Closer Look

MEMORANDUM

FDA Advisory Committee - Bristol-Myers Squibb/AstraZeneca's dapagliflozin July 19, 2011; Silver Spring, MD

Executive Highlights

In a packed room in the Silver Spring, MD Hilton, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee discussed the efficacy and safety of BMS/AZ's SGLT-2 inhibitor dapagliflozin, the first drug in its class to come under FDA review. After a full day of discussion, the panel ultimately voted 6-9 against approval of dapagliflozin, primarily due to unexpected safety signals seen - though weak, the main controversy ultimately rested on whether to explore the signals pre- or post-marketing. In this report, we bring you our takeaway themes of the panel, commentary behind each panelist's final vote for or against dapagliflozin approval, and a review of BMS/AZ and FDA's morning presentations.

When providing rationales for their votes at the end of the day, panelists on both sides of the vote voiced similar concerns about safety uncertainties that remain - bladder and breast cancer risk, and to a lesser extent hepatotoxicity - with dapagliflozin treatment. The major difference was that those that voted 'yes' emphasized that a post-marketing study was the only realistic way to assess these risks, while many who voted 'no' requested additional data pre-approval, without providing concrete recommendations on how to better characterize these risks in a pre-approval setting. Those favoring approval cited dapagliflozin's novel mechanism of action and efficacy and tolerability advantages (specifically, lack of hypoglycemia and weight gain). Some of those against approval were concerned with the paucity of data for specific subgroups, the potential use of dapagliflozin in renally impaired individuals, and the lack of PK/PD data. We find it unfortunate that BMS/AZ did not have overrepresented data in ethnic minorities and the elderly since this objection was fairly predictable. Surprisingly, not much discussion during the day centered on urinary or genital tract infections, and Patient Representative Cassandra McIntyre (Mitchellville, MD) was the only one who mentioned them in her closing comments. Looking forward, we see this as a positive for the SGLT-2 inhibitor class, given that such infections appear to be a class-wide effect; we do note that these effects may still be of concern in routine clinical practice.

The FDA is expected to make a final decision on dapagliflozin by its PDUFA date of October 28, 2011; we also expect to hear a decision in fall 2011 in the EU, as dapa was submitted in late 2010. From the day's proceedings and the metabolic division's recent track record, in all likelihood it appears that BMS/AZ will receive a complete response letter, requesting additional analyses, and potentially additional studies, prior to approval. While this is not the ideal outcome for BMS/AZ, it has become more or less status quo in this era of FDA conservatism for new diabetes drugs (excluding me-too drugs) to receive at least one CRL before gaining approval (Bydureon, Afrezza, and Linjeta have all yet to receive approval...). We await the final decision on dapagliflozin, which will almost certainly be a complete response letter, though it is possible we could see a narrow approval, given the conversation today. We note that although the official vote on the panel was negative on approval, the discussion demonstrated that many expect approval and the main question is how to best manage the process leading up to and following approval. Given that safety signals won't be reconciled pre-approval, and given major patient needs for alternatives in the near term, we expect to see approval in the next year combined with long- term post-marketing studies. We look forward to updates on other SGLT-2 inhibitors, such as J&J's canagliflozin (phase 3), BI/Lilly's empagliflozin (BI10773 - phase 3), Chugai's tofogliflozin (CSG452 - phase 3), Pfizer's compound (phase 2), Lexicon's dual SGLT-1/SGLT-2 inhibitor LX4211 (phase 2b), Astellas' ASP-1941 (phase 2-3), Taisho's TS-071 (phase 2), and GSK/Kissei's 1614235 (phase 1).

