AZ's DEPICT 1 trial of SGLT-2 inhibitor Farxiga (dapagliflozin) in type 1 diabetes just reported full results this morning at EASD 2017. The results were simultaneously published in the Lancet Diabetes & Endocrinology. Our initial reaction? Extremely positive. This data shows promise for dapagliflozin (and maybe other SGLT-2 inhibitors, down the line) to become a viable therapeutic option for people with type 1 diabetes, particularly those in-need of additional glycemic control and weight loss not achieved on insulin alone. Notably, DEPICT 1 was the first phase 3 trial of an SGLT-2 inhibitor in type 1 diabetes to report - J&J's Invokana (canagliflozin) remains in phase 2 for type 1, while Lilly/BI's Jardiance (empagliflozin) is in phase 3. Lexicon's SGLT-1/2 dual inhibitor sotagliflozin is also in phase 3 for a type 1 indication, and we saw brand new inTandem3 data just yesterday.

From a baseline 8.5%, mean A1c declined 0.4% with dapagliflozin 5 mg vs. placebo and 0.5% with dapagliflozin 10 mg vs. placebo (both p<0.001). CGM readings showed 52% (12.5 hours), 55% (13.2 hours), and 44% (10.6) time-in-range for 5 mg dapa, 10 mg dapa, and placebo, respectively, and weight loss was also 3%-4% greater with dapagliflozin vs. placebo (p<0.0001). Incredibly reassuring was the lack of any imbalance in DKA, with an event rate of 1% in the 5-mg group (four patients - two due to insulin pump failure, one to missed insulin dose), 2% in the 10-mg group (five patients - one attributed to pump failure, three to missed insulin dose, and one to alcohol), and 1% in the placebo group (three patients - one due to pump failure, one to missed insulin dose, one to stress). DEPICT 1 protocol recommended no more than 20% reduction in total daily insulin dose, based on evidence from prior studies. In general, we're reminded that the field still lacks clarity on best practice DKA management, but as adjunct type 1 therapies show promising phase 3 data (both dapagliflozin and SGLT-1/2 dual inhibitor sotagliflozin, with Lexicon's inTandem3 presented yesterday), this will hopefully come to light. This is just a summary of the results, and we provide much more granular detail below!

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SGLT-2 Inhibitors: Novel Therapies for Type 1 Diabetes

UNMET NEED AND ADJUNCT NON-INSULIN THERAPIES

Chantal Mathieu, MD (UZ Gasthuisberg, Lueven, Belgium)

Dr. Chantal Mathieu opened this symposium with an argument of what we should look for in adjunct type 1 diabetes therapies: (i) more stable glucose profiles, (ii) less weight gain, and (iii) less hypoglycemia. Equally important is what's missing from this list, namely the reduction of insulin dose. While clinical trials in type 1 diabetes tend to report this (and while observers tend to focus on it), Dr. Mathieu maintained that decreasing insulin requirements should not be a goal independent of bringing down hypoglycemia risk. She

outlined insulin's key physiological role in suppressing hepatic glucose production, lipolysis, and lipogenesis. People with type 1 diabetes, whose beta cells aren't secreting enough insulin, thus rely on exogenous insulin doses that shouldn't necessarily be dramatically reduced even with adjunct treatment. Dr. Mathieu emphasized the importance of time-in-range and the value of CGM in clinical trials to analyze this (foreshadowing what DEPICT 1 CGM data would show…). Notably, she also chaired an earlier EASD symposium on Sanofi/Lexicon's SGLT-1/2 dual inhibitor sotagliflozin and the inTandem3 trial in type 1 diabetes. DKA was more common in the sotagliflozin arm (3%) vs. placebo (0.6%), a finding that has elicited mixed reactions, though in our view the efficacy data far outweighs this manageable safety risk. Dr. Mathieu shared her invaluable clinical perspective, that these agents (both dapagliflozin and sotagliflozin) could be highly-effective therapeutic tools for type 1 diabetes, but that they should be used in "expert hands," with strong education on both the provider side and the patient side.

