CLOSER LOOK

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

September 12-16, 2016; Munich, Germany; Day #3-4 Highlights - Draft

Executive Highlights

Greetings from Munich, Germany! The 52nd annual EASD congress is forging ahead full-throttle, and in this report, we bring you our top 10 highlights from days #3-4 of the conference. Sad about that one talk you had to miss on Sunday, Monday, or Tuesday? Not to worry - you can read our top takeaways from day #1 and day #2. And don't forget to check out our suggestions for things to do in Munich as you make the most of your last few days in this beautiful city!

Without further ado, our highlights:

Diabetes Drug Highlights

1. 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.

2. 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, demonstrating very impressive A1c and body weight reductions.

3. 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 patients with type 2 diabetes.

4. Dr. Brett Lauring (Merck, Kenilworth, NJ) presented findings from the phase 3 VERTIS SITA2 trial demonstrating significant A1c reductions for Merck's SGLT-2 inhibitor candidate ertugliflozin as an add-on to DPP-4 inhibitor Januvia (sitagliptin) and metformin in patients with type 2 diabetes (n=463).

5. Drs. Wendy Lane and Carol Wysham presented data from the SWITCH 1 and SWITCH 2 trials demonstrating a reduced risk of hypoglycemia with Novo Nordisk's next-generation basal insulin Tresiba (insulin degludec) compared to Sanofi's Lantus (insulin glargine) in patients with type 1 and type 2 diabetes, respectively. We were impressed by the newly-shared numbers needed to treat and by the patient-reported outcome.

6. A morning symposium shared a critical unsolved dichotomy in type 2 diabetes: strong enthusiasm for combination therapy, but poor tools to actually guide clinician decision-making and profile patients. Can we truly individualize therapy right now?

Diabetes Technology Highlights

7. JAMA published Medtronic's MiniMed 670G US pivotal trial as a two-page Research Letter, concurrently presented as an oral presentation. We saw the data in at ADA, but it was excellent to see the visibility in JAMA (even as a "research letter"), and we were glad to see several metrics we did not see in the ADA poster.

8. In a huge outcomes victory for CGM, a randomized crossover trial in type 1s with impaired hypo awareness demonstrated a significant 53% fewer severe hypoglycemia events with CGM vs. SMBG (14 events vs. 34 events; p=0.03). The well-conducted study was concurrently published in the Lancet Diabetes and Endocrinology and showed many positive CGM outcomes.

9. We talked to two interesting startups in the exhibit hall: (i) Keya, a Bluetooth-enabled, CE-marked meter that measures both blood glucose and ketones on the same strip (UK Launch by end of 2016); and (ii)

Kaleido, a colorful CE-marked patch pump expected to launch in the Netherlands and UK by the end of this year.

Big Picture Highlights

10. After accepting the 2016 EASD/Novo Nordisk Foundation Diabetes Prize for Excellence, the brilliant Dr. Andrew Hattersley asserted that precision medicine in diabetes is a reality now, though widespread implementation into clinic practice is more challenging than the science itself.

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Diabetes Drug Highlights

1. 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.

2. 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). 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). 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.

3. 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 patients 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). 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. Notably, semaglutide showed significant reductions in the proportion of participants who experienced severe or blood glucose-confirmed symptomatic hypoglycemia. See our detailed discussion and commentary below for more details on this and other adverse events.

4. Dr. Brett Lauring (Merck, Kenilworth, NJ) presented findings from the phase 3 VERTIS SITA2 trial demonstrating significant A1c reductions for Merck's SGLT-2 inhibitor candidate ertugliflozin as an add-on to DPP-4 inhibitor Januvia (sitagliptin) and metformin in patients with type 2 diabetes (n=463). A 5 mg dose of ertugliflozin lowered A1c by a mean 0.8% after 26 weeks, while a 15 mg dose lowered A1c by 0.9% (baseline A1c=8%, p=0.001 for both vs. placebo). For comparison, the placebo group experienced a substantially smaller 0.1% A1c reduction. The between-group difference in glucose-lowering was apparent at six weeks and increased through the end of the 26-week study period. Among patients treated with 5 mg ertugliflozin, 32% achieved A1c <7% vs. 17% in the placebo group (p<0.001 for both doses based on adjusted odds ratio). An even higher 40% of patients in the 15 mg ertugliflozin group achieved this A1c target (p<0.001). Ertugliflozin treatment added to sitagliptin and metformin also demonstrated a significant improvement on a number of additional secondary endpoints, namely (i) weight loss; (ii) reductions in fasting plasma glucose; and (iii) reductions in systolic blood pressure. Weight loss amounted to an average of 3.3 kg (~7.3 lbs) in the 5 mg arm (p<0.001) and 3 kg (~6.6 lbs) in the 15 mg arm (p<0.001), compared to 1.3 kg (~2.9 lbs) in the placebo arm. Fasting plasma glucose was 25 mg/dl lower after 26 weeks in the 5 mg ertugliflozin group and 31 mg/dl lower in the 15 mg group compared to placebo (p<0.001 for both). There was a 4 mmHg drop in systolic blood pressure, on average, for patients given a 5 mg

