CLOSER LOOK

FDA Advisory Committee Meeting for Novo Nordisk's Semaglutide

October 18, 2017; Silver Spring, MD; Full Report - Draft

Executive Highlights

An FDA Advisory Committee just cast 16 votes in favor of approval for Novo Nordisk's once-weekly GLP-1 agonist semaglutide this afternoon in Silver Spring! There was one member of the committee who abstained from voting, leading to a final tally of 16-0 from the 17-person panel. Though advisors unanimously voiced concerns regarding the retinopathy signal in SUSTAIN 6 (HR=1.76, 95% CI: 1.11-2.78), there was consensus that this risk should be addressed through a warning on the product label. All 17 voting members (endocrinologists, cardiologists, ophthalmologists, statisticians, and patient/consumer representatives) agreed that the benefits to semaglutide therapy far outweigh the possible risks - or rather, the possible risk, singular. Retinopathy-aside, panelists endorsed semaglutide's strong safety profile, comparable to that of existing GLP-1 agonists and the greater ease of use of this compound. Ultimately, this was a nerve-wracking, but very exciting day for the diabetes field. Patients and providers could soon achieve better glucose-lowering and weight loss (all without hypoglycemia) with a new, potent GLP-1 agonist available in US pharmacies. Novo Nordisk submitted a New Drug Application (NDA) for semaglutide in December 2016, and an FDA decision is expected by year-end. We can't say with certainty what this decision will be, and we wouldn't dare jinx it, but Advisory Committees have historically been very influential. The company issued a press release announcing today's positive vote once it was finalized around ~5 pm Eastern time.

On this page, you'll find four themes exploring the vote of confidence in semaglutide. It was a packed day of discussion and debate, covering retinopathy as well as glycemic and weight loss efficacy, CV safety (with a strong hint toward cardioprotection), adherence, and outcomes beyond A1c - these latter two points were highlighted during the Open Public Hearing portion of the afternoon in particular, which we also summarize below - three members of our team, including Payal Marathe, Abigail Dove, and Ann Carracher. Lastly, we end this report with a description of each voting member's rationale for supporting semaglutide approval, or in the case of Dr. Yves Rosenberg, for abstaining.

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Top Four Highlights

1. RETINOPATHY DOMINATES ALL DAY: ADVISORY COMMITTEE ADVOCATES FOR SEMAGLUTIDE APPROVAL WITH CLEAR DESCRIPTION OF RISK ON THE LABEL

A day's worth of back-and-forth on semaglutide/retinopathy risk culminated in a clear consensus: While we shouldn't ignore the signal in SUSTAIN 6, it isn't sufficient to block drug approval, but rather, warrants precautionary language on the product label. In justifying their votes, each and every panelist endorsed this view, and we certainly expect to see a warning of some sort on semaglutide's label based on current empirical knowledge. The committee wasn't entirely convinced of Novo Nordisk's alternative explanations for retinopathy risk (high baseline A1c, rapid A1c decline, pre-existing retinopathy, and "early worsening phenomenon" rather than a safety concern inherent to the semaglutide molecule), but still underscored a favorable risk/benefit profile for this advanced agent. Even ophthalmologist Dr. Frederick Ferris (National Eye Institute, Bethesda, MD), who took greatest issue with the methods of data collection for retinopathy in SUSTAIN 6 ("I'm confused and appalled") voted favorably, arguing "I wouldn't take these retinopathy findings to mean that this drug shouldn't be put on the market." We firmly agree with the committee's position, and we'll be curious to see what language appears on the semaglutide product label in reference to retinopathy - especially since for many patients, the drug may ultimately help prevent retinopathy and other complications (this would be a decade long trial and there is zero evidence to prove this now - it's just our hunch for this and all GLP-1s). Novo Nordisk's proposal for risk minimization includes background to inform proper patient selection. High baseline A1c, rapid/steep A1c reductions, and pre-existing retinopathy are all known risk factors for new-onset or worsening retinopathy, and patients/HCPs should be made aware. As a reminder (and in fact we had forgotten this), insulin products actually already feature a cautionary statement along these lines under "adverse reactions": "Intensification or rapid improvement in glucose control has been associated with transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy." We imagine this sets a solid precedent for approval of an agent with very potent glucose-lowering properties, and it could also serve as a template for the semaglutide product label. It's interesting that we absolutely never hear about this as a risk factor.

