Closer Look

MEMORANDUM

FDA advisory panel votes 10-5 in favor of approving J&J's SGLT-2 inhibitor Invokana (canagliflozin) - January 11, 2013

Executive Highlights

- After considering data on renal, cardiovascular, and bone safety, the FDA EMDAC panel voted 10-5 in favor of approving canagliflozin. We think they were moved largely because of influential and very hitting advisors.
- Renal safety was the most controversial issue; many suggested restricting canagliflozin's use in patients with moderate renal impairment.

The FDA advisory committee meeting for canagliflozin focused primarily on renal safety and potential cardiovascular concerns, while placing less emphasis on bone mineral density and genitourinary infections (the latter was surprising). As the day's discussion progressed, it became increasingly more apparent that the drug's label will likely have some restriction on its use in patients with renal impairment given that (i) its efficacy decreases with decreasing renal function; (ii) the drug lowered eGFR more persistently in patients with moderate renal impairment (eGFR 45-60 ml/min/1.73 m2); and the risk of adverse events was higher in this patient population. We are curious if potentialrestrictions might take the form of stopping rules, dose restrictions, or strict eGFR cut-offs. The discussion on cardiovascular safety was not as controversial as we initially imagined it would be given the dramatically increased hazard ratio for MACE+ events seen in the first 30 days of CANVAS. Instead, the panelists' greatest concerns were the increases in LDL cholesterol associated with canagliflozin use and the potential increased risk of stroke found in the meta-analysis of pooled phase 2/3 studies.

In the end, most panelists voting in favor of drug approval concluded that canagliflozin offered significant benefits to people with normal or mildly impaired renal function (eGFR >60 ml/min/1.73 m2) and that the cardiovascular concerns raised by the FDA were not too troubling. They also, for the most part, agreed that the benefit/risk profile in people with moderate renal impairment could warrant restriction in this population and that the potential risk for increased stroke and the long-term effects of elevated LDL cholesterol on hard CV outcomes should be monitored in long-term studies. Most panelists who voted against approval cited the drug's potential for renal harm as the primary factor influencing their decision, though some also expressed concern about lack of long-term data on the effects of LDL elevation and the potentially elevated stroke risk. J&J proposed that patients at risk for adverse events (eGFR <60 ml/min/ 1.73 m2, those 75 years or older, or those using loop diuretics) start on the 100 mg dose of canagliflozin to reduce the risk of harm, and to only move to the 300 mg dose if 100 mg was not effective. However, panelists contended that the 100 mg dose was not efficacious in this population, meaning all patients would have to take the 300 mg dose anyway. Thus, as Dr. Abraham Thomas stated, more work might need to be done to find an appropriate dosing scheme for this population.

This report also includes a panelist-by-panelist breakdown of voting members' rationales behind their votes. Lastly, we've included some thoughts on where SGLT-2 inhibitors might fit in the treatment paradigm. It is a shame that the SGLT-2 class, thus far, does not seem like it will be as easy to take or easy to prescribe as we had once hoped. We see them as a good second- or third-line therapy, most likely behind metformin and DPP-4 inhibitors. J&J is also developing canagliflozin as a fixed-dose combination with metformin (both an immediate and extended release version), which may receive a decision December 2013 (see our report at https://closeconcerns.box.com/s/crzvl60rhlqe0y2kkndu).

Table of Contents

Executive Highlights

RENAL SAFETY

- **J&J, the FDA, and panelists appeared to agree that, for people with normal renal function or mild renal impairment (eGFR ≥60 ml/min/1.73m2), renal safety of canagliflozin was not a great concern.** Speakers for J&J and the FDA presented data showing that after an initial large percentage decrease in eGFR, eGFR began to rise again to approach baseline. J&J noted that canagliflozin's impact on eGFR is reversible after treatment discontinuation, and panelists did not express much concern about this pattern in people with normal renal function and mild renal impairment.
- **The FDA and members of the panel expressed significant concern about canagliflozin's use in people with moderate renal impairment (eGFR 30-60 ml/min/ 1.73m2).** J&J described the drop in eGFR seen in people with moderate renal impairment as having a similar pattern to that of people with normal renal function and mild renal impairment. However, the FDA stated (using the same graph as J&J's) that changes in eGFR over time in people with moderate renal impairment had a distinct and worse pattern, as the drop in eGFR in this population appeared to be more persistent than in the population with better renal function. Additionally, the FDA presented data from people with high cardiovascular risk, showing that there was little to no improvement in eGFR following the initial decrease.
- **J&J, the FDA, and the panel agreed that canagliflozin's glycemic efficacy decreases with worsening renal function.** J&J's dedicated phase 3 trial in patients with moderate renal impairment (now referred to as "renal impairment study") revealed lower placebo-adjusted mean A1c reductions for canagliflozin 100 mg (0.3%) and 300 mg (0.4%) compared to those observed in phase 3 trials with other patients populations (placebo-adjusted A1c reductions of 0.6-0.9% for the 100 mg dose and of 0.7% to 1.2% for the 300 mg dose). In a pooled population analysis that included participants from this trial, as well as a subset of patients from one trial in older patients, a trial assessing canagliflozin as monotherapy, and the cardiovascular outcomes trial CANVAS (median baseline eGFR of 50 ml/min/1.73m2), the placebo-adjusted A1c for the 100 mg dose was 0.4% and was 0.5% for the 300 mg dose.
- **Interestingly, while members of the panel seemed to agree that canagliflozin's decreased efficacy in people with impaired renal function tilted the benefit/risk ratio toward risk, J&J framed it quite differently, stating that people with renalimpairment have so few diabetes drug options that *any* additional A1c lowering options that come without the risk for edema or hypoglycemia would be beneficial.** A subanalysis of the pooled population analysis described above showed that canagliflozin's glycemic efficacy is better in patients in the top half of moderate renal impairment (eGFR of 45- 60 ml/min/1.73m2) than those in the bottom half (30-45 ml/min/1.73m2; see table below). Panelist Dr. Julia Lewis (a nephrologist from Vanderbilt who made astute comments all day) expressed doubt about whether the 0.2-0.4% A1c reduction seen with people in the lower end of moderate renal impairment was large enough to justify the eGFR decline. University of Chicago nephrologist Dr. George Bakris (speaking on behalf of J&J) urged panelists "not to throw the baby out with the bathwater" and to consider that a 0.5%