dose of ertugliflozin vs. a 1 mmHg drop for patients on placebo (p=0.019). Patient taking the 15 mg dose experienced a mean 5 mmHg decline in systolic blood pressure (p=0.002). Ertugliflozin was well-tolerated in the trial. For more, including commentary from our exclusive interview with Merck's Associate VP of clinical research in diabetes and endocrinology Dr. Sam Engel, see our detailed discussion and commentary below.

5. Drs. Wendy Lane and Carol Wysham presented data from the SWITCH 1 and SWITCH 2 trials demonstrating a reduced risk of hypoglycemia with Novo Nordisk's next-generation basal insulin Tresiba (insulin degludec) compared to Sanofi's Lantus (insulin glargine) in patients with type 1 and type 2 diabetes, respectively. Much of this data was previously shared in a pair of late-breaking posters at ADA 2016. As previously shared, SWITCH 1 found a 11% reduction in severe or blood-glucose confirmed symptomatic hypoglycemia (p<0.0001), a 36% reduction in severe or blood glucose-confirmed nocturnal symptomatic hypoglycemia (p<0.0001), and a 35% reduction in severe hypoglycemia (p<0.05) in the maintenance period with Tresiba vs. Lantus in patients (n=501) with type 1 diabetes. In patients with type 2 diabetes (n=721) in SWITCH 2, Tresiba treatment produced a 30% reduction in severe or blood-glucose confirmed symptomatic hypoglycemia (p<0.0001) and a 42% reduction in severe or blood glucose-confirmed nocturnal symptomatic hypoglycemia (p<0.0001) in the maintenance period compared to Lantus (rates of severe hypoglycemia were low in both groups and numerically but not significantly lower with Tresiba). The oral presentations EASD 2016 shared impressive new number needed to treat (NNT) figures. In SWITCH 1, 1 patient with type 1 diabetes would only need to be treated for four months to prevent one incident of symptomatic confirmed hypoglycemia. 1 patient would need to be treated for one year to prevent a nocturnal symptomatic confirmed hypoglycemia event and 3 patients would need to be treated for one year to prevent a severe hypoglycemia event. In SWITCH 2, 1 patient would need to be treated for one year to prevent one incident of overall symptomatic confirmed hypoglycemia and 3 patients would need to be treated for one year to prevent one incident of nocturnal symptomatic confirmed hypoglycemia. While the severe hypoglycemia difference was non-significant in the maintenance period due to low events, analysis of the full treatment period revealed a statistically significant 51% reduction in severe hypoglycemia (p<0.05) for Tresiba, with an associated NNT of 21. These very low numbers needed to treat across both trials certainly make a strong case for the non-glycemic benefits of next-generation basal insulin Tresiba. Novo Nordisk plans to submit the SWITCH 1 and 2 data to the FDA by the end of the month - we hope an expanded indication can help make the case to payers on the value of this product. In light of the greater attention to "outcomes beyond A1c" made at the FDA in late summer, we hope that patient engagement with "time in zone" will enable hypoglycemia data to be used on labels.

- **Very notably, Dr. Wysham shared TRIM-H patient-reported outcomes data from SWITCH 2, demonstrating improvements in daily function, diabetes management, emotional well-being, sleep disruption, work productivity, and TRIM-H total score with Tresiba. This seems like a very positive instrument and as the field moves toward greater standardization, we hope this tool is examined closely.** Both Tresiba-treated and Lantus-treated patients reported improvements in all of these outcomes in the first phase of the trial, though patients on Tresiba reported greater improvements than those on Lantus. Notably, however, those who switched from Lantus to Tresiba in the second, crossover phase of the study continued to report improvements in every outcome. On the other hand, patients who switched from Tresiba to Lantus in the second phase of the trial reported declines in daily function, diabetes management, emotional well-being, sleep disruption, and TRIM-H total score (and no change in work productivity).

