There seems to be an extension study for EDITION I exploring an adaptable injection profile - when might that read out? You commented on the significance on nocturnal hypoglycemia, what about the non-significance on overall?

A: Identification of the benefit of a product takes a large volume study. Characteristics of the patients in EDITION I and II were quite unusual. One reason why did this study first was to stress test the product. If we were going to find something meaningful here, the probability of the product to deliver could be speculated to be really meaningful. These studies will be followed by other ones. What you see is consistency on hypoglycemia wherever you look for it. In the degludec experience, the titration phase was problematic. The meta-analysis often times showed that there was excess hypoglycemia during titration, and then it flipped. However what you see with U300 glargine is consistency in the hypoglycemia benefit no matter when in the trial you are. The extension study on EDITION I will report relatively soon. Studies will deliver as planned. 2013 is the year when all of the studies will be released.

Q: Can you say you have not seen any CV event signals with U300 thus far? What's your level of confidence that the FDA won't make you do a CVOT prior to approval? Can you remind us what you're thinking in terms of timing for biosimilar Lantus in the US and Europe?

A: The molecular entity is identical. What changes between U300 and Lantus is the volume. The volume delivers a different PK/PD. However the patient exposure - how much insulin present in blood stream of the patient - is very similar to Lantus. What U300 does is redistribute the presence of insulin in the blood stream so you have a super flat profile. Honestly it's hard to think of a rational for a CV study. In discussing and hearing reactions to the presentation EDITION I at ADA from KOLs, no one considered that as a likely request. One company has been announcing they are developing biosimilar glargine - Lilly. Based on information we have, we could expect Lilly to be in position to launch in the US and in Europe by 2015.

Q: So you have not seen any CV signals with U300?

A: EDITION I is only one study, and it shows an absolute balance.

Q: The level of severe hypoglycemia was 5% with U300 vs. 5.7% for Lantus in EDITION I; that was roughly 12% reduction. Is that meaningful? Especially against Tresiba, which showed a bit less than 20% reduction? Do you think this may become a claim of superiority for marketing purposes?

A: From a statistical point of view, this is inappropriate. Studies should have a pre-specified hypothesis being tested. In this case, the relative risk for nocturnal hypoglycemia had a decrease of 21% in EDITION I and a 15% decrease in the degludec study. I think all we can do when we do studies is formulate hypothesis and test them. If, afterwards, we initiate a post-hoc analysis, we obviously always find something. So what I would like to say to you is that the assessment of severe hypoglycemia needs to come from a meta-analysis of all studies. What we've seen here today is rarely seen with degludec - the consistency of information with hypoglycemia. Although we only mention topline data for EDITION II, we were pleased to see the same consistency.

Q: One question on the EDITION program: it looks like Lilly is running a blinded trial for its novel basal while your EDITION is entirely open label. What conversations did you have with regulators? Does that matter? Additionally, on the price of Lyxumia - you've shown volume share in Germany, what does that mean in terms of value share and Lyxumia pricing?

A: When preparing the phase 3 study, it was done in consultation with regulatory agencies. So the characteristics of the study were ostensibly discussed. What creates a barrier to blinding in this case is the device. So the possibility of carrying on the study was limited to having in unblinded, and this was obviously part of our submitted dossier. On Lyxumia price, we can clearly say we don't want that to be a barrier to market access. It is priced roughly at parity to Byetta across markets, which is similar to about

1.2 mg Victoza.

Q: Following up on the favorable PK/PD profile - can you give commentary on the timing and flexibility of dosing vs. Lantus? Especially in the extreme dosing interval of eight to 40 hours vs. Lantus' more rigorous 24-hour dosing plan.

A: Today what we have is what we've presented at ADA. We see the PK/PD in multiple doses suggest a longer duration of action. We will explore how this translates into flexibility. Today we are limited to the information we have, which is what you just saw. The tail of the glucose infusion rate appears to be significantly longer with U300 when compared to Lantus.

Q: U300 is the same molecule as Lantus, so I guess it will be considered under an sNDA. So am I correct in assuming you will have a six-month review by the FDA? Can you comment on the risk of having an advisory committee meeting? On prices, apparently you have set the precedent not to look for too high of a premium. Why not go for a high premium if you have some good data like this confirmed in the next studies?

A: I can't comment from the point of view of the regulators, but what I can tell you is that we're planning to submit the dossier in 2014. FDA has had an evolving approach to the requirement for advisory committee meetings, so it would be purely speculative to give any answer. On pricing strategy, we consider that this would be a new generation of insulin that really brings an added value for patients eligible to insulin. On the other hand, we don't want price to be barrier to broad expansion. So I am indicating that we would have a price in the same range as Lantus, but potentially at a slight premium. It has nothing to do with the value profile of the product that we are building, but we just don't want price to be a barrier to growth and expansion to this new solution for people living with diabetes.

-- By Eric Chang, Adam Kraus, Jessica Dong, Nina Ran, Lisa Rotenstein, Manu Venkat, Katrina Verbrugge, Vincent Wu, and Kelly Close