- **The safety front was the major source of discussion all day. Panelists expressed concern over the uncertainties about the data with regards to bladder and breast**

cancer risk with dapagliflozin, while acknowledging the potential contribution of detection bias. Cancer specialist Steven Piantadosi, MD (Cedars-Sinai Medical Center, Los Angeles, CA) characterized the uncertainties that remain regarding potential cancer risk with dapagliflozin. On the one hand, risk ratios of bladder and breast cancer for the drug are four-to- five-fold higher than placebo (but not statistically significant); on the other hand, there is no clear mechanism for carcinogenicity, no evidence of mutagenicity from preclinical studies, and some of the effect could be attributable to detection bias. Dr. Piantadosi was clear to emphasize that even though detection bias may have played a role, it would not likely have accounted for all or even the bulk of the difference in cancer rate observed between dapagliflozin and placebo; he suggested that it is likely dapagliflozin would be left with a risk ratio of greater than two. Ellen Seely, MD (Harvard Medical School, Boston, MA) emphasized the need to explore the issue of detection bias in more depth, given that mammograms become easier to perform when obese patients lose weight, and that hydration could also affect imaging - this was an interesting point. Abraham Thomas, MD, MPH (Henry Ford Hospital, Detroit, MI) subsequently suggested that there was potential detection bias for bladder cancer as well, given that increased urinary tract infections (UTIs) may have led to increased follow-up analyses and greater detection of hematuria; Sanjay Kaul, MD (Cedars-Sinai Medical Center, Los Angeles, CA) and Enrico Veltri, MD (Sanofi, Bridgewater, NJ) commented that detection bias for bladder cancer seemed less plausible, given that the frequency of UTIs is much higher in females, thus, there would have to be a high predisposition for males to develop bladder cancer in order for Dr. Thomas' hypothesis to hold. All panelists agreed on one point - the need for further investigation and characterization of the potential cancer risk of dapagliflozin. Based on his estimates, Dr. Kaul noted that in order to address these uncertainties, a large trial with between 30,000-100,000 patients would need to be conducted; as such, he believed the trial would be more appropriate in the postmarketing setting- this suggested this his view of the benefit-risk tradeoff rested on more benefit fromdapagliflozin. Other panelists asked the FDA to clarify whether they had solidified the duration and size of the eventual outcomes study with BMS; the FDA responded they had not finalized anything as of yet.

- **In the rationale to the final vote, 11 of the 15 panelists specifically referenced cancer risk as an important safety issue requiring further study.** In general, there seemed to be consensus among those who voted for the approval of dapagliflozin regarding the unrealistic nature of assessing cancer risk in a pre-approval setting, given the required duration and sample size of such a study. On the other hand, several panelists who voted against the approval of dapagliflozin requested additional data on cancer risk in a pre-approval setting - we heard such requests from Cassandra McIntyre (Mitchellville, MD), Doris Strader, MD (University of Vermont College of Medicine, Burlington, VT), Edward Gregg, PhD (Center for Disease Control and Prevention, Atlanta, GA), Peter Savage, MD (NIDDK, NIH, Bethesda, MD), and Eric Felner, MD (Emory University School of Medicine, Atlanta, GA). While the 'yes' voters justified assessing cancer risk in a post-approval setting by providing specific sample sizes, the 'no' voters did not offer any specific insights on how to assess cancer risk in a pre-approval setting (in the short- term).
- **Bemoaning the paucity of data surrounding hepatotoxicity, the panel called for more stringent guidelines on the monitoring of liver disease in diabetes trials.** Withonly one patient considered the victim of "probable" drug-induced liver injury, the majority suggested that little could be concluded from the available data - though regardless of the overall balance in hepatotoxicity between the arms, many saw the event as cause of concern and reason for further study. The conversation quickly moved from the specific (while there was some debate, many suggested it was unlikely a case of autoimmune hepatitis, as the sponsor put forth) to the theoretical, as specialists acknowledged that even the process of defining "probable" drug-induced liver injury carries inherent uncertainty. Led by Doris Strader, MD (University of Vermont, Burlington, VT), a few panelists called for more rigid and mandatory guidelines on the monitoring of liver function in clinical trials as well, so that sparse data could be better interpreted in the future - Dr. Strader suggested the high rates of underlying liver disease and concomitant use of hepatotoxic medications such as statins would make this particularly applicable in diabetes. However, likely given the

uncertainty of the situation, no panelists offered specific suggestions for how to evaluate the hepatotoxicity of dapagliflozin moving forward.