6. A morning symposium highlighted a critical unsolved dichotomy in type 2 diabetes: strong enthusiasm for combination therapy (Dr. Stefano Del Prato), but poor tools to actually guide clinician decision making and profile patients (Dr. John Wilding). Can we truly individualize therapy right now? Dr. Del Prato gave many compelling arguments in favor of early combination therapy: pathogenetic complexity of type 2, complementary treatment modes of action, balances efficacy and side effects, potentially more sustained efficacy (to reduce the risk of long-term complications), and better therapy individualization. But then Dr. Wilding followed with a reality check - it is extremely difficult for clinicians to know what drug to choose for a particular patient at a given point in time. The guidelines don't give enough

tools to make precision estimates, do not consider recent outcome trials (they aren't updated frequently enough), and don't account for variability of response to treatment. As just one example, Dr. Wilding pointed out the remarkable spectrum of individual patient responses in a dapagliflozin trial: weight change ranged from -15 kg to +10 kg, while A1c changes ranged from -2% to +4%! Dr. Wilding also showed a slide with 21 different factors to consider when choosing a drug (see below), an overwhelming task even for the best clinicians. Still, both speakers seemed to lean towards greater use of SGLT-2s and GLP-1s, given the cardioprotective results (EMPA-REG, LEADER) and weight loss without hypoglycemia. We appreciated Dr. Wilding's insightful concluding series of questions, (see below) particularly his suggestion that we need more n=1 trials in diabetes - what is best for me? We think greater use of CGM in type 2 diabetes would help a lot here, particularly something as low-hassle as FreeStyle Libre Pro, which seems ideally designed as a companion diagnostic for prescribing type 2 diabetes drugs. Dr. Wilding noted that prospectively testing every combination and sequence of drugs would not be practical, but pharmacogenomics, other biomarkers (C-peptide), and big data may help HCPs make better treatment choices in the future. We hope digital tools from tech-pharma partnerships (IBM Watson/Novo Nordisk, Sanofi/Verily) can make serious progress on this front.

