CLOSER LOOK

European Association for the Study of Diabetes (EASD) 2016 Annual Meeting

September 12-16, 2016; Munich, Germany; Full Report - GLP-1 Agonists - Draft

Executive Highlights

From SUSTAIN 6, DURATION-8, and ADJUNCT ONE full results, to new data on oral semaglutide, to additional analyses of LEADER results, GLP-1 agonists were a major presence at this year's EASD. This meaty chapter of our EASD 2016 coverage includes themes, symposia, oral presentations, and posters on GLP-1 agonist agents. Talk titles highlighted in yellow were some of our favorites from the meeting, reflecting what we found to be most notable. Talk titles highlighted in blue are new full report additions, and were not part of our daily highlights coverage during the conference.

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Themes

GLP-1 AGONIST SEMAGLUTIDE, INJECTABLE AND ORAL

- **Novo Nordisk's next-generation, once-weekly injectable GLP-1 agonist semaglutide made a big splash at this year's EASD meeting, headlined by the positive SUSTAIN 6 cardiovascular outcomes results.** In the trial, semaglutide demonstrated a 26% risk reduction (95% CI: 0.58-0.95; p<0.001 for non-inferiority; p=0.02 for superiority) for the primary endpoint of three-point MACE (CV death, non-fatal MI, and non-fatal stroke). For comparison, LEADER

showed a 13% risk reduction for Novo Nordisk's Victoza (liraglutide) and EMPA-REG OUTCOME showed a 14% risk reduction for Lilly/BI's SGLT-2 inhibitor Jardiance (empagliflozin), with both CVOTs relying on the same three-point MACE used in SUSTAIN 6, and IRIS showed a 24% risk reduction in fatal/non-fatal MI and stroke in insulin resistant stroke survivors (without diabetes) for Takeda's TZD Actos (pioglitazone). Among the components of the primary outcome, semaglutide significantly reduced the risk of non-fatal stroke by 39% (HR=0.61; 95% CI: 0.38-0.99; p=0.04) - this appeared to have driven the achievement of the primary endpoint. Non-fatal MI also trended toward reduction, though the result was not significant (HR=0.74; 95% CI: 0.51-1.08; p=0.12). Notably, the Kaplan-Meier curves for cardiovascular death in the semaglutide and placebo arms were virtually superimposable (HR=0.98; 95% CI: 0.65-1.48; p=0.92). For comparison, the LEADER trial for Novo Nordisk's other GLP-1 agonist, Victoza (liraglutide), found a highly significant 22% reduction in cardiovascular death with liraglutide (HR = 0.78; 95% CI: 0.66-0.93; p=0.007). We expect the lack of clear cardiovascular mortality benefit might be due to the small size and short duration of the trial, contributing to a very low event number (44 adjudicated CV deaths and 46 adjudicated CV deaths).

- **While the results are certainly impressive, the small size of the trial and the resultant fairly large confidence intervals engendered reservations from some thought leaders.** Dr. Philip Home pointed out that it might be more accurate to categorize the risk reduction in the primary endpoint as 5%-42%, based on the confidence intervals, rather than 26%. We can't overlook the shorter span and smaller number of MACE events incurred during this CVOT, of course. Follow-up on the primary endpoint continued for only two years in SUSTAIN 6, whereas LEADER followed-up for a minimum of 3.5 and a maximum of five years and EMPA-REG OUTCOME followed-up for four years. The direct impact of a shorter CVOT is fewer MACE events - 254, 1,302, and 772 in SUSTAIN 6, LEADER, and EMPA-REG OUTCOME, respectively. As a result, it wouldn't be possible to say that the results would definitely support a cardioprotective indication, given the complexities of the regulatory system - indeed, Novo Nordisk has already shared that it intends to conduct a larger CVOT powered for superiority for semaglutide. Despite the differences in trial size, Dr. Steven Marso emphasized that SUSTAIN 6 has more in common with LEADER than not in terms of the patient population enrolled, the endpoints, etc.
- **Among the safety outcome measures collected, the most notable finding was a significantly increased in the risk for retinopathy (HR=1.76; 95% CI: 1.11-2.78; p=0.02).** Retinopathy complications, defined as vitreous hemorrhage, onset of diabetes-related blindness, or need for treatment with an intravitreal agent or retinal photocoagulation, appeared at a rate of 3% in the semaglutide group (50 events) vs. 1.8% in the placebo group (29 events). Of course, these are small event numbers and, while the findings are disturbing, they are not altogether surprising. Both Dr. Tina Vilsbøll, in presenting the clinical and metabolic outcomes of SUSTAIN 6, and Dr. Home noted that several previous studies, including the DCCT/EDIC trial, have found an association between rapid glucose-lowering and worsening of retinopathy. That said, the increased risk will surely be worrisome for some, including potentially regulatory agencies. There is nothing possible to say at this stage - there are equal chances this is "spurious correlation" or chance - or that this is a negative finding - and a trial will need to be done to ascertain this (perhaps a two-year trial - hard to say at this stage). In the LEADER trial, treatment with liraglutide also hinted at a trend toward increased retinopathy (HR=1.15; 95% CI: 0.87-1.52; p=0.33), but those results were non-significant. A larger trial would certainly be able elucidate this potential connection.
- **Impressively, all five other trials in the phase 3 SUSTAIN program were presented at EASD 2016 as well.** SUSTAIN 3 (head-to-head vs. AZ's Bydureon [exenatide once-weekly], previously presented at ADA 2016) and SUSTAIN 4 (head-to-head vs. Sanofi's Lantus [insulin glargine]) were presented as oral presentations, while

SUSTAIN 1 (monotherapy vs. placebo), SUSTAIN 2 (head-to-head vs. Merck's Januvia [sitagliptin], previously presented at ADA 2016), and SUSTAIN 5 (add-on to basal insulin) were presented as posters. As a whole, semaglutide demonstrated an impressive combination of A1c efficacy and weight loss, with the expected GI side effects. Together with the unexpected and highly impressive SUSTAIN 6 results, we expect the phase 3 program will make a compelling package for regulatory submission, expected in 4Q16.

- **In terms of the earlier-stage diabetes pipeline, we were particularly impressed by the much-anticipated full results from the phase 2 dose-ranging and escalation trial of Novo Nordisk's once-daily oral formulation of GLP-1 agonist semaglutide.** The double-blind, randomized, parallel-group trial (n=632) consisting of an impressive nine arms: five with escalating doses of oral semaglutide (2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg), two comparator arms with placebo and injectable semaglutide (1 mg dose), and two dose escalation arms in which oral semaglutide was titrated up to 40 mg over either eight weeks or over 26 weeks. Topline results for this trial were shared over a year and a half ago, in February 2015, noting dose-dependent improvements in A1c and comparable weight loss to the once-weekly injectable semaglutide formulation at the highest dose. The full results offered much more granularity on the specific A1c and body weight reductions with each of the five oral semaglutide doses compared to placebo and injectable semaglutide. Oral semaglutide demonstrated significantly greater A1c reductions than placebo at each of the five doses studied, with a very impressive 1.9% reduction at the 40 mg dose, matching the injectable semaglutide reduction and a 1.6% difference from placebo (baseline A1c=8.1%, p<0.0001). Participants experienced a dose-dependent mean body weight reduction of up to 6.9 kg (~15 lbs) in the 40 mg dose arm (p<0.0001). For comparison, participants in the placebo arm lost an average of 1.2 kg (~2.6 lbs) and those in the injectable semaglutide arm lost an average of 6.4 kg (~14 lbs). Furthermore, a greater proportion of participants on all doses of oral semaglutide were able to achieve an A1c target <7% or body weight loss 35% compared to placebo. See the detailed discussion and commentary for more details on these results and on the adverse event data.
    - **The robust results demonstrating the ability of an oral peptide formulation to match the efficacy of its injectable counterpart were extremely encouraging.** Semaglutide is the first peptide to advance into phase 3 development as an oral medication within the diabetes field and we hope its success could potentially pave the way for oral insulin as well (though the dose titration and narrow therapeutic range pose of insulin pose additional challenges on that front - Novo Nordisk recently completed a phase 2a trial for its oral insulin and we're eagerly looking forward to results there as well). That said, the 40 mg dose needed to match the efficacy of injectable semaglutide is much higher than the three doses that have been advanced into phase 3 (3 mg, 7 mg, and 14 mg). Despite the lower dose, the phase 2 results suggest that we might be able to expect A1c reductions between 1.5% and 1.7% and weight loss between 5 kg and 6 kg (11 lbs-13 lbs) with the highest 14 mg dose. The phase 3 PIONEER development program is underway, with all studies initiating enrollment throughout 2016 and we absolutely cannot wait to see the results in a few years.

CO-ADMINISTRATION COMBINATIONS

- *Several talks at EASD discussed the use of multiple diabetes therapies in combination, with a particular spotlight on dual therapy with GLP-1 agonists and SGLT-2 inhibitors - assessed for the first time in the* **DURATION-8 trial.** Results from the DURATION-8 trial showed improved glycemic control and cardiovascular risk factors with dual therapy consisting of AZ's once-weekly GLP-1 agonist Bydureon (exenatide) and AZ's SGLT-2 inhibitor Farxiga (dapagliflozin) vs. either drug as monotherapy. After 28 weeks, patients (n=695) in all three arms of the study - exenatide and dapagliflozin, exenatide alone, and dapagliflozin alone - experienced impressive reductions in A1c: -2.0% (95% CI: -2.1 to -1.8), -1.6% (-1.8 to -1.4), and -1.4% (-1.6 to -1.2) respectively (baseline A1c=9.3%). However, the exenatide/dapagliflozin dual therapy reduced baseline A1c to a

significantly greater extent than either monotherapy: a -0.4% improvement versus exenatide (95% CI: -0.6 to -0.1; p=0.004) and a -0.6% improvement versus dapagliflozin (95% CI: -0.8 to -0.3; p<0.001). Furthermore, exenatide/dapagliflozin dual therapy demonstrated superiority to either monotherapies for all secondary endpoints, including fasting plasma glucose, postprandial glucose, systolic blood pressure, and weight loss.

FIXED-RATIO COMBINATIONS

- **GLP-1 agonist/basal insulin products were a major focus within the realm of fixed-ratio combinations, with new post-hoc analyses of LixiLan-O and LixiLan-L.** Dr. Boris Kovatchev (University of Virginia, Charlottesville, VA) presented on LixiLan-O, "deconstructing" the A1c-lowering effect of Sanofi's iGlarLixi (lixisenatide/insulin glargine) into the impact of each individual component on fasting and postprandial glucose, separately. Insulin glargine lowered average glucose (mean of seven-point SMBG measures) by 45 mg/dl (p<0.0001) and lixisenatide lowered average glucose by 34 mg/dl (p<0.0001) over 30 weeks. When put together as iGlarLixi, the combination caused a more substantial 61 mg/dl drop in average glucose (p<0.0001). Glucose variability (measured by the High Blood Glucose Index) declined by a mean of 6.3 from a baseline of 9.8 if treated with insulin glargine alone, by 5.3 from a baseline of 10.4 if treated with lixisenatide alone, and by 8.3 from a baseline of 10.3 if given iGlarLixi. Then, using vector analyses, Dr. Kovatchev suggested that the postprandial effect of lixisenatide might have a greater impact on iGlarLixi's reduction of glycemic variability than on its reduction of overall plasma glucose. While this information is certainly helpful to theorists and academic researchers, we think "time in zone" data would be more understandable for patients and many HCPs. Dr. Vanita Aroda (Medstar Health Research Institute, Washington, DC) presented on LixiLan-L, sharing a post-hoc analysis to show that participants treated with iGlarLixi were 30% more likely to reach A1c <7% with no weight gain and 11% more likely to reach A1c <7% with no weight gain or documented hypoglycemia (p<0.0001 for both comparisons vs. insulin glargine alone). The issue arose that while LixiLan-L touts the result of no increased hypoglycemia risk with iGlarLixi, we might expect a reduced risk of hypoglycemia, because a basal insulin/GLP-1 agonist combination should have an insulin sparing effect. Dr. Aroda noted that disappointingly, no such insulin sparing was observed in LixiLan-L.
    - **Notably, GLP-1 agonist/basal insulin combinations were also a recurring theme at last year's EASD meeting in Stockholm.** We noted the buzz surrounding these products, which as a class, are perhaps the most highly-anticipated fixed-ratio or fixed-dose combinations for type 2 diabetes care. We're eager to see these combination therapies (which have been "on the horizon" for some time now) in real-world clinical practice, although we have to wait a little while longer still in the US - the FDA recently delayed approval for Sanofi's iGlarLixi (insulin glargine/lixisenatide) and for Novo Nordisk's IDegLira (insulin degludec/liraglutide) by three months each. As we've noted recently, we've a bit worried about payers missing the forest for the trees and not wanting to pay for combination therapy before monotherapy no matter how patients are doing - oh, please say it isn't so.