- **Independent commentator Dr. Emily Chew (NIH, Bethesda, MD) set the stage for this retinopathy discussion by reviewing "early worsening phenomenon."** She wasn't at all surprised to see an uptick in retinopathy with semaglutide treatment, given the profound A1c-lowering that occurs with this advanced therapy. Prior research has established how steep A1c reductions (both large and fast, which are more likely to occur from a high baseline A1c) can spur greater retinopathy events short-term. In the DCCT, many old-timers like Kelly will remember that patients randomized to intensive control vs. conventional care experienced a transient increase in retinopathy during the first two years of the study. Long-term, intensive care was correlated with as much as 76% reduction in retinopathy in the DCCT, and indeed tight glycemic control is still recommended practice to prevent microvascular complications, including eye disease. Dr. Chew outlined similar findings from the UKPDS - a transient increase in retinopathy with aggressive therapy, but a meaningful benefit over 12 years in terms of microvascular risk reduction. "Early worsening is very familiar to all of us in diabetic retinopathy research," she claimed, "and the legacy effect of intensive glycemic control has a huge impact that far outweighs transient retinopathy." This was a powerful message that reappeared throughout the day. Harvard's Dr. Lloyd Paul Aiello rehashed the DCCT data pointing to early worsening phenomenon, emphasizing that the later divergence of curves is much, much wider than the initial difference in absolute risk with intensive glycemic control. This also speaks to an overarching theme of this Advisory Committee meeting, in that semaglutide's benefits to glucose control should be more important to FDA at this stage than its possible relationship to retinopathy since the latter is a manageable risk.
- **Dr. Stephen Gough, Senior Principal Clinical Scientist at Novo Nordisk, presented a post-hoc analysis of SUSTAIN 6 looking at magnitude of A1c-lowering after 16 weeks:**

Participants with A1c drop >1.5% at week 16 experienced the highest frequency of retinopathy events, and Dr. Gough reminded the Advisory Committee that 236 patients on semaglutide achieved this level of A1c decline vs. only 76 patients on placebo. He concluded that the signal in SUSTAIN 6 is thus "consistent with glycemia-related early worsening phenomenon." Diabetes thought leaders have acknowledged that A1c-lowering in SUSTAIN 6 was greater than what is seen in most CVOTs due to semaglutide being a very potent anti-hyperglycemic compound. This aligns with Dr. Gough's commentary, and given what we know about insulin initiation leading to temporary spikes in retinopathy, it follows logically that a powerful glucose-lowering drug like semaglutide would also be associated with this transient phenomenon.

- **Members of the Advisory Committee were hesitant to fully accept this hypothesis around glucose control as a mediator for retinopathy risk. Dr. Erica Brittain (NIH, Bethesda, MD) characterized it as "plausible, but far from convincing at this point."** Several panelists emphasized that the SUSTAIN 6 retinopathy findings cannot be ruled-out as early worsening phenomenon without longer-term data on semaglutide. The DCCT and UKPDS continued well past two years. The good news on this front is that Novo Nordisk is already planning to conduct a larger, post-marketing CVOT for semaglutide with longer study duration - retinopathy data from this post-approval trial could answer the committee's concerns. Dr. Cecilia Low Wang (University of Colorado, Aurora, CO) called attention to the fact that the analysis of A1c decline at week 16 was post-hoc rather than pre-specified, which makes it interesting and hypothesis-generating but not conclusive. Dr. Daniel Budnitz (CDC, Atlanta, GA) captured the panel's overall sentiment: "Glucose control is certainly a mediator, but is it the only mediator? We just don't know yet." Notably, the FDA presented its own analysis of how glycemic control may have confounded the SUSTAIN 6 results. After adjusting for A1c-lowering in the first 16 weeks, the agency found a muted, non-significant risk for diabetic retinopathy associated with semaglutide (HR=1.22, 95% CI: 0.71-2.90, which crosses the line of unity). The most likely explanation at this point, according to FDA's Dr. Andreea Lungu, is that there was a direct effect of semaglutide on retinopathy risk alongside an indirect mediating effect of dramatic blood sugar reductions.
- **Pre-existing retinopathy is another established risk factor for subsequent eye complications, and Novo Nordisk's presentation highlighted how the SUSTAIN 6 safety finding was driven by individuals with baseline retinopathy.** Of 79 adjudicated retinopathy events (50 in the semaglutide group, 29 in the placebo group), 84% occurred in patients with retinopathy at study start, and 29% occurred in patients with proliferative retinopathy at baseline. Pre-existing diabetic retinopathy led to a higher incidence of the composite endpoint (retinal photocoagulation, vitreous hemorrhage, treatment with intravitreal agents, or diabetes-related blindness) across both treatment arms. Voting panelist Dr. Melissa Li-Ng (Cleveland Clinic, OH) pointed out that "not everyone gets diabetic retinopathy," and that among those patients who do experienced this complication, "sometimes it seems to get worse no matter what you do." In her view, treating retinopathy in the real world requires broad familiarity among HCPs with risk factors (such as pre-existing eye disease), but this isn't a public health problem that's going to be exacerbated or solved by semaglutide. Novo Nordisk briefly mentioned two other relevant risk factors: (i) the baseline A1c of SUSTAIN 6 participants experiencing retinopathy was high, at 9.4% (vs. 8.7% for the overall study population), which could have spurred faster, steeper A1c decline, and (ii) concomitant insulin use was more common among individuals experiencing retinopathy (76% vs. 58% for the overall study population) which suggests an even more aggressive glucose-lowering regimen.
- **Many presenters pointed to the therapies available to effectively treat diabetic retinopathy, which seemed to tip any undecided voters over the edge, toward semaglutide approval.** As Dr. Chew put it, "treatments are highly-effective these days - to have vision loss would requires tens of thousands of patients." The two ophthalmologists on the Advisory Committee, Dr. Ferris and Dr. Luciano Del Priore (Yale University, New Haven, CT), also highlighted the well-established practice guidelines for retinopathy screening (more frequent with a