Diabetes Technology Highlights

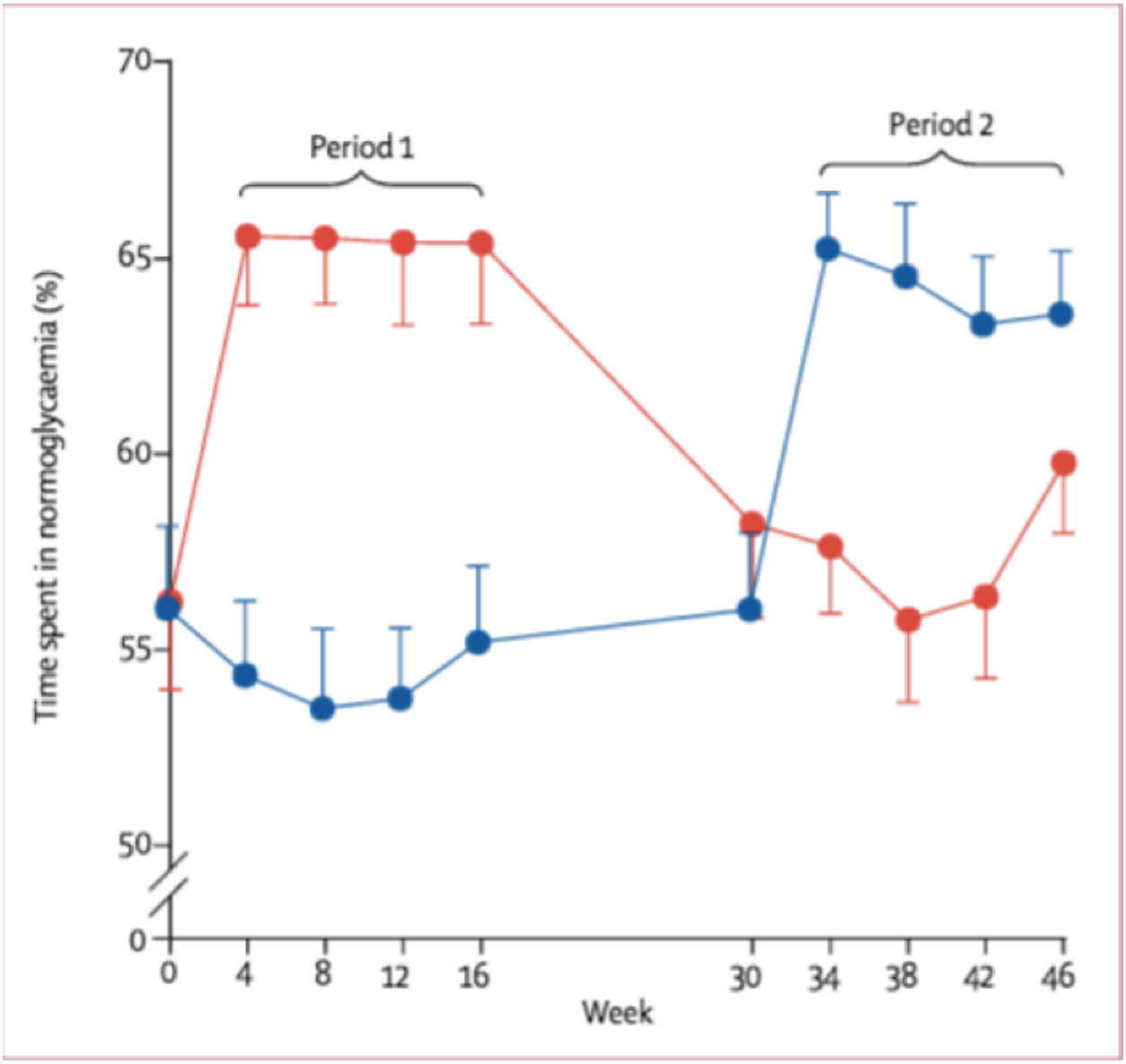
7. Today, *JAMA* published Medtronic's MiniMed 670G US pivotal trial as a two-page Research Letter, concurrently presented as an oral presentation by Dr. Richard Bergenstal this afternoon. We saw the data in a late-breaking ADA poster in June, but it was excellent to see the visibility in *JAMA* (even as a "research letter"), and we were glad to see several metrics we did not see in the ADA poster: mean and median glucose in the trial (~150 mg/dl); time spent >300 mg/dl (a strong 26% decline), nocturnal time-in-range data (excellent), within-day coefficient of variation, and median values for all CGM metrics. The data is otherwise identical to what we saw at ADA and reinforces the topline takeaways: (i) a strong safety profile; (ii) a solid 0.5% reduction in A1c from a low baseline (7.4%); (iii) excellent hypoglycemia avoidance (time ≤70 mg/dl declined 44%; (iv) outstanding efficacy overnight (75% time in 70-180); and (v) much-improved accuracy for Enlite 3 (MARD: 10.3%). A group of serious luminaries in the field authored the *JAMA* letter - Drs. Rich Bergenstal, Satish Garg, Stu Weinzimer, Bruce Buckingham, Bruce Bode, Bill Tamborlane, and Fran Kaufman. We assume this could not be an "original article" as a single arm, non-randomized study, which Medtronic obviously choose for speed and getting to market quickly - we're glad to see that was prioritized over a perfect pre-market RCT that gets published in long-form in a major journal, but takes longer to complete. As would be expected, the *JAMA* Research Letter places less focus on efficacy: "Safety" is the first word in the piece's title, "Table 1" shows device related adverse events ("Table 2" shows the study outcomes), and no p-values are shown comparing the two-week baseline to the intervention period. We hope readers can infer the efficacy from the Research Letter's table, though it will be interesting to see if closed loop shows better "real-world" efficacy than in trials. Managing expectations will of course be critical as this comes to market, something we heard over and over again at ADA. The 670G was submitted to FDA in June, and as of the 2Q16 call earlier this month, was "on track" for approval by April 2017.

- **To us, the big takeaway is that the 670G is safe and effective (even in a motivated patient population), and it will be a good first-generation starting point to learn and improve upon.** Patients in the pivotal clearly loved the system (80% chose to continue using it), a sign that these first-gen products will appeal to current pumpers. Though we've heard the 670G requires a fair amount of setup and the user interface needs improvement, it should reduce burden from what many are currently doing every day, and it certainly gives amazing peace of mind overnight and a great morning glucose to start the day.