- **Although hepatotoxicity was a major point of discussion during the meeting, few panelists mentioned it as a reason for their final votes.** Indeed, hepatologist Doris Strader, MD (University of Vermont, Burlington, VT) was the only one who considered it separately from cancer (rather than lumping it in with cancer as a safety issue requiring follow- up). She noted that the reason she prioritized liver concerns over cancer might have to do with her relative familiarity with each area. (We wonder if the other panelists' limited mention of hepatotoxicity reflected a generally greater comfort with cancer epidemiology compared to Hy's Law and liver chemistry, or if the potential cancer risk was simply thought more plausible and worrisome.) Of those who mentioned safety concerns, a handful specifically referred to liver disease. Some panelists proposed that liver concerns need to be addressed prior to approval; a few others noted the difficulty of studying such low-frequency events in clinical studies.
- **The panelists were in accordance that dapagliflozin showed no conclusive efficacy in patients with moderate renal impairment.** Led by nephrologist Kevin McBryde, MD (NIDDK, Bethesda, MD), many questioned the use of the 45 ml/min/1.73 m2 cut-off to narrow to the 3A stage of moderate impairment, noting that the MDRD formula used to estimate GFR tends to lose accuracy in this range and that labs can vary in their calculation method - given the 3A/3B distinction is not used in the US, many questioned its clinical relevance as well. At best, Sanjay Kaul, MD (Cedars-Sinai Medical Center, Los Angeles, CA) suggested the data was "hypothesis-generating," and many agreed an independent prospective trial would be necessary to validate any claim of efficacy in this population. In terms of monitoring renal function to ensure efficacy is maintained, Dr. McBryde and Ellen Seely, MD (Harvard Medical School, Boston, MA) proposed screening kidney function in patients on dapagliflozin regularly (minimum of annually) - given the limited data, they suggested if eGFR levels drop below 60 ml/min/1.73 m2 or if there is evidence of microalbuminuria, it should be seen as a "stop sign" for dapagliflozin treatment. While the panelists clearly hoped for a more specifically defined efficacy subset, these requirements could be clarified on the drug's eventual labeling - thus we suggest narrowing the efficacy population will likely be viewed as less relevant to the final approval decision than broader safety concerns. However, we do note that in his voting rationale, Dr. McBryde highlighted the general paucity of pharmacodynamic/ pharmacokinetic data, particularly in patients with proteinuria - given the agency's sensitivity to requests from the panelists, this may be more impactful if additional pre-marketing study is requested.
- **Despite the pre-panel hype around urinary tract infections and genital infections, there was relatively little discussion around these safety issues among the panel.** In fact, on the fourth voting question, which addressed genital-urinary infections and bone safety, chairman Abraham Thomas, MD, MPH (Henry Ford Hospital, Detroit, MI) had to kick-start thediscussion on both topics, given the lack of panel participation. He was the only one to comment on UTIs in the entire discussion and noted that although there was no signal of increased pyelonephritis (kidney infection as a result of UTI) with dapagliflozin treatment, further studies should assess the drug's impact of longer-term use. We are curious whether the focus on genital-urinary infections was minimal due to the potential severity of other safety issues (hepatotoxicity, cancer risk), given that we expect this to be a class issue that will re-surface for future SGLT-2 inhibitors. We suspect that if there had been fewer other safety issues to discuss, the panel may have had more complaints about this. That said, there is some upside for other companies that there was not much attention paid here, since there is now a precedent of some kind.
- **The open public hearing included notably fewer commenters than at recent advisory committee meetings; one speaker called for imminent conditional approval, while two others argued for substantially more pre-approval study.** Kelly Close (Close Concerns, San Francisco, CA) said that dapagliflozin, as a novel drug that lowers blood sugar without hypoglycemia or weight gain, is encouraging from a patient perspective, especially given the novel mechanism and