DEPICT 1: STUDY DESIGN AND BASELINE CHARACTERISTICS

Lars Hansen, MD (BMS, Princeton, NJ)

In this introduction to the trial, Dr. Lars Hansen provided an impressive amount of detail on baseline characteristics of the study population and study protocols (we were particularly interested in the recommendations around DKA, and appreciated the specificity). DEPICT 1 was conducted at 143 centers across 17 countries. At baseline, participants (n=833) had a mean A1c of 8.5%, mean age of ~42 years, mean diabetes duration of ~20 years, mean daily insulin dose of ~60 units, and mean BMI of 28 kg/m² (indicating overweight) - we note that this pool was comprised of patients in definite need for further A1c reductions and weight loss. Participants were randomized 1:1:1 to dapagliflozin 5 mg (n=277), dapagliflozin 10 mg (n=296), or placebo (n=260). All study drugs were on top of a patient's background insulin regimen. After randomization, the study was designed to include a 24-week, double-blind treatment period, followed by an un-blinded 28-week treatment period. The 24-week data was presented and published today in the Lancet Diabetes & Endocrinology. The primary outcome was change in A1c at 24 weeks with dapagliflozin 5 mg or 10 mg vs. placebo, and secondary outcomes included changes in total daily insulin dose, body weight, mean 24-hour glucose, mean amplitude of glucose excursion (MAGE), time-in-range between 70-180 mg/dl, and proportion of patients achieving an A1c decrease of ≥0.5% without severe hypoglycemia. The study enrolled slightly more females than males, and >95% of participants were white. Moreover, ~60% of participants were from Europe and 27% from North America, the rest from Latin America and Asia-Pacific. Approximately 63% of participants were using MDI, with about 37% using an insulin pump; 33% of participants used CGM at baseline.

- **Based on a phase 2 pilot study of dapagliflozin in type 1 diabetes, and a post-hoc analysis splitting insulin dose adjustments above and below 20%, investigators decided to cap insulin dose reductions at 20% in DEPICT 1 to counter DKA risk.** In the pilot, decreasing insulin by >20% was associated with an increase in ketogenesis. Following the first dose of dapagliflozin in DEPICT 1, patients/providers were recommended to reduce total daily insulin dose (including basal and bolus) up to but no more than 20%. Insulin adjustment followed throughout the treatment period. Study participants were given a combined meter for glucose/ketones and were instructed to fingerstick at least four times per day, as well as to check beta-hydroxybutyrate levels at any sign of DKA or illness, independent of SMBG values (we imagine this alerting of patients to early signs of possible DKA could be immensely valuable in the real world, though more much consensus is needed on how DKA should be most effectively monitored in real clinical practice settings).

DEPICT 1: EFFICACY AND SAFETY DATA

Paresh Dandona, MD (State University of New York, Buffalo, NY)

Dr. Paresh Dandona presented the safety and efficacy data from DEPICT 1, both decidedly positive. Results were published simultaneously in the Lancet Diabetes & Endocrinology. Both doses of dapagliflozin met the primary endpoint of change in A1c over 24 weeks: the 5 mg dose gave a 0.4% drop vs. placebo, while the 10 mg dose gave a 0.5% drop vs. placebo (both p<0.0001). A1c reduction was consistent across doses. Dr.

Dandona pointed out that a 0.25% A1c decline was observed between the screening visit and randomization (he described this as unsurprising, because people experiencing challenges with their glucose management often show improvement with additional "attention," i.e. enrollment in a clinical trial), with a clear additional benefit to dapagliflozin therapy after randomization. Total daily insulin dose fell 9% vs. placebo for the 5 mg dose of dapagliflozin and 13% vs. placebo for the 10 mg dose (both p<0.0001). Percent change in body weight vs. placebo was -3% for the 5 mg dapa dose and -4% for the 10 mg dose (both p<0.0001). Moreover, weight loss was continuous and there was very little flattening of the curve over six months, leading Dr. Dandona to conclude that more weight loss can be expected long-term (we eagerly await DEPICT 1 trial extension data to see for ourselves). Hypoglycemia was well-balanced across all treatment arms, and the proportion of patients with an A1c reduction of ≥0.5% without severe hypoglycemia was >50% for both SGLT-2 doses compared to ~25% for placebo.