8. In a huge outcomes victory for CGM, a randomized crossover trial in type 1s with impaired hypo awareness demonstrated a significant 53% fewer severe hypoglycemia events with CGM vs. SMBG (14 events vs. 34 events; p=0.03). The study was concurrently published in the *Lancet Diabetes and Endocrinology*. The very well conducted trial (out of the VU university hospital and Dr. Hans DeVries' group at Academic Medical Center, both in Amsterdam) randomly assigned 52 patients to either (i) 16 weeks of CGM followed by SMBG (n=26); or (ii) 16 weeks of SMBG followed by CGM (n=26). A

12-week washout came in between the periods, and the study enrolled type 1 adults with impaired hypoglycemia awareness, a baseline A1c of 7.5%, a mean age of 49 years, 31 years of diabetes duration, and 56% MDI users. The CGM study phase used the Medtronic Enlite CGM running on the Veo pump, but used only as a *receiver* (no low glucose suspend turned on). A blinded iPro2 device collected CGM data during the SMBG phase. The primary endpoint, time-in-range (70-180 mg/dl), significantly improved during the CGM phase: 65% with CGM vs. 55% with SMBG ($p<0.0001$), translating to 2.3 extra hours in range per day with CGM. This included a 40% reduction in time spent <70 mg/dl with CGM (6.8% vs. 11.4%; $p<0.0001$) and 15% less time spent >180 mg/dl (28.2% vs. 33.2%; $p<0.0001$). Severe hypoglycemia (requiring third-party assistance) was actually a secondary endpoint, but it was still powerful to see the huge change in this high-risk population - that the SMBG phase included 34 severe hypoglycemia events in 52 patients over 16 weeks was striking. Notably, the proportion of patients with ≥1 severe hypoglycemia event was 10 (CGM) vs. 18 (SMBG), translating to a compelling 0.48 odds ratio (borderline significant at $p=0.06$). A1c was not significantly different (-0.1%), meaning glycemic control was not ceded for the hypoglycemia benefits - yes! CGM surprisingly did not significantly improve awareness of hypoglycemia (as measured by Gold Score) after 16 weeks, though perhaps a longer trial would be needed. Interestingly, Lilly and Sanofi funded the trial. We think the results would be even better with a more recent device.

- **This trial further builds the case for CGM's cost-effectiveness (even with an older CGM sensor), and we especially hope it helps with European reimbursement. The publication neatly summarized the study implications**: "In earlier trials, CGM did not live up to the expectations of the diabetes community regarding its ability to reduce severe hypoglycemia. However, our findings here support the benefit of CGM, both with and without combining it with continuous subcutaneous insulin infusion, for improving glycemic control and diminishing severe hypoglycemia in adult patients with type 1 diabetes and impaired awareness of hypoglycemia, who are at highest risk of severe hypoglycemia."
- **There was no carryover effect, meaning the time-in-range improvement from CGM came solely from wearing it and using the data real-time (not a learning effect that persisted).** See below for the time-in-range outcome for the CGM-SMBG sequence (red line) and SMBG-CGM sequence (blue line). CGM immediately benefited time-in-range, and as soon as it stopped, patients returned to their baseline. There was also no interaction between insulin treatment modality (MDI vs. pump), confirming Dexcom's recent studies (DIaMonD study, COMISAIR) showing the benefits of CGM in MDI users.



9. We talked to two interesting tech startups in the exhibit hall: (i) Keya, a Bluetooth-enabled, CE-marked meter that measures both blood glucose and ketones on the same strip (UK Launch by end of 2016); and (ii) Kaleido, a colorful CE-marked patch pump expected to launch in the Netherlands and UK by the end of this year. The former was brand new to us, while we saw the latter at EASD 2015.

