Executive Highlights

This document contains our coverage of GLP-1 agonists at ADA 2016. Immediately below, we include our themes from the category, followed by detailed discussion and commentary. Talk titles highlighted in yellow were among our favorites from ADA 2016; those highlighted in blue are new full report additions from our daily coverage.

Themes

- **While LEADER was arguably one of the more likely diabetes drug CVOTs to demonstrate cardioprotection, the results were nonetheless surprisingly positive (from a historical sense) and monumental - cardioprotection and renal protection announced simultaneously.** There has been speculation about the potential for cardioprotection with GLP-1 agonists for some time due to the class' positive effects on weight, blood pressure, and lipids and possible direct effects on the heart and vasculature. Novo Nordisk had expressed cautious optimism in several quarterly updates (most recently in 3Q15) that LEADER would be more likely than most CVOTs to reveal any benefit that existed due to its greater individual patient exposure compared to other trials (mandated minimum exposure of 3.5 years per patient and total exposure of over 30,000 patient-years). That said, there were also many reasons to expect a neutral outcome: the trial was only powered to show non-inferiority, it enrolled a high-risk patient population, any effect of GLP-1 agonists on CVD was expected to be subtle and gradual, and the only other GLP-1 agonist CVOT to report (ELIXA for Sanofi's lixisenatide) had demonstrated neutral results. In that context, these results were certainly a pleasant surprise and a groundbreaking moment for the type 2 diabetes field.
- **The early consensus seems to be that the benefits in LEADER were most likely related to atherosclerosis.** This was the main hypothesized mechanism of CV benefit for GLP-1 agonists before the results were released, as the class positively affects a number of endpoints related to atherosclerosis (e.g., glucose, blood pressure, weight) and may have direct effects on reducing arterial plaque. Speakers at the press briefing for LEADER and in the main results presentation agreed that the results appeared consistent with an atherosclerotic mechanism: the effects took some time to appear and increased over the course of the trial, and they were relatively consistent across multiple atherosclerotic endpoints. This is in marked contrast with the EMPA-REG OUTCOME results for Lilly/BI's Jardiance (empagliflozin), which demonstrated an immediate effect on heart failure and CV mortality and little to no signal of an effect on MI or stroke. While we expect plenty of further speculation and investigation of the exact mechanism of benefit in LEADER (Dr. Laurie Baggio offered a few specific hypotheses in her discussant presentation), the field appears to be closer to a consensus hypothesis in this case compared to EMPA-REG OUTCOME.
- **We have many remaining questions about the clinical implications of the results that could take years to resolve.** Dr. John Buse (University of North Carolina, Chapel Hill, NC) emphasized in his concluding presentation that the results should only be applied to the specific patient population enrolled in LEADER - those with longstanding type 2 diabetes and high CV risk. We expect that any updates to the Victoza label and to type 2 diabetes treatment guidelines will only be applied to this population in the absence of what would be a very expensive trial in a lower-risk population. However, we also imagine that many clinicians may incorporate the results into their risk/benefit calculus for Victoza even for lower-risk patients. We are also very curious to see what the implications will be for Saxenda (liraglutide 3.0 mg for obesity), which is unlikely to undergo a

CVOT of its own. We would love to see Novo Nordisk conduct a CVOT for the more potent GLP-1 agonist semaglutide in patients with obesity and without type 2 diabetes, though we understand such a trial would also be very expensive. The question of a GLP-1 agonist class effect on CV outcomes is sure to be a hot topic for the next several years as CVOTs for other agents report results. In the near term, we expect the results to bolster the class as a whole but to disproportionately benefit Victoza until additional CVOTs report data. It will be very interesting to see how clinicians weigh the demonstrated CV benefits with Victoza against advantages like once weekly dosing with Lilly's Trulicity (dulaglutide) or guaranteed adherence with Intarcia's ITCA 650 (implantable exenatide mini-pump).

- **We are very curious to see how the LEADER and EMPA-REG OUTCOME results will be judged relative to each other.** Will GLP-1 agonists and SGLT-2 inhibitors (or the specific agents in each class that have demonstrated CV benefit) both be considered preferred second-line treatments for all patients at high CV risk? Will the recommendations be different depending on the specific type of CV risk (i.e., empagliflozin for heart failure and liraglutide for atherosclerosis)? The prospect of combination therapy with two drugs that reduce CV risk by different mechanisms is also an intriguing one, though one attendee during a Tuesday session on EMPA-REG OUTCOME raised the possibility that the two mechanisms could actually work against each other if liraglutide reduces ketone body production that is contributing to the benefit with empagliflozin.
- **Large-scale changes to the FDA's 2008 CV Guidance appear increasingly unlikely now that two CVOTs have reported positive results.** The consensus opinion has certainly changed from a year ago, when the streak of four completely neutral trials (SAVOR, EXAMINE, TECOS, and ELIXA) had raised questions about whether the value of these trials was worth the massive investment. Now that two trials have revealed important benefits that might otherwise have remained unknown, we have heard several speakers (including Dr. Darren McGuire and Dr. Steve Nissen at AACE) argue strongly that the field is getting its money's worth from these studies. Even some previous opponents of the FDA Guidance have changed their opinions over the past year - for example, Dr. Silvio Inzucchi (Yale University, New Haven, CT) stated at EASD that he was prepared to completely revise his previous assessment of the requirements in light of the EMPA-REG OUTCOME results. At the same time, the FDA officially eliminated the Risk Evaluation and Mitigation Strategy for rosiglitazone last December, effectively declaring the main rationale for the 2008 Guidance to be invalid. We also continue to question whether an across-the-board CVOT requirement with the same guidelines for all diabetes drugs is the most effective tool to assess the risks and benefits of new products. We believe that a more nuanced approach, in which drugs with a signal for CV risk would be required to conduct a safety trial and those with potential for benefit would be required or incentivized to conduct a superiority trial, would offer the most value to the field.
- **Data presented at this year's ADA illustrated a number of exciting potential future directions for the GLP-1 agonist class - the question is whether there will be a market for all of them.** We expect that the demonstration of a cardioprotective effect for Novo Nordisk's Victoza (liraglutide) in LEADER will likely spur growth of the entire class and provide some disproportionate benefit for Victoza. Over the long term, it is possible that some clinicians will use CVOT results as a key differentiating factor when choosing among different agents in the class, at least for their higher-risk patients. This will likely depend in large part on the consistency of results from future GLP-1 agonist CVOTs. Combinations with basal insulin represent another exciting advance for the GLP-1 agonist class; at this year's ADA, we saw full phase 3 results for Sanofi's iGlarLixi (lixisenatide/insulin glargine) combination, which is expected to receive US and EU regulatory decisions this year. Novo Nordisk's Xultophy (insulin degludec/liraglutide) is also on track for a US decision this year and is already available in Europe. Impressive new data for Novo Nordisk's semaglutide (in type 2 diabetes and obesity) reinforced its potential as a versatile, possibly best-in-class molecule, while results from the FREEDOM-2 trial of Intarcia's ITCA 650 (implantable exenatide mini-pump) underscored the advantages of an agent that offers guaranteed adherence.

We are excited about the potential for all of these products to help expand usage of the GLP-1 agonist class in both type 2 diabetes and obesity, which we have long felt is underutilized. It is not clear at this point whether all the options can find their own niche within the class or whether one or two will emerge as the clear preferred options.

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INTRODUCTION, STUDY RATIONALE, AND DESIGN

John Buse, MD, PhD (University of North Carolina, Chapel Hill, NC)

Dr. John Buse (UNC, Chapel Hill, NC) kicked off the session with an introduction to the background and design of the LEADER trial. He acknowledged the enormous scope of the study and the people who made it possible with an impressive slide reviewing the key numbers for the trial: LEADER enrolled 9,340 patients in 32 countries across 410 sites over five years. In total, an astounding 11,000 people worked on the trial to collect 27.6 million data points over 13,500+ monitoring visits, resulting in information on almost 30,000 patient-years of exposure to liraglutide. LEADER was a double-blind, randomized, placebo-controlled, time- and event-driven trial: participants were treated for at least 3.5 years and no more than 5 years and the trial was to accumulate at least 611 events included in the primary endpoint (CV death, non-fatal MI, and non-fatal stroke). Key secondary outcomes included an expanded composite endpoint of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, unstable angina pectoris requiring hospitalization, and hospitalization for heart failure. All-cause death and each individual component of the expanded CV composite were considered as secondary endpoints as well. Participants had type 2 diabetes with an A1c ≥7% and fell into one of two high cardiovascular risk categories: (i) at least 50 years old with established CVD or chronic renal failure or (ii) at least 60 years old with risk factors for CVD. Participants could be diabetes drug-naïve, on oral diabetes medications, or on basal or premix insulin. Patients on GLP-1 agonists, DPP-4 inhibitors, pramlintide, or rapid-acting insulin were excluded from the trial, as were those with type 1 diabetes or a familial or personal history of multiple endocrine neoplasia type 2 (MEN-2) or medullary thyroid cancer (MTC). Participants were treated according to standard of care guidelines with target A1c ≤7%, blood pressure 130/80 mmHg, and LDL cholesterol <100 mg/dl (<70 mg/dl in patients with previous CV events). Statins were recommended for all patients and aspirin or clopidogrel were recommended for patients with prior CV events. Events were adjudicated by an external committee made up of subcommittees each focused on cardiovascular, microvascular, pancreatitis-related, or neoplasm-related events.

STUDY POPULATION

Neil Poulter, FMedSci (Imperial College London, London, UK)

Dr. Neil Poulter reviewed the characteristics of the LEADER study population, emphasizing that this was truly a global effort (32 countries, 30% of participants from North America, 35% from Europe, 8% from Asia, and 27% from the rest of the world). He also highlighted the trial's very impressive retention rate: 97% of participants in both groups completed the trial and there were only 29 dropouts whose vital status was unknown at the end of the study. The study population was 64-65% male, with an average age of 64 and an average diabetes duration of 13 years, which Dr. Poulter noted is significantly longer than in most diabetes trials. Baseline A1c was fairly high at 8.7%, likely due to the lack of an upper A1c limit in the entry criteria. Baseline BMI was 32.5 kg/m², baseline weight was 92 kg (~203 lbs), baseline blood pressure was fairly well controlled at 140/77 mmHg, and 18% of participants had heart failure at baseline. The liraglutide and placebo groups were well matched for all baseline characteristics. Over 80% of participants fell into the higher-risk group of patients ≥50 with existing CVD or CKD, and many had more than one qualifying condition. Consistent with this high level of risk, over 90% of patients were on antihypertensive therapy, 40% on diuretics, 75% on lipid-lowering medications (which Dr. Poulter described as suboptimal), and just under 70% on platelet inhibitors. Metformin was by far the most commonly used diabetes medication (used by approximately 75% of participants), followed by sulfonylureas at 50% and insulin at 45%. Dr. Poulter also highlighted the impressive treatment exposure in the trial, with a median exposure time of just over 3.5 years and patients spending an average of 83%-84% of the time on study drug.