background of eye disease). These remarks generated a sense of confidence in the room that retinopathy risk is manageable. Even if all of Novo Nordisk's detailed hypotheses are unfounded and there's no mediating effect of rapid A1c decline or pre-existing retinopathy (which is extremely unlikely - we find the evidence to be quite compelling), semaglutide could still help many people with diabetes reach A1c and body weight goals, because patients/providers are equipped with clear guidelines on monitoring the eyes and with retinopathy treatments if necessary. During this discussion, we were reminded of CANVAS results and the nearly two-fold risk increase for lower limb amputations associated with J&J's SGLT-2 inhibitor canagliflozin (Invokana). There are key differences between this SGLT-2 CVOT and SUSTAIN 6, but perhaps the most important is that the diabetes field is more advanced in retinopathy guidelines and treatment options. After all, there's no "reversing" an amputation, and while we'd love to see diabetes care providers monitoring the feet more regularly and intervening at the sight of infection, peripheral vascular disease, or an ulcer, our sense is that there's less understanding currently of best practice in foot care vs. eye care. It is our impression (no data) that plenty of patients do not get their eyes regularly checked and that doing so would help enormously.

- **Importantly, FDA consulted separately with a group of ophthalmologists on semaglutide/retinopathy as well, and this cohort found no reason to restrict patient population or dose titration at all.** The group consulted saw certain problems with data collection in SUSTAIN 6, namely that dilation was not required and that eye exams could be performed by a trial investigator or by a local optometrist; more standardized protocol would have been preferred and this points yet again at many issues that are not yet standardized in outcomes trials. Retinopathy was scored differently in this CVOT than it typically is in the real world, using categories of "normal," "abnormal," and "abnormal/clinically-significant," and the composite endpoint looked at advanced eye disease (vitreous hemorrhage, diabetes-related blindness) closer to the symptomatic, intervention stage (photocoagulation, intravitreal agents) instead of at step-wise progression on the ETDRS scale (Early Treatment Diabetic Retinopathy Study) like in the DCCT. These protocol issues led to Dr. Ferris' "confused and appalled reaction." In the end, however, committee members felt that this possibility for statistical noise had no substantive bearing on the data or their impression of the data. That said, again, we believe there could be considerably more focus on standardization.

2. FDA'S PREFERRED ANALYSIS STILL SIGNIFICANTLY FAVORS SEMAGLUTIDE ON A1C AND WEIGHT LOSS EFFICACY

Dr. Andreea Lungu presented the FDA's preferred statistical analysis of the SUSTAIN 1-5 pivotal program, reporting slightly smaller but still highly significant improvements in A1c and body weight with semaglutide vs. comparators. If we needed any more convincing that this GLP-1 agonist candidate is highly efficacious on key diabetes parameters, this was it. Novo Nordisk's full analysis encompassed all randomized participants who received at least one dose of study drug, and used Mixed Model Repeated Measures (MMRM) testing, but the FDA's preferred analysis involves multiple imputation of missing data based on retrieved dropouts followed by an ANOVA model. Using this preferred method, the FDA calculated A1c treatment differences for the 0.5 mg and 1.0 mg doses of semaglutide as 1.2% and 1.4% in SUSTAIN 1 (vs. placebo), 0.6% and 0.8% in SUSTAIN 2 (vs. sitagliptin), 0.5% in SUSTAIN 3 (only 1.0 mg dose; vs. exenatide extended-release), 0.3% and 0.6% in SUSTAIN 4 (vs. insulin glargine), and 1.1% and 1.6% in SUSTAIN 5 (vs. placebo). Further, the FDA calculated weight loss treatment differences for the 0.5 mg and 1.0 mg doses of semaglutide as 5.8 lbs and 7.8 lbs (SUSTAIN 1), 5.5 lbs and 8.4 lbs (SUSTAIN 2), 6.3 lbs (1.0 mg only, SUSTAIN 3), 9.0 lbs and 12.3 lbs (SUSTAIN 4), and 4.9 lbs and 10.4 lbs (SUSTAIN 5). As with the sponsor's analyses, the FDA-calculated 95% CI for every single A1c and weight loss change indicated significant benefit favoring semaglutide. Moreover, even though the margin of treatment difference was generally smaller with the FDA analysis vs. the original Novo Nordisk analysis, it was only slightly so and still supported incredible efficacy (i.e. in SUSTAIN 1, Novo Nordisk reported A1c treatment differences of 1.5% and 1.6% for 0.5 mg and 1.0 mg semaglutide, respectively). We also heard several mentions throughout the day of head-to-head data comparing semaglutide to an existing diabetes therapy, and in particular, to an