future potential to combine the agent with other classes. She asked the panelists to foster innovation while mitigating risk as much as possible by considering narrow labeling and/or post-approval studies to mitigate its risks as appropriate. More broadly, she encouraged the agency to measure how its policies shape early-stage development in specific therapeutic areas (e.g., to assess the effect of pre-approval cardiovascular requirements on investment and preclinical study in diabetes). Specifically, she expressed concern about lack of predictability from FDA advisory panels and declining investment in the diabetes arena. She also thanked the FDA and the advisory panel for their work to date and commented upon the "under-resourced" agency, implying this was also a negative for both patients as well as providers. Diana Zuckerman, PhD (National Research Center for Women and Families, Washington, DC) said that the risks of bladder and breast cancer stood out to her. Given the cancer issues, other safety and efficacy concerns, and her assessment that diabetes is "not an emergency situation," she told the panel members that they "don't have to rush this drug to market." Concluding the 15-minute hearing, Sidney Wolfe, MD (Health Research Group of Public Citizen, Washington, DC) reviewed dapagliflozin-associated concerns about cancer, hepatotoxicity, genital and urinary tract infections, and hematocrit changes. He said that approving dapagliflozin would mean treating a surrogate marker of disease (A1c) while increasing the risk of other diseases, whereas not approving the drug would be "a public health move in the right direction."

COMMENTARY FROM VOTING COMMITTEE MEMBERS - "YES VOTES"

- **Ellen Seely, MD (Harvard Medical School, Boston, MA) voted for approval, citing the need for additional treatments in the diabetes armamentarium, especially ones that are weight neutral or promote weight loss.** She emphasized that in her view, dapagliflozin should only be used in overweight or obese patients with normal renal function or mild renal dysfunction. Consistent with her comments earlier in the day, Dr. Seely felt that there was good reason to suspect detection bias for both bladder and breast cancer with dapagliflozin treatment. She expressed her opinion that asking companies to power studies for the outcomes of bladder and breast cancer would be largely impractical, and would halt the development of drugs that have such unexpected signals. Dr. Seely suggested that cancer risk should be assessed in the postmarketing setting, along with microalbuminuria; in addition, the sponsor could consider conducting a prospective study to explore the efficacy of dapagliflozin in those with moderate renal impairment. From a patient perspective, as we did on the Contrave panel, we reallyappreciated Dr. Seely's views, which really seemed to incorporate a strong patient perspective. We are very pleased that she is now a permanent member of the Endocrinologic and Metabolic Drugs Advisory Committee; her term began in late April 2011 and will go until 2014.
- **Abraham Thomas, MD, MPH (Henry Ford Hospital, Detroit, MI) voted for the approval of dapagliflozin, emphasizing the benefits of dapagliflozin's mechanism and the unrealistic nature of assessing cancer risk in a pre-approval setting.** He emphasized that long-term follow-up will be necessary to further establish the risk of liver toxicity, bladder cancer, and breast cancer; however, given the estimated required patient population of 30,000-100,000, he did not believe it was "realistic for drug development to make this a pre-marketing requirement." Interestingly, he cautioned against extrapolating safety of dapagliflozin from patients with familial glucosuria (condition involving a genetic mutation in SGLT-2), after referencing that patients with a similar defect leading to hypertriglyceridemia demonstrate no elevated risk of coronary events. Finally, he mentioned the importance of considering several other issues, including dehydration, syncope (leading to injuries), and quality of life; however, he did not believe these concerns warranted delaying approval of the drug.
- **Cancer specialist Steven Piantadosi, MD, PhD (Cedars-Sinai Medical Center, Los Angeles, CA) said he was in favor of approving dapagliflozin, emphasizing the compound's "quite strong" efficacy and its novel mechanism of action.** Balancing his optimism for the compound, he expressed concern about the weak evidence available for the potentially substantial cancer risk. Earlier in the day, Dr. Piantadosi expressed serious concerns about the cancer risk associated with dapagliflozin treatment, noting that the risk ratio of bladder

and breast cancer was four-to-five times more than comparator and could not be explained solely due by detection bias. However, he noted that a study to adequately cancer risk would require a large number of subjects, and such a trial would not realistically be able to be conducted in a premarketing setting.