CLINICAL AND METABOLIC OUTCOMES

Bernard Zinman, MD (Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario, Canada)

Dr. Bernard Zinman (University of Toronto, Canada) presented the key clinical and metabolic outcomes from the study. At three years post-randomization (a pre-specified time point), mean A1c in the liraglutide-treated group was 0.4% lower than in the placebo-treated group (p<0.001), despite the instructions to treat to a target A1c of 7% in both groups. The gap in A1c diminished throughout the trial, largely due to an intensification of other agents in the placebo group. The proportion of patients on metformin, sulfonylureas, alpha-glucosidase inhibitors, TZDs, glinides, and insulin was fairly evenly matched between the two groups at the start of the trial, but more participants in the placebo group initiated treatment with these classes (particularly insulin and sulfonylureas) throughout the trial. Other clinical and metabolic outcomes of interest include 2.3 kg weight loss with liraglutide compared to placebo at three years (p<0.001), a 1.2 mmHg decrease in systolic blood pressure (p<0.001), a 0.6 mmHg increase in diastolic blood pressure (p=0.004), a 3 beats/min increase in heart rate (p<0.001), a 1.6 mg/dl decrease in LDL cholesterol (p=0.02), and a non-significant 0.3 mg/dl increase in HDL cholesterol (p=0.07). Dr. Zinman generally characterized these outcomes as expected effects associated with liraglutide and suggested that the increase in diastolic blood pressure and decrease in LDL cholesterol were not clinically significant. During the trial, a greater proportion of participants in the placebo group initiated new cardiovascular medications such as antihypertensive therapies, diuretics, lipid-lowering drugs, platelet aggregation inhibitors, or other anti-thrombotic medications. The LEADER study also investigated health-related quality of life measures, as measured by the EQ-5D index score (which assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the EQ-5D VAS score (a visual scale of health state from 0 to 100 representing worst and best health, respectively). Based on the index score, both liraglutide and placebo reduced participants' quality of life, but liraglutide offered a 0.018 index score improvement over placebo (p=0.034). Liraglutide also offered a 1.3 point advantage on the VAS score (p=0.03). We were extremely pleased to see quality of life measures included in the study and hope that this kind of patient-centered metric could help encourage greater coverage from payers.

CARDIOVASCULAR OUTCOMES

Steven Marso, MD (UT Southwestern, Dallas, TX)

Interrupted multiple times by applause, Dr. Steven Marso presented the primary results from the LEADER trial. He emphasized the consistency of the effect for all the outcomes measured, noting that every single endpoint had a point estimate <1 that fell within a narrow range from 0.6-0.98. Taken together, these results fit the pattern that most in the field had predicted any positive CVOTs for diabetes drugs would show: risk reduction for multiple CV outcomes that appeared gradually and increased over time. This is in marked contrast with the EMPA-REG OUTCOME results for Lilly/BI's Jardiance (empagliflozin), which demonstrated an immediate benefit for CV death and hospitalization for heart failure and little to no signal of benefit for other endpoints. As several speakers noted, the LEADER results appear more likely to be mediated through a reduction in atherosclerosis, whether that is due to indirect effects (reductions in A1c, weight, blood pressure, etc.) or direct effects on the heart or blood vessels.

- **Primary outcome:** The hazard ratio for the primary outcome of three-point MACE (non-fatal MI, non-fatal stroke, and CV death) was 0.87 (95% CI: 0.78-0.97; p<0.001 for non-inferiority; p=0.01 for superiority), translating to a significant 13% risk reduction. Dr. Marso noted that the event rate (3.7 events/100 patient-years) was two-fold higher than projected, perhaps due to the high percentage of participants with existing CVD. The magnitude of the effect was consistent and robust in a number of sensitivity analyses, with the point estimate ranging from 0.82-0.87 and the upper bound of the 95% confidence interval consistently <1.
- **Individual components:** While all three components of the primary endpoint contributed to the benefit, the most robust effect was a 22% risk reduction for CV death (HR = 0.78; 95% CI: 0.66-0.93; p=0.007; 497 events). The Kaplan-Meier curves for the two groups began to separate 12-18 months into the trial and continued to diverge until the end of treatment. The results for non-

fatal MI and non-fatal stroke trended in the right direction but were not statistically significant. The hazard ratio for non-fatal MI was 0.88 (95% CI: 0.75-1.03; p=0.11, 598 events) and the hazard ratio for non-fatal stroke was 0.89 (95% CI: 0.71-1.11; p=0.30; 336 events). Dr. Marso pointed out that the shape of the curves for non-fatal MI followed the same pattern as those for CV death and for the primary endpoint - initial separation between 12 and 18 months and continued divergence over the course of the trial - perhaps suggesting that the risk reduction might have become statistically significant over a longer time period.

- **Subgroup analyses:** There was no significant heterogeneity of the effect on the primary endpoint in subgroups divided by sex, age, region, race, ethnicity, BMI, A1c, diabetes duration, heart failure status, or anti-diabetic therapy. The two subgroups with a p-value for interaction <0.05 (with the caveat that the analyses did not control for multiplicity of testing) were CVD status and renal function. The point estimate for the group with established CVD was 0.83, while the point estimate for the group with CV risk factors was 1.2. Dr. Marso attributed this to the fact that the vast majority of trial participants fell into the first category, which had a much higher event rate; the lower-risk group most likely did not accumulate enough events to show a benefit. By renal function, the point estimate for patients with an eGFR <60 ml/min/1.73 m^2 was 0.69 while the point estimate for patients with an eGFR >60 was 0.94.
- **Key secondary outcome:** Results for an expanded MACE endpoint (including coronary revascularization and hospitalization for heart failure or unstable angina in addition to the primary endpoint) demonstrated a significant 12% risk reduction (HR = 0.88; 95% CI: 0.81-0.96; p=0.005).
- **All-cause mortality:** The liraglutide group experienced a significant 15% risk reduction in all-cause mortality (HR = 0.85; 95% CI: 0.74-0.97; p=0.02), accounted for by the significant reduction in CV death and comparable rates of death from non-CV causes. Dr. Marso noted that these curves also separated after 12-18 months (much later than in EMPA-REG OUTCOME) and continued to diverge throughout the trial.
- **Heart failure:** Results for the much-watched endpoint of hospitalization for heart failure also trended in a positive direction but did not reach statistical significance (HR = 0.87; 95% CI: 0.73-1.05; p=0.14).

MICROVASCULAR OUTCOMES

Johannes Mann, MD (Friedrich Alexander University of Erlangen, Erlangen, Germany)

While microvascular outcomes usually don't receive as much attention as cardiovascular results at CVOT sessions, the topic turned out to be one of the real positives of the entire LEADER session. We were very surprised to see a 16% statistically improvement in time to first microvascular event (encompassing renal and ophthalmic adverse outcomes; 95% CI: 0.73-0.97, p=0.02), driven entirely by a 22% statistically significant improvement in renal outcomes (95% CI: 0.67-0.92, p=0.003). There was no statistically significant improvement in eye outcomes - the hazard ratio was 1.15 (95% CI: 0.87-1.52, p=0.33). The Kaplan-Meier curves for renal outcomes separated one year into the study and continued to diverge throughout the study. The renal benefit was driven primarily by a difference in the diagnosis of persistent macroalbuminuria (HR=0.74, 95% CI: 0.60-0.91).

- **The implications of this strong renal benefit are substantial, perhaps even prompting consideration of a dedicated chronic kidney disease trial for liraglutide.** While improvements in risk factors like glucose and blood pressure could explain some of the benefit, newer evidence suggests that there might be a direct effect at play, involving GLP-1 receptor-stimulated relaxation of muscles around glomeruli (the functional filtering units of the kidney).
- **The patient population in LEADER had a fairly high level of microvascular disease at baseline:** around 2.5% of patients had an eGFR below 30 ml/min/1.73m^2, ~20% were between 30 and 59 ml/min/1.73m^2, and ~41% were between ml/min/1.73m^2.

- **The specific outcomes assessed in the category of microvascular disease were as follows:**
    - **Renal:** (i) New onset of persistent macroalbuminuria - as mentioned above, this was the renal sub-outcome that drove the improvement, (ii) persistent doubling of serum creatinine, (iii) need for continuous renal replacement therapy, and (iv) death due to renal disease.
    - **Eye:** (i) Need for retinal photocoagulation or treatment with intravitreal agents, (ii) vitreous hemorrhage, and (iii) diabetes-related blindness.

SAFETY

Michael Nauck, MD, PhD (Diabeteszentrum Bad Lauterberg, Germany)

Dr. Michael Nauck (St. Josef Hospital, Bochum, Germany) presented safety and adverse event data from LEADER. Most notably, treatment with liraglutide was associated with a 20% risk reduction for confirmed hypoglycemia with a blood glucose ≤56 mg/dl (HR=0.80, CI: 0.74-0.88, p<0.001) and a 31% risk reduction for severe hypoglycemia requiring assistance (HR=0.69, CI: 0.51-0.93, p=0.016). We expect that this reduction in hypoglycemia risk is largely or at least somewhat attributable to the smaller number of participants in the liraglutide group initiating insulin or sulfonylurea therapy during the trial. The results demonstrate the real-world, long-term benefits of using GLP-1 agonists as an alternative to therapies that increase hypoglycemia risk, and we imagine they could further strengthen the case for GLP-1 agonists (or even GLP-1 agonist/basal insulin combinations) as a first injectable option ahead of insulin. Interestingly, Dr. Anne Peters suggested at The diaTribe Foundation/TCOYD forum later that evening that the overall cardiovascular benefit in LEADER may be at least partially attributable to the lower use of sulfonylureas/ insulin and lower hypoglycemia rates in the active treatment group rather than to specific benefits associated with liraglutide - we wonder whether this opinion will be widely shared and whether it will become a significant part of the debate over the results.

- **Total, serious, and severe adverse event rates were generally similar between the liraglutide and placebo groups.** As expected, a higher proportion of patients experienced nausea, vomiting, and diarrhea leading to discontinuation in the liraglutide group (p<0.001 for each). Abdominal pain and discomfort were also significant adverse events resulting in treatment discontinuation (p=0.03 for pain, p=0.002 for discomfort). Decreased appetite was also significantly more prevalent in the liraglutide-treated group (p=0.01). Liraglutide also produced a statistically significant increase in acute gallstone disease (145 events vs. 90 in placebo, p<0.001) and acute cholecystitis (36 vs. 21 in placebo, p=0.046). Injection site reactions were higher in the liraglutide-treated group as well (32 vs. 12 in placebo, p=0.002).
- **There was a signal toward increased risk of any, malignant, and benign neoplasms by 12%, 6% and 16%, respectively, but the increase was not significant for each.** Interestingly, by type, liraglutide produced a statistically significantly reduced risk of prostate cancer (HR=0.54, CI:0.34-0.88) and leukemia (HR=0.36, CI:0.13-0.99), though Dr. Nauck acknowledged that the number of events was very small. Pancreatic carcinomas were numerically higher in the liraglutide group (13 vs. 5), but the difference was not statistically significant. There were no cases of medullary thyroid carcinoma in the liraglutide-treated group and one in the placebo group. Acute and chronic pancreatitis rates in the liraglutide group were not significantly different from the placebo group.
- **However, both all-cause serious and severe adverse event rates were lower in the liraglutide group than in the placebo group** - in fact, serious adverse events overall were significantly lower in the liraglutide group (p=0.01). We expect at least part of this was driven by the reduced risk of hypoglycemia in the liraglutide-treated group compared to the placebo group.

CONCLUSION

John Buse, MD, PhD (University of North Carolina, Chapel Hill, NC)

Dr. John Buse contextualized the LEADER results by discussing potential mechanisms of benefit, clinical implications, and comparisons to results from other CVOTs for diabetes drugs. He stressed from the outset that directly comparing results from two separate trials is an "entirely inappropriate activity" due to differences in study population, definition and adjudication of events, secular trends in diabetes management, and the countries where the studies were conducted. With that in mind, Dr. Buse shared that he was "nevertheless going to engage in that activity," suggesting that the divergent results from LEADER and ELIXA (CVOT for Sanofi's lixisenatide) could have been due either to differences in study design or intrinsic differences between the molecules. He contrasted the benefits seen in LEADER with those in EMPA-REG OUTCOME, suggesting that the LEADER benefit was more likely mediated through a reduction in atherosclerosis while the EMPA-REG results may have been due to an osmotic effect or an impact on fuel energetics. Dr. Buse offered minimal commentary on the clinical implications of the results but stressed that the conclusions need to be limited to high-risk patients. Like previous speakers, he closed by highlighting the trial's impressive retention and follow-up, suggesting that the trial conduct should inspire strong confidence in the results.