A1c reduction for those with an eGFR of 45- 60 ml/min/1.73 m2 was still a real benefit. During the panelists' remarks on whether the drug should be approved, they generally agreed that some level of restriction is required, but did not reach a consensus regarding whether the cut-off should be 45 ml/min/1.73m2 (to include some people with moderate renal impairment) or the more restrictive threshold of 60 ml/min/1.73m2.

	Placebo-adjusted mean A1c change	
Canagliflozin dose	**eGFR 30-45 ml/min/1.73m2**	**eGFR 45-60 ml/min/1.73m2**
100 mg	-0.2% (n=118)	-0.5% (n=208)
300 mg	-0.4% (n=1.22)	-0.5% (n=232)

- **J&J and the FDA appeared to disagree over the significance of the increased rate of adverse events (AEs) among people with moderate renal impairment - the panel took a middle position, expressing surprise that canagliflozin was not associated with a greater elevation in renal-related AEs.** Speakers for J&J stated that there was only a slight increase in the frequency of all AEs in the renal impairment data set (75.3% for canagliflozin 300 mg [n=365] vs. 74.0% for canagliflozin 100 mg [n=338] vs. 70.4% [n=382] for placebo), and emphasized that these events were not more severe in intensity than in the placebo group: 14.1% of participants on canagliflozin experienced a severe AE (SAE) compared to 19.6% of those on placebo. Canagliflozin was not associated with an increase in SAEs leading to treatment discontinuation or death. However, the FDA showed that canagliflozin was associated with a more dramatic increase in renal-related adverse events among people with moderate renal impairment compared to those with normal renal function or mild renal impairment (see table below). Some panel members expressed the concern that canagliflozin use might aggravate renal disease; these included Dr. Julia Lewis, who found it hard to believe that the drug would not cause more acute renal failure. Additionally, in Dr. Abraham Thomas' (acting panel chairperson; Henry Ford Hospital, Detroit, MI) summary statement on the benefit-risk of canagliflozin in patients with moderate renal impairment, he expressed the panel's surprise that there were not more acute kidney injury events due to the volume depletion observed early on.

	Proportion of participants with at least one renal-related adverse event	
	Population with baseline eGFR of 48.2 ml/min/1.73m2 (DS2)	**Population with baseline eGFR of 88.1 ml/min/1.73m2 (DS1)**
Placebo	3.7%	0.6%
Canagliflozin 100 mg	8.9%	0.6
Canagliflozin 300 mg	9.3%	1.7%

- **If canagliflozin is ultimately approved, presumably its label will restrict its use in the renally impaired population - the question is to what extent.** Combined with the drug's genitourinary side effects, canagliflozin may turn out to be less "hassle-free" to take and prescribe than KOLs initially thought the SGLT-2 inhibitor class could be. We're interested in what percentage of type 2 patients needing second- or third-line therapy have some degree of renal impairment, as a high percentage would suggest a smaller potential market penetration for canagliflozin.

- **J&J's proposed a dosing scheme for people with moderate renal impairment to help mitigate the risks associated with them using canagliflozin, but panelists questioned its effectiveness given the low efficacy associated with the 100 mg dose.** J&J described both doses as "clinically meaningful" and showed that in the renal impairment study (n=269; baseline A1c=8.0%), as well as in the pooled population analysis (n=1,085; baseline A1c=8.1%), a higher proportion of people using canagliflozin 100 mg or 300 mg achieved an A1c <7.0% than people on placebo (see table below; p-values were not provided). However, Dr. Sanjay Kaul questioned if it is "clinically relevant" for only ~25% of such patients to reach goal when on canagliflozin 100 mg; Dr. Julia Lewis described the canagliflozin 100 mg dose as being "totally not efficacious" and hypothesized that practically all patients with moderate renal impairment would therefore be put on the 300 mg dose; she also expressed concerns that J&J had not actually demonstrated that starting people with moderate renal impairment on 100 mg and then moving them up to 300 mg would be safer or better. In this spirit, Dr. Abraham Thomas' summary statement on the benefit-risk of canagliflozin in patients with moderate renal impairment (question one) noted the uncertainty of whether people with moderate renal impairment will experience glycemic benefits with canagliflozin 100 mg; he stated that more work might need to be done on the proposed dosing scheme for this population.