existing GLP-1 agonist (AZ's Bydureon in SUSTAIN 3, Lilly's Trulicity in SUSTAIN 7). These remarks further reinforced semaglutide's glycemic and weight loss efficacy. The emphasis on head-to-head studies eventually emerged as a sign of semaglutide's potential to be a significant stride forward in diabetes care, beyond what patients are currently able to achieve with existing treatment options.

3. COMMITTEE AGREES ON STRONG SAFETY PROFILE FOR SEMAGLUTIDE, RETINOPATHY-ASIDE

In addition to efficacy, panelists also agreed on semaglutide's strong safety profile (notwithstanding the retinopathy discussion). There was no dispute during discussion question no. 4 that SUSTAIN 6 convincingly established CV safety for semaglutide, and a few voting members hinted at possible cardioprotection, though in the words of Dr. William Hiatt (University of Colorado, Aurora, CO): "This was clearly a safety study, not an efficacy study, which hasn't been discussed here, and I think that's appropriate." He was alluding to the fact that Novo Nordisk does not expect a CV indication based on SUSTAIN 6 data. The company is planning on a larger, post-market CVOT of semaglutide, and many panelists (Dr. Susan Yanovski, Dr. Brendan Everett, and others) seemed optimistic that this will yield positive results. Beyond CV safety, voting members agreed that semaglutide's safety profile is consistent with its class of GLP-1 agonists. Dr. Cecilia Low Wang (University of Colorado, Aurora, CO) advised that cancer risk be monitored for this drug class, mostly because it's still relatively new. She pointed to a slight imbalance in breast cancer trending against semaglutide - in the phase 3a pool of studies, five cases of breast cancer were observed in semaglutide-treated patients vs. three in comparator arms, but we are keeping in mind that these event rates were very low. A large registry to investigate medullary thyroid carcinomas (MTCs) with GLP-1 agonists is ongoing - this was a major theme at the Victoza Advisory Committee (to discuss a CV indication) in June, though panelists were unconvinced that this is a substantial safety concern in humans, as all evidence thus far has been collected from animal models. Lastly, we were glad to hear the GLP-1/pancreatitis issue put to bed during today's FDA meeting (despite elevation in amylase and lipase with semaglutide treatment, there was no correlation to pancreatitis).

4. OPEN PUBLIC HEARING SPEAKERS EMPHASIZE ADHERENCE, WEIGHT LOSS, OUTCOMES BEYOND A1C

Thirteen clinicians, patients, and advocates spoke during today's Open Public Hearing, twelve in favor of semaglutide's approval. Representing AACE, Dr. Lawrence Blonde opened the session by highlighting the need for effective anti-hyperglycemic agents that do not increase risk of hypoglycemia. Dr. Tamara Darsow represented the ADA, noting the need for drugs that can help manage weight and CV risk. Multiple providers with experience in clinical trials of semaglutide spoke to the unique level of success, treatment satisfaction, and feelings of agency/control that Novo Nordisk's candidate gave to participating patients. We also heard commentary on the benefits of once-weekly dosing for adherence (a key consideration), and the esteemed Dr. Robert Ratner, former Chief Scientific Officer at the ADA, described the need for a broad spectrum of treatment options to enable personalized care. Boy was this eloquent! Three patients who had taken semaglutide in clinical trials shared their experiences, citing weight loss of 30-60 lbs and A1c-lowering from 8.1% to 5.4%, 7.7% to 6.5%, and 7.5% to 5.7%. Wow! None of these patients has found a drug as efficacious as semaglutide (including Novo Nordisk's liraglutide, branded Victoza and dosed once-daily) since going off semaglutide. One patient in particular, Mr. Dennis Murphy, is currently taking Trulicity (Lilly's dulaglutide), Actos (Takeda's TZD pioglitazone), glimepiride, Januvia (Merck's DPP-4 sitagliptin), and Invokana (J&J's SGLT-2 canagliflozin) to hit an A1c of 6.5% - admittedly, an impressive number - but he reached 5.7% on semaglutide alone. Virginia Valentine gave an eloquent nurse practitioner view as well as a patient view, as someone who has extensive experience with the GLP-1 class and what patients and providers still need. Three of our associates, Payal Marathe, Abigail Dove, and Ann Carracher, offered remarks highlighting positive thought leader opinions on semaglutide, data indicating that semaglutide provides what patients want in a diabetes drug, and how semaglutide approval could improve patient access to and provider awareness of GLP-1 agonists. The only critical comments of the OPH focused on the need for more subgroup analyses exploring safety and efficacy in racial minorities, women, and those over 65 years-old. Full details on each speaker's comments are below. We have also made public full transcripts of the speeches from Ms. Marathe, Ms. Dove, and Ms. Carracher.