- **Dr. Buse believes that the "substantial differences" between the results from LEADER and ELIXA could be due either to differences in trial design or intrinsic drug-specific differences.** He noted that ELIXA had a different primary endpoint (four-point MACE) and recruited an even higher-risk patient population (patients with a recent acute coronary syndrome event) than LEADER. The nature of the population appeared to have an impact on the pattern of events (the majority of events occurred at the beginning of the trial) and may have impacted the results as well. However, Dr. Buse also stressed that lixisenatide and liraglutide are very different molecules both in terms of structure and pharmacokinetics. Lixisenatide is an analog of the Gila monster-derived exenatide while liraglutide is an analog of human GLP-1, and liraglutide has a much longer half-life and provides 24-hour coverage. We imagine that the PK differences in particular could very likely have contributed to the discrepancy on CV outcomes; future CVOTs for other GLP-1 agonists should provide more insight on this question.
- **Dr. Buse contrasted the gradual, consistent benefit in LEADER with the more immediate and unexpected benefit in EMPA-REG OUTCOME.** He argued that while the hazard ratio for the primary endpoint was "remarkably similar" (13% vs. 14%) in the two trials, the overall picture was very different. EMPA-REG OUTCOME showed a rapid separation between groups followed by maintenance of the difference, whereas the curves in LEADER began to separate within the first 18 months and continued to diverge for the rest of the trial. Similarly, while both studies showed the most profound benefit on CV death, LEADER showed much more consistent results across other outcomes. Dr. Buse suggested that the pattern and timing of responses in LEADER is more consistent with an effect on atherosclerosis, while the main hypotheses at this point for the EMPA-REG OUTCOME results relate to osmotic diuresis and fuel energetics.

DISCUSSANT

Laurie Baggio, PhD (Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario, Canada)

Dr. Laurie Baggio's discussant presentation explored possible mechanistic explanations for the effects observed in LEADER. Regarding the surprisingly large benefit seen on nephropathy, Dr. Baggio suggested that improvements in risk factors like glucose, oxidative stress, weight, blood pressure, and inflammation played an indirect role, but there also exists the tantalizing possibility that liraglutide could be acting directly to reduce filtration pressures in the glomerulus (the functional filtration unit of the kidney), preventing them from burning out. On the observed increase in gallstones, Dr. Baggio speculated on potential mechanisms (weight loss in known to cause an increase in gallstones), but concluded by highlighting the dearth of data in this area, characterizing gallstones as a major area for future investigation on GLP-1 agonists. In her conclusion, Dr. Baggio stated that it is a "huge advantage" for

patients to know that liraglutide reduces mortality, cardiovascular death, MI, and kidney disease, though they must balance those benefits against increases in nausea, vomiting, diarrhea, and gallstone disease.

- **Improvements in cardiovascular risk factors likely explain the lion's share of the MACE reduction seen with liraglutide, but Dr. Baggio did not rule out the possibility of direct GLP-1-receptor-mediated action directly on the heart.** Evidence is mixed on whether GLP-1 receptors are present in cardiac ventricles. The evidence is clearer on the improvements in risk factors, including body weight, blood vessel health, diuresis, natriuresis, reducing inflammation, glucose control, postprandial lipids, coagulation, and reduced hypoglycemia. However some of these risk factors that were measured, such as blood pressure, did not change enough to explain much of the overall cardiovascular benefit seen in the trial.
- **Dr. Baggio appeared unconvinced that GLP-1 agonists are the best option for patients with advanced heart failure.** She pointed that existing outcomes studies, including LEADER, do not suggest a benefit of GLP-1 agonists on heart failure. In her words, there is no reason to avoid using a GLP-1 agonists in a patient with early-stage heart failure, but that prescribers "may want to think twice" in patients with more advanced heart failure. In any case, SGLT-2 inhibitors (or at least empagliflozin from EMPA-REG OUTCOME data) appear to do better with reducing the incidence of heart failure.
- **Dr. Baggio briefly discussed the increase in heart rate seen with liraglutide, but suggested that LEADER does not provide sufficient information to assess the issue one way or the other.**
- **The increases in amylase and lipase are hard to assess, given that their levels are usually variable and often elevated in type 2 diabetes patients who are otherwise asymptomatic.** In fact, 23% of LEADER patients had elevated levels of the enzymes at baseline. Amylase and lipase levels are examined because they are diagnostic for pancreatitis, but overall the pancreatitis data were reassuring, as is experimental evidence that GLP-1 agonists do not promote acinar cell inflammation or proliferation.
- **LEADER was not powerful or long enough to provide a definitive answer on liraglutide and cancer.** Dr. Baggio sees the GLP-1/cancer question as a valid one, in light of evidence that GLP-1/GLP-1 agonists can reduce apoptosis, increase intestinal mass, and increase beta cell mass. She suggested that it will be helpful to know when in LEADER the cancer cases occurred.

Oral Presentations: Treatment Choices after Orals in Type 2 Diabetes

EFFICACY AND SAFETY OF ONCE-WEEKLY SEMAGLUTIDE VS. SITAGLIPTIN AS ADD-ON TO METFORMIN AND/OR THIAZOLIDINEDIONES AFTER 56 WEEKS IN SUBJECTS WITH TYPE 2 DIABETES

Bo Ahrén, MD, PhD (Lund University, Sweden)

In the double-blinded, double-dummy, active-controlled, parallel-group SUSTAIN 2 trial (n=1231), semaglutide 0.5 mg produced a 0.77% greater A1c reduction (p<0.0001) and semaglutide 1.0 mg produced a 1.06% greater A1c reduction (p<0.0001) than Merck's Januvia (sitagliptin 100 mg) after 56 weeks of treatment. Participants had type 2 diabetes and were on metformin, TZDs, or both. In total, semaglutide 0.5 mg produced a 1.3% A1c reduction and semaglutide 1.0 mg produced a 1.6% A1c reduction, compared to sitagliptin's 0.5% A1c reduction (baseline A1c=8.1%, p<0.0001). Participants treated with semaglutide 0.5 mg and 1.0 mg experienced a 17.4 mg/dl and 26.74 mg/dl reduction in fasting plasma glucose (FPG), respectively, compared to participants treated with sitagliptin (baseline FPG=169.4 mg/dl, p<0.0001). Overall, participants experienced FPG reductions of 37.4 mg/dl, 46.7 mg/dl, and 20.8 mg/dl on semaglutide 0.5 mg, semaglutide 1.0 mg, and sitagliptin, respectively. End-of-trial 7-point SMPG profiles were lower at every point for participants treated with semaglutide compared to sitagliptin and compared to baseline. 78% of participants in the semaglutide 1.0 mg group and 69% of participants in the semaglutide 0.5 mg group achieved an end-of-trial A1c of <7.0% at 56 weeks, compared to 36% of the sitagliptin-treated group.

66% of the semaglutide 1.0 mg group and 53% of the semaglutide 0.5 mg group achieved a target A1c of ≤6.5% at 56 weeks, compared to 20% of the sitagliptin-treated group.

- **62% of participants on semaglutide 1.0 mg and 46% of participants on semaglutide 0.5 mg achieved ≥5% weight loss, compared to 18% of participants in the sitagliptin group.** Furthermore, 24% of participants in the semaglutide 1.0 mg group and 13% of participants in the semaglutide 0.5 mg group experienced even more impressive weight loss of ≥10%, compared to just 3% of the sitagliptin-treated group. Semaglutide 0.5 mg and 1.0 mg produced a 2.37 kg (~5.22 lbs) and 4.22 kg (~9.3 lbs) greater weight loss, respectively, than sitagliptin (p<0.0001). In total, participants on semaglutide 0.5 mg lost a mean 4.3 kg (~9.5 lbs) of body weight while participants on semaglutide 1.0 mg lost a mean 6.1 kg (~13.4 lbs), compared to 1.9 kg (~4.2 lbs) with sitagliptin (baseline body weight=89 kg [~196 lbs]). Like the A1c results, Dr. Ahrén highlighted the early and dramatic divergence in weight loss between the semaglutide and the exenatide groups.
- **74% of participants in the semaglutide 1.0 mg group and 63% of participants in the semaglutide 0.5 mg group achieved a composite endpoint of (i) A1c <7.0%, (ii) no severe or blood-glucose confirmed symptomatic hypoglycemia, and (iii) no weight gain.** Only 27% of participants in the sitagliptin-treated group were able to achieve this endpoint. Thus, participants on semaglutide appear 2-3 times more likely to achieve this very clinically relevant composite outcome.
- **Overall, serious, and severe adverse event rates were comparable across all three treatment groups, though adverse events leading to discontinuation were higher in the two semaglutide groups.** Not surprisingly, Dr. Ahrén attributed the higher discontinuation rate of the semaglutide groups to increased GI side effects - 18% of participants in both semaglutide groups experienced nausea at least once throughout the study (vs. 7% in the sitagliptin group), 13% experienced diarrhea (vs. 7%), and 8%-10% experienced vomiting (vs. 3%). That said, Dr. Ahrén emphasized that the vast majority of cases of nausea were classified as "mild," the percentage of patients experiencing nausea at any single time point in the study never exceeded 10%, and the percentage of patients experiencing nausea tapered off as the trial progressed. Hypoglycemia, pancreatitis, and malignant neoplasms were similar across all the groups. Participants in the two semaglutide groups experienced a 2 beats/min increase in heart rate, compared to a 1 beat/min increase in the sitagliptin group.

SUSTAIN 2 Results Summary

Treatment	**Semaglutide 0.5 mg**	*Difference between 0.5 mg and sitagliptin*	**Semaglutide 1.0 mg**	*Difference between 1.0 mg and sitagliptin*	**Sitagliptin 100 mg**
A1c	-1.3%	-0.77%, p<0.0001	-1.6%	-1.06%, p<0.0001	-0.5%
Fasting Plasma Glucose (FPG)	-37.4 mg/dl	-17.4 mg/dl, p<0.0001	-46.7 mg/dl	-26.74 mg/dl, p<0.0001	-20.8 mg/dl
% Achieving A1c <7.0%	69%		78%		36%
% Achieving A1c <6.5%	53%		66%		20%

Weight	-4.3 kg (~9.5 lbs)	-2.37 kg (~5.22 lbs), p<0.0001	-6.1 kg (~13 lbs)	-4.22 kg (~9.3 lbs), p<0.0001	-1.9 kg (~4.2 lbs)
% Achieving ≥5% Body Weight Loss	62%		46%		18%
% Achieving ≥10% Body Weight Loss	13%		24%		3%
% Achieving A1c <7.0% with no severe/symptomatic hypoglycemia and no weight gain	63%		74%		27%

EFFICACY AND SAFETY OF ONCE-WEEKLY SEMAGLUTIDE VS. EXENATIDE ER IN SUBJECTS WITH TYPE 2 DIABETES (SUSTAIN 3)

Andrew Ahmann, MD (Oregon Health & Science University, Portland, OR)

In the open-label, active-controlled, parallel-group SUSTAIN 3 (n=813) trial, participants treated with semaglutide 1.0 mg experienced a 0.62% greater A1c reduction (p<0.0001) than participants treated with exenatide ER 2.0 mg (AZ's once-weekly Bydureon). Overall, those in the semaglutide-treated group experienced a mean A1c reduction of 1.5%, compared to a 0.9% reduction in the exenatide-treated group (baseline A1c=8.3%, p<0.0001). Dr. Ahmann emphasized that the A1c curves for the semaglutide and exenatide groups diverged early on and stayed significantly different throughout the trial. End-of-trial 7-point SMBG profiles were lower at every point for participants treated with semaglutide compared to exenatide and compared to baseline, though the difference appeared to be less dramatic than the separation between the semaglutide and sitagliptin SMPG profiles (as expected, given the generally accepted greater glucose-lowering efficacy of GLP-1 agonists compared to DPP-4 inhibitors) - it would have been more helpful from our view to have CGM data than SMBG data. 67% of participants in the semaglutide group achieved an end-of-trial A1c of <7.0% at 56 weeks, compared to 40% of the exenatide-treated group. 47% of the semaglutide group achieved a target A1c of ≤6.5% at 56 weeks, compared to 22% of the exenatide-treated group.