Detailed Discussion and Commentary

Symposium: SUSTAIN 6

STUDY DESIGN AND BASELINE CHARACTERISTICS

Lawrence Leiter, MD (St. Michael's Hospital, Toronto, Canada)

Dr. Lawrence Leiter provided an overview of the trial design and baseline population characteristics in the SUSTAIN 6 cardiovascular outcomes trial (CVOT). SUSTAIN 6 was a double-blind, randomized, placebo-controlled, time- and event-driven trial: 3,297 individuals with type 2 diabetes from 230 sites across 20 countries were enrolled so long as they were (i) ≥ 50 years old with evidence of CVD (83% of subjects) or ≥ 60 years old with subclinical evidence of CVD (17% of subjects); (ii) diabetes drug-naïve, or on 0-2 oral

diabetes agents with or without basal or premix insulin; and (iii) had an A1c ≥ 7.0%. Clinicians were repeatedly encouraged to treat according to local standard of care guidelines to achieve optimal glycemic control. Participants were randomized in a 1:1:1:1 fashion to 1.0 mg semaglutide, 0.5 mg semaglutide, or volume-matched placebos and were observed for 109 weeks (104-week treatment period followed by a 5-week follow-up period). The trial required at least 122 primary events (cardiovascular death, non-fatal MI, and non-fatal stroke) to achieve appropriate statistical power, though the trial yielded more than double that minimum number of events. Key secondary outcomes included time to first occurrence of an expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, revascularization, unstable angina requiring hospitalization, and hospitalization for heart failure). All-cause death and each individual component in the expanded composite CV outcome were pre-specified secondary outcomes as well. The outcomes addressing secondary safety and efficacy objectives included glycemic control, body weight, patient-reported outcomes, microvascular outcomes (retinopathy and nephropathy), and adverse events (including hypoglycemia). Dr. Leiter noted that the study was extremely well-executed, given that 98.0% of patients completed the trial (those in the semaglutide group were slightly more likely to drop out, most commonly due to the documented GI consequences of GLP-1 therapy), and the vital status of 99.6% was known at trial's end.

- **Baseline characteristics were well-balanced between the semaglutide-treated arms and placebo.** The study population had a mean age of 65 years, body weight of 92 kg (~202 lbs), 14-year diabetes duration, and 8.7% baseline A1c. Notably, a high proportion of patients had hypertension (~93%) and ischemic heart disease (~61%) at baseline, and many were taking CV medications - ~94% were on anti-hypertensive agents, ~73% on statins, and ~76% on anti-thrombotics. In addition, ~58% of the subjects were on some sort of insulin therapy, and ~84% were taking non-insulin glucose-lowering medications, the most prevalent being metformin (~73%) and sulfonylureas (~43%).

CARDIOVASCULAR OUTCOMES

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

Cardiologist Dr. Steven Marso presented the headlining cardiovascular outcomes from SUSTAIN 6. Novo Nordisk's next-generation once-weekly GLP-1 agonist semaglutide demonstrated a 26% (!) risk reduction for the primary endpoint of three-point MACE (CV death, non-fatal MI, and non-fatal stroke), eliciting a loud round of applause and joyful murmuring from the audience. This primary outcome occurred in 7% of semaglutide patients (n=1,648) titrated to a dose of either 0.5 mg or 1.0 mg of the agent vs. 9% of the placebo group (n=1,649) over 104 weeks, producing a hazard ratio of 0.74 (95% CI: 0.58-0.95; p<0.001 for non-inferiority; p=0.02 for superiority). Dr. Marso emphasized that the point estimates for the primary outcomes continued to favor placebo across subgroup analyses for sex, baseline age, baseline BMI, baseline A1c, baseline duration of diabetes, and region, with hazard ratios ranging from 0.58 to 0.84. The p-value for interaction among subgroups within each category was non-significant, suggesting that the results are consistent across all subgroups. Similarly, the point estimates for subgroup analyses of race, ethnicity, baseline heart failure status, history of MI/stroke, cardiovascular disease status, insulin treatment at baseline, and eGFR at baseline (<60 ml/min/1.73m² and <30 ml/min/1.73m²) were all to the left of or right at unity and the p-values for interaction for all were non-significant.

- **The 26% risk reduction for the composite primary endpoint is remarkable!** For comparison, LEADER showed a 13% risk reduction for Novo Nordisk's Victoza (liraglutide) and EMPA-REG OUTCOME showed a 14% risk reduction for Lilly/BI's SGLT-2 inhibitor Jardiance (empagliflozin), with both CVOTs relying on the same three-point MACE used in SUSTAIN 6. That said, in a conversation with us, Dr. Philip Home (Newcastle University, UK) suggested that reporting the relative risk reduction as being in the range of 5%-42% would be more accurate, given the large confidence intervals. Within this context, the SUSTAIN 6 results are consistent with the LEADER results. We also can't overlook the shorter span and smaller number of MACE events incurred during this CVOT. Follow-up on the primary endpoint continued for only two years in SUSTAIN 6, whereas LEADER followed-up for a minimum of 3.5 and a maximum of five years and

EMPA-REG OUTCOME followed-up for four years. The direct impact of a shorter CVOT is fewer MACE events - 254, 1,302, and 772 in SUSTAIN 6, LEADER, and EMPA-REG OUTCOME, respectively. As a result, it wouldn't be possible to say that the results would definitely support a cardioprotective indication, given the complexities of the regulatory system - indeed, Novo Nordisk has already shared that it intends to conduct a larger CVOT powered for superiority for semaglutide. Despite the differences in trial size, Dr. Marso emphasized to us that SUSTAIN 6 has more in common with LEADER than not in terms of the patient population enrolled, the endpoints, etc.

- **Individual components of primary outcome:** Among the components of the primary outcome, semaglutide significantly reduced the risk of non-fatal stroke by 39% (HR=0.61; 95% CI: 0.38-0.99; p=0.04). Non-fatal MI also trended toward reduction, though the result was not significant (HR=0.74; 95% CI: 0.51-1.08; p=0.12). Notably, the Kaplan-Meier curves for cardiovascular death in the semaglutide and placebo arms were virtually superimposable (HR=0.98; 95% CI: 0.65-1.48; p=0.92). For comparison, the LEADER trial for Novo Nordisk's other GLP-1 agonist, Victoza (liraglutide), found a highly significant 22% reduction in cardiovascular death with liraglutide (HR = 0.78; 95% CI: 0.66-0.93; p=0.007). We expect the lack of clear cardiovascular mortality benefit might be due to the small size and short duration of the trial, contributing to a very low event number (44 adjudicated CV deaths and 46 adjudicated CV deaths).
- **Key secondary endpoints:** Semaglutide demonstrated a significant 26% risk reduction for the expanded composite outcome (cardiovascular death, non-fatal MI, non-fatal stroke, revascularization, and hospitalization for unstable angina or heart failure) (HR=0.74; 95% CI: 0.62-0.89; p=0.002). The composite endpoint of non-fatal MI, non-fatal stroke, and all-cause mortality (replacing cardiovascular mortality) was reduced by 23% (HR=0.77; 95% CI: 0.61-0.97; p=0.03). Like the cardiovascular mortality results, the Kaplan-Meier curves for all-cause mortality were largely superimposable with 62 deaths in the semaglutide group and 60 deaths in the placebo group (HR=1.05; 95% CI: 0.74-1.50; p=0.79).
- **Revascularization:** Revascularization, including both coronary and peripheral revascularization, was also significantly reduced by 35% with semaglutide treatment (HR=0.65; 95% CI: 0.50-0.86; p=0.003). This event occurred in 83 participants in the semaglutide group and 126 participants in the placebo group, driving event rates of 5% and 8%, respectively. All other individual components were not significantly different from placebo.
- **Hospitalization for unstable angina and for heart failure:** Neither hospitalization for unstable angina nor for heart failure with semaglutide treatment achieved a significant difference from placebo. The hazard ratio point estimate for unstable angina requiring hospitalization was 0.82 (95% CI: 0.47-1.44; p=0.49), with 22 events in the semaglutide arm and 27 events in the placebo arm. The hazard ratio for hospitalization for heart failure slightly favored placebo, but the wide confidence intervals suggest no significant relationship between semaglutide treatment and increased risk of hospitalization for heart failure (HR=1.11; 95% CI: 0.77-1.61; p=0.57).
- **As expected, semaglutide treatment produced modest increases in heart rate and decreases in systolic blood pressure.** Pulse increased 2.1 beats/min and 2.4 beats/min in the 0.5 mg and 1.0 mg dose groups, respectively. Systolic blood pressure decreased 1.27 mmHg with semaglutide 0.5 mg and 2.59 mmHg with semaglutide 1.0 mg.

CLINICAL AND METABOLIC OUTCOMES

Tina Vilsbøll, MD (University of Copenhagen, Copenhagen, Denmark)

Dr. Tina Vilsbøll presented the key clinical and metabolic outcomes from the SUSTAIN 6 trial, overviewing semaglutide's efficacy outcomes (in terms of A1c and weight reductions) and microvascular outcomes (encompassing renal and opthalamic complications). At the pre-specified time point of two years post-randomization, mean A1c in the semaglutide vs. placebo groups was 0.66% lower for the 0.5 mg dose and 1.05% lower for the 1.0 mg dose, both of which were statistically significant (baseline A1c=8.7%; p<0.0001). Similarly, mean body weight (baseline = 92 kg) *in the semaglutide vs. placebo groups was 2.87 kg (~6.3 lbs)*

lower for the 0.5 mg dose and 4.35 kg (~10 lbs) lower for the 1.0 mg dose (baseline=92 kg [~203 lbs); p<0.0001 for both). The microvascular outcome measures collected were a double-edged sword, showing an encouraging decreased risk of nephropathy (HR= 0.64; 95% CI: 0.46-0.88; p=0.005) and a concerning increase in the risk for retinopathy (HR=1.76; 95% CI: 1.11-2.78; p=0.02).

- **Retinopathy complications appeared at a rate of 3% in the semaglutide group (50 events) vs. 1.8% in the placebo group (29 events), a 1.2% absolute risk increase and a 76% relative risk increase.** Of course, these are very small event numbers but the increased risk of retinopathy complications (which were defined in this study as vitreous hemorrhage, onset of diabetes-related blindness, or need for treatment with an intravitreal agent or retinal photocoagulation) will surely be worrisome for some, including potentially regulatory agencies. That said, Dr. Visbøll emphasized that all of the patients that experienced worsening retinopathy had pre-existing retinopathy at baseline. Among the five semaglutide-treated patients with onset of diabetes-related blindness during the trial, all had proliferative retinopathy at baseline according to Dr. Visbøll. There is nothing possible to say at this stage - there are equal chances this is "spurious correlation" or chance - or that this is a negative finding - and a trial will need to be done to ascertain this (perhaps a two-year trial - hard to say at this stage). 50 vs. 29 events are simply too small numbers to confidently assess, especially given the multiple endpoints at play in this trial. A larger trial would certainly be able elucidate this potential connection. It is concerning that in the LEADER trial, treatment with liraglutide also hinted at a trend toward increased retinopathy (HR=1.15; 95% CI: 0.87-1.52; p=0.33), although those results were non-significant.
    - **Certainly these findings are disturbing on the face of it, but they do not come completely unexpectedly.** Dr. Visbøll mentioned that rapid glucose lowering is associated with worsening of retinopathy, as reported in the DCCT/EDIC study - although the applicability of this finding to the SUSTAIN 6 results is not yet clear, it's important to think about this particularly related to the very small numbers shown. In a conversation with us, Dr. Philip Home (Newcastle University, Newcastle, UK) echoed this sentiment, also noting a similar finding in the Kroc study in the 1980s. He explained that the mechanism is believed to be reduction of blood flow in a damaged vasculature previously protected by the high blood flow (through vascular dilatation) of hyperglycemia, which is consistent with the large improvement in A1c also seen after intensive glucose lowering. It will be great to hear opinions on various approaches, keeping in mind what will keep things easy for patients and HCPs - we would not want to see complicated regimens that would threaten adherence. We wondered if possibly a slower dose titration or if more gradual treatment intensification (perhaps to a DPP-4 inhibitor or an SGLT-2 inhibitor, or even a less potent GLP-1 agonist before initiating semaglutide) could help ameliorate some of this risk among patients with pre-existing retinopathy but this is pure speculation and we will look forward to amassing expert views.
- **Renal complications appeared at a rate of 3.6% in the semaglutide group (59 events) vs. 6.0% in the placebo group (99 events), an impressive 36% risk reduction.** The renal benefit was driven primarily by a difference in the diagnosis of persistent macroalbuminuria, which occurred at a rate of 2.5% in the semaglutide group, versus 4.9% with placebo. This parallels the nature of the renal benefits reported in the LEADER trial (HR=0.88; 95% CI: 0.67-0.92, p=0.003), which were also driven by reductions in macroalbuminuria. Renal complications (which were defined in this study as new onset of persistent macroalbuminuria, persistent doubling of serum creatinine, need for continuous renal replacement therapy, or death due to renal disease) are among the costliest of diabetes complications, so it is very encouraging to see evidence of renal protective effects in a second member of the GLP-1 agonist class. As of now it remains unclear whether these renal benefits are due to improvements in glucose control and blood pressure or are instead the product of a direct effect of semaglutide on the kidney. We will be awaiting further dissection of these renal findings, and perhaps even a dedicated chronic kidney disease trial for semaglutide (which has been suggested for liraglutide). If Novo Nordisk does undertake a dedicated chronic

kidney disease trial, we expect it would be for semaglutide as management has stated that it will focus more of its resources on semaglutide, which it views as the more efficacious and potent GLP-1 agonist molecule - it's also, presumably, easier to prescribe for HCPs and use for patients. We're curious if it would be possible to conduct a single combined outcomes trial that both rigorously assesses the cardiovascular benefit (as Novo Nordisk is already planning on initiating) and the potential renal benefit. Of course, this trial would be massive and likely very costly, though we expect less costly than conducting two separate outcomes trials. Compared to the overall costs of kidney disease, it is very very low.