- **Sanjay Kaul, MD (Cedars-Sinai Medical Center, Los Angeles, CA) voted to approve dapagliflozin, agreeing with Dr. Piantadosi that a study that could properly assess cancer risk would not be feasible in a premarketing setting.** Dr. Kaul noted that the label should be restricted to patients with normal renal function and mild renal dysfunction, and that it should include a box warning on potential cancer risk until the uncertainties are resolved. Always thorough, practical, and forward looking in his responses, Dr. Kaul also delineated the characteristics of the population he would like to see enrolled in the future outcomes trial - an enriched population, of which over half have prior cardiovascular disease, over half have longstanding diabetes (eight-10 years in duration, at least half are over the age of 65, and more than one quarter are over the age of 75). In addition, Dr. Kaul suggested that a trial in patients with moderate renal insufficiency is warranted in the postmarketing setting to better characterize the efficacy of dapagliflozin in this subpopulation. Lastly, he urged the FDA and panelists to keep in mind that it is the discussion and deliberation that matters most at advisory committee meetings, as opposed to the vote count.
- **Terry Smith, MD (University of Michigan, Ann Arbor, MI) voted for the approval of dapagliflozin; in his comments, he remarked that it was not an easy decision.** He was satisfied with the efficacy, not only as standalone therapy, but also for its potential to be used in combination with other diabetes drugs. In terms of post-approval studies, he was in support for further defining the target population (especially the older patients who may be prone to hypoglycemia), PK studies in patients with proteinuria, and long-term studies to establish the risk of bladder and breast cancer and hepatotoxicity.
- **Ed Hendricks, MD (Center for Weight Management, Sacramento, CA) voted in favor of approval on the basis of clinical relevance.** Contrasting dapagliflozin with many currently available options, he praised the drug for its effects on weight loss and insulin- independent mechanism of action; he also commended its potential ease of use as an oral medication. While he suggested safety issues were of some concern, he was satisfied that "post- marketing study would settle some of those issues." Encouragingly, he acknowledged that there is a limit to what can be learned from clinical trials and advocated to the agency that understanding that limit was critical to "taking medicine forward and introducing innovative things." He concluded with a tongue-in-cheek compliment to the sponsors for "the courage to bring the drug forward to this particular board" - suggesting some acknowledgement of the committee's track record of late.

COMMENTARY FROM VOTING COMMITTEE MEMBERS - "NO VOTES"

- **After voting against approval of dapagliflozin, Peter Savage, MD (NIDDK, NIH, Bethesda, MD) stated that it was not a clear-cut decision, though he did express a general desire for more data around cancer, minority groups, and renal function in elderly patients.** His safety concerns were compounded by the notion that dapagliflozin, if approved, could be used in "potentially millions of people." While he was not specific regarding additional data for cancer, he noted that another study "showing a non-significant pattern" would make him more comfortable on the carcinogenicity front. He was also concerned about efficacy in elderly populations, given the declining renal function commonly observed in these patients. Overall, Dr. Savage was not extremely specific in his requirement for pre-approval studies and was also not an active contributor to the discussion throughout the panel.
- **While speaking in positive overtones, Eric Felner, MD (Emory University School of Medicine, Atlanta, GA) voted against the approval of dapagliflozin.** He prefaced his rationale with praise for the drug's effects on A1c, weight loss, and usefulness as an add-on, noting that he would "love to see it get approved." However, similar to other dissuading panelists, he spoke

abstractly about the unacceptable level of uncertainty surrounding breast and bladder cancer risk. Notably, he concluded by suggesting that he didn't think "it would take a large study to get approved" - we assume this would mean relegating any large-scale outcomes trials to post-marketing study.