- **52% of participants treated with semaglutide in SUSTAIN 3 achieved ≥5% weight loss, compared to 17% of those treated with exenatide.** 21% of semaglutide-treated patients achieved ≥10% weight loss compared to only 4% of exenatide-treated patients. Participants treated with semaglutide experienced a 3.78 kg (~8.3 lbs) greater weight loss than those treated with exenatide (p<0.0001). In total, the semaglutide-treated group experienced a mean weight loss of 5.6 kg (~12.3 lbs) compared to a mean weight loss of 1.9 kg (~4.2 lbs) with exenatide (baseline body weight = 95.8 kg [~211 lbs]).
- **With semaglutide treatment, 57% of participants were able to achieve a composite endpoint of A1c <7% with no severe or symptomatic hypoglycemia and no weight gain.** This is about twice the proportion of participants in the exenatide-treated group that achieved this composite endpoint (29%).
- **Overall adverse events were similar between the semaglutide and the exenatide groups, but serious AEs, severe AEs, and AEs leading to discontinuation were slightly higher in the semaglutide group (9% vs. 7%).** This was likely driven by the increased GI side effects seen with semaglutide. In particular, as was previously reported, participants in the semaglutide group experienced almost twice as much nausea as those in the exenatide group (22%

vs. 12%). Participants in the semaglutide group also experienced higher rates of diarrhea (11% vs. 8%), decreased appetite (8% vs. 5%), vomiting (7% vs. 6%), dyspepsia (7% vs. 5%), and constipation (6% vs. 5%). The side effect profile is consistent with what has been reported across the SUSTAIN phase 3 development program. Our sense is that semaglutide is a more potent GLP-1 agonist, offering greater A1c and weight loss efficacy - though some suggest it may have an accompanying higher GI side effects, with most in single digits, we're not too worried about that - although to what degree "hand holding" in the trial would have reduced those reporting nausea etc we don't know. Either way, there are obviously a high percentage of patients that would seem to be able to benefit from this therapy and we look forward to seeing the move toward the market for it.

- **The SUSTAIN 2 and SUSTAIN 3 results were some of the most highly anticipated from the phase 3 development program for semaglutide.** Novo Nordisk is positioning semaglutide as a next-generation GLP-1 agonist with greater A1c efficacy, greater weight loss, and potential additional benefits (such as *cardioprotection* and positive effects on NASH). The results drive home semaglutide's superiority on the A1c and weight loss front compared to other incretins. We'd love to see how semaglutide stacks up against Lilly's new GLP-1 agonist Trulicity (dulaglutide), which has been garnering rave reviews from patients and providers. We'd also be highly interested in seeing a head-to-head trial of injectable semaglutide vs. an SGLT-2 inhibitor - and it goes without saying that we'd love to see how they work together. The *PIONEER* phase 3 development program for the oral formulation of semaglutide does includes a trial against Lilly/BI's Jardiance (empagliflozin).

SUSTAIN 3 Results Summary

Treatment	**Semaglutide 1.0 mg**	**Exenatide ER 2.0 mg**	*Difference between semaglutide and exenatide*
A1c	-1.5%	-0.9%	-0.62%, p<0.0001
% Achieving A1c <7.0%	67%	40%	
% Achieving A1c <6.5%	47%	22%	
Weight	-5.6 kg (~12.3 lbs)	-1.9 kg (~4.2 lbs)	-3.78 kg (~8.3 lbs), p<0.0001
% Achieving ≥5% Body Weight Loss	52%	17%	
% Achieving ≥10% Body Weight Loss	21%	4%	
% Achieving A1c <7.0% with no severe/symptomatic hypoglycemia and no weight gain	57%	29%	

SUPERIOR EFFICACY OF ITCA 650 VS. SITAGLIPTIN IN UNCONTROLLED TYPE 2 DIABETES ON METFORMIN: THE FREEDOM-2 RANDOMIZED, DOUBLE-BLIND, 1-YEAR STUDY

Julio Rosenstock, MD (Dallas Diabetes and Endocrine Center, Dallas, TX)

Dr. Julio Rosenstock presented results from the phase 3 FREEDOM-2 study demonstrating significantly greater A1c reductions (1.5% vs. 0.8%; p<0.001) and weight loss (4 kg vs. 1.3 kg; p<0.001) with Intarcia's

ITCA 650 vs. Merck's Januvia (sitagliptin). Intarcia announced topline results from the trial in August. The double-blind trial randomized 535 patients with type 2 diabetes on metformin to receive either ITCA 650 + oral placebo or Januvia + implantable placebo for 52 weeks. Patients received the initiation dose of ITCA 650 for 13 weeks and switched to the maintenance dose for the remaining 39 weeks. The A1c difference between the groups was already significant at six weeks and stabilized at week 26; final reductions were 1.5% with ITCA 650 vs. 0.8% with Januvia (baseline = 8.6%-8.7%; p<0.001). ITCA 650 also produced significantly greater reductions in fasting plasma glucose (47 mg/dl vs. 28 mg/dl; p<0.001). Weight loss followed a similar pattern as the A1c reductions, with a fairly early separation that stabilized at around week 26 and remained stable throughout the trial. The final weight reduction was 4 kg (~8.8 lbs) with ITCA 650 vs. 1.3 kg (~2.9 lbs) with Januvia (baseline BMI = 33 kg/m²; p<0.001). ITCA 650 was also superior in terms of the percentage of patients achieving the composite endpoint of A1c reduction >0.5% and weight loss ≥2 kg (61% vs. 28%; p<0.001) and the percentage achieving A1c targets of <7% (61% vs. 42%) and <6.5% (44% vs. 21%). As expected, there were more GI events in the ITCA 650 group, though the discontinuation rates due to these events were low (4.5% for nausea and 2.3% for vomiting). Importantly, the rate of procedure-related adverse events was quite low (<1%) in both groups. Dr. Rosenstock also emphasized that nausea rates peaked when the initial dose was started and when the dose was escalated, but rates were quite low throughout the rest of the trial.

- **We are particularly impressed with the durability of the A1c and weight reductions - the difference between the groups held steady from week 26 through the end of the trial.** We also found the results for the composite endpoint especially compelling and expect that payers will as well. Intarcia has reported results from three additional trials for ITCA 650: results from FREEDOM-1 and FREEDOM-HBL demonstrating significant A1c reductions vs. placebo were presented at ADA 2015 and topline results from the FREEDOM-CVO trial demonstrating a neutral effect on CV outcomes were announced in May. The impressive efficacy and guaranteed adherence should make ITCA 650 an appealing option for a wide range of patients and could significantly expand use of the GLP-1 agonist class, although we would not be surprised if the product's commercial performance falls a bit short of the extremely high expectations that some in the field have set for it, particularly less informed investors looking at the first year or two. We have big expectations that the GLP-1 field will continue to grow, and expect Intarcia to be a meaningful part of this. We appreciate very much Intarcia's focus on helping improve patient adherence and engagement and look very forward to seeing how the launch emerges. Ideally, this therapy will continue the path that a range of companies are trying to take to make various therapies easier to prescribe and take and stay on.

Questions and Answers

Q: Are there any issues around removal in terms of fibrosis?

A: There were no issues of fibrosis. The technique has been highly revised. It's now done with a delivery device and different tools to ensure the placement is very superficial. Before there was not a tool to really make sure the device was not placed too deep. Now they have a device where you can't get too deep, so that's no longer an issue.

Q: Do you have to take the device out to change the dose?

A: Yes. This device could be used for six months, and eventually it will be one year. Taking it out takes less than two minutes.

EFFICACY AND DURABILITY OF EXENATIDE IN COMBINATION WITH PIOGLITAZONE VS. BASAL-BOLUS INSULIN IN POORLY CONTROLLED TYPE 2 DIABETIC PATIENTS: THE QATAR STUDY

Muhammad Abdul-Ghani, MD, PhD (UT Health Science Center, San Antonio, TX)

Dr. Muhammad Abdul-Ghani presented results of the QATAR study, demonstrating that the addition of exenatide in combination with pioglitazone in poorly controlled type 2 diabetes patients (on metformin/

SFU) produces greater A1c reductions with less hypoglycemia and weight gain compared to basal-bolus insulin therapy. This study randomized poorly controlled type 2 diabetes patients on maximal dose of metformin/SFU to either once-weekly exenatide plus pioglitazone (n=112) or basal (glargine)-bolus (aspart) insulin (n=114). Follow-up visits were conducted monthly for the first six months and then every two to three months afterwards. At six and 12 months, the exenatide/pioglitazone arm (baseline A1c of ~10%) achieved A1c levels of 6.5% and 6.2%, respectively, compared to the insulin arm's achievement of 7.5% and 7.3% at 6 and 12 months, respectively - that's a pretty big difference and excellent results, especially given the high baseline A1c. In addition, more participants in the insulin therapy arm failed to achieve the A1c goal <7% compared to the combination therapy arm (63% vs. 17%). Regarding adverse events, the exenatide/pioglitazone group experienced significantly less hypoglycemia (0.21 vs. 0.67 events/patient year) and gained less weight (0.7 kg vs. 3.1 kg). On the other hand, the combo therapy arm saw greater edema, injection site bumps, nausea, and other GI side effects. But ultimately, these findings are promising and highlight the rising potential and greater enthusiasm for various forms of combination therapies. The TZD element of the combination was great to see, particularly as this is now a generic drug - we've heard when it is taken in lower doses, there are often significantly fewer side effects and we'd love to know more on that. These results reinforce our thinking that early and mid-stage in diabetes treatment, prandial insulin is going to be chosen a smaller percentage of the time given other alternatives - we believe the other alternatives will also keep patients alive longer and that more will eventually need prandial insulin as the "lifespan" will continue to expand. We just hope an "elderly well" rather than an "elderly unwell" will start to emerge. Although we hear a lot of negativity about SFUs, we'd also love to see "all" patients get "the best one."

Questions and Answers

Q: What did you do with the SFUs? Did you continue it or what?

A: Yes, the treatments were added on top of SFUs and metformin. Participants were also allowed to adjust meds throughout the study.

Q: You noted there was more edema in the combo therapy - was that related to CHF?

A: It was peripheral edema. Only three patients discontinued due to the edema.

Q: One third of your patients had nausea in the combo therapy. Most of these patients also had severe insulin resistance. Did you check the food intake with nausea in relation to the weight changes?

A: No, we didn't but it's an interesting point. [Editor's note - we're surprised this wasn't checked. This was an early question/criticism of Amylin's Byetta and proved to be unfounded.]

Dr. Julio Rosenstock (Dallas Diabetes and Endocrine Center, Dallas, TX): This is very interesting data. These patients have more than ten years of diabetes and A1cs of 10% on metformin and SFUs. The A1c reductions are so impressive. I've never seen anything like this. I wish my patients were in the QATAR study.