    - **Dr. Home noted that these nephropathy findings are encouraging, but do not directly address renal function.** This would require assessment of eGFR, which we hope will appear in later analyses of the SUSTAIN 6 data.

- **Semaglutide demonstrated significant improvements in a variety of additional efficacy outcomes related to A1c and weight reduction, which were sustained over the 2 year treatment period.** Semaglutide was efficacious in reaching A1c goals: 39% and 49% of participants in the semaglutide 0.5 mg and 1.0 mg arms respectively achieved an A1c <7% vs. 16% and 15% with equivalent doses of placebo ($p<0.0001$ for both); 23% and 34% of participants on semaglutide 0.5 mg and 1.0 mg respectively achieved an A1c <6.5% vs. 7% and 8% with equivalent doses of placebo ($p<0.0001$ for both). Furthermore, after 104 weeks, a higher proportion of semaglutide-treated patients were able to achieve 5% and 10% weight loss. 36% (versus 18%) of patients in the low dose arms and 47% (versus 19%) of patients in the high dose arms achieved 5% weight loss. 13% (versus 6%) of patients in the low dose arms and 20% (versus 7%) of patients the high dose arms achieved 10% weight loss. Dr. Vilsbøll highlighted this latter finding as particularly notable; indeed, it is quite impressive that 1.0 mg semaglutide produces such substantial weight loss in as many as 1 in 5 patients.
- **Additionally, semaglutide demonstrated significant improvements on a range of patient-reported outcomes (PROs), as assessed by the SF-36v2 survey.** Encouragingly, the 1.0 mg semaglutide demonstrated statistically significant improvements on ALL (!) patient-reported outcomes assessed, including physical functioning, bodily pain, general health, vitality, social functioning, and mental health (The 0.5 mg semaglutide dose produced positive trends in these PROs, but only general health reached statistical significance). We applaud the trial designers for including PROs in this analysis. To our knowledge (and we need to check this!) this is the first time such outcomes have been assessed in a CVOT, and we hope this more holistic and patient-centered approach becomes the standard going forward.
- **Patients in the semaglutide and placebo groups alike experienced similar low rates of hypoglycemia.** Severe or blood-glucose confirmed hypoglycemia occurred at a rate of 23.1% (191 events) and 21.7% (178 events) in the 0.5 mg and 1.0 mg semaglutide groups, respectively, and 21.5% (177 events) and 21.0% (173 events) in the corresponding placebo groups. Severe hypoglycemia occurred at a rate of 1.7% (14 events) and 1.3% (11 events) in the 0.5 mg and 1.0 mg semaglutide groups, respectively, and 1.5% (12 events) and 2.1% (17 events) in the corresponding placebo groups.

SAFETY OUTCOMES

Stephen Bain, MD (Swansea University, UK)

Dr. Stephen Bain stepped up next to discuss additional safety outcomes of interest. Treatment discontinuation due to an adverse event was higher among semaglutide patients (214 cases amounting to 12% of the 0.5 mg group and 15% of the 1.0 mg group) vs. placebo (110 cases amounting to 6% of the 0.5 mg group and 8% of the 1.0 mg group), although the total numbers of adverse events and serious adverse events were greater for placebo vs. semaglutide. Adverse events occurred in 90% of patients on 0.5 mg semaglutide vs. 91% of their placebo counterparts, and in 89% of patients on 1.0 mg semaglutide vs. 89% of their placebo counterparts. Serious adverse events (including death, life-threatening episodes, and hospitalizations) occurred in 35% of patients on 0.5 mg semaglutide vs. 40% of their placebo counterparts, and in 34% of patients on 1.0 mg semaglutide vs. 36% of their placebo counterparts. Researchers focused on

many adverse events in SUSTAIN 6 that have been raised as points of consideration for GLP-1 agonists and other incretin-based therapies, such as GI side-effects, pancreatitis, and neoplasms, particularly in the pancreas.

- **Nausea was the no. 1 factor leading to discontinuation of treatment, accounting for nearly 5% of premature cessation in the 1.0 mg semaglutide arm.** There were 233 nausea events reported in the 0.5 mg semaglutide group (75% mild, 21% moderate, 5% severe) vs. 79 in the 0.5 mg placebo group (72% mild, 27% moderate, 1% severe), and 285 nausea events in the 1.0 mg semaglutide group (66% mild, 28% moderate, 5% severe) vs. 95 in the 1.0 mg placebo group (82% mild, 18% moderate, 0% severe).
- **Diarrhea occurred 279 times in the 0.5 semaglutide group vs. 161 times in placebo, and 251 times in the 1.0 mg semaglutide group vs. 113 times in placebo.** As was the case for nausea, a majority of these events were mild.
- **There were 128 vomiting events among patients on 0.5 mg semaglutide vs. 53 in the corresponding placebo group; there were 173 vomiting events among patients on 1.0 mg semaglutide vs. 43 in the corresponding placebo group.** Once again, as was seen in the data on nausea and diarrhea, a majority of these cases were mild.
- **Acute pancreatitis occurred in 0.7% of patients on 0.5 mg semaglutide vs. 0.4% of their placebo counterparts, and in 0.4% of patients on 1.0 mg semaglutide vs. 1.1% of their placebo counterparts.** In total, there were nine semaglutide-treated patients and 12 placebo patients who experienced acute pancreatitis. There were no instances of severe pancreatitis observed during the trial.
- **Adverse events related to the gallbladder were reported in 4%, 3%, 5%, and 3% of the 0.5 mg semaglutide, 1.0 mg semaglutide, 0.5 mg placebo, and 1.0 mg placebo arms, respectively.** Gallbladder adverse events included cholelithiasis and cholecystitis acute.
- **The frequency of malignant neoplasms was similar across treatment arms, and the hazard ratio for pancreatic cancer was 0.25 in favor of semaglutide (though this ratio was not statistically significant).** In total, pancreatic cancer affected one individual in the semaglutide group and four individuals in the placebo group during the study period. The hazard ratio for total neoplasms, encompassing those that were benign, was 1.12 in favor of placebo; however, this value was once again not statistically significant.

DISCUSSANT

Lars Rydén, MD, PhD (Karolinska Institute, Stockholm, Sweden)

Dr. Lars Rydén endeavored to contextualize the SUSTAIN 6 results, providing a historical perspective on the path to modern CVOTs and a comparison to other neutral and positive CVOTs for diabetes drugs that have reported in the last few years. Dr. Rydén congratulated the trial lead investigators for a "carefully planned, well performed, objectively reported" trial and underscored that he would not be nitpicking the details of the trial design or interpretation. Instead, he emphasized that both the 26% relative risk reduction and the 2.3% absolute risk (from 8.9% to 6.6%) in the primary endpoint with semaglutide treatment is substantial and clinically meaningful. He pointed out that cardiologists are often pleased if new platelet therapies are able to demonstrate a much smaller absolute risk reduction.

- **Regarding the mechanism of action,** Dr. Rydén emphasized that the results appear to be driven by a positive impact of semaglutide on non-fatal stroke and non-fatal MI. Considered along with the benefit on risk reduction for revascularization and the slow onset of benefit, Dr. Rydén suggested that semaglutide's cardioprotective effect could be mediated through a delay in progression or even regression of atherosclerosis. Dr. Rydén also suggested that duration of action may account for the heterogeneity seen in the large 26% risk reduction observed in SUSTAIN 6 compared to the smaller - but still positive - 13% risk reduction of liraglutide in LEADER and to the neutral ELIXA results for lixisenatide (Sanofi's Lyxumia/Adlyxin). Lixisenatide is a short-acting

GLP-1 agonist, while liraglutide is a longer-acting GLP-1 agonist and semaglutide (as a once-weekly injection) is longer-acting still. He hypothesized that the bioavailability of the GLP-1 agonist must last at least through an entire day to demonstrate a cardioprotective benefit.

- **In a comparison to the LEADER and EMPA-REG OUTCOME trials,** Dr. Rydén highlighted that both the relative and absolute risk reduction was greater in SUSTAIN 6. Semaglutide's relative risk reduction of 26% and absolute risk reduction of 2.3% compares to liraglutide's relative risk reduction of 13% and absolute risk reduction of 1.9% and empagliflozin's relative risk reduction of 14% and absolute risk reduction of 1.6%. Dr. Rydén also pointed out that the A1c reduction in SUSTAIN 6 was greater than in the LEADER and EMPA-REG OUTCOME trials: a placebo-adjusted difference of 0.8%, compared to 0.4% and 0.2%. As expected for a pre-approval safety trial, the follow-up duration in SUSTAIN 6 was shorter at 2.1 years compared to 3.8 years for LEADER and 3.1 years for EMPA-REG OUTCOME.
- **Regarding the retinopathy data,** Dr. Rydén largely deferred to future clinical or registry-based trials. He pointed out that the LEADER trial had also observed a 15% increase in retinopathy, though it was not statistically significant, but ultimately suggested that time will tell how much of a concern this finding is. We were a little disappointed that Dr. Rydén did not dig into the retinopathy outcomes more - though of course he was already fitting a lot into the mere 10 minutes he was allotted already! - and we expect we'll hear much discussion of this finding in the coming months.
- **Dr. Rydén concluded with three main areas of impact for the SUSTAIN 6 results in his view:** (i) raising interest in mechanistic studies delineating mechanisms and refining treatment; (ii) catalyzing the initiation of new clinical trials investigating the combination of a GLP-1 agonist and an SGLT-2 inhibitor; and (iii) creating an immediate therapeutic option for a sizeable and vulnerable patient population.

CLOSE CONCERNS QUESTIONS

Q: Is the remarkable 26% risk reduction for three-point MACE a product of smaller sample size of events? How much of this risk reduction should be attributed to the smaller number of MACE events?

Q: Will empirical support for semaglutide's CV benefits make an even stronger case for the CV benefits of Victoza (liraglutide)? Will this influence the FDA's decision to revise the Victoza label?

Q: What is the prospective timeline for a larger CVOT of semaglutide that includes a higher number of MACE events on par with LEADER or EMPA-REG OUTCOME?

Q: Does the physiological action of semaglutide directly increase retinopathy risk?

Q: How will follow-up research unpack the association between semaglutide and eye complications?

Q: Do the significant weight loss results foreshadow semaglutide's potential as an obesity drug, paralleling Saxenda (high dose liraglutide)?

Q: Does SUSTAIN 6, in conjunction with LEADER, offer support for a cardioprotective class effect of GLP-1 agonists?

Q: Is there an aspect of the once-weekly formulation (perhaps improved adherence) that causes more powerful CV effects vs. the once-daily formulation?

Q: Given the more dramatic 24% risk reduction on three-point MACE vs. Victoza's 13% risk reduction, does semaglutide have more potential as a cardioprotective agent in a lower-risk patient population vs. liraglutide?

DURATION-8 STUDY: DAPAGLIFLOZIN AND EXENATIDE QW COMBINATON

Cristian Guja, MD (University of Medicine and Pharmacy, National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania)

Dr. Cristian Guja (University of Medicine and Pharmacy, Bucharest, Romania) presented the results of the DURATION-8 trial demonstrating improvement of glycemic control and of some cardiovascular risk factors with dual therapy consisting of AZ's once-weekly GLP-1 agonist Bydureon (exenatide) and AZ's SGLT-2 inhibitor Farxiga (dapagliflozin) vs. either drug as monotherapy. After 28 weeks, patients (n=695) in all three arms of the study - exenatide and dapagliflozin, exenatide alone, and dapagliflozin alone - experienced impressive reductions in A1c: -2.0% (95% CI: -2.1 to -1.8), -1.6% (-1.8 to -1.4), and -1.4% (-1.6 to -1.2) respectively, from a baseline A1c of 9.3%. Interestingly, Dr. Guja noted that the trial enrolled participants with a baseline A1c of 8%-12% to minimize the risk of potential hypoglycemia if the trial enrolled participants with a lower A1c. The A1c reduction of 1.4% in the standalone dapagliflozin arm is certainly very robust for an SGLT-2 inhibitor, which is undoubtedly at least partly attributable to the high baseline A1c. That said, the exenatide/dapagliflozin dual therapy reduced still produced a significantly greater A1c reduction than either monotherapy: a -0.4% improvement versus exenatide (95% CI: -0.6 to -0.1; p=0.004) and a -0.6% improvement versus dapagliflozin (95% CI: -0.8 to -0.3; p<0.001). Given the potential for additive CV risk reduction stemming from both classes (this still has to be proven, of course), the positives in taking the two compounds together may be even larger. Although no labels have yet been updated in the US concerning cardiovascular or renal risk reduction, we imagine this is a "when" not "if" and the number of trials to happen in combinations in the coming years should provide great learning and excitement for now to improve public health. The full results from the trial were simultaneously published in The Lancet Diabetes and Endocrinology.