Open Public Hearing Summaries

- **Dr. Lawrence Blonde (Oschner Medical Center, New Orleans, LA):** The highly-regarded Dr. Lawrence Blonde spoke on behalf of AACE, which doesn't advocate for the approval of any specific medication, but is greatly concerned with the unmet need in diabetes care for therapies that address hyperglycemia without increasing hypoglycemia or body weight. Throughout Dr. Blonde's remarks, it became clear that semaglutide fits this niche perfectly. We appreciated the shoutout to the "outcomes beyond A1c" movement right off the bat (this continued throughout OPH, indicating that what really matters to real-world patients and HCPs is factors like hypoglycemia, time-in-range, weight, etc.). To help committee members grasp the scale of the US obesity epidemic, Dr. Blonde cited the most recent NHANES data from 2015-2016: 40% of adults and 19% of youth have obesity, up from 37% and 17% just two years ago. This is a clear public health problem, he argued, and semaglutide's weight loss effects should not be under-valued.
- **Ms. Virginia Valentine (La Clinica Esperanza, Albuquerque, NM):** Ms. Virginia Valentine described once-weekly dosing as a very meaningful improvement in GLP-1 agonist therapy. In her experience, she finds that patients consistently prefer once-weekly doses to once-daily doses - lower injection burden is a piece of this, but it also decreases the daily burden of diabetes, reminding the individual less often of his/her chronic disease. Ms. Valentine underscored her belief that retinopathy risk will be manageable in the real world (she subscribes to the early worsening phenomenon, supported by the DCCT). Overall, she gave a resounding endorsement of semaglutide as a new addition to the diabetes toolkit, and it was fascinating to hear her perspective on what will make her patients happier and healthier (truly enhancing their quality of life).
- **Dr. Vanita Aroda (MedStar Health Research Institute, Hyattsville, MD):** Dr. Vanita Aroda, a principal investigator on three semaglutide clinical trials, characterized this drug as a tool that providers can use to help frustrated patients regain a sense of control and overcome feelings of guilt/inadequacy. We loved her candor! As a practicing endocrinologist, Dr. Aroda has 15 years of experience treating diabetes, and the most frequent concerns she encounters are (i) that patients are taking their medications but still have high blood glucose; and (ii) that they cannot seem to lose the weight they want to get rid of. Both concerns carry a strong sense of guilt. One patient in particular - engaged enough to bring in her diary, medications, and meter - was told by her well-intentioned physician to just "try harder." With semaglutide, Dr. Aroda has witnessed a requisite tool that can help patients achieve glycemic control and battle excess weight, even when they have tried and failed with other agents. As a sidenote, we have heard that Dr. Aroda is moving to Boston - all Boston clinics should move as quickly as possible to attract her to their work. She is one of the major young shining lights in the field - an expert researcher as well as an incredibly highly valued patient advocate.
- **Mr. Christopher Wayne-Brown (Selma, NC):** Mr. Christopher Wayne-Brown was the first patient representative to speak during OPH. His story was powerful, to say the least. Mr. Wayne-Brown lost 30 lbs in a semaglutide clinical trial, and his A1c declined from 8.1% at baseline to 5.4% by end of study. Afterward, he continued with daily Victoza (liraglutide) injections, but regained 15 lbs while his A1c "rose slowly to a barely acceptable number." These numbers speak for themselves, and Mr. Wayne-Brown established how excited he would be if his doctor could prescribe semaglutide, for him and for others living with diabetes. Notably, on adherence, he commented that once-weekly injections were definitely more convenient compared to his once-daily doses of Victoza.
- **Mr. James Thomas Conner (Irving, TX):** Mr. James Conner recalled the frustration of switching back-and-forth between metformin and pioglitazone since his diabetes diagnosis in 2001, and the difficulty of maintaining his A1c goals in the midst of long, stressful hours at work (a challenge, he pointed out, that only increases with age). Semaglutide put a temporary stop to this: Mr. Connor optimistically noted that during his approximately nine-month enrollment in the semaglutide arm of one of the SUSTAIN studies, his A1c fell from 7.7% to 6.5%, and he lost a remarkable 40 pounds. He was so pleased with this brief experience with semaglutide (and so

disappointed that he can no longer take the drug now that the trial has ended) that he has enrolled in another study in hopes of again being randomized to the treatment arm and reaping the benefits of what he characterized as this extremely effective agent.