CLINICAL IMPACT OF TITRATABLE FIXED-RATIO COMBINATION OF INSULIN GLARGINE/ LIXISENATIDE VS. EACH COMPONENT ALONE IN TYPE 2 DIABETES INADEQUATELY CONTROLLED ON ORAL AGENTS: LIXILAN-O TRIAL

Julio Rosenstock, MD (Dallas Diabetes and Endocrine Center, Dallas, TX)

Dr. Julio Rosenstock presented results from the phase 3 LixiLan-O trial demonstrating significantly greater A1c reductions with Sanofi's iGlarLixi (formerly LixiLan) vs. either of its components in patients with type 2 diabetes on oral agents. Sanofi announced topline results from the trial in July 2015 and the dataset was included in the company's briefing documents for the recent FDA Advisory Committee meeting for iGlarLixi. The open-label trial randomized 1,170 patients with type 2 diabetes not at goal on metformin and another oral agent to receive either iGlarLixi (n=469), Lantus (insulin glargine; n=467), or lixisenatide (n=234) for 30 weeks. A1c reductions were significantly greater with iGlarLixi (1.6%) vs. both Lantus (1.3%) and

lixisenatide (0.9%) (baseline = 8.1%; p<0.0001). A significantly higher percentage of patients achieved an A1c <7% with the combination (74%) compared to Lantus (59%) and lixisenatide alone (33%). Fasting plasma glucose reductions were comparable with iGlarLixi (62 mg/dl) and Lantus (59 mg/dl) and less impressive with lixisenatide (27 mg/dl) (baseline = 176-178 mg/dl; p<0.0001). As expected, lixisenatide's greatest contribution was on postprandial glucose. iGlarLixi was superior to both Lantus (by 43 mg/dl) and lixisenatide (by 20 mg/dl) on two-hour postprandial glucose; the combination was superior to Lantus (by 38 mg/dl) but inferior to lixisenatide (by 16 mg/dl) on postprandial glucose excursions. Seven-point glucose profiles showed lower overall glucose throughout the day with iGlarLixi and lower peaks compared to Lantus, especially at breakfast (we'd love in the future CGM use). The combination also demonstrated a 1.4 kg weight benefit compared to Lantus and allowed a significantly higher percentage of patients to achieve the composite endpoint of A1c <7% with no weight gain (43% vs. 25% with Lantus and 28% with lixisenatide).

- **Especially relevant in light of the recent IGlarLira AdComm discussion, Dr. Rosenstock highlighted the potential for dosing flexibility with the two iGlarLixi pens.** Sanofi plans to market iGlarLixi in two pens, one (pen A) with a 2:1 insulin glargine/lixisenatide ratio and insulin doses ranging from 10-40 U/day and another (pen B) with a 3:1 insulin glargine/ lixisenatide ratio and insulin doses ranging from 40-60 U/day. Dr. Rosenstock emphasized that this allows insulin titration up to 60 U without going above the maximum dose of 20 mcg lixisenatide. Data on the final dose distribution in LixiLan-O showed that 56% of patients achieved good control with pen A, 44% required intensification to pen B, and only 8% reached the maximum dose of 60 U without achieving target. A number of panelists at the AdComm meeting expressed concerns about distinguishing between the two pens and about the nomenclature of "units" used to dose the combination. These concerns were fairly unexpected to us, and we hope Sanofi and the FDA can work together to resolve them in short order.
- **Adverse events were generally similar between groups in the trial.** Nausea rates were substantially lower with iGlarLixi (9.6%) compared to lixisenatide (24%), confirming one of the main expected with these combinations compared to GLP-1 agonists alone. Dr. Rosenstock highlighted the fact that only 0.4% of the iGlarLixi group discontinued treatment due to nausea (compared to 2.6% in the lixisenatide group). The rate of documented symptomatic hypoglycemia was low and comparable between the iGlarLixi and Lantus groups (1.4 vs. 1.2 events/patient-year).

Questions and Answers

Q: Given the short duration of action of lixisenatide, might it make more sense to use it twice a day?

A: That sounds like common sense but you don't need to. With the results you get, why would you need to? You get an effect on postprandial glucose mainly in the morning, you do have some carry over for lunch, and by dinner there's not much, but you get down to 6.5%. We shouldn't use it twice a day because it's not approved. (Editor's note - we think this question is interesting - as we continue to emphasize, the over-emphasis on A1c is troubling. We are curious if twice-daily dosing might get more of the 26% of patients who did not reach 7% A1c to 7% or lower.)

Q: Would you use it twice a day if A1c deteriorates over time?

A: I don't know. We need longer-term studies.

Q: I'd like to see a study where you challenge the fixed-ratio combination not only to glargine + lixisenatide but to degludec + liraglutide, comparing the fixed ratio with split injections. I think it would highlight the convenience of the fixed ratio and on the other side the ability to individualize the combination because we know patients have different characteristics.

A: There's no question that what you suggest would be a nice study. The question is whether simultaneous therapy is better than sequential. All these years we've done sequential. We have a bit of indirect evidence on this from GetGoal Duo 1, where patients were on basal insulin for 12 weeks and then added lixisenatide. That got people down to 7% and here we got down to 6.5%. The important bottom line is that we get down to 6.5%.

The same was true with IDegLira. Both combinations get people down to levels we were never able to get before with any of the components alone.

Q: What concentration of insulin glargine was used?

A: U100.

Oral Presentations: Beyond Basal Insulin in Type 2 Diabetes - Treatment Intensification Options

EFFICACY AND SAFETY OF THE INSULIN GLARGINE/LIXISENATIDE FIXED-RATIO COMBINATION VS. INSULIN GLARGINE IN PATIENTS WITH T2DM: THE LIXILAN-L TRIAL

Vanita Aroda, MD (MedStar Health Research Institute, Hyattsville, MD)

The highly respected Dr. Vanita Aroda presented results from the phase 3 LixiLan-L trial demonstrating significantly greater A1c reductions with Sanofi's iGlarLixi (formerly LixiLan) vs. Lantus (insulin glargine) in patients with type 2 diabetes on basal insulin, driven by improvements in postprandial glucose. Sanofi announced topline results from the trial in September 2015 and the dataset was included in the company's briefing documents for the FDA Advisory Committee meeting for iGlarLixi. The open-label trial randomized 736 patients not at goal on basal insulin and oral drugs to treatment with iGlarLixi (n=367) or Lantus (n=369) for 30 weeks. The insulin glargine dose in both groups was titrated to a fasting glucose target of 80-100 mg/dl and the dose was capped at 60 U/day (to match the maximum dose in the combination). A1c reductions were significantly greater with iGlarLixi (1.2%) than Lantus (0.6%) (baseline = 8.1%). A significantly higher percentage of patients achieved an A1c <7% with iGlarLixi (55%) than with Lantus (30%; p<0.0001). Fasting plasma glucose reductions were similar in both groups (21 mg/dl vs. 23 mg/dl), as expected given the almost identical average daily doses of insulin glargine at the end of the trial (46 vs. 47 U). The main contribution of lixisenatide to the combination was on postprandial glucose: iGlarLixi produced significantly greater reductions in both two-hour postprandial glucose (85 mg/dl vs. 25 mg/dl) and postprandial excursions (70 mg/dl vs. 8 mg/dl) compared to Lantus. Seven-point glucose profiles illustrated this improvement in postprandial control, particularly after breakfast. iGlarLixi led to a 1.4 kg weight benefit and comparable hypoglycemia rates to Lantus. The combination also allowed a greater percentage of patients to achieve an A1c <7% without weight gain (34% vs. 13%), an A1c <7% without hypoglycemia (32% vs. 19%), and an A1c <7% without weight gain or hypoglycemia (20% vs. 9%) - while the benefit is encouraging, the low absolute percentages in both groups illustrate the remaining need for more effective therapies.

Questions and Answers

Q: Do you think the weight loss is less when lixisenatide is used in combination with insulin vs. separately when added to insulin or without insulin?

A: I would refer you to the LixiLan-O trial, where we saw greater weight loss with lixisenatide alone. Here we have mitigation of the weight gain with insulin glargine.

Q: But the average weight loss seems to be less here than when you add on a GLP-1 agonist without insulin or even separately.

A: Part of it might be the final dose, which was 17 mcg of lixisenatide on average.

Q: I'm guessing the combination was administered before breakfast. Was the administration of glargine alone done at the same time?

A: Glargine could be administered at any time and it was consistent throughout the trial. The combination was injected an hour before breakfast.

Q: From the seven-point profile, it's obvious that the main effect is on that first meal, yet it was a fixed schedule of dosing before breakfast. Do you think the results would be different if it was administered with the largest meal rather than breakfast? My patients don't all eat breakfast, and dinner is typically the biggest meal in the US.

A: That's an intriguing question that can only be answered by a trial. There was a sub-study looking at dosing at the main meal vs. the morning and the main effect seems to be in the morning, but we would need a trial to know.

Q: You didn't save a single dose of insulin by adding lixisenatide and you had the same rate of hypoglycemia. Is there any information on the PK/PD data? Were the profiles of both components really preserved? It seems like a very weak effect.

A: The PK data were consistent with what was seen in the lixisenatide standalone program. Your point is appreciated that there's not necessarily an insulin-sparing effect. I would also state here that we had a greater A1c reduction down to 6.9% without increased hypoglycemia. We're looking at two different end A1cs with comparable hypoglycemia.

Q: Looking at the meal data in the control group, you still have glucose values of 230 mg/dl two hours after a meal - people are clearly not well controlled. Would you anticipate different results if you had a more well-controlled group?

A: The 230 mg/dl was from a mechanistic substudy highlighting the mechanism of action of iGlarLixi on postprandial glucose. The 7-point SMPG, reflective of control in the comparator group, showed the control we typically see with titration with insulin glargine (postprandial glucose of 160s-190s during the day). This, along with detailed review of titration, superimposable fasting glucoses, and insulin doses all support appropriate titration in the control group.

PATIENTS WITH T2D TREATED WITH INSULIN DEGLUDEC/LIRAGLUTIDE (IDEGLIRA) HAVE A GREATER CHANCE OF REACHING GLYCEMIC TARGETS WITHOUT HYPOGLYCEMIA AND WEIGHT GAIN THAN WITH INSULIN GLARGINE (IG)

Ildiko Lingvay, MD, MPH (University of Texas Southwestern Medical Center, Dallas, TX)

Dr. Ildiko Lingvay (University of Texas Southwestern Medical Center, Dallas, TX) presented a post-hoc analysis of DUAL V trial focusing on patients who were able to achieve fasting plasma glucose (FPG) and A1c targets (FPG <130 mg/dl or A1c <7%) in the trial. DUAL V, which was previously presented at ADA 2015, demonstrated striking A1c and weight benefits with Novo Nordisk's fixed-ratio GLP-1 agonist/basal insulin combination Xultophy (insulin degludec/liraglutide) over basal insulin Lantus (insulin glargine) intensification in 557 patients with type 2 diabetes who were already on Lantus and metformin (-0.6% and -3 kg [7lbs], p<0.001 for both). In this post-hoc analysis, Dr. Lingvay showed that significantly more participants in the trial who were treated with Xultophy and achieved a FPG <130 mg/dl did so without hypoglycemic episodes (57.9% of those in the Xultophy arm were able to do so, compared to 40.9% of those in the Lantus arm, p<0.0001). More participants achieving the target FPG with Xultophy did so without weight gain as well (54.3% of Xultophy arm vs. 24% of Lantus arm, p<0.0001). Impressively, 41% of participants who achieved a FPG <130 mg/dl in the Xultophy arm did so without either hypoglycemia or weight gain, while only 14% of those in the Lantus arm did so (p<0.0001). Similarly, greater proportions of patients in the Xultophy arm were able to (i) achieve an A1c <7%, (ii) achieve an A1c <7% with no hypoglycemia, and (iii) achieve an A1c <7% with no hypoglycemia or weight gain. This held true for regardless of baseline A1c (≤7.5%, >7.5%-≤8.5%, and >8.5%). Dr. Lingvay also showed that participants on Xultophy were able to achieve the FPG target <130 mg/dl more quickly than participants on Lantus, despite those participants taking lower insulin doses than those in the Lantus arm throughout the trial.

IMPROVED GLYCEMIC CONTROL AND WEIGHT LOSS WITH ONCE-WEEKLY DULAGLUTIDE VS. PLACEBO, BOTH ADDED TO TITRATED DAILY INSULIN GLARGINE, IN TYPE 2 DIABETES PATIENTS (AWARD-9)

Paolo Pozzilli, MD (University Campus Bio-Medico, Rome, Italy)

In front of a standing-room-only crowd, Dr. Paolo Pozzilli presented the results of AWARD-9, a double-blind, 28-week superiority trial comparing the effects of Lilly's Trulicity (dulaglutide) vs. placebo on A1c and weight when added to insulin glargine in type 2 diabetes patients. The trial randomized 300 patients with inadequate glycemic control (A1c of 7-10.5%) to dulaglutide 1.5 mg (n=150) or placebo (n=150) on top

of once-daily glargine titrated to a FPG target of 71-99 mg/dl (± metformin). Baseline characteristics were similar between both groups (please see below). Data at 28 weeks show that compared to placebo, dulaglutide provided significantly greater reductions in A1c (-0.7% vs. -1.4%, respectively), and in fasting serum glucose (28 vs. 45 mg/dl, respectively; p<0.001 for both comparisons). No difference in the rate of hypoglycemia was observed. Patients on dulaglutide experienced a weight loss (4.2 lbs [1.91 kg]), compared to a weight gain with placebo (1.1 lbs [0.50 kg]; p<0.001). In addition, insulin glargine requirements were statistically significant lower in the dulaglutide group (13U) vs. the placebo group (26U).