- **In a conversation with AZ's VP of Global Medicines Development, Dr. Elisabeth Bjork, we learned more about the additive effects of Bydureon and Farxiga on A1c.** Namely, Dr. Bjork articulated how diabetes drugs are mostly baseline-dependent - as one product in this combination improves a patient's glycemic control, the second will have a marginally smaller impact on A1c, although the essential takeaway is that exenatide and dapagliflozin in combination achieved superior A1c reductions vs. either agent alone. Dr. Bjork also remarked that there is interesting potential for the additive cardioprotective effects of Bydureon and Farxiga, especially since the dominant thought is that SGLT-2 inhibitors and GLP-1 agonists operate through distinct mechanisms of action when it comes to cardioprotection. There's no CVOT in the works for this combination per se, although EXCEL (for exenatide) and DECLARE (for dapagliflozin) are ongoing and will reveal any impact of these drugs on MACE events and CV mortality. Finally, Dr. Bjork explained that the baseline A1c of 9.3% was an important piece of this study because these are the patients who might benefit most from a combination therapy when uncontrolled on metformin alone.
- **Exenatide/dapagliflozin dual therapy demonstrated superiority to either monotherapies for all secondary endpoints.** Dual therapy produced significantly greater reductions in fasting plasma glucose (FPG) than exenatide or dapagliflozin monotherapy (-3.61 mmol/l [65 mg/dl] vs. -2 mmol/l [36 mg/dl] and -2.7 mmol/l [49 mg/dl]; p<0.001). The same was true for reductions in postprandial glucose (PPG) (-4.83 mmol/l [87 mg/dl] vs. -3.31 mmol/l [87 mg/dl] and -3.41 mmol/l [61 mg/dl]; p<0.0001) and reductions in systolic blood pressure (-4.2 mmHg vs. -1.3 mmHg and -1.8 mmHg; p<0.007).
- **Furthermore, dual therapy with exenatide and dapagliflozin produced greater weight loss (-3.41 kg [~7.5 lbs] vs. -1.54 kg [~3.4 lbs] and -2.19 kg [~4.8]; p<0.001) and a greater proportion of patients with weight loss of 5% or more (33% vs. 14% and 20%; p<0.001).** Dr. Guja noted that the weight loss effects of the co-administration appear to be additive. Notably, participants with a baseline A1c between 8% and 9% appeared to experience a greater, more additive weight loss benefit from the co-administration of the two products. In this

subgroup, participants treated with both dapagliflozin and exenatide experienced a mean 4.5 kg (~10 lbs) weight reduction, compared to 1.9 kg (~4.2 lbs) in the standalone exenatide group and 2.2 kg (~4.9 lbs) in the standalone dapagliflozin group (p<0.001 for the combination compared to both exenatide and dapagliflozin). In comparison, participants with a baseline A1c³9% treated with both dapagliflozin and exenatide experienced a mean weight loss of 2.6 kg (~5.7 lbs), compared to 1.2 kg (~2.6 lbs) in the standalone exenatide group and 2 kg (~4.4 lbs) in the standalone dapagliflozin group (p<0.01 vs. exenatide, non-significant vs. dapagliflozin). Based on these promising results, we'd be especially eager to see a trial of co-administration of the two products in patients with lower A1cs down to 7.5%.

- **Adverse events occurred with approximately equal frequency in each group: exenatide plus dapagliflozin (57%), exenatide alone (54%), and dapagliflozin alone (52%).** Respectively, serious adverse events occurred evenly across all groups (4% vs. 3% and 4%), as did adverse events leading to discontinuation (4% vs. 5% and 2%). The most commonly-occurring adverse events were: (i) diarrhea (4% vs. 6% and 3%); (ii) injection-site nodules (8% vs. 6% and 5%); (iii) nausea (5% vs. 7% and 3%); and (iv) urinary tract infections (4% vs. 5% and 6%). No major, minor, or severe hypoglycemia events occurred throughout the trial. There was only one case of diabetic ketoacidosis in the trial that occurred in the standalone exenatide arm. There was one case of pancreatitis in the standalone exenatide arm and one case in the combination treatment group. As expected, the rate of genital mycotic infections in the co-administration and standalone dapagliflozin arms were higher than in the exenatide arm (4%, 6%, and 2%, respectively). Overall, this adverse event profile seems very positive.

PATHOPHYSIOLOGICAL BASIS OF SGLT-2 INHIBITOR/GLP-1 AGONIST COMBINATION

Ele Ferrannini, MD (University of Pisa, Italy)

In a discussion immediately preceding the discussion of the DURATION-8 results, the highly renowned Dr. Ele Ferrannini (University of Pisa, Italy) argued that co-administration of GLP-1 agonists and SGLT-2 inhibitors is both rational and likely to work. He emphasized the distinct mechanisms of action of the two drugs (pointing out SGLT-2 inhibitors' non-insulin-dependent glucose lowering) and the impressive benefits both classes appear to offer in terms of weight loss and potential cardioprotection. Notably, pointing out that it would be impossible for us to empirically evaluate every single possible combination of diabetes drugs with rigorous randomized controlled clinical trials, Dr. Ferrannini advocated for a "rational" approach to determining which drugs should be used together in combination therapy - SGLT-2 inhibitors and GLP-1 agonists certainly seem to fit the bill and there's already been some very cogent discussion by Professor Philip Home on how it may be possible to profile cohorts of patients by their profile (complications etc).

Symposium: Liraglutide Effect and Action in Diabetes

EVALUATION OF CARDIOVASCULAR OUTCOME RESULTS - A LONG-TERM EVALUATION (LEADER)

Rury Holman, MD (University of Oxford, UK); John Buse, MD (University of North Carolina, Chapel Hill, NC); Steven Marso, MD (UT Southwestern, Dallas, TX); Michael Nauck, MD (Diabeteszentrum Bad Lauterberg, Germany); Johannes Mann, MD (Friedrich Alexander University of Erlagen, Germany)

In a symposium largely recapping LEADER cardiovascular outcomes trial data for Novo Nordisk's GLP-1 agonist Victoza (liraglutide), we saw several new sub-analyses of the cardiovascular, renal, and pancreatic data. The double-blind, randomized, placebo-controlled, time- and event-driven LEADER trial (n=9,340) results were originally presented ADA 2016, demonstrating a 13% relative risk reduction for the primary outcome of three-point MACE (cardiovascular death, non-fatal MI, and non-fatal stroke) and a 16% improvement in microvascular outcomes (driven entirely by a 22% improvement in renal outcomes), among a barrage of other secondary endpoints. See our detailed coverage of the ADA 2016 LEADER results presentation for more.

- **Dr. Johannes Mann (Friedrich Alexander University of Erlagen, Germany) presented an expanded analysis of the microvascular outcomes from the LEADER trial.** The microvascular benefit - or, perhaps more accurately, the renal benefit - was driven primarily by a 26% reduction in the onset of persistent macroalbuminuria with liraglutide (HR=0.74, 95% CI: 0.60-0.91) and a 19% reduction in urinary albumin-creatinine ratio, a measure of microalbuminuria (HR=0.31, 95% CI: 0.76-0.86). Dr. Mann also revealed two new findings from the ongoing subgroup analysis of the LEADER trial's renal data: (1) Among participants with kidney disease (eGFR <60 ml/min/1.73 m2) there was a 22% reduction in time to first renal event (HR: 0.78; 95% CI: 0.56-1.09); (2) Among participants with severe kidney disease (30-60 ml/min/1.73 m2) or end-stage renal disease there was a 27% reduction in time to next additional composite renal outcome (HR: 0.73; 95% CI: 0.50-1.07). The trial investigators had previously shared that the hazard ratio point estimate for participants was 0.94 (95% CI: 0.83-1.07). The full subgroup analysis is expected in two months at the upcoming American Society of Nephrology meeting, but these two findings provide the intriguing suggestion that liraglutide's renal benefits may be particularly applicable to patients already experiencing renal disease. The implications of this strong renal benefit are substantial, and may even prompt consideration of a dedicated chronic kidney disease trial for liraglutide. We are curious whether this effect of liraglutide is a consequence of improvements in renal risk factors like glucose and blood pressure, or whether it is a direct effect (GLP-1 is known to mediate the muscles around renal glomeruli, the functional filtering units of the kidney). These results should surely result in much more robust discussion on this front.
- **Highly regarded cardiovascular expert Dr. Steven Marso shared additional analyses of the heart failure data from LEADER.** The combined endpoint of hospitalization for heart failure and all-cause death was reduced by 13% in the overall trial (95% CI: 0.77-0.97). Recognizing that heart failure is of particular interest to many given the conditions significant in EMPA-REG OUTCOME and DPP-4 inhibitor CVOTs thus far, Dr. Marso also shared two subgroup analyses examining cardiovascular outcomes in patients with and without heart failure at baseline. The hazard ratio for the primary three-point MACE endpoint among patients without heart failure at baseline was 0.85 (95% CI: 0.76-0.96) while the hazard ratio among patients with heart failure at baseline was 0.94 (95% CI: 0.72-1.21). While the risk reduction was not significant among patients with heart failure, the point estimate trended in the right direction and the p-value for interaction between the two subgroups was non-significant at 0.53. Among participants without heart failure at baseline, the hazard ratio for hospitalization for heart failure throughout the trial was 0.82 (95% CI: 0.65-1.04). Among participants with heart failure at baseline, the hazard ratio was 0.95 (95% CI: 0.71-1.28) - like the MACE results, the point estimate here trended in the right direction and the p-value for interaction between the two groups was non-significant at 0.45.
- **A more detailed sub-analysis of the LEADER trial presented by Dr. Michael Nauck (Diabeteszentrum Bad Lauterberg, Germany) supported the initial finding that liraglutide does not increase the incidence of pancreatitis, though a wide confidence interval prevents us from ruling out the possibility entirely.** Nineteen events of acute pancreatitis occurred in 18 patients on liraglutide, compared to 33 events in 25 patients on placebo. Dr. Nauck shared a graph depicting time to acute pancreatitis in the Victoza-treated vs. placebo groups and reported a hazard ratio of 0.78 over in favor of liraglutide. However, due to the confidence interval for the hazard ratio ranging from 0.42-1.44, Dr. Nauck stated that "we cannot rule out the possibility that liraglutide could have a minute enhancement of risk for pancreatitis." Based on this sub-analysis, the worst case scenario would be a 44% greater risk of acute pancreatitis associated with liraglutide (or a best case scenario of a 58% risk reduction in pancreatitis). There were very low rates of neoplasms in LEADER, Dr. Nauck continued, which poses a challenge in precise determination of pancreatic cancer risk. The rate of pancreatic cancer was 0.3% in the liraglutide group and 0.1% in the placebo group, representing a hazard ratio of 2.59, though Dr. Nauck reiterated the high amount of uncertainty linked to this value. Overall, the results are reassuring and further support the general consensus that the benefits of GLP-1 agonist treatment outweigh the small possible risks of pancreatitis.

DOSE-DEPENDENT GLUCOSE LOWERING AND BODY WEIGHT REDUCTIONS WITH THE NOVEL ORAL FORMULATION OF SEMAGLUTIDE IN PATIENTS WITH EARLY TYPE 2 DIABETES

Melanie Davies, MD (University of Leicester, UK)

Dr. Melanie Davies (University of Leicester, UK) presented much-anticipated full results from the phase 2 dose-ranging and escalation trial of Novo Nordisk's once-daily oral formulation of GLP-1 agonist semaglutide. The double-blind, randomized, parallel-group trial (n=632) consisting of an impressive nine arms: five with escalating doses of oral semaglutide (2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg), two comparator arms with placebo and injectable semaglutide (1 mg dose), and two dose escalation arms in which oral semaglutide was titrated up to 40 mg over either eight weeks or over 26 weeks. Topline results for this trial were shared over a year and a half ago, in February 2015, noting dose-dependent improvements in A1c and comparable weight loss to the once-weekly injectable semaglutide formulation at the highest dose. The full results offered much more granularity on the specific A1c and body weight reductions with each of the five oral semaglutide doses compared to placebo and injectable semaglutide. Oral semaglutide demonstrated significantly greater A1c reductions than placebo at each of the five doses studied: 0.7% with the 2.5 mg dose (baseline A1c=8%, p=0.0069), 1.2% with the 5 mg dose (baseline A1c=7.8%, p<0.0001), 1.5% with the 10 mg dose (baseline A1c=7.8%, p<0.0001), 1.7% with the 20 mg dose (baseline A1c=7.9%, p<0.0001), and 1.9% with the 40 mg dose (baseline A1c=8.1%, p<0.0001). For comparison, the placebo arm experienced an A1c reduction of 0.3% (baseline A1c=8%) and the injectable semaglutide arm experienced an A1c reduction of 1.9% (baseline A1c 7.8%, p<0.0001 vs. placebo).