- **After coming into the meeting "on the fence and leaning toward yes," David Capuzzi, MD, PhD (Thomas Jefferson University, Philadelphia, PA) voted against approval 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.** He noted the value of an agent that acts independently of insulin secretion and sensitization, and he stated his belief that there were no "untoward" effects of glycosuria. He said that the drug's ease compared to "fancy creative peptides" (presumably GLP-1 receptor agonists) makes it particularly suited to elderly patients, whom he said generally have less time left to live. However, he was concerned by the lack of "fairly basic" subpopulation analysis and limited data on protein binding and gastrointestinal absorption. He said that given the wide range of clinicians treating people with diabetes and the general ease of access to medications, there is a need for clearer safety guidelines than are currently possible. He expressed his hopes that these issues could be resolved; he said that dapagliflozin "would be a great way to lower blood glucose" and tentatively likened it to adjunctive cholesterol-lowering drugs (bile acid binders, ezetimibe) that can be added to statins.
- **Noting that she changed her mind "about four times during the last ten seconds" before voting, Erica Brittain, PhD (National Institute of Allergy and InfectiousDiseases, Bethesda, MD) ultimately voted against the approval of dapagliflozin.** She said it was "the closest of calls," emphasizing that primarily, she just wanted to get more information on the safety of dapagliflozin, and that the timing of the collection of such data was somewhat a secondary concern. Dr. Brittain suggested that the proposed CV outcomes trial could be monitored as it progresses for cancer and hepatotoxicity risks, and that information could be used to change whatever decision is made later this year.
- **Edward Gregg, PhD (Center for Disease Control and Prevention, Atlanta, GA) voted "no" on the basis of uncertainty surrounding breast and bladder cancer risk.** While he also noted a lack of clarity on which specific populations would not benefit from the drug, Dr. Gregg indicated his primary motivator was the magnitude of the risk ratio for both cancers ("If it were 1-2 I would dismiss it, but 4-5 I just can't" - though we question what the ratios would be if the cases of cancer occurring with only short-term exposure were excluded from calculations). He put forth that the purpose of phase 2 and 3 trials in his eyes is to identify concerns such as these that need more evaluation pre-marketing. Similar to Dr. Felner, he did not think a "large, definitive trial" would be necessary to solidify cancer risk, though he did not put forth specific recommendations for what type of trial he would require to support approval.
- **Agreeing with her colleagues who voted both 'yes' and 'no,' Consumer Representative Ida Spruill, PhD, RN (Medical University of South Carolina, Charleston, SC) voted "no" based on the limited enrollment of subgroups with high burdens of diabetes (e.g., African-American and elderly patients).** She said that as a diabetes nurse educator she had initially been excited about dapagliflozin for its wide-ranging efficacy and ease of use. However, she said that as a consumer representative she had thought that "something was missing" on data in subgroups with high diabetes incidence, and she called for additional data on efficacy in these populations prior to approval. We were surprised and rather disappointed that BMS/AZ had not had higher numbers in racial sub-groups that are hit disproportionately hard in diabetes; this issue has come up in other panels, and it is something that is possible for companies to address. We felt that Spruill may well have voted for rather than against approval had this issue not been a showstopper for her. While we don't think the consumer or patient representatives votes "count" as much as the other members of the Advisory Committee, for the sake of optics if nothing else, it would have been great to have seen a 8-7 vote rather than a 9-6 vote, and this would have been the case had this

enrollment question been handled differently. We do recognize this is challenging, but given the burden of diabetes, we would suggest different CROs are used in different geographic areas if the best-known CROs cannot help with this issue. We also believe CROs have a larger responsibility to advise companies on how to obtain more representative panels (we recognize that the racial breakdown does match the US but given the disproportionate burden of diabetes on minorities, we believe that the request for higher representation is reasonable).