	Proportion of Participants Achieving A1c <7.0%	
	Renal Impairment Study	**Pooled Renal Impairment Population**
Canagliflozin 100 mg	27.3%	17.4%
Canagliflozin 300 mg	32.4%	24.5%
Placebo	17.2%	31.9%

CARDIOVASCULAR SAFETY

- **The cardiovascular safety concerns raised during the meeting included increased LDL cholesterol, the elevated hazard ratio for stroke in the pooled meta-analysis of phase 2 and 3 studies, and an imbalance in MACE+ events (CV death, myocardial infarction, stroke, hospitalized unstable angina) seen in the first 30 days of theCANVAS study.** The panelists expressed the most concern over the increase in LDL and the potentially elevated risk of stroke.
- **J&J argued persuasively that the early MACE+ imbalance in the CANVAS study was likely due to chance, and most panelists seemed to agree.** However, most panelists also agreed that the one-year data currently available were too short to draw real conclusions about CV outcomes. Among the five panelists who voted against approval, only one cited CV safety as the primary reason for his negative vote.
- **Panelists worried that long-term data had not yet been ascertained to examine whether the increase in LDL cholesterol will affect outcomes.** Canagliflozin was associated with a dose-dependent increase in LDL cholesterol (4.4 mg/dl and 8.2 mg/dl placebo- adjusted increase with canagliflozin 100 mg and 300 mg, respectively, from a baseline of 106.6 mg/dl). Smaller increases in non-HDL cholesterol, ApoB, and LDL particle number were also observed. J&J suggested that these observations be taken into consideration with canagliflozin's favorable effects on CV risk factors - increases in HDL cholesterol, neutral effect on LDL/HDL ratio, decreases in triglycerides, decreases in systolic and diastolic blood pressure, improved glycemic control, and decreased body weight. Panelists recognized the balance in positive and negative effects on CV risk factors, but stressed the need for longer-term data to examine outcomes.

- **Panelists also expressed concern over the potentially elevated risk of stroke.** The only component of MACE+ that had a hazard ratio greater than 1.0 was fatal and non-fatal stroke, which had a hazard ratio of 1.47 (95% CI: 0.83-2.59). J&J argued that this reported increase was likely due to a chance difference given several observations: 1) there was no evidence of hypercoagulability due to dehydration from volume depletion; 2) the Kaplan-Meier curves for stroke diverged after 18 weeks, whereas volume depletion events occurred mostly in the first 12 weeks; and 3) there was a lack of dose-relationship for strokes, whereas a dose-relationship was observed for AEs related to volume depletion. J&J presented an additional meta-analysis requested by the EMA using an extended dataset that added an additional 80 events to the dataset submitted to the FDA - under this analysis, the hazard ratio for stroke dropped to 1.29 (95% CI: 0.80-2.09). In the end, panelists acknowledged that stroke may be a potential concern, but that a more definitive answer could be reached at the conclusion of CANVAS. Some panelists, including biostatistician Dr. Erica Brittain (NIAID, Bethesda, MD), expressed comfort in that all of the other components of MACE+ favored canagliflozin. On the other hand, Dr. Abraham Thomas warned that MACE components can meaningfully diverge, citing ACCORD as an example. Disappointingly, when panelists asked J&J what the nature of the strokes was to gain a better understanding of the strokes' clinical implications, J&J was not able to provide such characterization.
- **The elevated risk of MACE+ events seen in the first 30 days of the CANVAS cardiovascular outcomes trial was not of great concern to panel members.** As a reminder, while the hazard ratio for MACE+ from the pooled meta-analysis of phase 2 and 3 trials (HR=0.91; 95% CI: 0.68-1.22) fell well-below the FDA's pre-approval 1.8 upper-bound requirement, an imbalance in MACE+ events in canagliflozin-treated patients was observed in the first 30 days of the CANVAS trial (HR=6.49; 95% CI=0.85-49.64). J&J argued that the considerable month-to-month variability in the frequency of events made it likely that the imbalance in MACE+ for the first 30 days was due to chance: there was a very low event rate in the placebo group in the first 30 days (one event, compared to 13 events in the canagliflozin group [with a 1:2 placebo:treatment randomization]), which J&J noted was lower than is typically seenin a cardiovascular outcomes trial. In contrast, in months two, three, and four, the event rate was markedly higher in the placebo group than in the canagliflozin group. Panelists were largely supportive of J&J's efforts to meet (and exceed) the FDA's pre-approval CV requirements. They generally agreed that the post-hoc nature of the 30-day analysis, as well as the lack of proportionality in events (1 observed vs. 3.76 expected placebo events based on the placebo event rate during the entire trial), likely made this analysis immaterial without other supporting evidence of cardiovascular concern.
- **As another argument for why the increase in early MACE+ was not drug-related, J&J called into question the plausibility of a relationship between the increased early MACE+ events and volume depletion due to the drug's diuretic effect.** As a reminder, because of its osmotic diuretic effect, canagliflozin causes increased urine volume and, thus decreased intravascular volume) Volume-related AEs were very much dose-related, but the MACE+ events were equally distributed across the two canagliflozin doses; most volume-related AEs took place over the first 90-120 days whereas the imbalance in MACE+ events occurred only in the first 30 days; finally, there were no reports of volume depletion-related symptoms in patients with MACE+ (e.g., dizziness and hypotension were the most commonly reported AEs related to volume). The FDA, however, stated that narrative reports of patients with MACE+ in the first 30 days following randomization were not detailed enough to allow assessment of these patients' volume status in relation to the MACE+ event.
- **Panelists, including the shrewd Dr. Sanjay Kaul (Cedars-Sinai Heart Institute, Los Angeles, CA), strongly urged the FDA to ensure that J&J complete the CANVAS study with integrity and in a timely manner should canagliflozin be approved** in order to put concerns about long-term outcomes associated with elevated LDL, risk of stroke, and early event imbalances in CANVAS to rest. In a conversation we had after the Advisory Committee meeting with Dr. Kirk Ways (Janssen VP, Therapeutic Area Head, Metabolism/GI), he explained how continuing

the CANVAS study will help determine if there is a cardiovascular signal for canagliflozin several years sooner than a new post-approval cardiovascular outcome trial would. We note that CANVAS' estimated primary completion date is April 2013 (ClinicalTrials.gov Identifier: NCT01032629).