- **Oral semaglutide demonstrated dose-dependent, significantly greater reductions in fasting plasma glucose (FPG) compared to placebo:** 1 mmol/l (18 mg/dl) with the 2.5 mg dose (p=0.0078), 1.5 mmol/l (27 mg/dl) with the 5 mg dose (p<0.0001), 2.3 mmol/l (41 mg/dl) with both the 10 mg and 20 mg doses (p<0.0001 for both), and 2.8 mmol/l (50 mg/dl) with the 40 mg dose (p<0.0001), compared to 0.1 mmol/l (1.8 mg/dl) with placebo. That said, the FPG reduction at the highest 40 mg oral dose didn't quite match the 3.1 mmol/l (56 mg/dl) observed with injectable semaglutide (p<0.0001 vs. placebo).
- **Oral semaglutide produced dose-dependent reductions in body weight.** Participants experienced a mean body weight reduction of 2.1 kg (~4.6 lbs) in the 2.5 mg dose arm (non-significant vs. placebo), 2.7 kg (~6 lbs) in the 5 mg dose arm (just barely non-signifcant at p=0.0577), 4.8 kg (~11 lbs) in the 10 mg dose arm (p<0.0001), 6.1 kg (~13 lbs) in the 20 mg dose arm (p<0.0001), and 6.9 kg (~15 lbs) in the 40 mg dose arm (p<0.0001). For comparison, participants in the placebo arm lost an average of 1.2 kg (~2.6 lbs) and those in the injectable semaglutide arm lost an average of 6.4 kg (~14 lbs). We were impressed to see that, at the highest dose, the oral formulation of semaglutide was able to match that of the injectable version. Injectable semaglutide is currently in phase 2 for obesity and we're curious if an obesity indication for oral semaglutide could eventually be possible, though of course it could be cost-prohibitive given that 40 mg once-daily is 280x the dose of 1 mg once-weekly (pricing could also change - it would not necessarily need to be linear).
- **A greater proportion of participants on all doses of oral semaglutide were able to achieve an A1c target <7% or body weight loss >5% compared to placebo.** 44% of participants treated with 2.5 mg oral semaglutide were able to achieve an A1c<7% (p=0.0142 vs. placebo), as did 81% of participants treated with 5 mg, 84% of participants treated with 10 mg, 86% of participants treated with 20 mg, and 90% of participants treated with 40 mg (p<0.0001 for 5, 10, 20, and 40 mg vs. placebo). For comparison, 28% of participants in the placebo arm and 93% of participants in the injectable semaglutide achieved this goal. In terms of weight loss, a significantly greater proportion of participants in the 10 mg, 20 mg, and 40 mg dose arms were able to achieve body weight reductions ³5% compared to placebo (56% of participants, 64%, and 71%, respectively, p<0.0001). 21% of participants in the 2.5 mg and 5 mg groups achieved this goal, a non-significant

difference statistically from the 13% in the placebo group that did so. For comparison, 66% of participants in the injectable semaglutide group were able to achieve this goal.

- **Adverse event rates were dose dependent and ranged from 67%-81%.** For comparison, adverse event rate in the placebo arm was 68% and in the injectable semaglutide arm was 81%. Notably, however, serious adverse event rate was much lower for every dose of oral semaglutide compared to placebo (1.4%-3% in the oral semaglutide groups vs. 7% in the placebo group). Fast dose escalation of oral semaglutide appeared to be associated with a higher rate of both overall and serious adverse events (86% and 7%, respectively). Treatment discontinuations were higher in all oral semaglutide groups compared to placebo, ranging from 6% to 27% compared to 1.4% with placebo. The treatment discontinuation rate of injectable semaglutide was 15%. As expected, GI side effects were the most common adverse events, with nausea rates of 33%-34% in the 10, 20, and 40 mg dose groups (compared to 13%-14% in the 2.5 and 5 mg dose groups, 1.4% in the placebo group, and 32% in the injectable semaglutide group). Vomiting occurred in 16%-22% of participants in the 10, 20, and 40 mg oral semaglutide groups, compared to 6% in the 2.5 and 5 mg groups, 4% in the placebo group, and 9% in the injectable semaglutide group. We're curious if the higher rate of vomiting in the oral semaglutide groups may be due to a specific aspect of the mechanism of oral delivery. Diarrhea rates varied across the oral semaglutide dose groups with no clear dose relationship, ranging from 7% in the 2.5 mg group to 14% in the 40 mg group to a high of 23% in the 10 mg group. Diarrhea rates in the placebo group were 10% and 15% in the injectable semaglutide group. Reductions in systolic blood pressure across all doses of oral semaglutide and heart rate increases with the 10 mg and higher doses were comparable to that observed with injectable semaglutide.
- **In terms of safety:** overall hypoglycemia rate was low, with only two cases of severe hypoglycemia reported in the trial - one in the injectable semaglutide arm and one in the fast dose escalation oral semaglutide arm. Three patients in the trial experienced pancreatitis, two taking oral semaglutide and one taking injectable semaglutide. Three neoplasms were reported as well, two in oral semaglutide-treated arms (one malignant and one benign) and on in the injectable semaglutide arm. Notably, two cardiovascular events occurred in the 71-participant placebo arm while three cardiovascular events occurred in the combined oral semaglutide arms (totaling 491 patients). While it's obviously impossible to draw any conclusions from such low numbers, taken together with the positive SUSTAIN 6 cardiovascular outcome results for injectable semaglutide, it certainly suggests optimism for a cardiovascular benefit for the oral formulation as well - we look forward to *PIONEER 6* shedding more light on this and other important complication questions in the coming years.

Oral semaglutide phase 2 efficacy results summary

	A1c reduction (p-value vs. placebo)	*Fasting plasma glucose (FPG) reduction (p-value vs. placebo)*	*Body weight reduction*	*Proportion achieving A1c <7% (p-value vs. placebo)*	*Proportion achieving body weight reduction ³5%*
2.5 mg oral semaglutide	0.7% (p=0.0069)	18 mg/dl (p=0.0078)	2.1 kg (~4.6 lbs)	44% (p=0.0142)	21% (p=0.1226)
5 mg oral semaglutide	1.2% (p<0.0001)	27 mg/dl (p<0.0001)	2.7 kg (~6 lbs) (p=0.0577)	81% (p<0.0001)	21% (p=0.1875)
10 mg oral semaglutide	1. 5% (p<0.0001)	41 mg/dl (p<0.0001)	4.8 kg (~11 lbs) (p<0.0001)	84% (p<0.0001)	56% (p<0.0001)

20 mg oral semaglutide	1.7% (p<0.0001)	41 mg/dl (p<0.0001)	6.1 kg (~13 lbs) (p<0.0001)	86% (p<0.0001)	64% (p<0.0001)
40 mg oral semaglutide	1.9% (p<0.0001)	50 mg/dl (p<0.0001)	6.9 kg (~15 lbs) (p<0.0001)	90% (p<0.0001)	71% (p<0.0001)
1 mg injectable semaglutide	1.9% (p<0.0001)	56 mg/dl (p<0.0001)	6.4 kg (~14 lbs) (p<0.0001)	93% (p<0.0001)	66% (p<0.0001)
placebo	0.3%	1.8 mg/dl	1.2 kg (~2.6 lbs)	28%	13%

EFFICACY AND SAFETY OF ONCE-WEEKLY SEMAGLUTIDE VS. ONCE-DAILY INSULIN GLARGINE IN INSULIN-NAIVE SUBJECTS WITH TYPE 2 DIABETES (SUSTAIN 4)

Hans DeVries, MD (University of Amsterdam, the Netherlands)

Dr. Hans DeVries (University of Amsterdam, Amsterdam, the Netherlands) presented full results from the SUSTAIN 4 trial, demonstrating the superiority of Novo Nordisk's once-weekly GLP-1 agonist semaglutide versus once-daily insulin glargine (Sanofi's Lantus) at improving glycemic control in participants with type 2 diabetes. We first saw topline data from this study at Novo Nordisk's Capital Markets Day and in a poster at AACE 2016. In this open-label, active-controlled, parallel-group, trial (n=1089), insulin-naïve patients with type 2 diabetes were randomized to one of two doses of semaglutide (0.5 mg and 1.0 mg) once weekly or insulin glargine once-daily for 30 weeks. Primary endpoint results showed impressive A1c reductions of 1.2 % and 1.6% with the two respective doses of semaglutide, representing A1c reductions of 0.38% and 0.81% greater than the 0.8% A1c reduction observed in the insulin glargine active comparator group (baseline A1c=8.2%; p<0.0001). Likewise, semaglutide 0.5 mg and 1.0 mg was efficacious in reaching A1c goals. 58% and 73% of participants respectively achieved an A1c <7% with semaglutide vs. 38% with insulin glargine (p<0.0001). Moreover, 37% and 54% of participants on semaglutide respectively achieved an A1c <6.5% vs. 18% with insulin glargine (p<0.0001).

- **Semaglutide was superior to insulin glargine at reducing body weight.** Participants experienced weight loss of 3.5 kg (~7.7 lbs) and 5.2 kg (~11.5 lbs) with the two respective semaglutide doses vs. 1.2 kg (~2.6 lbs) weight gain with insulin glargine (p<0.0001 for both). Additionally, 37% and 51% of participants given semaglutide 0.5 mg and 1.0 mg achieved ³5% weight loss, compared to 5% with insulin glargine (p<0.0001 for both).8% of patients in the semaglutide 0.5 mg dose group (p=0.0002) and 16% of patients in the 1.0 mg dose group (p<0.0001) achieved ³10% weight loss, compared to 2% with placebo.
- **Semaglutide showed significant reductions in the proportion of participants who experienced severe or blood glucose-confirmed symptomatic hypoglycemia.** Of the participants in the semaglutide 0.5 mg and 1.0 mg groups, 4.4% and 5.6% experienced hypoglycemia, vs. 10.6% in the insulin glargine group (p<0.0001). This distinction was particularly stark among the subset of participants taking a sulfonylurea: 8.1% and 8.6% hypoglycemia rates with semaglutide vs. 18.1% with placebo. Among participants not on a sulfonylurea, hypoglycemia rates were lower and did not differ between the treatment groups (0.6% and 2.3% vs. 2.3%).
- **Adverse events were similar between the semaglutide and insulin glargine arms (70% and 73% vs. 65%), but the semaglutide 0.5 mg and 1.0 mg groups had a higher number of serious AEs (6% and 5% vs. 5%), severe AEs (7% and 6% vs. 3%), and AEs leading to discontinuation (6% and 8% vs. 1%).** As is to be expected for the GLP-1 agonist class, gastrointestinal-related adverse events were the most commonly reported: compared to participants in the insulin glargine arm, participants in the two semaglutide arms experienced more nausea (21% and 22% vs. 4%), diarrhea (16% and 19% vs. 4%), vomiting (7% and 10% vs. 3%), and dyspepsia (3%

and 7% vs. 1%). Other adverse events included decreased appetite (7% and 6% vs. 0%), increased lipase (10% and 8% vs. 4%, nasopharyngitis (12% and 8% vs. 12), and headache (5% and 6% vs. 6%).

    - **Additional safety data** included six fatalities (4 in the semaglutide arms, 2 in the insulin glargine arm), five malignant neoplasms (4 in the semaglutide arms, 1 in the insulin glargine arm), two incidences of pancreatitis (both in the 0.5 mg semaglutide arm), and three instances of cholelithiasis (both in the semaglutide arms).

- **Dr. DeVries (and one very astute questioner from the audience!) commented that the SUSTAIN 4 trial's main limitation was less-than-aggressive titration of insulin glargine in the active-control arm.** Daily glargine doses began at a rather low 10 units/day and were gradually titrated up to a mean dose of 29.2 units/day by the end of the 30 week trial. Dr. DeVries acknowledged that more aggressive titration may have resulted in less of an A1c difference between the semaglutide and insulin glargine groups, but also noted that such a situation would have produced a greater difference in weight loss between the two treatments. Furthermore, he noted that the 29.2 units/day dose of insulin glargine is "rather typical" for clinical trials and may reflect real life insulin titration more accurately.

UNCONTROLLED TYPE 2 DIABETES PATIENTS ON METFORMIN MONOTHERAPY: RESULTS OF THE FREEDOM-2 STUDY

Julio Rosenstock, MD (UT Southwestern, Dallas, TX)

Dr. Julio Rosenstock reviewed the results of the FREEDOM-2 study investigating Intarcia's implantable exenatide mini-pump ITCA 650 (60 mcg/day) vs. Merck's Januvia (sitagliptin) in patients with type 2 diabetes on metformin (n=535). Dr. Rosenstock previously presented these results at ADA 2016. The trial demonstrated significantly greater A1c reductions (1.5% vs. 0.8%) and weight loss (4 kg vs. 1.3 kg) with ITCA 650 vs. Januvia after 52 weeks (p<0.001 for both; baseline A1c = 8.5% in the ITCA 650 group and 8.7% in the Januvia group). ITCA 650 was also superior in terms of the percentage of patients achieving a secondary composite efficacy endpoint (>0.5% A1c reduction and ≥2 kg weight loss) and the percentage of patients achieving an A1c <7%. See our coverage of the results presentation at ADA 2016 for more - we were particularly impressed by the durability of the A1c and weight reductions. As a reminder, ITCA 650 is the first implantable GLP-1 agonist delivery therapy under development, and involves a small matchstick sized device placed subdermally for 6-12 month intervals in a simple outpatient procedure. Although not touched upon in Dr. Rosenstock's presentation, earlier this year Intarcia also announced positive topline results from the FREEDOM-CVO pre-approval cardiovascular outcomes trial (n=~4,000) demonstrating non-inferiority for the primary endpoint of four-point MACE (cardiovascular death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina) with ITCA 650 vs. placebo. Given this growing body of impressive clinical trial data and the potential adherence advantage of ITCA 650 over existing injectable GLP-1 agonist options, the product certainly has significant disruptive potential. That said, we really think it's just going to expand the market if all goes well - we think the entire GLP-1 market has major potential to expand, particularly with the advent of using more real-time "intermittent" professional CGM. According to Intarcia, preliminary plans are ongoing for a larger CVOT for ITCA 650 designed to demonstrate superiority in cardiovascular outcomes and an NDA submission for ITCA 650 is expected in 4Q16.