- **Providing the nephrology perspective, Kevin McBryde, MD (NIDDK, NIH, Bethesda, MD) provided a passionate speech justifying his negative vote, focusing on the lack of data on the effects of dapagliflozin in patients with proteinuria.** In his rationale for voting against the approval of dapagliflozin, Dr. McBryde began offering a theoretical explanation: "I have learned in my career to have a tremendous amount of respect for the proximal tubule of the kidney…to block SGLT-2 and say it will have no effect is giving tremendous discredit to the proximal tubule." His primary complaint was the scarcity of data on dapagliflozin in patients with proteinuria, given that the drug is 91% protein-bound and that patients with proteinuria are known to induce drug resistance. He referenced familial glucosuria patients, noting that they are often children suffering from growth delay, dehydration, electrolyte imbalances, etc. However, aside from renal impairment, Dr. McBryde was also uncertain aboutthe specific indications BMS/AZ were targeting and was uncomfortable about the "potentially wide distribution" given the aforementioned safety concerns.
- **Doris Strader, MD (University of Vermont College of Medicine, Burlington, VT) suggested the potential risk of subjecting patients to "life-threatening complications" currently overwhelmed the benefits of dapagliflozin.** While she acknowledged the challenges of conducting conclusive studies pre-marketing, she indicated such concerning issues could not be ignored in her decision-making. Similar to Dr. McBryde, she was also surprised by the absence of pharmacodynamic and pharmacokinetic study results. As the resident hepatologist, she noted that hepatotoxicity is "always of concern to me" as well, though she was unsure whether one case was enough to support any correlation - rather, she suggested the case demonstrated the need for more rigorous and well-defined guidelines on the monitoring of liver disease in diabetes trials.
- **Patient Representative Cassandra McIntyre (Mitchellville, MD) voted a decisive "no," saying that BMS/AZ need to obtain more data about risks for hepatic disease, breast and bladder cancer, and genital and urinary tract infections.** She noted that dapagliflozin is innovative and could be useful for people with type 2 diabetes, but she believes that patients lack data to make an informed decision about whether to use the drug. She said that it is better to have these data prior to approval rather than risk losing public trust if risks are confirmed post-approval; she did not discuss the practicality of screening for rare events in pre- approval trials.

--by Joseph Shivers, Sanjay Trehan, Vincent Wu, and Kelly Close

Appendix 1: Dapagliflozin Advisory Committee Morning Highlights - July 19, 2011

This was distributed mid-day on July 19.

The morning portion of the dapagliflozin advisory committee meeting consisted of sponsor (BMS/AZ) presentations, FDA presentations, and clarifying questions from the committee. In general, BMS/AZ focused on the clinical development program for dapagliflozin and proposed post-marketing studies. BMS chose their presenters well, enlisting very well regarded Dr. John Buse (University of North Carolina, Chapel Hill, NC) and Dr. James Gavin (CEO and CMO, Healing Our Village) to discuss the medical need for new diabetes treatments and the overall risk/benefit of dapagliflozin. In the clarifying questions to the sponsor, panelists fielded questions on a broad range of topics, with no overwhelming emphasis on one safety issue. However, after FDA medical reviewer Dr. Somya Dunn (Clinical Reviewer, Division, CDER, FDA) highlighted cancer risk and Hy's Law (drug-induced liver injury) as the primary safety concerns from the FDA's perspective, the panel's following questions were largely focused around assessing and extrapolating cancer risk associated with dapagliflozin treatment.