- **Dr. Helena Rodbard (Endocrine and Metabolic Consultants, Rockville, MD):** Dr. Helena Rodbard called semaglutide the most effective medicine she's ever seen. Over the course of her career, Dr. Rodbard has been involved in >90 clinical trials and has enrolled 24 patients in studies of semaglutide. She expressed that she was "tremendously impressed" by the efficacy and safety of the once-weekly GLP-1 agonist, on A1c-lowering but also lack of hypoglycemia, improvements in systolic blood pressure, and clinically-meaningful weight loss. Dr. Rodbard was gratified to hear how much better patients felt on semaglutide, and she shared that *every* patient asked if it was possible to continue on the drug when their clinical trial enrollment ended, as they preferred it to their previous medication. In Dr. Rodbard's words, "semaglutide represents a major advancement in the treatment of people with type 2 diabetes, and I hope it will soon be approved for use in the US and become available to patients."
- **Dr. Robert Ratner (Georgetown University, Washington, DC):** Personalized medicine was the core theme of Dr. Robert Ratner's OPH remarks, and he positioned semaglutide as an important addition to the diabetes toolkit so that patients/providers can have better conversations and decide (through shared decision-making) on the best therapy for the individual. His thoughts on the retinopathy signal were similar in tone: "Put the numbers in the package insert, let us know what we can talk about in terms of safety and efficacy." He added that semaglutide could be particularly advantageous in patients with diabetes and comorbid renal disease, since SGLT-2 inhibitors have to-date been "problematic" in this subpopulation.
- **Mr. Dennis Murphy (UT Southwestern, Dallas, TX):** Mr. Dennis Murphy spoke as another patient voice during OPH, sharing another moving personal story. Mr. Murphy is currently taking Trulicity (Lilly's dulaglutide), Actos (Takeda's TZD pioglitazone), glimepiride, Januvia (Merck's DPP-4 sitagliptin), and Invokana (J&J's SGLT-2 canagliflozin) to hit an A1c of 6.5% - admittedly, an impressive number - but he reached 5.7% on semaglutide alone. He urged the Advisory Committee to vote in favor of semaglutide approval, because it offers a level of glycemic control unattainable with what's currently out there.
- **Dr. Megan Polanin (National Center for Health Research, Washington, DC):** In the only critical remarks of OPH, Dr. Megan Polanin urged the committee to ask the sponsor to reanalyze data for all demographic groups, to conduct more studies in underrepresented populations, and to extend follow-up periods to determine safety. Dr. Polanin enumerated several concerns related to semaglutide's efficacy and safety in minority populations, women, and the elderly - she felt these groups were inadequately assessed in the semaglutide pivotal program. She noted that in SUSTAIN 1, semaglutide was less effective in people of non-white race. However, we suggest in response that this discrepancy could be attributed to issues of adherence, which most likely stem from social/environmental causes rather than from the molecule itself. While we agree that racial minorities are often underrepresented in clinical trials across the board, particularly when one considers the prevalence of diabetes in minority populations, there's no scientific reason to suspect that safety and efficacy data will not generalize for semaglutide. As Dr. Hiatt pointed out, there are no subgroup interactions for gender, nationality, age, or race in the forest plots of MACE events.
- **Ms. Ann Carracher (Close Concerns, San Francisco, CA):** Our very own Ms. Ann Carracher took the podium on behalf of The diaTribe Foundation where she is a volunteer. She described a need to increase awareness of the GLP-1 agonist class among real-world patients - these are some of the most advanced treatments on the market, and yet only a small proportion of patients are on them and only a small proportion of page views on diaTribe.org (0.5%) go to resources focused on GLP-1 agents. She advocated strongly for semaglutide's approval, alluding to impressive head-to-head data from SUSTAIN 7 (vs. Lilly's once-weekly GLP-1 agonist dulaglutide). Click here for her full remarks.