- **The rate of retention was similar between the dulaglutide and placebo groups (92% and 89%, respectively). The two groups also had similar baseline characteristics,** with an average age of 60 years, percent female of 41%-43%, percent Caucasian of 92%-95%, BMI of 33 kg/m^2, diabetes duration of 13 years, A1c of 8.3%-8.4%, fasting serum glucose of 156-157 mg/dl, and percent on metformin of 87%-89%.

Table: 28-week data on the effect of dulaglutide vs. placebo on glucose measurements, weight, and glargine requirements.

Primary Endpoint	Dulaglutide	Placebo	Difference	p value
A1c reduction (%)	1.44	0.67	0.77	p <0.001
% pt with A1c <7%	69%	35%	--	p <0.001
% pt with A1c <6.5%	51%	17%	--	p <0.001
Reduction in FSG (mg/dl)	45	28	17	p <0.001
Weight change	-1.91 kg (4.2 lbs)	+0.50 kg (1.1 lbs)	-2.41 kg (5.3 lbs)	p <0.001
Change in glargine dose	13U	26U	-13U	p <0.001

- **Hypoglycemia rates between the two groups were similar.** The dulaglutide and placebo groups had similar rates of overall hypoglycemia (82% vs. 76%, respectively), documented symptomatic hypoglycemia (53% vs. 45%, respectively), and nocturnal hypoglycemia (42% vs. 43%, respectively). The dulaglutide group had one episode of severe hypoglycemia, compared to zero in the placebo group.
- **Regarding adverse events, more gastrointestinal symptoms were observed in the dulaglutide groups.** Dr. Pozzilli noted that these events only led to discontinuation of therapy in very few patients.

Questions and Answers

Q: Can you give us an idea on how the insulin was adjusted?

A: The basal insulin glargine dose was given according to the classical algorithm used for a patient with basal-only insulin. It was then titrated by two units.

Q: You had a baseline A1c of 8.4%, which came down to about 7%. But you only had a fraction of people achieve an A1c <7%, suggesting that there were non-responders. Did you look at those non-responders?

A: The patients had an excellent response if you look at the standard deviation. You see that there is minimal variation, suggesting that nearly all the patient responded to therapy. The difference between the two groups was highly significant between the two groups.

Dr. Stefano Del Prato (University of Pisa, Italy): There is something that is not completely clear to me. People in the placebo group required 26 more units of glargine compared to 13 units for dulaglutide, yet there was no difference in the rate of hypoglycemia. What is the

explanation? Because one of the things that we have been exposed to is that the combination of insulin plus a GLP-1 agonist often comes with a reduction in hypoglycemia. Is it because of the titration?

A: Yes, I think it is the titration.

Oral Presentations: Obesity and Related Conditions

SEMAGLUTIDE REDUCES APPETITE AND ENERGY INTAKE, IMPROVES CONTROL OF EATING, AND PROVIDES WEIGHT LOSS IN SUBJECTS WITH OBESITY

John Blundell, PhD (University of Leeds, UK)

Dr. John Blundell presented positive results on reductions in energy intake and appetite with once-weekly GLP-1 agonist semaglutide in people with obesity. This double-blind, crossover study examined the mechanisms of weight loss of semaglutide (dose-escalated to 1.0 mg) vs. placebo in 30 participants with obesity and without type 2 diabetes (baseline BMI of 34 kg/m²). At 12 weeks, the results found a reduction in body weight, with decreases in energy intake, appetite, and food intake along with overall improved control of eating. Specifically, findings demonstrated that ad libitum energy intake was lower with semaglutide vs. placebo at lunch (5 hours after standardized breakfast), evening meal, and snacks with relative reductions of 35%, 18%, and 22%, respectively. In addition, the semaglutide group achieved weight loss of 5 kg (with greater loss of fat mass compared to lean mass) vs. a small increase of 0.97 kg with placebo. Fasting overall appetite scores also indicated reduced appetite with semaglutide vs. placebo (p=0.0023), while nausea ratings were similar - suggesting that this effect was independent of side effects. Additionally, results from the overall appetite-suppression score and control of eating questionnaire indicated less cravings and greater control of eating. Notably, participants had greater reductions in energy intake of food groups of high fat and traditionally more "appealing" foods, which reflected the results from the Leeds food preference task. Dr. Blundell noted that the semaglutide group experienced a reduction in resting metabolic rate. These findings further confirm to us the impressive versatility of semaglutide, as the product has been suggested to be studied in several indications beyond type 2 diabetes, including NASH, obesity, and a range of macrovascular and microvascular complications - see more on this from our Novo Nordisk 1Q16 report. We have certainly seen significant enthusiasm for the GLP-1 agonist class within obesity - as already pioneered by Novo Nordisk's Saxenda (liraglutide 3.0 mg) - and the eating behavior-specific findings from this study direct us back to potential mechanisms within the brain and its reward circuitry, which is marking itself as a fast growing area of research for obesity.

Questions and Answers

Q: Do you think the changes in resting metabolic rate are accounted for by the degree of weight loss?

A: Yes, when weight is lost rapidly, the body adjusts. This can drive appetite and make energy expenditure more efficient. When body weight was entered into the analysis as a co-variate, the effect of semaglutide on RMR was no longer significant.

DAPAGLIFLOZIN + EXENATIDE QW REDUCED BODY WEIGHT AND IMPROVED GLUCOSE TOLERANCE IN NONDIABETIC OBESE ADULTS: A RANDOMIZED, PLACEBO-CONTROLLED, PHASE 2 STUDY

Jan Eriksson, MD, PhD (Uppsala University, Uppsala, Sweden)

Results from a phase 2 proof of concept study (n=50) of combination therapy with AZ's Farxiga (dapagliflozin) and Bydureon (exenatide once weekly) demonstrated significant ~4 kg weight loss and glycemic improvements vs. placebo in patients with obesity but not diabetes. Participants in the double-blind, single-center study were randomized to receive either active treatment or double placebo for 24 weeks, followed by a 28-week open-label extension study; data from the extension study will be presented at EASD in September. After 24 weeks, the combination led to significant placebo-adjusted weight loss of 4.1 kg (baseline weight = 103-106 kg [227-234 lbs]; baseline BMI = 35-36; p=0.0007) or 4.2% (p=0.0005). As in

most obesity drug trials, there was a wide range of responses, but far more patients achieved ≥5% weight loss with the active treatment than with placebo (36% vs. 4%). MRI analysis of body composition showed that almost all of the weight loss was due to loss of adipose tissue, with no significant change in lean tissue. The combination also produced a modest but significant 0.2% placebo-adjusted A1c reduction (baseline = 5.6%, p=0.0004), a significant drop in the proportion of patients with impaired fasting glucose and impaired glucose tolerance, and a significant placebo-adjusted blood pressure reduction of 6.4 mm Hg (p=0.026). Adverse events were fairly balanced, with slightly more GI side effects in the active treatment group.

- **These results are encouraging, though as noted during Q&A, the real test will be how the combination stacks up against each of its components alone.** AZ is currently conducting a phase 3 study (n=660) of that comparison in patients with type 2 diabetes that is expected to complete in December 2017 (primary completion May 2016). As presenter Dr. Jan Eriksson noted, GLP-1 agonist/SGLT-2 inhibitor combinations are very appealing for obesity due to their complementary mechanisms of weight loss (calorie loss with the SGLT-2 inhibitor and reduced appetite/caloric intake with the GLP-1 agonist). The same could also be said for glycemic control, as the reduction in glucagon production with GLP-1 agonists could help mitigate the increased glucagon production that blunts some of the efficacy of SGLT-2 inhibitors. We expect AZ to focus primarily on type 2 diabetes with this combination but find the potential in obesity very interesting as well, particularly for a GLP-1 agonist with more potent weight effects like Novo Nordisk's Saxenda (liraglutide 3.0 mg) or semaglutide.

Questions and Answers

Q: Could you clarify the timing of the last dose vs. the glucose measures?

A: A glucose tolerance test was performed at baseline and at 24 weeks. The dose was taken half an hour before the glucose tolerance test was started.

Q: Although I acknowledge this was a proof of concept trial, why didn't it include monotherapy + placebo arms? You're really asking whether there's a synergistic or additive effect and this study didn't answer that.

A: It's a proof of concept for the combination and we showed robust weight loss vs. placebo, but I agree, we want a study against monotherapies as well. That would have increased the study size so we couldn't have done it at a single center.

Oral Presentations: Hypoglycemia Potpourri

EFFECTS OF GLP-1 INFUSION ON ENDOTHELIUM AND ATHEROTHROMBOTIC BALANCE DURING HYPOGLYCEMIA IN HEALTHY INDIVIDUALS

Stephen Davis, MD (University of Maryland, Baltimore, MD)

Dr. Stephen Davis shared results from two randomized, double blind trials (n=22) evaluating the impact of GLP-1 on endothelial health and atherothrombotic balance during hypoglycemia (50 mg/dl) in participants without diabetes. Results showed that atherothrombotic and inflammatory mediators ICAM-1, VCAM-1, PAI-1, E-Selectin, and Endothelin were all reduced during hypoglycemia with GLP-1 infusion as compared to placebo. Further, nitric oxide and other non-nitric oxide mediated vasodilation were also improved with GLP-1 (p<0.05) vs. control. GLP-1 infusion did not significantly impact glucose kinetics, catecholamines, insulin, glucagon, growth hormone, or free fatty acids. According to Dr. Davis, these data indicate that GLP-1 has acute protective effects on endothelial function and reduces pro-atherothrombotic, pro-inflammatory, and pro-coagulant responses during moderate hypoglycemia. We would expect that the protective effects of the GLP-1 infusion would translate to the GLP-1 agonist class and we are especially curious as to how these effects would play out in those with hypoglycemia unawareness and impaired counter-regulatory hormone reactions to hypoglycemia.

EFFECT OF EXENATIDE ONCE WEEKLY ON GLYCEMIC FLUCTUATIONS IN PATIENTS WITH T2D (1014-P)

J Frias, J Ruggles, S Zhuplatov, S Nakhle, E Klein, R Zhou, L Shi, and P Strange

Dr. Frias et al. conducted a randomized, controlled, double blind study investigating the effects of AZ's Bydureon (exenatide once weekly) on glucose fluctuations in patients with type 2 diabetes. The study recruited 117 adult patients well-controlled on metformin (A1c 7-10%), who were randomized to open-label metformin XR (1500 or 2000mg daily) plus double-blinded Bydureon 2.0 mg (n=61) or placebo (n=56). Glucose concentration was measured via the Dexcom G4 CGM every 5 minutes during the last week before randomization (baseline), as well as during weeks 4 and 10. Compared to placebo, Bydureon provided significantly greater reductions in 24-h mean glucose on day six of week four (5.3 mg/dl vs. 26.0 mg/dl, respectively) and on day six of week 10 (3.0 mg/dl vs. 30.8 mg/dl, respectively). Similar results were observed for fasting plasma glucose (FPG), postprandial glucose (PPG), and mean amplitude of glycemic excursions (MAGE) (please see table 1 below). Those on Bydureon experienced a significant increase in the time spent in euglycemia (70-180 mg/dl) from baseline to week four and week 10 (p<0.001 for both) - this was secondary to reductions in time spent in hyperglycemia (>180 mg/dl), with no increase in the time spent in hypoglycemia (<70 mg/dl); the finding was not observed in the placebo group. The authors concluded that Bydureon provides robust effects on measures of glycemic fluctuation at week four that persist to week 10.