- **The FDA received some criticism over its decision to use interim data in an approval decision.** While J&J's decision to begin its CVOT prior to submitting an NDA means that it will have CV outcomes data far ahead of anyone that begins a CVOT post-approval, it also means that the interim CANVAS data raised questions that are difficult to address. Dr. Kaul in particular questioned whether Janssen's CV analysis - in relying heavily on interim CANVAS data - was "faithful to the spirit of the [FDA CV assessment] guidelines." The FDA responded to these concerns by noting that the CV guidance is "dynamic" and still evolving. We imagine that if the FDA itself isn't clear about what it believes on CV risk and how trials should be developed, those active in drug development could find the process of trial design and seeking approval to be increasingly frustrating. We believe this is another example of how uncertainty about FDA requirements raises the risk of diabetes drug development, and we hope the FDA works toward greater clarity and transparency in the future.
- **Quite strikingly, panelists invoked rosiglitazone as a cautionary tale numerous times throughout the afternoon discussion.** As a reminder, an LDL increase was initially observed with rosiglitazone, when most other CV risk markers looked favorable, and the drug was approved before ascertaining long-term data on CV outcomes.

RISK OF GENITOURINARY INFECTION

- **Neither the FDA nor panel members focused on canagliflozin's association with an increased risk for urinary tract infections (UTIs) and genital mycotic infections.** This established side effect of the SGLT-2 inhibitor drug class appears to be uncontroversial because it responds well to treatment although we will have to monitor how inconvenient it is. During J&J's presentations, Dr. Peter Stein emphasized that though UTIs and genital infections occurred more frequently in people taking canagliflozin, they were rarely serious or led to discontinuation, and were balanced between the two doses. Notably, they generally could be treated with standard antifungal therapy. Notably, the FDA presented data showing that the rate of recurrence for both male and female genital mycotic infections was higher in people taking canagliflozin (22% for both genders) those on placebo (0% among men and 10% among women). It is our understanding that infections often occur shortly after onset of therapy, but how much of an inconvenience this side effect actually is for patients (and therefore how much it could impact adherence) will depend on the risk of such infections over a longer time period than has been reported so far and how troubling it is to actually address the challenge. .

FRACTURES AND BONE MINERAL DENSITY

- **Panelists expressed little concern over canagliflozin's potential effects on bone health**, with only two panelists offering their thoughts during the corresponding FDA discussion question. Dr. Abraham Thomas, MD (Henry Ford Hospital, Detroit, MI) questioned whether the changes in bone turnover markers and bone density were due to weight loss, or whether they would persist in the long run even after weight loss plateaus. He noted that, if canagliflozin were positioned for use early in the treatment paradigm as some KOLs have suggested in the past, the effects of its long-term use could be particularly harmful in adolescents and young adults, who have not yet reached peak bone strength. Dr. Abraham called for long-term data to shed more light onto this issue. In his response, Janssen's bone expert Dr. John P. Bilezikian (Columbia University School of Medicine, New York, NY) agreed that long-term follow-up is required and remarked that the effects on bone turnover and density may be related to weight loss; however, the imbalance of upper limb fractures observed in the phase 3 trials still has an uncertain cause, as it does not appear to be attributable to changes in bone strength, metabolic parameters, bone mineral density, or bone turnover markers.

COMMENTARY FROM VOTING COMMITTEE MEMBERS - "YES" VOTES (10)