Questions and Answers

Q: Are there any data on patient reported outcomes, quality of life, and how patients perceive this compared to other treatments?

A: I think there is data on that, but I haven't seen it yet. [This would be interesting to see - essentially the questioner was asking for a patient preference study.]

Q: Do you have data to show glucose variability over weeks and days?

A: Great suggestion. I want to use CGM in future studies like this. **** note - please pull this to the top and put it in the intro - this is a big deal ….

Q: Is there any contraindication in patients taking anti-coagulants or anti-aggregants?

A: There was no sign of extra bruising in these patients. ITCA-650 requires only a very tiny incision. It's no big deal. You can see the device in the exhibit hall!

Oral Presentations: GLP-1 Receptor Agonists: Combinations, Type 1 Diabetes, and Long-term Use

EFFICACY AND SAFETY OF LIRAGLUTIDE ADDED TO INSULIN TREATMENT IN TYPE 1 DIABETES, THE ADJUNCT ONE TREAT-TO-TARGET RANDOMIZED TRIAL

Bernard Zinman, MD (University of Toronto, Canada)

Dr. Bernard Zinman (Mount Sinai Hospital, Toronto, Canada) presented long-awaited full results from the ADJUNCT ONE trial of Novo Nordisk's Victoza (liraglutide) in type 1 diabetes, demonstrating modest reductions in A1c, body weight, and insulin dose and less-welcome increases in adverse events. The randomized, double-blind, placebo-controlled compared the efficacy and safety of three doses of liraglutide - 0.6 mg, 1.2 mg, and 1.8 mg - to placebo in patients with type 1 diabetes (n=1,398) over 52 weeks of treatment. The trial found a modest, dose-dependent effect for liraglutide on A1c: mean placebo-adjusted reductions were 0.2% with the 1.8 mg dose (baseline A1c=8.14, p<0.05), 0.15% with the 1.2 mg dose (baseline A1c=8.16 mg, p<0.05), and 0.09% with the 0.6 mg dose (baseline A1c 8.16%, non-significant compared to placebo). Dr. Zinman emphasized that the placebo group in the trial also experienced a significant improvement in A1c (of course! It's a randomized controlled trial!) and the additional liraglutide-associated reductions should be considered in this context. All three doses of liraglutide also produced statistically significant body weight reductions: -4.9 kg (~11 lbs) with the 1.8 mg dose (p<0.05), -3.55 kg (~8 lbs) with the 1.2 mg dose (p<0.05), and -2.19 kg (~5 lbs) with the 0.6 mg dose (p<0.05). Furthermore, treatment with the two higher doses of liraglutide led to modest but statistically significant reductions in insulin dose of about 0.08 units and 0.05 units per unit of insulin compared to the placebo group, respectively (p<0.05 for both). A greater proportion of patients on the two higher doses achieved a composite outcome of an A1c <7% and no severe hypoglycemia compared to placebo as well: 18% of participants were able to achieve this goal in the 1.8 mg dose group (p=0.0024) and 20% of participants were able to in the 1.2 mg dose group (p=0.0003). For comparison, less than 10% of participants in the placebo group were able to achieve this composite goal.

- **The adverse event profile of liraglutide in ADJUNCT ONE raised several potential safety concerns.** As expected, nausea was the most common adverse event, the association was dose-dependent, and the nausea rates subsided over time. More worrisome was the 31% increase in symptomatic hypoglycemia in the 1.8 mg group (p=0.0081) and the 27% in the 1.2 mg group (p=0.0219) - symptomatic hypoglycemia was numerically increased in the 0.6 mg group but was not statistically significant. This translated to 16.5 hypoglycemic events per patient year of exposure for the 1.8 mg dose and 16.1 events per patient year of exposure for the 1.2 mg dose. On the other hand, adjudicated confirmed severe hypoglycemia trended lower in the liraglutide-treated groups (hazard ratios of 0.85, 0.61, and 0.64 in the 1.8 mg, 1.2 mg, and 0.6 mg groups, respectively), though the confidence intervals were very wide and none of the differences were statistically significant due to low event rates. Our guess is that the insulin reduction just wasn't quite enough as the GLP-1 ramped up and we think this could've been managed over time. We would've been very interested to see the "time in zone" profile had patients worn CGM - we think the trial was done before the best CGM tools were available. Of bigger concern was the more than three-fold, statistically significant increase in hyperglycemia with ketosis with the highest 1.8 mg dose of liraglutide (HR=2.22; 95% CI: 1.13-4.34; p=0.0205). Hyperglycemia with ketosis was also increased in the 1.2 mg and 0.6 mg groups, though the results were not statistically significant. Notably, there were eight episodes of full-blown diabetic ketoacidosis (DKA) in ADJUNCT ONE, all of which occurred in the liraglutide-treated groups (three episodes in the 1.8 mg group, one episode in the 1.2 mg group, and four episodes in the 0.6 mg group). Dr. Zinman noted that all the cases of DKA occurred in patients with no detectable C-peptide levels and suggested in Q&A that liraglutide has differential effects in patients with type 1 diabetes with and without C-peptide, though he acknowledged that the number of patients with C-peptide was too low to conduct a rigorous analysis of this. Overall, however, Dr.

Zinman concluded that the safety signals combined with the modest efficacy demonstrated by liraglutide in this trial limits its value and utility in patients with type 1 diabetes - we agree with this although we think the way that outcomes could be done today are different from back then and we do think GLP-1 is still of interest to type 1 patients - but difficult to know how to personalize for which patients and safety issues are definitely greater than we had realized (though some would still want to figure out how to use GLP-1 because the risk/benefit in their view would be worth it). Based on these results, Novo Nordisk announced its decision not to pursue a type 1 diabetes indication for Victoza over a year ago (concurrent with the release of the topline data). At the time, little detail on the adverse event profile was provided. While the increase in hypoglycemia and hyperglycemic ketosis, as well as the decision not to pursue an expanded indication, are very disappointing, we're intrigued by the possibility of a subset of patients with type 1 diabetes responding better to treatment. We hope that future studies can perhaps dig further into the efficacy and safety of liraglutide among patients with type 1 diabetes and some degree of remaining C-peptide, though we recognize that Novo Nordisk has many other ongoing projects in diabetes on which it is focused.

SWITCHING FROM SITAGLIPTIN TO LIRAGLUTIDE IN SUBJECTS WITH TYPE 2 DIABETES: ANALYSIS OF COMPOSITE ENDPOINTS FROM THE LIRA-SWITCH RANDOMIZED TRIAL

Timothy Bailey, MD (AMCR Institute, Escondido, CA)

Dr. Timothy Bailey presented results from the LIRA-SWITCH trial, which we first got a glimpse of at ENDO 2016. The trial's findings showed that at 26 weeks, adults with type 2 diabetes who switched from Merck's DPP-4 inhibitor Januvia (sitagliptin, n=407) to Novo Nordisk's GLP-1 agonist Victoza (liraglutide) achieved greater A1c reductions compared to those who continued Januvia treatment (n=204) (-1.1% vs. -0.5%; baseline A1c of 8.2%-83%). In addition, the Victoza arm experienced greater body weight reductions compared to the Januvia arm (-3.3 kg vs. -1.6 kg) (baseline weight of 89 kg-91 kg). Dr. Bailey particularly highlighted Victoza's superiority in a number of composite endpoints, including the proportion of patients in each treatment group who reached an A1c <7% with no weight gain and no confirmed hypoglycemia at 26 weeks. Of all participants switched to liraglutide therapy, 48% achieved this composite endpoint, compared to only 24% of the sitagliptin group. This corresponds to an odds ratio of 3.4 (p<0.0001). Additionally, 53% of Victoza-treated participants experienced an A1c reduction of >1% with no weight gain vs. 29% of Januvia-treated participants (OR=2.85, p<0.0001), 48% of Victoza-treated participants reached A1c <7% with no weight gain vs. 24% of Januvia-treated participants (OR=3.34, p<0.0001), and 45% of Victoza-treated participants reached A1c <7% with no weight gain and systolic blood pressure <140 mmHG vs. 19% of Januvia-treated participants (OR=3.88, p<0.0001). Dr. Bailey underscored that each of these composite endpoints, and especially the outcome on A1c <7% alongside no weight gain or hypoglycemia, is valuable - these are the endpoints that are "most meaningful to patients," he argued. We definitely agree. There are so many outcomes that matter to patients beyond A1c-lowering (as hammered home at the August FDA workshop on outcomes beyond A1c), and we were happy to see this focus on hypoglycemia, body weight, and blood pressure in a LIRA-SWITCH post-hoc analysis.

Questions and Answers

Q: It seems that when you choose patients for these trials, the mean A1c is always <9%. Can you comment on that?

A: Qualifications for this trial were relatively narrow - an A1c between 7.5-9.5% - so the average baseline A1c we saw was expected. There were a few people in the study with A1c >9%, but not many. I think that's fine, because our target group should be baseline a little below 9% A1c. In most countries, we see clinical inertia, where therapies are not switched until A1c is quite high. Historically, we've endorsed one target to reach, and a separate target A1c where providers actually do things differently. I believe the target to take action should be much closer to the target A1c. If you're not reaching goals, switch therapies. The optimal thing is to test therapies in patients who are failing above goals of 7% or 8%.

Q: Since you only reached glycemic targets in half of patients, isn't that a hint that you should start earlier and switch treatments at an even lower A1c?

A: Indeed, this is a common theme. It's why so many patients have an A1c >9%, because of providers' inertia to take action until A1c is already quite high.

Q: Since only half of patients reached targets, even in the liraglutide group, what's your view on leaving sitagliptin and adding in liraglutide or another GLP-1 agonist?

A: That's been proposed, but the data doesn't suggest an additional benefit that would justify the additional cost. Where I live, the cost of sitagliptin is ~$6/day. Even if there was a marginal clinical benefit, this wouldn't be economically cost-effective.

Q: Do you have any data on double diabetes, the coincidence of having both type 1 and type 2 diabetes?

A: Yes, it's possible to develop both. These patients would presumably be on a background of insulin therapy. I don't have data on double diabetes, per se.

Q: Can you talk a little bit about the safety profile of these two drugs?

A: So far, we haven't seen a greater incidence of pancreatitis predicted by switching from sitagliptin to liraglutide. That said, in patients with a history of pancreatitis, you wouldn't want to use either of these agents.

THE DIFFERENTIAL AND COMBINED ACTION OF INSULIN GLARGINE AND LIXISENATIDE ON THE FASTING AND POST-PRANDIAL COMPONENTS OF GLUCOSE CONTROL

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

Dr. Boris Kovatchev presented a new post-hoc analysis of the phase 3 LixiLan-O trial of Sanofi's iGlarLixi (insulin glargine/lixisenatide), which found distinct and differential effects of each component agent on fasting and postprandial glucose. Initial results from LixiLan-O demonstrated that iGlarLixi produces greater A1c reductions than insulin glargine (Sanofi's Lantus) or lixisenatide (Sanofi's Lyxumia) alone. Dr. Kovatchev positioned this post-hoc as a "deconstruction" of the A1c lowering effect, as the analysis elucidated the specific impact of each drug on fasting and postprandial glucose. Insulin glargine lowered average glucose (mean of seven-point SMBG measures) from 10.2 mmol/l (184 mg/dl) at baseline to 7.7 mmol/l (138 mg/dl) at 30 weeks (a 2.5 mmol/l [45 mg/dl] drop, p<0.0001) and lixisenatide lowered average glucose from 10.4 mmol/l (187 mg/dl) at baseline to 8.5 mmol/l (153 mg/dl) at 30 weeks (a 1.9 mmol/l [34 mg/dl] drop, p<0.0001). When put together as iGlarLixi, the combination lowered average glucose from 10.4 mmol/l (187 mg/dl) to 7.0 mmol/l (126 mg/dl), marking a more substantial 3.4 mmol/l (61 mg/dl, p<0.0001) decline. Dr. Kovatchev noted that this glucose effect is not completely additive, and explained how this indicates some overlap in the type of hyperglycemia (fasting or postprandial) targeted by each component, glargine and lixisenatide. Similarly, the effects of insulin glargine and lixisenatide on glucose variability and glycemic exposure are not completely additive. Patients' glucose variability, as measured by the High Blood Glucose Index (HBGI), declined by a mean of 6.3 from a baseline of 9.8 if treated with insulin glargine alone, by 5.3 from a baseline of 10.4 if treated with lixisenatide alone, and by 8.3 from a baseline of 10.3 if given iGlarLixi. Glycemic exposure, as measured by area under the curve, fell ~34 mmol-hr/l from a baseline of 144 mmol-hr/l in the glargine group, fell ~27 mmol-hr/l from a baseline of 147 mmol-hr/l in the lixisenatide group, and fell ~48 mmol-hr/l from a baseline of 146 mmol-hr/l in the iGlarLixi group. Using vector analyses of the contributions of insulin glargine and lixisenatide to iGlarLixi's effect, Dr. Kovatchev suggested that the postprandial effect of lixisenatide might have a greater impact on iGlarLixi's reduction of glycemic variability than on its reduction of overall plasma glucose. While this information is certainly helpful to theorists and academic researchers, we think "time in zone" data would be more understandable for patients and some HCPs.