- **Ms. Abigail Dove (Close Concerns, San Francisco, CA):** Ms. Abigail Dove, an associate on the therapy team at Close Concerns, represented dQ&A during OPH. She pulled insights from a survey of 10,000 people with diabetes, highlighting what patients care about most - time-in-range (or put another way, less hypoglycemia), weight loss, and a once-weekly dosing regimen. All of these qualities apply to semaglutide, and Abigail thus advocated for approval on the basis of filling gaps in diabetes care (for example, <17% of people with type 2 diabetes in the dQ&A survey felt that their current medication regimen was "very successful" at "reaching, or keeping to, a healthy weight"). Click here for her full remarks.
- **Ms. Payal Marathe (Close Concerns, San Francisco, CA):** Our own Ms. Payal Marathe summarized dominant opinion from diabetes thought leaders on semaglutide: exceptionally positive. She emphasized the agent's glycemic efficacy, profound weight loss benefits, and potential for greater adherence due to a lower injection burden. Last year, IMS Health attributed $4 billion in US healthcare system costs to poor adherence in diabetes. Payal also highlighted semaglutide's glucose-dependent mechanism, which confers lower hypoglycemia risk. Click here for her full remarks.
- **Dr. Tamara Darsow (ADA, Arlington, VA):** Dr. Tamara Darsow represented the ADA, noting the need for drugs that can help manage weight and CV risk. Both of these outcomes beyond A1c are incorporated into the ADA's 2017 Standards of Care, she explained, and it's important for therapy to keep up with these shifting demands of patient care. Notably, Dr. Darsow spoke during OPH at the Victoza Advisory Committee meeting as well, outlining the unmet need in addressing residual CV risk in people with diabetes. Though a CV indication was not on the table today, we sensed a positive outlook from Dr. Darsow that semaglutide may eventually join the ranks of liraglutide and empagliflozin as cardioprotective diabetes drugs.

Commentary from Voting Members

YES

- **Dr. Michael Blaha (John Hopkins University, Baltimore, MD) highlighted the weight loss results on semaglutide as extremely clinically-important.** He suggested that weight loss may be driving some of the glycemic benefits in SUSTAIN studies. He did express interest in further investigation of the mechanism causing retinopathy in SUSTAIN 6, and also pointed to a potential CV benefit from this trial.
- **Dr. Daniel Budnitz (CDC, Atlanta, GA) voted yes, and expressed a desire for information to be provided as "number needed to treat" and "number needed to harm" with respect to retinopathy on the semaglutide product label.** He hopes a long-term CVOT will include a study of retinopathy, after which labeling could potentially be reversed.
- **Harvard's Dr. Brendan Everett voted yes, and stated that it's a shame CV benefit was not formally evaluated in SUSTAIN 6.** Dr. Everett explained his view that the retinopathy signal is real despite inconsistent ascertainment, and like Dr. Budnitz, he sees an opportunity to nest a small, focused retinopathy study within a larger CVOT.
- **Dr. Cecilia Low Wang (University of Colorado, Aurora, CO) found the 1.76 hazard ratio for retinopathy particularly high and suggested a trial pitting semaglutide against an active comparator giving similar A1c reductions,** but still found the efficacy and safety data compelling enough to vote yes.
- **Dr. James Neaton (University of Minnesota, Minneapolis, MN) was impressed with 99% follow up in a CVOT, but was unimpressed with the way retinopathy data was collected.** He suggested the FDA should study the issue further. We agree and wish we could see more standardization in these trials.

- **Dr. Thomas Weber (Duke University, Durham, NC) was compelled by the sustained glycemic and weight loss improvements,** but admitted concern over incomplete patient adherence to eye monitoring follow up.
- **Chairperson Dr. Peter Wilson (Emory University, Atlanta, GA) voted yes, suggesting a registry of those similar to the SUSTAIN 6 population and with background retinopathy on several classes of drugs, as well as a new CVOT of people with mild retinopathy to follow long-term progression.**
- **Obesity specialist Dr. Susan Yanovski (NIDDK, Bethesda, MD) thought the proportion of patients achieving clinically-meaningful weight loss was impressive and found the retinopathy risk manageable.** She also noted a suggestion of CV benefit.
- **Statistician Dr. Erica Brittain (NIH, Bethesda, MD) voted an "uncomfortable" yes, worried that we'll never know if there's a benefit on retinopathy longer-term.** She trusted the ophthalmologists around the table that retinopathy risk could be managed.
- **Ophthalmologist Dr. Frederick Ferris (National Eye Institute, Bethesda, MD) voted yes, as the primary outcome was clearly met and adverse events were mostly expected and not worrisome.** He noted that it would be prudent for anyone suddenly improving their blood glucose to get regular eye exams, thought it wise to indicate such on the label, and would like to see an analysis excluding those with proliferative retinopathy.
- **Cleveland Clinic's Dr. Melissa Li-Ng felt that risks of worsening retinopathy were manageable and was convinced by A1c, weight, and blood pressure data.** For her, the once-yearly screening for retinopathy recommended by the ADA, increased depending on severity, is sufficient. We would love to know in the "real world" how often this happens - this is addressable.
- **Dr. Paul Palevsky (University of Pittsburg, PA) voted yes, emphasizing that the benefit seen with semaglutide outweighs the modest concern over retinopathy.** He proposed a label addition advising monitoring for retinopathy, and a longer study with documented retinal exams.
- **Consumer representative Ms. Suzanne Robotti (New York, NY) voted yes despite feeling that side-effects and adverse events will cause many to stop using the drug.** She also expressed concern over a lack of diversity in trial participants and subgroup analyses.
- **Ophthalmologist Dr. Luciano Del Priore (Yale University, New Haven, CT) found the risk:benefit ratio of semaglutide extremely favorable, and was compelled by the retinopathy explanation offered by the DCCT.** His main concern is that patients will be treated but not carefully screened for retinopathy. As noted, this is addressable.
- **Expert cardiologist Dr. William Hiatt (University of Colorado, Aurora, CO) was convinced by the strong impact semaglutide has on A1c, but thinks a properly powered CVOT with a representative sample should be carried out.** While he thinks the retinopathy concern is likely real, it should be handled as a labeling issue and does not demand further study, in his view.
- **Patient representative Mr. Richard Lumley can't wait to tell his doctor that he voted on this panel and, while he doesn't find vomiting and diarrhea very exciting, is convinced by the A1c-lowering, weight, and blood pressure benefits.** Notably, he also touted the once-weekly dosing of semaglutide.