- **The influential Dr. Sanjay Kaul, MD (Cedars-Sinai Heart Institute, Los Angeles, CA) voted "yes," with one caveat: the drug should not be used in those with moderately impaired renal function**. He did not specify an eGFR threshold, though he seemed to imply the entire <60 ml/min/m2 population. Dr. Kaul noted that this patient population was underrepresented in the trials, and since canagliflozin's glycemic efficacy was reduced at the same point that adverse events increased two- to four-fold, more data should be collected in this population. We thought this was a very rational approach, and certainly one that emphasizes personalized medicine. On the issue of strokes, Dr. Kaul asked for greater detail to better characterize whether the events were disabling. Regarding the 30-day CANVAS CV data, he thought it was difficult to make much of it, though he was also not willing to completely dismissit. Last, given the chronic nature of diabetes, Dr. Kaul expressed concern that the CANVAS dataset was only one year long. Always thorough, practical, and forward looking, Dr. Kaul's insights and perspectives have been of consistently very high value and we believe he will continue to be extremely influential at Advisory Committee meetings.
    - **Much of Dr. Kaul's commentary in the afternoon elucidated concerns about the FDA's cardiovascular guidance, process for cardiovascular assessment, and trial design.** He was particularly skeptical that the Agency and companies could ensure trial integrity for an ongoing cardiovascular outcomes trial that will continue post-approval ("as a general rule, unblinding a trial is not a good thing unless there are compelling circumstances. I don't hear those compelling circumstances"). Dr. Kaul also wondered whether CANVAS was faithful to the spirit of the diabetes drug cardiovascular guidance - while the guidance suggests a meta-analysis of phase 2 and phase 3 trials, he noted that 80% of canagliflozin's CV data came from an interim analysis of an ongoing phase 3 trial (i.e., CANVAS). He also noted that the approval of canagliflozin would set a precedent, since he was not aware of the FDA ever having approved a drug based on an interim analysis from an ongoing trial.
- **Masterful chair Dr. Abraham Thomas, MD (Henry Ford Hospital, Detroit, MI) seemed to speak with an eye toward approval, noting his general comfort with the data and confidence that more was coming.** He acknowledged that there are "definite benefits, and there are risks," but he was "reassured" that the CANVAS trial will accumulate enough MACE events. Despite the issues of a potentially higher risk for stroke and elevations in cholesterol, he did not think there was enough data to make a final determination. Dr. Thomas also harkened back to over-the-counter obesity therapies, where FDA used surveillance and epidemiological data to remove drugs from the market. He emphasized that canagliflozin should have long-term follow-up through registry data, surveillance data, and data from HMOs. As we've come to expect, we were impressed by his thoughtfulness and his masterful ability to summarize the often-diffuse discussion in a concise and informative manner.
- **Dr. Julia Lewis, MD (Vanderbilt University, Nashville, TN) voted "yes" based on the company's reasonable approach, though expressed concerned about use of canagliflozin in renally impaired patients.** Her vote reflected "great faith in my FDA colleagues" to ensure that canagliflozin's label would prevent use of the drug in patients with a low eGFR (<45 ml/min/1.73 m2). Like Dr. Kaul, she found it "disconcerting" that canagliflozin had less glucose-lowering effects and as many or more side effects in this population ("I hate for my patients to not get a drug, but I'm concerned about it doing more harm than good [in those who are renally impaired]"). She was skeptical that the 100 mg dose would be appropriate in those with renal impairment, since the lower efficacy would push prescribers to increase the dose to 300 mg. Dr. Lewis also raised the issue of drug-drug interactions, since the use of anti-fungal medications would be more common due to higher rates of UTIs. She reiterated other panelists' requests that the CANVAS trial be completed in a timely manner. Dr. Lewis was new to the EMDAC panel, and we

found her to be one of the most astute and detail-oriented panelists of the day. We hope she remains on for future Advisory Committees.

- **Ms. Rebecca Killion (Patient Representative) thought canagliflozin was "very encouraging" from a patient point of view.** She liked that it improved A1c and addressed concerns about weight and hypoglycemia, issues she said most people with diabetes deal with. Additionally, Ms. Killion highlighted how a new mechanism of action "represents a step forward." She acknowledged that every drug has risks ("this story is still unfolding") and is not appropriatefor use in all populations, but expressed confidence that such issues will be worked out with canagliflozin. In what we thought was a good point, Ms. Killion expressed concerns about patient adherence to canagliflozin due to the prevalence of UTIs - she asked whether infections were typically seen at therapy initiation and dissipated over time, or whether the rate was constant. From the data presented, it appeared that the accrued rate of infections began to increase right at therapy initiation and flatten around 26 weeks, with further flattening around 52 weeks. Ms. Killion also brought an excellent patient perspective to the discussion of CV risk assessment for diabetes drugs, "As a patient, it's been a concern of mine that we have to be very careful not to overburden the R&D process. We all know we need new and better drugs for diabetics. But if we hold out the approval of drugs until the conclusion of long term CVOTs, that will stall and chill development - we can't have that as a diabetic population." Ultimately, we began referring to the summary of her many and varied conclusions as "stay safe, stay sane.'
- **Dr. Erica Brittain, PhD (NIAID, NIH, Bethesda, Maryland) voted in favor of approval, noting canagliflozin's robust efficacy (perhaps even superiority) and "fairly promising" cardiovascular picture.** She thought the results were strong enough to outweigh the lingering renal safety and bone issues, along with the "slightly confusing" cardiovascular picture. Dr. Brittain wasn't really sure what to make of the 30-day cardiovascular data, though she highlighted that the survival curves do turn around in the right direction. She found it comforting that the increased risk of stroke was an outlier in the MACE+ analysis, since all the other components had hazard ratios less than one. She also concurred with other panelists that the risk-benefit tradeoff for renally impaired patients "is clearly less clear cut."
- **Dr. David Cooke, MD (Johns Hopkins, Baltimore, MD) voted "yes" based on canagliflozin's efficacy and "sufficiently reassuring" safety data.** He cautioned that the risk data is incomplete at this point, but he thought it was good enough to justify the efficacy data and approval. Dr. Cooke also mentioned the risks of "putting excessive burden on the development and delivery of these medications to a very important and needy population." On the cardiovascular risk front, he thought that the 30-day data and the stroke data were something to be considered, but they will be borne out in the long-term data. Dr. Cooke was also quite comfortable that canagliflozin was easily well below the 1.8 threshold for approval.
- **Dr. David Malarkey, DVM, PhD (National Institute of Environmental Health Sciences, NIH, Research Triangle Park, NC)** favored approval of canagliflozin, citing its "relatively low risk" and "nicely done" animal studies. He voiced unanswered concerns about the long-term effects of canagliflozin, but overall felt that the benefits outweighed the risks. Dr. Malarkey was also confident that the FDA's pre-approval CV threshold of 1.8 had been met, and his biggest concern was the angst of fellow panelists more than his own.
- **Dr. Michael Proschan, PhD (NIAID, NIH, Bethesda, MD) was persuaded by canagliflozin's abundance of safety data, which was more than any other diabetes drug.** Fellow panelists also convinced him of the benefits of a new drug class that has an insulin-independent mechanism. Regarding overall cardiovascular events, there was no question in his mind that canagliflozin met the 1.8 threshold ("they've demonstrated what they need to"). Like many other panelists, Dr. Proschan still had unanswered questions about the stroke data.
- **Dr. Paul Palevsky, MD (University of Pittsburgh, Pittsburgh, PA) voted "yes," but with concerns about use of canagliflozin in the renally impaired** (eGFR <45 ml/min/1.73 m2).