Questions and Answers

Q: What was the dose of glargine for the combination therapy group vs. the insulin glargine only group?

A: As I recall, it was lower in the combination group, but I can't give you the exact numbers.

Q: On mechanism of action: Do you presume these effects are observed because of the gastric emptying effect of lixisenatide?

A: Yes, that was the original thought.

Q: When you're talking about postprandial glucose, are you addressing all meals or just breakfast?

A: Average across all meals.

Q: The effect of insulin glargine on postprandial glucose was more than the effect of lixisenatide on postprandial glucose, despite the notion that insulin glargine is working mostly on the fasting glucose axis. Can you explain that, please?

A: Yes, you're right. That's because insulin glargine is still bringing the entire glucose curve down.

EFFICACY AND SAFETY OF LIXILAN, A FIXED-RATIO COMBINATION OF INSULIN GLARGINE PLUS LIXISENATIDE IN TYPE 2 DIABETES NOT ADEQUATELY CONTROLLED ON BASAL INSULIN: LIXILAN-L TRIAL

Vanita Aroda, MD (Medstar Health Research Institute, Washington, DC)

Dr. Vanita Aroda reviewed major findings from the LixiLan-L trial comparing Sanofi's combination drug iGlarLixi (insulin glargine/lixisenatide) to Lantus (insulin glargine) alone. These data were also presented at ADA 2016, and Dr. Aroda shared that the results had just been accepted for publication. The critical takeaway, she articulated, is that treatment with iGlarLixi lowered A1c to 6.9% vs. 7.5% with Lantus from a baseline A1c of 8.1% in both groups. She also discussed composite endpoints - a theme of this session, as speakers highlighted GLP-1 agonist combinations for their multifaceted effects on various aspects of diabetes. Participants treated with the combination product were 30% more likely to reach A1c <7% with no weight gain at week 30 (p<0.0001), 13% more likely to reach A1c <7% with no documented hypoglycemia at week 30 (no p-value calculated), and 11% more likely to reach A1c <7% with no weight gain or documented hypoglycemia at week 30 (p<0.0001). During Q&A, the issue arose that while LixiLan-L touts the result of no increased hypoglycemia risk with iGlarLixi, we might actually expect a reduced risk of hypoglycemia, because a basal insulin/GLP-1 agonist combination should have an insulin sparing effect. Dr. Aroda noted that disappointingly, no such insulin sparing was observed in the trial.

Questions and Answers

Q: You said you were happy about no extra hypoglycemia, probably referring to the fact that with the fixed-dose combination you achieved better A1c, and lower glucose translates to greater hypoglycemia risk. But on the other hand, if in one group the reduction of glucose rests on insulin only and in the other group there's some component contributed by a GLP-1 agonist (which alone should not cause hypoglycemia), shouldn't there be hope of reducing hypoglycemia? And that's not what we see in these data.

A: To clarify, I didn't say I was happy. You're right, it doesn't appear that iGlarLixi has an insulin sparing effect.

Q: Did you measure heart rate in the two groups? Is there a way to split this combo into two injections/day?

A: There was maybe a 1 beat/minute difference between the iGlarLixi and Lantus treatment groups, but nothing notable. We did look at the percentage of patients with heart rate >120 beats/minute, and there were none. Sponsors have chosen to pursue once-daily dosing based on earlier studies which didn't demonstrate pronounced benefits of twice-daily injections of this class of product, but this investigation hasn't been done with iGlarLixi, specifically.

Q: What was the difference for patients using sulfonylureas vs. not?

A: Sulfonylureas were discontinued during run-in.

Q: Why are patients, on average, needing the same insulin dose, in both groups?

A: That's an astute observation, and it points to lixisenatide not having an insulin sparing effect.

Q: Let's think about an international population. In some places, culture emphasizes big dinners. In other places, it's the norm to eat a big breakfast. Did you see cross-cultural differences?

A: Great point. This isn't something we analyzed.

FACTORS ASSOCIATED WITH THREE YEARS OF RESPONSE TO A1C GOAL WITH EXENATIDE QW OR INSULIN GLARGINE: RETROSPECTIVE ANALYSIS OF DURATION-3

Michael Trautmann, MD (Diabetes Research, Hamburg, Germany)

Germany's Dr. Michael Trautmann presented a new retrospective analysis of DURATION-3, a head-to-head study comparing AZ's Bydureon (exenatide once-weekly) with Sanofi's Lantus (insulin glargine). He outlined one goal of this post-hoc analysis was to pinpoint specific factors that predict a patient's long-term success on the once-weekly GLP-1 agonist, although there were few differences at baseline between sustained responders (individuals who achieved an A1c <7% at 26 weeks and maintained an A1c <7% for 80% of the next 11 visits, including at least one of two visits in the last six months) and non-sustained responders (individuals who achieved an A1c <7% at 26 weeks but did not maintain this for 80% of the remaining 11 visits). Of 233 participants randomized to exenatide therapy, 53 (or ~23%) were sustained responders, vs. 31 (~14%) of 233 participants randomized to insulin glargine alone. Comparing baseline characteristics of 84 sustained responders vs. 91 non-sustained responders, this post-hoc analysis found no significant differences in starting A1c (7.8% for the sustained responders vs. 8.1% for the non-sustained responders), fasting plasma glucose (8.9 mmol/l vs. 9.6 mmol/l, respectively), or postprandial glucose (11.1 mmol/l for both arms). It certainly would be helpful to be able to predict response to relatively expensive GLP-1 agonists prior to starting therapy, but the benefits of these agents are such that it is probably worthwhile for a wide range of patients to at least try them. Indeed, Dr. Trautmann emphasized that long-term, over seven years (in fact, this is the longest spanning clinical study of a GLP-1 agonist), treatment with once-weekly exenatide increases a patient's chances of sustained improvements in A1c and body weight vs. treatment with insulin glargine alone.

DURATION-1 EXTENSION IN PATIENTS WITH TYPE 2 DIABETES: EFFICACY AND TOLERABILITY OF EXENATIDE ONCE-WEEKLY OVER 7 YEARS

Athena Phillis-Tsimikas, MD (Scripps Diabetes Institute, La Jolla, CA)

Dr. Athena Phillis-Tsimikas discussed a seven-year follow-up to the DURATION-1 study of AZ's Bydureon (exenatide once-weekly) comparing completers vs. non-completers. She emphasized that a once-weekly, 2 mg injection of the GLP-1 agonist, alongside regular screening visits, was a rather intensive regimen to continue for seven years, which is why there were only 122 completers out of the 293 participants from the initial 30-week assessment. Seven-year completers of DURATION-1 experienced a mean 2.2% A1c reduction in the first year of treatment ($p<0.05$), and although A1c bounced back slightly, the average reduction from baseline at seven years was still significant at 1.5% ($p<0.05$). Among completers who had no new concomitant drugs added to their diabetes care (which most often was insulin), the results were even more impressive, with a mean 2.4% A1c reduction at one year ($p<0.05$) and a sustained 1.8% reduction at seven years ($p<0.05$). We expect this is a function of poorer response to Bydureon and long-term glucose control precipitating the intensification of therapy, rather than therapy intensification causing poorer glucose control. Similar sustained but attenuated trends were observed for fasting plasma glucose, though there did not appear to be a substantial difference among those with and without concomitant medications: Average lowering of fasting plasma glucose at one year was 2.7 mmol/l and 2.8 mmol/l for completers with and without new concomitant medications, respectively, and was 1.3 mmol/l for both groups at seven years ($p<0.05$ for all interactions). Weight loss was 4.7 kg on average for completers at one year and 3.9 kg at seven years ($p<0.05$ for both interactions). Meanwhile, completers with no new concomitant drugs saw a mean 5.7 kg weight loss at one year, which actually increased to a mean 6.5 kg weight loss at seven years

(p<0.05 for both interactions) - this is an exciting piece of data for type 2 diabetes care, as it reflects a possible sustained weight loss benefit of exenatide, which we have always assumed existed but did not have proof. Dr. Phillis-Tsimikas also reported that cholesterol and triglyceride levels declined significantly for completers over seven years, but notably, statin use increased during this study period as well, which makes it difficult to interpret the lipid effects of exenatide. In concluding her presentation, Dr. Phillis-Tsimikas listed a few limitations of this DURATION-1 follow-up - namely, that 59% (n=173) participants withdrew and that due to the intensity of the regimen, completers may have been more dedicated, motivated patients to begin with.

Questions and Answers

Q: Did beta cell function improve throughout the study? Will you continue to investigate effects on beta cell function after discontinuation of exenatide, to probe for durability?

A: I don't think that's planned, but you're absolutely right - it would be very interesting.

Posters

EFFICACY AND SAFETY OF SEMAGLUTIDE ONCE-WEEKLY VS. PLACEBO AS ADD-ON TO BASAL INSULIN ALONE OR IN COMBINATION WITH METFORMIN IN SUBJECTS WITH TYPE 2 DIABETES (SUSTAIN 5)

H Rodbard, I Lingvay, J Reed, R De La Rosa, L Rose, D Sugimoto, E Araki, P-L Chu, N Wijayasingh, P Norwood

A Novo Nordisk poster unveiled the full results of the SUSTAIN 5 trial, which demonstrated superior glycemic control and weight loss for next-generation once-weekly GLP-1 agonist semaglutide versus placebo in patients with type 2 diabetes on basal insulin. As was previously reported in the topline results, adults with type 2 diabetes inadequately managed with basal insulin alone or in combination with metformin (n=397) achieved superior A1c reductions of 1.4% and 1.8% after 30 weeks of add-on treatment with 0.5 mg and 1.0 mg of semaglutide, respectively, compared to a 0.1% reduction with placebo (mean baseline A1c=8.4%, p<0.0001). Semaglutide also demonstrated superior weight loss (3.7 kg-6.4 kg vs. 1.4 kg; baseline = 92 kg), and insulin dose reductions (10%-15% vs. 3%). The full results shared impressive data on the proportion of semaglutide-treated patients that were able to achieve an A1c target <7%, an A1c target <6.5%, a weight loss of 5% or more, a weight loss of 10% or more, and a composite endpoint of A1c<7% without hypoglycemia or weight gain. We also got a glimpse at semaglutide's impact on fasting plasma glucose (FPG), mean 7-point self-monitored plasma glucose (SMPG), insulin dose, and blood pressure and saw more granularity on the adverse event data. See below for a deep dive into these long-awaited results.

- **From the full results, we further learned that higher proportions of semaglutide-treated participants achieved their A1c targets and weight loss goals.** For participants receiving 0.5 mg and 1.0 mg semaglutide, 61% and 79% achieved an A1c <7%, compared to 11% with placebo (p<0.0001). 41% and 61% of subjects respectively achieved an A1c <6.5%, compared to 5% with placebo (p<0.0001). Additionally, 42% and 66% of subjects given 0.5 mg and 1.0 mg semaglutide achieved 5% weight loss, compared to 11% with placebo (p<0.0001 for both). Furthermore, a higher proportion of participants taking semaglutide achieved 10% weight loss or greater (9% with the 0.5 mg dose [p=0.04] and 26% of patients with the 1.0 mg dose [p<0.0001], compared to 3% with placebo). Finally, the full results revealed that a significantly higher proportion of subjects achieved the triple goal of A1c <7% without severe or BG-confirmed symptomatic hypoglycemia and without weight gain: 54% and 67% respectively with 0.5 mg and 1.0 mg semaglutide, versus 7% with placebo.
- **New efficacy data also elaborated upon the secondary outcomes of mean fasting plasma glucose (FPG), mean 7-point self-monitored plasma glucose (SMPG), and blood pressure.** From a baseline of 8.6 mmol/l (154 mg/dl), mean FPG decreased by 1.6 mmol/l (29 mg/dl) and 2.4 mmol/l (43 mg/dl) in the semaglutide 0.5 mg and 1.0 mg groups, respectively, significant reductions as compared to the 0.5 mmol/l (9 mg/dl) FPG reduction seen in the placebo

group (p=0.0002 and p=0.0001, respectively). Furthermore, mean 7-point SMPG decreased by 2.5 mmol/l (45 mg/dl) and 3.0 mmol/l (54 mg/dl) in the semaglutide treatment groups, respectively, significantly more than the 0.8 mmol/l (14 mg/dl) reduction observed in the placebo group (p=0.0001 for both). Postprandial increments for mean 7-point SMPG also decreased significantly more in the 0.5 mg and 1.0 mg semaglutide groups (-0.8 mmol/l [14 mg/dl] and -1.2 mmol/l [22 mg/dl], respectively), versus a 0.2 mmol/l [4 mg/dl] reduction in the placebo group (p=0.003 and p<0.0001, respectively). The larger 1.0 mg semaglutide dose was significantly more effective at reducing systolic blood pressure than placebo (-6.29 mmHg; p=0.0007). The 0.5 mg semaglutide dose also reduced systolic blood pressure, but the reduction was not significantly different from that seen with placebo.