- **Opening the session, Dr. Mary Parks (Director, Division of Metabolism and Endocrinology Products, CDER) commended industry representative Dr. Enrico Veltri (Vice President, US Medical Affairs, Sanofi) for his three years of participation on the Endocrinologic and Metabolic Drugs Advisory Committee, presenting him with a plaque for his service.** We appreciated this gesture, as serving on an advisory committee is likely no easy task, is of paramount importance in influencing the direction of regulation, and likely goes widely unrecognized in the public.
- **During BMS' discussion on the safety of dapagliflozin, Dr. Jim List (Executive Director, Global Clinical Research - CV/Metabolics, BMS) highlighted that there were no preclinical signals suggesting cancer or liver toxicity risk.** He noted that there was no compelling evidence to suggest the imbalances in bladder and breast cancer were drug induced, given the lack of biological plausibility, and the small number of cases. Subsequently, he pointed out the difficulties in assigning causality of liver injury, noting that in the one case of potential drug-induced liver injury (DILI), the three adjudicators all differed in their decisions - one thought DILI was probable, one thought it was possible, and one thought it was unlikely.
- **BMS focused on the comprehensiveness of its clinical development program for dapagliflozin, and the comprehensiveness of its approach.** Dr. Brian Daniels (Senior Vice President, Global Development and Medical Affairs, BMS) said that according to their estimates, dapagliflozin's clinical trial development program was the largest one submitted to the FDA for review thus far, with data for over 6,000 patients (over 4,000 on dapagliflozin). Noting that over 10,000 patients of a planned 16,000 have already been enrolled for the SAVOR cardiovascular outcomes trial for saxagliptin (Onglyza) in the 30 months following its approval, Dr. Daniels suggested that the company would proceed with a similar level of dedication for dapagliflozin in the postmarketing setting, with an outcomes trial, extensive pharmacovigilance, and observational studies.
- **BMS chose their presenters well, enlisting very well regarded Dr. John Buse (University of North Carolina, Chapel Hill, NC) and Dr. James Gavin (CEO and CMO, Healing Our Village) to discuss the medical need for new diabetes treatments and the overall risk/benefit of dapagliflozin.** In our opinion, both did a superb job in providing compelling arguments for the need for additional agents with novel mechanisms, good efficacy in lowering A1c, and little risk for hypoglycemia that cause weight loss, as the diabetes epidemic is still growing.
- **In the clarifying questions to the sponsor, panelists asked questions on a broad variety of topics, with no overwhelming emphasis on any specific safety issue.** Industry representative Dr. Veltri asked about markers of macrovascular risk - lipids, proinflammatory markers, and heart rate; Dr. Ellen Seely (Harvard Medical School, Boston, MA) inquired about the time course and recurrence of urinary and genital tract infections; Dr. Steven Piantadosi (Cedars-Sinai Medical Center, Los Angeles, CA) asked for malignancy rate ratios; Dr. Edward Gregg (CDC, Atlanta, GA) brought up efficacy in older populations; and Dr. Doris Strader (University of Vermont, Burlington, VT) inquired about the extent of BMS' evaluation of liver enzymes. Overall, a balanced set of questions in our view, with no major insights regarding dapagliflozin's approvability.
- **During the FDA presentation, Dr. Somya Dunn (Clinical Reviewer, Division, CDER, FDA) highlighted cancer risk and Hy's Law as the two major safety issues with dapagliflozin.** She noted that potential bladder and breast cancer risk were "of particular concern," and that one Hy's Law case in a clinical program is "worrisome;" to be fair, she acknowledged that it is difficult to assess the risk based solely on one case. Urinary and genital tract infections, while more common in dapagliflozin-treated patients, did not seem to be of much concern to Dr. Dunn.
- **In the clarifying questions to the FDA, panelists largely focused on cancer risk.** Notably, Dr. David Capuzzi (Thomas Jefferson University, Philadelphia, PA) commented that even though

there are "very soft numbers" with regards to the number of cases of cancer seen in the dapagliflozin clinical development program, he was "not comfortable with it," highlighting the severity of the cancers and the barriers to effective diagnosis. In addition, Dr. Piantadosi asked the FDA and BMS to delineate what the final number of cases of bladder and breast cancer the panelists should use in their deliberations. During the session, Dr. Sanjay Kaul (Cedars-Sinai Medical Center, Los Angeles, CA) asked for additional clarity on baseline CV characteristics of the study population. In general, we found the questions that were asked to the sponsor and to the FDA to be of a higher level of granularity than those asked at the advisory committee meetings for anti-obesity medications, presumably due to the panelists' greater familiarity with diabetes.

- **This one is hard to call so we won't even try.** We'll be back later with the vote.