He believed that the stroke data and 30-day cardiovascular data would not play out, both likely a reflection of statistical anomalies.

- **Dr. David Capuzzi, MD, PhD (Thomas Jefferson University, Philadelphia, PA) was quite negative on canagliflozin all day, though in the end he mistakenly voted "yes."** He seemed rather confused on what the final voting question was asking; following his official "yes" vote in favor of approval, Dr. Capuzzi began explaining his concerns with the drug and why he voted "no." Chair Dr. Thomas then interrupted him to confirm that he indeed meant to vote "yes." Dr. Capuzzi did not have an answer, and instead of waiting for one, Dr. Thomas moved on (it sort of felt like a timeout, perhaps appropriate since Dr. Capuzzi was already sitting in the corner). In comments made earlier in the day, Dr. Capuzzi was mainly concerned about the elevations in LDL cholesterol seen with canagliflozin, calling them "a problem" and "a really big issue." We found few of Dr. Capuzzi's comments throughout yesterday's committee to add value to the discussion at hand. As we understand it, this was his final advisory committee on the EMDAC panel.

COMMENTARY FROM VOTING COMMITTEE MEMBERS - "NO" VOTES (5)

- **Concerns about cardiovascular safety moved Dr. William Hiatt, MD (University of Colorado, Aurora, CO) to vote against approval.** He believed there were CV risks that had not been fully evaluated, a process he assumed would take about two years (i.e., following analysis of CANVAS's complete dataset). Dr. Hiatt thought the early 30-day CV risk signal likely wouldn't change, and a late risk signal could emerge based on the elevations in LDL cholesterol. He felt it was unlikely that the upper bound of the hazard ratio confidence interval would get to 1.8, though he could see it rising to 1.3 once more data is accumulated. He was looking for an answer in the totality of data, "which we don't have yet." Given his track record of voting (see Appendix), we were somewhat surprised to see Dr. Hiatt vote again approval of canagliflozin.
- **Dr. William Knowler, MD, PhD (NIDDK, NIH, Phoenix, AZ) was mainly concerned about use of canagliflozin as a monotherapy.** In providing his rationale, he said, "I think the drug would be acceptable as add-on therapy, but for a general indication including monotherapy, I cannot recommend it "due to lack of head-to-head data comparing canagliflozin and metformin. Dr. Knowler also wanted to see more than just one-year data to alleviate his concerns about the increases in lipids.
    - **Dr. Edward Gregg, PhD (Centers for Disease Control and Prevention, Atlanta GA) voted against approval due to the absence of two-year data and the concerning stroke data.** He admitted that canagliflozin had a diverse set of benefits, but stated that there were many lingering questions (bone density, fractures, renal function, volume depletion) that could not be answered without long-term data. He also would have liked to see quality of life datawe agree that this would have been valuable to see. In Dr. Gregg's view, canagliflozin's benefitswere also clouded by the lower efficacy in those with renal impairment, a target population. He was not concerned about the cardiovascular risk in the first 30 days, a finding he attributed to chance.
- **Dr. Peter Savage, MD (NIDDK, NIH, Bethesda, MD) was uneasy about the use of canagliflozin in people with moderate renal disease.** Dr. Savage felt the risk-benefit ratio was different in this group, and he was uncomfortable with the potential risk of kidney damage with long-term UTIs. Dr. Savage highlighted that canagliflozin could be useful in other parts of diabetic population - indeed, we would note that this particular rationale could have supported a "yes" vote (similar to Dr. Kaul) assuming a conditional approval with an appropriatecontraindication. Dr. Savage also felt there was "no evidence" that canagliflozin would be replacement for metformin, except in cases of GI side effects.
- **Dr. Nakela Cook, MD (NIH, Bethesda, MD) spoke sparingly during the day, but at the time of voting was concerned about the use of canagliflozin in those with moderate**

renal impairment. This factor, she said, "overrode" her vote. She did have concerns about cardiovascular risk, but expressed optimism that longer-term data would help with that.