- **Inside Biometrics:** We stopped by the Inside Biometrics booth to have a first look at the Bluetooth-enabled Keya Smart System, a meter that measures both blood glucose and ketone levels using the same strip. The device is about the size of a pack of cards (see picture here), has a very easy-to-use interface, and functions like a normal BGM, but automatically alerts users when their ketones are high. It received a CE mark back in May, and a UK launch is expected by the end of the year, with Germany to follow soon thereafter. FDA clearance is expected next year, though it has not yet been filed. Reps told us that the company has an existing integration agreement with Diasend (now merged with Glooko), and is working on an app that would offer actionable analytics - they seemed particularly excited about this because so little is known about the interactions between glucose and ketone levels. When asked about the possibility of a flash or continuous monitoring system, reps told us to keep an eye out for gen 2. Inside Biometrics will soon be ramping up, growing

their team from ~45 to ~60 people, outsourcing manufacturing of the meter (but not the strips), and establishing a branch in California. Pricing will be a big question for Keya. BGM is a very tough market for startups, but we are happy to see some novel innovation and a product that could conveniently address DKA. Most patients don't even know what their ketone levels should be, let alone have the supplies on-hand to measure them. This issue is only becoming more important as SGLT-2s are increasingly used in type 1 off label. We like the convenience of a normal meter that can measure ketones in the background, reducing the hassle of Abbott's Precision Xtra meter that requires separate blood glucose and ketone strips.

- **Kaleido:** We first saw Kaleido at last year's EASD, and the company received a CE Mark earlier this year. The very colorful patch pump is expected to launch in the Netherlands and UK by the end of this year. The approach resembles Cellnovo, giving patients two reusable pump units, a wireless controller handheld, and an insulin cartridge that connects to a short on-body infusion set (5 cm or 30 cm). Unlike Cellnovo or the OmniPod, the handheld doesn't have a built-in blood glucose meter, though the company recently added a bolus calculator. The body-worn pump and iPod-like handheld are both quite slim (measurements here), and the company has put a major emphasis on customizable color offerings. This is direct competition for Cellnovo, who has had a fairly slowly launch ramp in Europe.

Big Picture Highlights

10. After accepting the 2016 EASD/Novo Nordisk Foundation Diabetes Prize for Excellence, the brilliant Dr. Andrew Hattersley (University of Exeter, UK) asserted that precision medicine in diabetes is a reality now, though widespread implementation into clinic practice is more challenging than the science itself. Current professional society guidelines call for the tailoring treatments to the severity of diabetes (A1c), not the root cause. Dr. Hattersley illustrated, via a series of case studies, that shifting this paradigm to define and treat the causes of an individuals' diabetes can improve care. Each story began with a person who was diagnosed with type 1, type 2, or gestational diabetes (one was new British PM Theresa May!), and did not improve on insulin therapy. Each story concluded with an alternate diagnosis and proper treatment leading to better outcomes. For a large number of the cases, the patients actually had forms of monogenic diabetes, and could be easily controlled with an oral medication, diet adjustment, or even the cessation of treatment. For the less cut-and-dry, polygenic varieties of diabetes, Dr. Hattersley is banking on Big Data sets to help elucidate which genetic factors, or even clinical characteristics, correlate with which types of diabetes and which treatment to pair with each diagnosis. He cited MASTERMIND, a consortium that looked at ~50,000 patients in the UK, with preliminary findings that obese people and females see better outcomes on TZDs, while non-obese people and males have better outcomes on sulfonylureas. Indeed, when the GSK ADOPT trial was sub-analyzed, obese females displayed better and prolonged control using TZDs vs. sulfonylureas, while non-obese males showed the reverse (for about three years, after which the therapies appear equally effective). While there has been tremendous progress in the science of precision medicine in diabetes, people are still constantly misdiagnosed. This is in part because a lot of the monogenic forms are so rare that Dr. Hattersley believes some providers aren't considering them when evaluating patients, and in part because the medical education system has been teaching diabetes simply as type 1, type 2, and gestational for too long. Huge congratulations to Dr. Hattersley on winning the prestigious Prize for Excellence - precision medicine is an exciting but very early field at the moment, and we hope the reality eventually lives up to the hype.

Detailed Discussion and Commentary

Oral Presentations: GLP-1 RA: The Longer, the Better?

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 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 ³5% 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-NAÏVE 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.