ABSTAIN

- **The only non-yes vote came from the abstention of Dr. Yves Rosenberg (National Heart, Lung, and Blood Institute, Bethesda, MD), who thought there was ample reason to approve semaglutide but wanted to make a point that further studies should be performed.** He noted a "tremendous loss of opportunity" is not designing SUSTAIN 6 with a longer follow-up, and encouraged the creation of a retinopathy registry for the GLP-1 agonist class.

We believe it would be so easy to make at least "check ins" more common after these studies conclude and would like to see far more of this.

Interview with Dr. Todd Hobbs

- **In a separate call with our team, Novo Nordisk's Chief Medical Officer Dr. Todd Hobbs shared that he was very satisfied with the outcome of the meeting, not only the 16-0 vote, but the appreciation for semaglutide's favorable risk/benefit profile.** "We're happy that it wasn't 100% focused on retinal concerns," he stated, pointing to the "robust discussion" of glucose-lowering and weight benefits. In fact, Dr. Hobbs was pleasantly surprised that the Advisory Committee's conversation veered toward weight loss several times throughout the day, though it's easy to see how the impressive body weight results in SUSTAIN 1-6 would elicit positive reactions. During Dr. Anders Hvelplund's (Senior Director, Medical and Science, Novo Nordisk) presentation on the design of semaglutide, he explained that this compound was developed with weight loss in mind, and it's thus fitting that the potent GLP-1 agonist has applications in obesity as well (phase 3 obesity studies are slated to begin in the first half of 2018). The agent's combined glycemic and weight loss efficacy certainly contribute to a strong risk/benefit profile, and Dr. Hobbs also mentioned that clinical data on semaglutide was overall "solid from a safety standpoint."
- **In addressing the retinopathy concerns, Dr. Hobbs reminded us that SUSTAIN 6 was not designed to look rigorously at eye outcomes** (it was a CV trial, after all, with all microvascular effects as secondary endpoints). He acknowledged that spontaneous adverse event recording is probably not the optimal way to collect data on retinopathy complications, and explained that were the company to initiate another trial to further evaluate this microvascular risk, "yes, we would do it differently." Before planning any additional studies, Novo Nordisk will discuss with FDA to gauge level of concern. We are eager to see a larger, post-market CVOT for semaglutide aimed at demonstrating superiority, and as many Advisory Committee members stipulated, this could be a great opportunity to look closely at retinopathy over an extended duration. Dr. Hobbs underscored how cardiology experts on the panel seemed quite optimistic about semaglutide's potential to show CV efficacy - this was "encouraging" to hear, though the primary goal for Novo Nordisk right now is to get semaglutide approved by December, he articulated.
- **Dr. Hobbs drew our attention to an important benefit of once-weekly dosing - not only does this schedule improve adherence prospects (as was noted during OPH), but it makes the initiation process easier.** For injection-naïve patients in particular, he pointed out that starting a once-weekly regimen is a much more attractive offering vs. once-daily. Semaglutide's low injection burden could thus expand volume for the GLP-1 agonist class, and Dr. Hobbs emphasized that there's so much room for this class to grow - a very small proportion of the type 2 diabetes population is on GLP-1 therapy, and <50% of the HCPs Novo Nordisk engages with write GLP-1 agonist prescriptions. "One of our goals is for primary care physicians to be comfortable prescribing this," he added, and we definitely see how once-weekly injections would promote this. When we asked about adherence specifically, Dr. Hobbs suggested that real-world evidence will confirm semaglutide as a more patient-friendly GLP-1 agonist in this regard. Once-weekly dosing has a significant upside, but so does sustained glycemic and weight loss efficacy, which will encourage patients to stay on treatment as they continue to do well and feel successful.

-- by Ann Carracher, Payal Marathe, Abigail Dove, and Kelly Close