CLOSE CONCERNS' SPECULATIONS ON CANAGLIFLOZIN POSITIONING

- **Where could canagliflozin fall in the treatment paradigm?** This is of course an important question for any new type 2 diabetes therapy, especially as the number of drug classes continues to grow. We're glad to see more and more focus on personalized and individualized therapy, a development that we believe will accelerate in the coming years (especially as new classes continue to emerge and genetic testing gets better). The treatment paradigm question is also one with a variety of components to it besides safety and efficacy - factors like cost, physician awareness, dosing frequency, and professional position statements are also very key.
    - **We believe it is unlikely SGLT-2s will be used as a monotherapy.** The exception could be cases where metformin cannot be tolerated - but even then, we would guess the popularity, better side effect profile, long-term safety data, and likely lower cost of DPP-4 inhibitors would put them ahead of SGLT-2s as a monotherapy. Given their cost advantages and short-term efficacy (though generally accepted limited durability), we wonder if HCPs will continue to use sulfonylureas in the coming years - we hope this is not the case, as the drug class is associated with significant weight gain and hypoglycemia concerns. There is still a camp that favors use of low-dose pioglitazone, which now that it is generic, could be another option as well (although we have also heard lower dose TZD argument). Monotherapy obviously fails early in the progression of type 2 diabetes, and we believe HCPs will lean towards the safest and lowest cost therapies with the highest adherence. In our view, SGLT-2s just don't have an edge here. I
    - **We see the most likely use of SGLT-2s as a second-line or third-line therapy.** For the reasons cited above, we suspect providers will prefer metformin plus a DPP-4, a sulfonylurea, or low-dose pioglitazone; however, for those that cannot tolerate metformin, an SGLT-2 inhibitor on top of a DPP-4 inhibitor could be a logical option, though this would also be quite expensive. We cannot wait to see the results of the GRADE study, which will be a head-to-head comparison of the long-term effectiveness of the sulfonylurea Amaryl (glimepiride), the DPP-4 inhibitor Januvia (sitagliptin), the GLP- 1 agonist Victoza (liraglutide), and the basal insulin Lantus (glargine), each added on to metformin over four years. Notably, SGLT-2 inhibitors are not included; it will be interesting to see if the results of GRADE change clinical practice, and if so, how popular SGLT-2s will be by that point. The other important confound will be CVOT trials, which will start reporting in the coming years. Canagliflozin's CANVAS is slated to be the first ongoing CVOT to complete (in April 2013). Should an agent demonstrate cardioprotection, that could raise the bar for all other drug classes and thus change physician's decision making.
    - **Assuming that canagliflozin will be used as second- or third-line therapy, its labeling and any restrictions could heavily impact its uptake.** Should the FDA decide to prevent the use of canagliflozin in people with renal impairment (of course, thisdepends on the eGFR cut-off), the drug's use may be confined mostly to type 2 patients without a shorter disease duration, perhaps limiting its potential as a third-line therapy. Of course, this is simply food for thought and difficult to predict overall because of the heterogeneity of type 2 patients - on the flip side, we imagine that there will be patients with long-standing diabetes who do not have renal impairment and thus could benefit from the drug.
- **J&J indicated, in a conversation with us, that they have taken a type 1 diabetes indication into consideration, though we have not learned of any plans to initiate a trial in type 1.** We have several questions regarding whether similar (or more severe) safety concerns might also arise in the type 1 diabetes population. Since patients with type 1 diabetes would

likely begin therapy earlier in life, the lifetime risk for renal impairment, bone density loss, and genitourinary infection may intensify with longer exposure.

APPENDIX - PANELIST VOTING HISTORY

Panelists Voting "YES"

- **Dr. Sanjay Kaul, MD (Cedars-Sinai Heart Institute, Los Angeles, CA).** Previously, Dr. Kaul voted to approve dapagliflozin, noting that a study that could properly assess cancer risk would not be feasible in a premarketing setting. At the Advisory Committee meeting for CV risk assessment in obesity drug development, he voted "yes" to require obesity drugs with no CV risk signal to rule out a certain degree of excess CV risk, and supported a two-tiered approach that would allow for a pre-approval meta-analysis of phase 2/phase 3 data. In 2010, Dr. Kaul gave an impassioned speech on why Contrave should not be approved, arguing that Contrave failed to meet an efficacy margin that allows for an acceptable safety tradeoff consideration.
- **Dr. Abraham Thomas, MD (Henry Ford Hospital, Detroit, MI).** Dr. Thomas voted for the approval of dapagliflozin in 2011, emphasizing the benefits of the SGLT-2 inhibitor mechanism and the unrealistic nature of assessing cancer risk in a pre-approval setting. In addition, he voted in favor of approving Vivus' Qnexa (Qysmia) and Arena's Belviq (Lorqess) in their second go-arounds, and in favor of approving Orexigen's Contrave; however, he supported blanket CV risk assessment for future obesity drug development.
- **Dr. Julia Lewis, MD (Vanderbilt University, Nashville, TN) was new to the EMDAC committee.**
- **Ms. Rebecca Killion (Patient Representative)**. Most recently, Ms. Killion voted in favor of approving insulin degludec, viewing it as an important step forward in basal insulin therapy. At the 2008 FDA Advisory Committee meeting on the CV safety of diabetes medications, Ms. Killion voted against requiring all new type 2 diabetes drugs to demonstrate cardiovascular safety in a hard outcomes clinical trial or by other means, even if no concerning cardiovascular signal is observed in phase 2/3. She was in favor of approving liraglutide in 2009 and thought that the cardiovascular risk could be safely managed. In 2008, she was in favor of a post-marketing trial for saxagliptin. Ms. Killion has been a very recognized strong voice for improving the suite of therapy options for patients; we see it as a positive for patients and industry that she is on the EMDAC panel.
- **Dr. Erica Brittain, PhD (NIAID, NIH, Bethesda, Maryland).** Dr. Brittain voted against the approval of dapagliflozin, emphasizing that primarily, she wanted to get more information on the drug's safety, and that the timing of the collection of such data was somewhat a secondary concern. At the recent insulin degludec Advisory Committee meeting, Dr. Brittain voted against approval because the CV signal was too great not to be addressed first. She voted in favor of approving Arena's Belviq at its second Advisory Committee meeting, though was not happy about the abundant missing data. She also expressed some concern about the feasibility of conducting placebo-controlled trials post-marketing. At the Obesity CV Guidance Advisory Committee, Dr. Brittain voted in favor of additional CV safety assessment (a two-staged approach) since obesity drugs will target a sizeable population. At the Qnexa (Qsymia) panel, she voted in favor of approval "not without trepidation," especially with regards to cardiovascular risk.
- **Dr. David Cooke, MD (Johns Hopkins, Baltimore, MD)**. Dr. Cooke voted in favor of approval of Novo Nordisk's insulin degludec, because he believed the pharmacokinetics of insulin degludec represent an advance for the treatment of both type 1 and type 2 diabetes (though it was a tough decision). He stated that obviously there is concern about whether degludec increases cardiovascular risk, but that the risk is far from proven. Dr. Cooke commented that he thought it would be important for clinicians to have access to insulin degludec so they could decide whether the benefit/risk profile of the drug warrants its use on a patient-by-patient case.
- **Dr. David Malarkey, DVM, PhD (National Institute of Environmental Health Sciences, NIH, Research Triangle Park, NC).** Dr. Malarkey supported approval of Arena's Belviq at its