- **Both groups had eight patients withdraw from the study**, leading to a retention rate of 87% in the exenatide group (53 patients analyzed) and of 86% in the placebo group (48 patients).
- **Baseline characteristics were comparable between the two groups,** with an average age of 55-56 years, percent male of 55-57%, similar race breakdown, duration of diabetes of 9-10 years, pre-trial metformin dose of 1,875-1,925 mg, body weight of 90-91 kg, BMI of 32, A1c of 8.0-8.2%, fasting plasma glucose of 168-178 mg/dl, 2-h mean post-prandial glucose of 221 mg/dl, 24-h mean glucose of 184-186 mg/dl, and MAGE of 90-91.

Table 1: Effect of Bydureon vs. placebo on measures of glucose control and fluctuation

	Bydureon group	Placebo group	p value
	Change in 24-h mean glucose from baseline		
Week 4, day 6	-26.0	-5.3	p <0.001
Week 10, day 6	-30.8	-3.0	p <0.001
	Change in fasting plasma glucose, from baseline		
Week 4, day 6	-29.6	-1.9	p <0.001
Week 10, day 6	-41.9	-5.0	p <0.001
	Change in post-prandial glucose (after standard meal), from baseline		
Week 4, day 6	-32.1	-2.0	p <0.001
Week 10, day 6	-44.4	-6.0	p <0.001
	Change in mean amplitude of glucose excursions		
Week 4, day 6	-8.2	-3.8	---
Week 10, day 6	-15.2	+2.9	p <0.001

Table: Effect of Bydureon vs. placebo on time spent in euglycemia and hyperglycemia

	Time spent in euglycemia (70-180 mg/dl)		
	Baseline	Week 4	Week 10
EQW group	53%	71%*	77%#
Placebo group	55%	60%	58%
	Time spent in hyperglycemia (>180 mg/dl)		
	Baseline	Week 4	Week 10
EQW group	47%	29%	22%
Placebo group	45%	40%	42%

Numeric data was not provided for time spent in the hypoglycemia range (<70 mg/dl)

* p<0.001 for baseline vs. week 4 in the EQW group

# p<0.001 for baseline vs. week 10 in the EQW group

- **Serious adverse events were observed in four patients in the Bydureon group** (one case each of acute pancreatitis, non-cardiac chest pain, chest pain, and nephrolithiasis), as well as in one patient in the placebo group (upper respiratory tract infection). The investigators considered these events to be unrelated to treatment.

CONSISTENT OUTCOMES ACROSS DOSE RANGES WITH TITRATABLE LIXILAN, INSULIN GLARGINE/LIXISENATIDE FIXED-RATIO COMBINATION, IN THE LIXILAN-O TRIAL (1017-P)

R Henry, B Ahrén, M Davies, Y Wu, Y Handelsman, E Souhami, E Niemoeller, and J Rosenstock

Sanofi presented data from the LixiLan-O trial showing that iGlarLixi (formerly LixiLan; lixisenatide/ insulin glargine) was consistently safe and effective and produced minimal weight gain across all dose ranges. Primary results from the trial presented as an oral presentation demonstrated superior glycemic control with iGlarLixi vs. either component alone in patients with type 2 diabetes not at goal on oral medications. During the trial, the dose of insulin glargine (Lantus) was titrated weekly in both the iGlarLixi and insulin glargine groups to a fasting plasma glucose target of 80-100 mg/dl, with a cap of 60 U/day (the maximum dose available in the combination). In the iGlarLixi group, two different pens with different insulin glargine/lixisenatide fixed ratios were used depending on the required dose of insulin glargine. Patients requiring 10-40 U/day of insulin glargine were treated with the lower-dose pen (ratio of 2 U insulin glargine/1µg lixisenatide), while those requiring insulin glargine doses of 30-60 U/day were treated with the higher-dose pen (ratio of 3 U insulin glargine/1 µg lixisenatide). In this analysis, patients in the iGlarLixi group were divided into subgroups based on their final doses of insulin glargine (≤10-<20 U, ≥20-30 U, ≥30-≤40 U, and >40-≤60) and lixisenatide (≥5-<10 µg, ≥10-<15 µg, and ≥15-≤20 µg). A1c reductions, the percentage of patients achieving an A1c <7%, and the incidence of hypoglycemia in the iGlarLixi group were consistent across all dose categories, and the weight gain seen with insulin glargine alone was mitigated with all doses of iGlarLixi. The incidence of nausea/vomiting was low, which the authors attributed to the gradual titration of lixisenatide.

IMPACT OF BASELINE HBA1C, BMI, AND DIABETES DURATION ON THE EFFICACY AND SAFETY OF LIXILAN (INSULIN GLARGINE/LIXISENATIDE TITRATABLE FIXED-RATIO COMBINATION) VS. INSULIN GLARGINE AND LIXISENATIDE IN THE LIXILAN-O TRIAL (1028-P)

M Davies, L Leiter, G Grunberger, FJ Ampudia-Basco, B Guerci, C Yu, W Stager, E Niemoeller, E Souhami, and J Rosenstock

This analysis of the LixiLan-O trial demonstrated consistent efficacy and safety with Sanofi's iGlarLixi (formerly LixiLan; lixisenatide/insulin glargine) across subgroups divided by baseline A1c, diabetes duration, and BMI. Primary results presented as an oral presentation demonstrated superior glycemic control with iGlarLixi vs. either component alone in patients with type 2 diabetes not at goal on oral medications. In this analysis, participants were separated into groups by baseline A1c (<8% or ≥8%), duration of type 2 diabetes (<7 or ≥7 years) and BMI (<30 or ≥30 kg/m²). After 30 weeks, the results for A1c reductions, the percentage of patients with an A1c <7%, and hypoglycemia were consistent across all subgroups. iGlarLixi consistently led to significantly greater A1c reductions (~0.3% vs. insulin glargine and 0.7%-0.9% vs. lixisenatide) and more patients achieving an A1c <7% compared to both components; hypoglycemia was comparable between the iGlarLixi and insulin glargine groups. See the table below for detailed results.

Subgroup	iGlarLixi			Insulin Glargine			Lixisenatide	
	A1c Reduction	A1c <7%	Hypoglycemia	A1c Reduction	A1c <7%	Hypoglycemia	A1c Reduction	A1c <7%
A1c <8%	1.2%	83.8%	23.0%	0.8%	67.7%	22.4%	0.5%	50.5%
A1c ≥8%	1.9%	69.8%	27.9%	1.6%	53.9%	24.6%	1.1%	19.4%
Duration <7 years	1.5%	75.2%	21.3%	1.2%	61.9%	19.0%	0.8%	37.5%
Duration ≥7 years	1.6%	72.6%	28.8%	1.3%	57.4%	27.2%	0.7%	29.9%
BMI <30 kg/m²	1.6%	78.6%	31.6%	1.2%	57.9%	29.1%	0.7%	28.4%
BMI ≥30 kg/m²	1.5%	75.2%	22.0%	1.3%	62.2%	20.1%	0.8%	36.5%

EFFICACY AND SAFETY OF LIXILAN VS. INSULIN GLARGINE ACCORDING TO BASELINE CHARACTERISTICS IN PATIENTS WITH TYPE 2 DIABETES FROM THE LIXILAN-L TRIAL (1018-P)

C Wysham, R Bonadonna, V Aroda, MP Domingo, C Kapitza, W Stager, C Yu, E Niemoeller, E Souhami, and R Bergenstal

This analysis from the LixiLan-L trial demonstrated consistent efficacy and safety with Sanofi's iGlarLixi (formerly LixiLan; insulin glargine/lixisenatide) across subgroups divided by baseline A1c, diabetes duration, and BMI. Primary results from the trial presented as an oral presentation demonstrated superior glycemic control with iGlarLixi vs. insulin glargine (Lantus) in patients not at goal on basal insulin. In this analysis, participants were divided into groups based on their baseline A1c (<8% or ≥8%), time since diagnosis of type 2 diabetes (<10 or ≥10 years), and BMI (<30 or ≥30kg/m²). After 30 weeks, the results for A1c reduction, percentage of patients with an A1c <7%, and hypoglycemia were consistent across all subgroups. iGlarLixi consistently led to ~0.5% greater A1c reductions and ~20-30% more patients achieving

an A1c <7% compared to insulin glargine, and there were no significant differences in hypoglycemia between treatment groups. iGlarLixi also offered a significant weight benefit vs. insulin glargine in subgroups divided by baseline A1c and BMI (results for duration of diabetes subgroups not given. See the table below for detailed results.

Subgroup	iGlarLixi			Insulin Glargine		
	A1c Reduction	Percentage with A1c <7%	Hypoglycemia Incidence	A1c Reduction	Percentage with A1c <7%	Hypoglycemia Incidence
A1c <8%	0.8%	67.5%	32.7%	0.3%	45.4%	42.3%
A1c ≥8%	1.4%	44.5%	46.0%	0.8%	16.8%	42.6%
Duration <10 years	1.1%	56.0%	41.0%	0.6%	35.3%	36.7%
Duration ≥10 years	1.1%	54.3%	39.2%	0.6%	25.7%	46.7%
BMI < 30 kg/m²	1.1%	58.3%	47.7%	0.5%	27.6%	50.0%
BMI ≥30 kg/m²	1.1%	52.4%	34.3%	0.6%	31.1%	36.8%

LIRAGLUTIDE PROTECTS DIET INDUCED OBESITY THROUGH INDUCTION OF BROWN ADIPOGENSIS IN MICE (1966-P)

J Zhou, P Chandramani-Shivalingappa, and L Li

This poster presented data showing that liraglutide (Novo Nordisk's Victoza/Saxenda) reduced weight gain and obesity-related inflammation and upregulated genes related to brown fat tissue synthesis in mice. The experiment was conducted on four groups of C57black/6 mice that were fed either a normal (control) or a high fat sucrose diet (HFHSD) and were injected with either liraglutide or saline for five weeks. The mice were then massed and liver, fat and skeletal muscle tissue samples were taken for protein and RNA extraction. The results showed that liraglutide reduced weight gain and inflammation in mice fed a HFHSD to levels comparable to those of the mice receiving saline injections and eating a normal diet. Liraglutide also decreased paragonadal fat mass in HFHSD mice while inducing the expression of UCP-1 (a protein in brown adipose tissue that increases thermogenesis and metabolic rate) and three other related genes: PPAR-alpha, Cidea, CEBP-alpha and CEBP-beta. Liraglutide did not have any effect on fatty acid oxidation or synthesis. This study provides additional mechanistic explanations for the positive clinical results seen with liraglutide in obesity - in particular, we have not heard as much discussion about the connection to brown fat as we have about neural mechanisms of weight regulation - in fact, we haven't heard too much about brown fat as of late at all - a big change of late.

IDEGLIRA IS EFFICACIOUS ACROSS BASELINE HBA_{1C} CATEGORIES IN SUBJECTS WITH TYPE 2 DIABETES UNCONTROLLED ON SU, GLP-1RA OR INSULIN GLARGINE: ANALYSES FROM COMPLETED PHASE 3B TRIALS (925-P)

C Sorli, S Harris, E Jódar, I Lingvay, K Chandarana, J Langer, and E Jaeckel

Novo Nordisk presented a post hoc analysis of the phase 3b DUAL trials for GLP-1 agonist/basal insulin combination IDegLira (Xultophy; insulin degludec/liraglutide), showing that the drug's efficacy was consistent regardless of baseline A1c. The analysis included populations uncontrolled on a GLP-1 agonist

(DUAL III; IDegLira vs. continued GLP-1 agonist therapy), a sulfonylurea (DUAL IV; IDegLira vs. placebo) and insulin glargine (DUAL V; IDegLira vs. continued insulin glargine therapy). Patients in each trial were split into three different baseline A1c categories: ≤7.5%, >7.5-≤8.5% and >8.5%. In all categories, IDegLira led to significantly greater A1c reductions than the comparator therapy; as expected, the greatest reductions occurred in the highest baseline A1c category. See the table below for detailed results. Perhaps most impressively, IDegLira led to a mean final A1c <7% in all categories, underscoring its status as one of the most efficacious and versatile type 2 diabetes drugs available.