- **Over the 30-week trial, insulin dose decreased in all treatment doses.** Overall, subjects on semaglutide 0.5 mg and 1.0 mg decreased their insulin dose by 10% and 15%, versus 4% in the placebo group (p=0.0046 and p<0.0001, respectively, compared with placebo). Among patients with A1c >8.0% at screening, the semaglutide 0.5 mg and 1.0 mg groups reduced their insulin dose by 6% and 10%, versus 2% with placebo. Patients with A1c <8.0% at screening mandatorily reduced their insulin dose by 20% at the beginning of the trial to minimize hypoglycemia risk. By the end of the trial they had reduced their insulin dose from baseline by 18% and 24% with semaglutide 0.5 mg and 1.0 mg, versus 7% with placebo.
- **New safety data revealed that subjects given semaglutide 0.5 mg, 1.0 mg, and placebo experienced adverse events (AEs) in the proportions of 69%, 64%, and 58%, respectively.** 6.1%, 9.2%, and 6.8% of subjects respectively reported serious AEs across multiple organ classes, and 4.5%, 6.1%, and 0.8% permanently discontinued treatment due to AEs. Treatment with 0.5 mg and 1.0 mg semaglutide increased pulse rate by 1 and 4 beats per minute, respectively; by contrast, placebo decreased pulse rate by 1 beat per minute. No event adjudication committee (EAC)-confirmed pancreatitis events or fatal events were reported, but there were four instances of gallbladder disease and one instance of EAC-confirmed malignant neoplasm among the semaglutide-treated groups.
    - **As expected, the most frequent AEs in semaglutide-treated subjects were gastrointestinal, and mild to moderate in nature.** 11.4% and 16.8% of subjects treated with 0.5 mg and 1.0 mg semaglutide reported nausea, as compared to 4.5% of subjects on placebo.
    - **Severe or BG-confirmed symptomatic hypoglycemia occurred in 8.3%, 10.7%, and 5.3% of subjects treated with semaglutide 0.5, 1.0 mg and placebo.** The proportions of subjects experiencing hypoglycemia were comparable between the semaglutide and placebo groups among patients with A1c >8.0% at screening, but among patients with A1c <8.0%, hypoglycemia occurred in a higher proportion of the semaglutide-treated groups. We think that is manageable - this is expected given people had to reduce insulin and that's always a bit tricky (in the "real world" of course more people would go on this drug before going on to insulin).
- **Semaglutide is poised to become Novo Nordisk's star GLP-1 agonist once the patent for the hugely-successful Victoza (liraglutide) expires.** This new evidence demonstrating the safety and efficacy of semaglutide in combination with basal insulin therapy indicates that the drug has a promising future in store, and enhances our anticipation for Friday's announcement of the SUSTAIN 6 trial results, assessing cardiovascular outcomes for semaglutide.

EFFICACY AND SAFETY OF LIRAGLUTIDE ADDED TO CAPPED INSULIN TREATMENT IN TYPE 1 DIABETES, THE ADJUNCT TWO RANDOMIZED TRIAL

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The ADJUNCT TWO trial investigated the therapeutic efficacy of liraglutide (Novo Nordisk's Victoza) in patients with type 1 diabetes (n=835) as an adjunct to insulin treatment over 26 weeks, randomizing patients to either 0.6 mg, 1.2 mg, 1.8 mg, or placebo. Each dose of the GLP-1 agonist led to statistically significant A1c and body weight reductions vs. placebo. A1c-lowering was 0.24%, 0.23%, and 0.35% greater with the 0.6 mg, 1.2 mg, and 1.8 mg doses, respectively (baseline A1c=~8%; p<0.05). Estimated treatment difference in weight loss amounted to 2.2 kg, 3.7 kg, and 4.8 kg for the 0.6 mg, 1.2 mg, and 1.8 mg doses of liraglutide, respectively vs. placebo (p<0.05). Insulin requirements also decreased significantly for participants on liraglutide, with participants on 0.6 mg, 1.2 mg, and 1.8 mg liraglutide taking 0.05, 0.07, and 0.1 units less insulin per unit of insulin in the placebo group (p<0.05). At 26 weeks, 15% of patients treated with 1.8 mg liraglutide achieved an A1c reduction >1%, compared to 11% of patients on 1.2 or 0.6 mg of the agent and only 4% of patients receiving placebo injections. While the authors conclude that liraglutide added to insulin could be an effective glucose- and weight-lowering therapy for type 1 diabetes patients, they note that concerns over hypoglycemia may limit clinical use. Symptomatic hypoglycemia occurred most frequently in the 1.2 mg liraglutide arm of the study, affecting 175 or 84% of patients vs. 160 or 78% of patients on 1.8 mg liraglutide, 166 or 79% of patients on 0.6 mg liraglutide, and 162 or 78% of patients on placebo. In the 1.2 mg group, this represented a 31% increase in hypoglycemia over the placebo group. Additionally, liraglutide treatment increase the rate of hyperglycemic episodes with ketosis: liraglutide 1.8 mg was associated with a nearly four-fold increase in these events (HR=3.96, 95% CI=1.49-10.55, liraglutide n=42, placebo n=10). The most common adverse event in the trial was, as expected for a GLP-1 agonist, dose-dependent nausea and vomiting.

- **These results mirror that of the similarly-designed but larger ADJUNCT ONE trial (n=1,398 patients with type 1 diabetes followed for one year), which were presented at this meeting by Dr. Bernie Zinman.** The modest improvements in glycemic control and weight coupled with concerning safety signals in ketosis and hypoglycemia led Novo Nordisk to decline to pursue a type 1 diabetes indication for Victoza over a year ago. While Novo Nordisk certainly has many other projects within diabetes and obesity to which to turn its attention, we do still think GLP-1 agonists remain of interest for type 1 diabetes and we hope future studies can perhaps identify sub-populations of responders where the metabolic benefits may be enhanced and the safety concerns minimized - for instance, Dr. Zinman suggested in the ADJUNCT ONE presentation that patients with detectable levels of C-peptide may fare better and we wonder if the use of GLP-1 agonists in this population may potentially have a beta cell-protective effect. We would also love to see data on the impact of liraglutide or other GLP-1 agonists on time-in-range, as measured by CGM, and on patient-reported outcomes.

SAFETY AND EFFICACY OF IDEGLIRA TITRATED ONCE WEEKLY VERSUS TWICE WEEKLY IN PATIENTS WITH T2D UNCONTROLLED ON ORAL ANTIDIABETIC DRUGS: DUAL VI STUDY

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In this 32-week, open-label, non-inferiority trial, insulin-naïve patients (n=420) uncontrolled on metformin alone or on metformin/TZD (pioglitazone) therapy were randomized to once- or twice-weekly titration of Novo Nordisk's IDegLira (insulin degludec/liraglutide, branded Xultophy). Among the 210 patients on once-weekly titration, the average A1c drop was 2.1%, from a baseline of 8.2% to 6.1%. The mean A1c reduction for the twice-weekly titration IDegLira group (n=210) was also 2.1%, from a baseline of 8.1% to 6%, and the estimated treatment difference between the two dosing regimens was 0.12% (p=0.012 for non-inferiority). Similar proportions of each treatment group achieved target A1c: (i) ~90% of both dosing arms reached A1c <7%; (ii) 86% of once-weekly patients experienced A1c <7% with no hypoglycemia vs. 84% of twice-weekly patients; (iii) 84% of once-weekly patients reached A1c <6.5% vs. 85% of twice-weekly patients; and (iv) 79% of both groups experienced A1c <6.5% with no hypoglycemia. Fasting plasma glucose decreased by 4.3 mmol/l (77 mg/dl) with once-weekly IDegLira (from a baseline of 10.1 mmol/l) and by 4.6 mmol/l with twice-weekly IDegLira (from the same baseline of 10.1 mmol/l [182 mg/dl]), marking a 0.2 mmol/l (3.5 mg/dl) estimated treatment difference (p=0.2 for non-inferiority). The once-weekly titration group experienced 1 kg (2.2 lb) weight loss on average, compared to 2 kg (4.4 lb) mean weight loss for the

twice-weekly group - a statistically significant treatment difference (p=0.014). While the holistic safety profile was similar for both doses of IDegLira (253 adverse events in the once-weekly arm vs. 307 in the twice-weekly arm, affecting 49% and 51% of patients, respectively), hypoglycemia rates were noticeably higher for patients in whom the dose was titrated twice a week. Severe, symptomatic hypoglycemia occurred in 6% and 16% of the once- and twice-weekly titration groups, respectively, and in 1% and 7% of both groups respectively overnight. Overall, the results support the efficacy and safety of the simpler once-weekly titration strategy, which could help reduce the patient and provider burden associated with IDegLira initiation.

PATIENT-REPORTED OUTCOMES WITH ONCE WEEKLY DULAGLUTIDE VERSUS PLACEBO, BOTH IN COMBINATION WITH ONCE DAILY INSULIN GLARGINE (+/- METFORMIN) IN TYPE 2 DIABETES (AWARD-9)

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AWARD-9 was a 28-week, phase 3b, randomized study in patients with type 2 diabetes treated with or without metformin (≥1500 mg/day), who received weekly titrated basal insulin glargine with either 1.5 mg of dulaglutide (Lilly's Trulicity) or placebo. Dulaglutide (n=150) resulted in significantly greater reductions in A1c - 1.4% drop from an average baseline of 8.4% - and fasting plasma glucose - 2.5 mmol/l (45 mg/dl) decline from a baseline of 8.7 mmol/l (157 mg/dl) - vs. placebo (p<0.001). For comparison, the placebo group (n=150) saw an average A1c decline of 0.7% from baseline 8.3% and an average fasting plasma glucose decline of 1.6 mmol/l (29 mg/dl) from baseline 8.7 mmol/l (157 mg/dl). A larger proportion of dulaglutide-treated patients (67%) reached a target A1c <7% compared to placebo (33%, p<0.001). There was a greater observed increase in insulin glargine dose with placebo at 26u vs. dulaglutide at 13u (p<0.001), though the rate of hypoglycemia was similar in both groups (82% and 76% for dulaglutide and placebo arms, respectively). In addition, body weight decreased in the dulaglutide arm by a mean 1.9 kg (4.2 lbs) but increased in the placebo arm by 0.5 kg (1.1 lbs), both from a 93 kg (205 lbs) baseline (p<0.001). Nausea and diarrhea were common side-effects of dulaglutide, occurring with 12% and 11% frequency, respectively. These GI side-effects were less common for placebo-treated participants, at 1% and 4%, respectively. Importantly, investigators also looked at patient reported outcomes (PRO) in AWARD-9. PROs were administered at baseline and then again after 28 weeks of treatment, revealing significant improvements on weight-related quality of life metrics. Specifically, score on the "Impact of Weight on Self-Perceptions" test improved by a greater margin in dulaglutide-treated patients vs. placebo-treated patients - total transformed score at 28 weeks was 6.14 for the dulaglutide group (p<0.05 vs. baseline) vs. 0.07 for the placebo group (p<0.05). We greatly appreciated the inclusion of patient-reported outcomes data and hope to see greater standardization among trials and within the regulatory process on how these are measured.

EFFICACY AND SAFETY OF ONCE-WEEKLY SEMAGLUTIDE MONOTHERAPY VERSUS PLACEBO IN SUBJECTS WITH TYPE 2 DIABETES (SUSTAIN 1)

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SUSTAIN 6 may have been a looming highlight of EASD 2016, but other notable data from the SUSTAIN program for Novo Nordisk's GLP-1 agonist semaglutide was also presented in Munich, including this poster on SUSTAIN 1. The 30-week, phase 3a trial randomized 388 adults with type 2 diabetes to semaglutide 0.5 mg (n=129), semaglutide 1.0 mg (n=130), or placebo (n=129). A1c decreased by 1.5% and 1.6% with semaglutide 0.5 mg and 1.0 mg, respectively, and declined by <0.1% with placebo (baseline A1c=8%, p<0.0001 for both comparisons). Moreover, 66% and 65% of participants treated with semaglutide 0.5 mg and 1.0 mg, respectively, achieved target A1c <7% without severe or blood glucose-confirmed symptomatic hypoglycemia or weight gain, whereas only 19% of the placebo group achieved this composite endpoint. Improvement on seven-point self-monitored plasma glucose (SMPG) was found to be significant for 1.0 mg semaglutide vs. placebo - there was a 1.1 mmol/l (20 mg/dl) decrease in seven-point SMPG with 1.0 mg of the active agent vs. a 0.3 mmol/l (5.4 mg/dl) decrease with placebo (p=0.0014). Seven-point SMPG decreased by a mean 0.8 mmol/l (14 mg/dl) among patients on 0.5 mg semaglutide, but this treatment difference vs. placebo did not reach statistical significance. Mean body weight decreased by 4 kg (8.8 lbs)

and 5 kg (11 lbs) with semaglutide 0.5 mg and 1.0 mg, respectively, and by 1 kg (2.2 lbs) with placebo ($p<0.0001$ for both comparisons). Adverse event rates were comparable across groups and were reported in 64%, 56%, and 54% of participants on semaglutide 0.5 mg, semaglutide 1.0 mg, and placebo, respectively. As expected, the most frequent side-effects were GI-related (including nausea and diarrhea); there were no fatal adverse events reported throughout the trial period. In total, 47 participants discontinued treatment prematurely and were fairly well-balanced among the three groups - 17 from the 0.5 mg semaglutide arm, 16 from the 1.0 mg semaglutide arm, and 14 from the placebo arm.

-- by Abigail Dove, Helen Gao, Brian Levine, Payal Marathe, and Kelly Close