Oral Presentations: SGLT-2 Inhibitor Trials

EFFICACY AND SAFETY OF ERTUGLIFLOZIN IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS INADEQUATELY CONTROLLED ON THE DUAL COMBINATION OF METFORMIN AND SITAGLIPTIN: THE VERTIS SITA2 TRIAL

Brett Lauring (Merck, Kenilworth, NJ)

Dr. Brett Lauring presented findings from the phase 3 VERTIS SITA2 trial demonstrating significant A1c reductions for Merck's SGLT-2 inhibitor candidate ertugliflozin as an add-on to DPP-4 inhibitor Januvia (sitagliptin) and metformin in patients with type 2 diabetes (n=463). A 5 mg dose of ertugliflozin lowered A1c by a mean 0.8% after 26 weeks, while a 15 mg dose lowered A1c by 0.9% (baseline A1c=8%, p=0.001 for both vs. placebo). For comparison, the placebo group experienced a substantially smaller 0.1% A1c reduction. The between-group difference in glucose-lowering was apparent at six weeks and increased through the end of the 26-week study period. Among patients treated with 5 mg ertugliflozin, 32% achieved A1c <7% vs. 17% in the placebo group (p<0.001 for both doses based on adjusted odds ratio). An even higher 40% of patients in the 15 mg ertugliflozin group achieved this A1c target (p<0.001). Ertugliflozin treatment added to sitagliptin and metformin also demonstrated a significant improvement on a number of additional secondary endpoints, namely (i) weight loss; (ii) reductions in fasting plasma glucose; and (iii) reductions in systolic blood pressure. Weight loss amounted to an average of 3.3 kg (~7.3 lbs) in the 5 mg arm (p<0.001) and 3 kg (~6.6 lbs) in the 15 mg arm (p<0.001), compared to 1.3 kg (~2.9 lbs) in the placebo arm. Fasting plasma glucose was 25 mg/dl lower after 26 weeks in the 5 mg ertugliflozin group and 31 mg/dl lower in the 15 mg group compared to placebo (p<0.001 for both). There was a 4 mmHg drop in systolic blood pressure, on average, for patients given a 5 mg dose of ertugliflozin vs. a 1 mmHg drop for patients on placebo (p=0.019). Patient taking the 15 mg dose experienced a mean 5 mmHg decline in systolic blood pressure (p=0.002).

- **Dr. Lauring noted that the higher dose trended better on most primary and secondary outcome measures.** The exception was weight loss which was similar for both doses.
- **Ertugliflozin was well-tolerated,** showing no increased risk of urinary tract infections (4, 7, and 3 subjects in the 5 mg, 15 mg, and placebo groups, respectively), symptomatic hypoglycemia (6, 1, and 4 subjects in the 5 mg, 15 mg, and placebo groups, respectively), or hypovolemia (1, 0, and 1 subjects in the 5 mg, 15 mg, and placebo groups, respectively). As expected, the incidence of genital mycotic infections was higher in both males and females and the differences from placebo were statistically significantly different (p<0.05) for the 5 mg dose for males and the 15 mg dose for females (6, 9, and 1 subjects in 5 mg, 15 mg and placebo for females and 4, 3, and 0 subjects in 5 mg,

15 mg and placebo for males). All four of these adverse events types were pre-specified for further analysis in VERTIS SITA2, according to Dr. Lauring, because of concerns related to SGLT-2 inhibitor agents more generally.

- **According to an announcement released as soon as Dr. Lauring's presentation began, Merck and partner Pfizer will submit NDAs for standalone ertugliflozin, ertugliflozin/sitagliptin and ertugliflozin/metformin by the end of 2016.** Further regulatory submissions in international markets are expected in 2017.
- **In an interview with Dr. Sam Engel (Merck, Kenilworth, NJ), Associate VP of clinical research in diabetes and endocrinology, we learned that Merck views ertugliflozin as part of a larger strategy of developing diabetes therapies that patients can use at any point during the course of their care.** In other words, the people who could benefit from ertugliflozin and its combinations would span a wide spectrum encompassing patients regardless of diabetes duration, whether newly-diagnosed as a first-line therapy or already a few decades into diabetes management in need of therapy intensification. On a similar theme, Dr. Lauring argued during Q&A following his presentation that bringing a fourth SGLT-2 inhibitor to market would benefit patients by expanding choice. Ertugliflozin would join Lilly/BI's Jardiance (empagliflozin), Janssen's Invokana (canagliflozin), and AZ's Farxiga (dapagliflozin). He added that he's particularly enthusiastic about the therapeutic potential for a SGLT-2 inhibitor/DPP-4 inhibitor combination product. Right now, the only SGLT-2 inhibitor/DPP-4 inhibitor fixed-dose combination available in the US is Lilly/BI's Glyxambi (empagliflozin/linagliptin), while AZ's Qtern (dapagliflozin/saxagliptin) was recently approved in Europe. We expect the very neutral cardiovascular safety results for the sitagliptin component of the ertugliflozin/sitagliptin combination will be reassuring for many providers, though we expect much of the buzz for SGLT-2 inhibitors will continue to center around the empagliflozin franchise, at least until further cardiovascular outcomes trials are able to confirm a cardiovascular class effect.