2012 Advisory Committee meeting, since his concerns regarding carcinogenicity were reassured by the safety margins and prolactin data.

- **Dr. Michael Proschan, PhD (NIAID, NIH, Bethesda, MD).** At the meeting on CV risk assessment for obesity medications, Dr. Proschan voted for a two-stage approach using both a meta-analysis and a CV outcomes trial. In 2010, he voted against the approval of Qnexa (Qsymia) and Contrave, and for Belviq (Lorqess). With Contrave, he was concerned about CV safety, and with Qnexa, he was concerned with the neurological side effects, and wanted longer-term data.
- **Dr. Paul Palevsky, MD (University of Pittsburgh, Pittsburgh, PA).** We do not have any previous voting history on any diabetes- or obesity-related advisory committee in the last four years for Dr. Palevsky.
- **Dr. David Capuzzi, MD, PhD (Thomas Jefferson University, Philadelphia, PA).** Dr. Capuzzi voted against approval of dapagliflozin based on the dearth of pharmacokinetic (PK) and safety/efficacy data in several populations, including otherwise healthy patients with heart failure, the elderly, and the renally or hepatically compromised. That being said, he acknowledged the potential value of the SGLT-2 inhibitor class - a mechanism of action independent of insulin secretion and sensitization, and ease of use. Dr. Capuzzi also gave a relatively hard-to-follow explanation for voting against the approval of Belviq in 2012, and an indecisive vote against the approval of Qnexa (Qsymia) during its second review (before the vote, he asked if panelists could abstain from the vote; he was the only panelist to switch from an initial "yes" vote during the first panel to a "no" in the second).

Panelists Voting "No"

- **Dr. William Hiatt, MD (University of Colorado, Aurora, CO).** Dr. Hiatt favored approval of insulin degludec, citing the "onerous" burdens a pre-approval CV study would create. Dr. Hiatt voted in favor of approving Belviq during its second review, noting that the cancer risks had been defined and could be monitored post-marketing. At the Obesity CV Guidance Advisory Committee, he voted against additional requirements - Dr. Hiatt felt that if the FDA decided to impose a blanket CV requirement for anti-obesity drugs, then the Agency should be consistent and impose a similar requirement for all symptomatic drugs across all indications. At the Contrave Advisory Committee meeting, Dr. Hiatt voted for approval and noted that "a study pre- approval would likely kill development of the drug, and I'm just wrestling with what the message will be to the wider community. Requiring a 10,000-patient trial before approval in the future would be a steep hill to climb."
- **Dr. William Knowler, MD, PhD, MPH (NIDDK, NIH, Phoenix, AZ).** At the 2010 Avandia Advisory Committee meeting, Dr. Knowler voted for the drug to be removed from the market.
- **Dr. Edward Gregg, PhD (Centers for Disease Control and Prevention, Atlanta GA).** Dr. Gregg voted against the approval of dapagliflozin on the basis of uncertainty surrounding its breast and bladder cancer risk. Dr. Gregg voted against approval at the first Advisory Committee meeting for Belviq (Lorqess) and in favor at the second, the main difference being that Arena's additional data alleviated most of the safety concerns. He voted for the approval of Qnexa (Qsymia) in 2012, comforted by the proposed REMS program. At the Advisory Committee meeting on CV risk assessment for obesity drugs, Dr. Gregg voted "yes" and encouraged a meta- analysis of phase 2/3 trials to evaluate many safety concerns, including CV risk. Dr. Gregg was one of the few "yes" voters who expressed concern about a two-tiered approach to CV risk evaluation, noting that it may not provide clear guidance to sponsors.
- **Dr. Peter Savage, MD (NIDDK, NIH, Bethesda, MD).** Dr. Savage also voted against the approval of dapagliflozin; it was not a clear-cut decision for him, and he expressed a general desire for more data on cancer, minority groups, and renal function in elderly patients. Dr. Savage voted in favor of blanket CV risk assessment for obesity medications, given the checkered history of obesity medications and their potential for widespread use.

- **Dr. Nakela Cook, MD, MPH (NIH, Bethesda, MD).** We do not have any previous voting history on any diabetes- or obesity-related advisory committee in the last four years for Dr. Cook.

-- by Adam Brown, Hannah Deming, Jessica Dong, Nina Ran, and Kelly Close