Table: A1c Reductions Across Baseline A1c Categories in the DUAL Trials

	Overall	**Baseline A1c ≤7.5%**	**Baseline A1c >7.5%-≤8.5%**	**Baseline A1c ≥8.5%**
DUAL III	IDegLira (n=292): -1.3%	IDegLira (n=113): -1.0%	IDegLira (n=141): -1.4%	IDegLira (n=38): -1.9%
	GLP-1 (n=146): -0.3%	GLP-1 (n=66): -0.3%	GLP-1 (n=66): -0.3%	GLP-1 (n=14): -1.0%
DUAL IV	IDegLira (n=289): -1.5%	IDegLira (n=93): -1.0%	IDegLira (n=156): -1.5%	IDegLira (n=40): -2.1%
	Placebo (n=146): -0.5%	Placebo (n=48): -0.2%	Placebo (n=80): -0.6%	Placebo (n=18): -0.7%
DUAL V	IDegLira (n=278): -1.8%	IDegLira (n=63): -1.0%	IDegLira (n=102): -1.6%	IDegLira (n=113): -2.5%
	IGlar (n=279): -1.1%	IGlar (n=64): -0.5%	IGlar (n=118): -1.0%	IGlar (n=97): -1.7%

P=0.004 for DUAL III baseline A1c ≥8.5%; p<0.001 for all other categories

ITCA 650: A NOVEL THERAPEUTIC APPROACH TO TREATING TYPE 2 DIABETES (1027-P)

A Whitson, R Azeem, T Alessi, and M Baron

Intarcia presented a poster sharing the company's experience with the safety and tolerability of the implantation, replacement, and removal of their ITCA 650 exenatide mini-pump thus far from the FREEDOM phase 3 development program for the product. As of November 2015, physicians, registered nurses, and physician assistants had performed 18,383 placements, replacements, and removals of the product in 5,200 patients with type 2 diabetes across 493 clinical sites in 28 countries. There were no serious AEs observed and the poster characterized overall adverse events related to the procedure as generally mild, transient, and reflective of normal healing. Only 1% of procedures were originally unsuccessful (mostly because they were placed too deep in the skin). 0.19% of procedures resulted in discontinuation of treatment and 0.4% resulted in inadvertent expulsion/extrusion (Intarcia noted that this rate is lower than that seen in clinical trials of other implanted drugs). The experience of the implantation and removal procedure has been one of the biggest questions surrounding the potential uptake of ITCA 650. We will look forward to hearing from patients on what they thought of the procedure. Does it hurt? Is the implantable noticeable or uncomfortable post-placement? How easy is removal? A soon-to-be-published paper on treatment satisfaction outcomes in the phase 2 study for ITCA 650 should shed more light on these questions. All in all, these results demonstrating minor adverse events related to the procedure itself are reassuring and we hope bode well for future patients and physician acceptance of this novel delivery mechanism.

DURATION-1 EXTENSION IN PATIENTS WITH T2D: EFFICACY AND TOLERABILITY OF EXENATIDE ONCE WEEKLY (QW) OVER 7 YEARS (1041-P)

CH Wysham, A Philis-Tsimikas, EJ Klein, P Öhman, N Iqbal, J Han, and RR Henry

Findings of the seven-year extension period of the DURATION-1 study demonstrated that exenatide (QW) therapy for seven years was associated with significant, sustained reductions in A1c and weight, with infrequent insulin initiation and no new long-term safety findings. As background, the DURATION-1 study was a 30-week study that compared exenatide QW and twice daily in 295 patients with type 2 diabetes. During this seven-year extension period, patients received exenatide once weekly and visited every eight weeks during this period; glucose-lowering medication usage was noted and glycemic and weight data were analyzed. While there were 295 initial patients, 122 patients completed the extension period - while some of this was "regular" fall-off due to patients moving away and other typical reasons (see below), we do not have data on approximately 40% and we would be very curious to know how many patients left to go on other therapy like once weekly GLP-1, SGLT-2s, etc. Specifically, withdrawal reasons included withdrawn consent (27%), adverse events (12%), investigator decision (7%), lost to follow-up (7%), and glucose control lost (4%). Of the completers, 57 added a new glucose-lowering medication. Concomitant medications included metformin (84%), SFUs (59%), and TZDs (24%); 2% added long-acting insulin in years 2-5, 9% in year 6, and 12% in year 7. For those who followed through with the 7-year extension period, A1c decreased, FPG was significantly below the baseline after the extension period, and body weight decreased (the greatest decreases in body weight occurred in patients that did not take any new glucose-lowering medications). Specifically, at seven years, 46% of participants had A1c <7.0% and 30% had A1c ≤6.5%. Mean reductions at seven years were 1.5% in A1c (baseline of 8.2%); 24 mg/dl in FPG (baseline of 166 mg/dl); and 3.9 kg in weight (baseline of 101 kg). Even though there was a gradual increase in these three categories over time, the authors believed that this probably resulted from the time period's progression of diabetes, which makes sense. As for safety, out of all the patients who participated in the study, there were 71 serious adverse events, though mild GI and injection site adverse events primarily occurred in the initial 30 weeks. Ultimately, these findings show that the benefits of exenatide appear to be sustained over years of continued use, with no new long-term safety findings and very impressive duration of effect.

Symposium: Heart Failure and Diabetes

GLP-1 RA AND CARDIOVASCULAR PHYSIOLOGY - WILL THE CLINIC EVER CONFIRM THE MECHANISTIC STUDIES?

Mansoor Husain, MD (University of Toronto, Toronto, Canada)

Dr. Mansoor Husain presented various mouse and human studies demonstrating how incretin-targeted therapies affect the cardiovascular system through glycemic control, lipid control, weight loss, endothelial function, sodium and fluid excretion, blood pressure control, anti-inflammatory effects, plaque composition, a small increase in heart rate, cardioprotection in ischemia, and improved left ventricle function in heart failure. Dr. Husain also noted that although these effects apply to multiple incretin classes, GLP-1 agonists typically have a greater impact than DPP-4 inhibitors, as they lead to pharmacological levels of GLP-1 whereas DPP-4 inhibitors simply protect endogenous GLP-1 from degradation. Throughout the talk, Dr. Hussein kept returning to the idea that people who have diabetes have a slightly different profile of HFpEF and HFrEF (heart failure with preserved ejection fraction vs. heart failure with reduced ejection fraction) than those without diabetes. Dr. Husain also reviewed an analysis of studies examining the relationship between heart failure and intensive glucose lowering, remarking that the increased risk of heart failure with intensive treatment seems to be mostly attributed to TZDs rather than DPP-4 inhibitors (few GLP-1 agonists were evaluated in the review). Dr. Husain also presented results from a resent observational study (Filion et al, N Engl J Med, 2016) demonstrating that hospitalizations for heart failure did not increase with incretins vs. other oral anti-diabetic drugs for those with or without a history of heart failure. Finally, Dr. Husain pointed to the results from the LEADER trial for Novo Nordisk's Victoza (liraglutide) to highlight the potential impact that cardioprotective drugs could have on patients.

Questions and Answers

Q: How many patients do you see with heart failure, and what do you do when you see them? How do you follow up?

A: I consistently look for symptoms of heart failure, through a simple evaluation. I do this all on routine basis. However, if I see signs or symptoms, I move to image-based evidence to check to see if it is reduced ejection fraction or if the ejection fraction is preserved. Then, I make sure that blood pressure is well controlled.

Corporate Symposium: New Therapeutic Advances and Practical Strategies for Complementary Basal Insulin Plus Incretin System - Targeted Agents in Complex Patients with Diabetes (Supported by Sanofi Diabetes)

SUMMARY

Lawrence Blonde, MD (Ochsner Medical Center, New Orleans, LA); Juan Pablos Frias, MD (National Research Institute, Los Angeles, CA); Lawrence Leiter, MD (St. Michael's Hospital, Toronto, Canada); Julio Rosenstock, MD (Dallas Diabetes and Endocrine Center, Dallas, TX)

Dr. Julio Rosenstock opened the symposium with a discussion on the physiological basis for combination therapy and complementary pharmacologic approaches and mechanisms. He reviewed the current research on the combination of basal insulin with complementary therapies such as GLP-1 agonists to treat fasting plasma glucose and postprandial glucose in people with type 2 diabetes and addressed several key factors that affect patient adherence to glucose lowering medications, ultimately emphasizing that the GLP-1/basal insulin combination carries a low hypoglycemia risk and balances insulin's weight gain effects. Dr. Lawrence Leiter followed with a presentation on the role of post-prandial glucose (PPG), as he stressed that it contributes substantially to A1c and elevated PPG is associated with increased cardiovascular risk, especially in those on basal insulin and those older than 65 years. After reviewing evidence, he emphasized that prandial GLP-1 agonists have greater effects on gastric emptying and PPG compared to non-prandial GLP-1s, nicely complementing the effects of basal insulin on fasting glucose. Next, Dr. Lawrence Blonde gave an overview of the ADA/EASD roadmap for the management of type 2 diabetes and the differing roles of FPG and PPG dysregulation in contributing to overall hyperglycemia, as he highlighted the guidelines' stated role of basal insulin. Lastly, Dr. Juan Pablos Frias closed out with a discussion on the practical and mechanistic role of GLP-1 agonists for managing PPG in basal inuslin-treated patients, highlighting that this patient population typically requires additional PPG control and that currently available fixed-dose combinations may offer significant benefits with regards to side effects.

PANEL DISCUSSION

Q: Why should you take lixisenatide when liraglutide has been shown to reduce cardiovascular events? What are the differences between ELIXA and LEADER?

Dr. Leiter: These trials differ in ways beyond the drugs that were tested. The LEADER trial was done in patients with stable cardiovascular disease where patients had acute coronary symptoms in the ELIXA trial. Eighty percent of patients in LEADER had cardiovascular disease while 20% did not. We don't yet know the results of LEADER but we know that the starting A1c was higher, about 8.7%. In the absence of head-to-head trials it's difficult to come to a definite conclusion. It appears that the result from LEADER is positive and that ELIXA is neutral but we don't know if they were used in different clinical settings. The patients with acute coronary syndrome in ELIXA may be the right population to show safety and the wrong population to show efficacy - but it's because the FDA asked for safety and not efficacy. Patients with post acute coronary syndrome have a lot of cardiovascular events so it's an efficient way to do a study for safety.

Q: Is there any evidence or rationale in terms of protective effects of GLP-1 agonists on beta cell function?

Dr. Leiter: If you look at beta cell function as opposed to beta cell mass, there are some studies where, compared to insulin, the GLP-1 agonists do a better job of improving beta cell function. There was a three-

year study with exenatide compared to basal insulin and in that time, there was better beta cell function after using exenatide than when the patients were on insulin. This is with exenatide three times a day.

Dr. Rosenstock: It is conceivable that if you give short acting GLP-1 agonists, it reduces gastric emptying and there is less insulin and less exposure of nutrients to beta cells. Theoretically, for people with advanced diabetes, it is more dependent on gastric emptying.

Dr. Blonde: If you look at trials, almost all of them gave agents to people with longer duration of diabetes who are using two or more oral agents, and they got substantially good benefits. It appears beta cell function can be improved. They didn't use clamps but the idea is that most people with type 2 diabetes can lose beta cells but it may be reversible with appropriate treatments.

-- by Melissa An, Sadie Bronk, Helen Gao, Hannah Martin, Nina Ran, Emily Regier, Ava Runge, Sarah Wilkins and Kelly Close