Symposium: New Paths to Tight Glycemic Control

CLINICAL PROFILING AS A KEY TO OPTIMAL DRUG SELECTION

John Wilding, MD (University of Liverpool, UK)

Dr. Wilding gave this session on combination therapy a reality check - it is extremely difficult for clinicians to know what drug to choose for a particular patient at a given point in time. The guidelines don't give enough tools to make precision estimates, do not consider recent outcome trials (they aren't updated frequently enough), and don't account for variability of response to treatment. As just one example, Dr. Wilding pointed out the remarkable spectrum of individual patient responses in a dapagliflozin trial: weight change ranged from -15 kg to +10 kg, while A1c changes ranged from -2% to +4%! He also showed a slide with 21 different factors to consider when choosing a drug (see below), an overwhelming task even for the best clinicians. Like Dr. Del Prato, Dr. Wilding seemed to lean towards greater use of SGLT-2s and GLP-1s, given the cardioprotective results (EMPA-REG, LEADER) and weight loss without hypoglycemia. We appreciated his insightful concluding series of questions, (see below) particularly the suggestion that we need more n=1 trials in diabetes - what is best for me based on my data? We think greater use of CGM in type 2 diabetes would help a lot here, particularly something as low-hassle as FreeStyle Libre Pro, which seems ideally designed as a companion diagnostic for prescribing type 2 diabetes drugs. Dr. Wilding noted that prospectively testing every combination and sequence of drugs would not be practical, but pharmacogenomics, other biomarkers (C-peptide), and big data may help HCPs make better treatment choices in the future. We hope digital tools from tech-pharma partnerships (IBM Watson/Novo Nordisk, Sanofi/Verily) can make serious progress on this front.

Key Questions

- **Low weight/accelerated progression**. Can we accurately identify those who will need insulin early?
- **Glucose lowering drugs in obese/overweight type 2 diabetes**. Should we prioritize weight losing/neutral medications early - is the evidence strong enough?
- **Variability in response**: How do we know which is the right drug for each patients (n of 1 trials)?
- **Optimal sequencing** of treatment: which drug 1st, 2nd, 3rd?
- **Complications**: at what point to modify targets? Can we extrapolate from cardiovascular outcomes studies to lower risk populations?

Factors to Consider When Selecting Appropriate Drugs for Type 2 Diabetes

Patient Characteristics	Co-morbidity	Healthcare System
Patient Preference	Renal Function	Affordability
Age	Blood Pressure	Formulary/Guidelines
Gender	CVD	Education/training
BMI	Liver Function	
Ethnicity	Pancreatitis	
Driving?	Osteoporosis	
Disease Duration	Cognitive Function	
Occupation/hobbies	Frailty	
Lives alone? Social support?	Cancer	

FROM THE START: COMBINATION THERAPY

Stefano Del Prato, MD (University of Pisa, Italy)

Dr. Stefano Del Prato framed his talk on early combination therapy with a compelling slide to show what is at stake - an estimated ~170 million people with diabetes globally with neuropathy, ~160 million with retinopathy, ~150 million with overt nephropathy, ~80 million with coronary heart disease, and ~25 million with stroke (based on prevalence estimates and the global population of patients). He gave many strong arguments in favor of early combination therapy: pathogenetic complexity of type 2, complementary treatment modes of action, balances efficacy and side effects, potentially more sustained efficacy (to reduce the risk of long-term complications), and better therapy individualization. Dr. Del Prato highlighted "extra-glycemic properties" too, in the wake of cardiovascular benefit from LEADER and EMPA-REG and kidney function benefits for empagliflozin (Wanner et al., NEJM *2016). He urged caution in applying the high-risk population results to newly diagnosed individuals, but was clear that "we have to start factoring these results in." His talk ran through many combination therapies, but was not prescriptive - in Q&A he recommended clinicians choose the right combination based on the patient in front of them. (Admittedly this is extremely difficult, and the curious clinician seemed a bit let down.) Dr. Del Prato concluded that the field needs to change the type 2 diabetes treatment paradigm to start treating patients much earlier - no argument there.*

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