- **CGM readings showed 52% (12.5 hours), 55% (13.2 hours), and 44% (10.6) time-in-range for 5 mg dapa, 10 mg dapa, and placebo, respectively.** This translates to an extra ~2.2 hours in-range for low-dose dapagliflozin patients and an extra ~2.6 hours in-range for high-dose dapagliflozin patients vs. placebo - time spent feeling well, experiencing better quality of life (this is a tremendous increase!). In the placebo group, average adjusted interstitial glucose increased 5 mg/dl over 24 weeks; mean difference from placebo for the dapagliflozin groups was -15 mg/dl for 5 mg and -18 mg/dl for 10 mg (both p<0.001). Average adjusted MAGE at 24 weeks with placebo was 2 mg/dl; mean difference from placebo for the dapagliflozin groups was -17 mg/dl for low-dose and -19 mg/dl for high-dose (both p<0.0001).
- **24-hour CGM data indicates a blood glucose reduction in the early morning hours.** According to investigators, patients dosed dapagliflozin in the morning, and the greatest glucose-lowering effects seemed to occur near the end of the 24-hour dose cycle, around 7 am. This will require further analysis, and more study will be needed to fully comprehend the time-action profile of dapagliflozin in patients with type 1 diabetes, as well as how the "dawn effect" of early morning glucose increase is involved in this dynamic.
- **DKA has emerged as a key consideration in using SGLT-1/2 and SGLT-2 inhibitors in type 1 diabetes, but DEPICT 1 was reassuring on this front.** There was an event rate of 1% in the 5 mg group (four patients - two due to insulin pump failure, one to missed insulin dose), 2% in the 10 mg group (five patients - one attributed to pump failure, three to missed insulin dose, and one to alcohol), and 1% in the placebo group (three patients - one due to pump failure, one to missed insulin dose, one to stress). At least some of the favorable DKA outcomes seem to be attributable to the study guideline that total insulin should only be reduced up to 20% - patients were advised to eat extra carbs and dose insulin if they weren't taking a certain amount daily. It is our understanding that this lower limit of insulin reduction is paramount in preventing DKA, and we wonder if there was any cap on insulin reduction in any of the inTandem clinical trials for sotagliflozin.
- **The adverse event profile of dapagliflozin was otherwise as expected, with a greater frequency of genital mycotic infections** (12%, 11%, and 3% in the 5 mg, 10 mg, and placebo arms, respectively). Urinary tract infections, fractures, and hypotension/dehydration were all evenly balanced and rarely occurred. Hypoglycemia occurred in 79% of participants on the 5 mg dapa dose, 79% of those on the 10 mg dapa dose, and 80% of those taking placebo, while severe hypoglycemia occurred in 8%, 6%, and 7% of participants, respectively. Adverse events led to 23 discontinuations in total: six from the 5 mg dose, 8 from the 10 mg dose, and 9 from placebo.

COMMENTATOR

Maciej Malecki, MD (Jagiellonian University Medical College, Cracow, Poland)

Dr. Maciej Malecki provided independent commentary, offering a very positive view on DEPICT 1 trial design and results overall. In fact, one of his final slides read that "the DEPICT 1 study gives hope for prompt registration of dapagliflozin as an adjunct type 1 therapy" - indeed, we'd love to see Farxiga move closer to the type 1 market, and we keep our fingers crossed that upcoming results from DEPICT 2 and the DEPICT 1 trial extension support the strong safety/efficacy profile seen here. According to Dr. Malecki, it's a

shame the DEPICT 1 investigators didn't formally assess patient quality of life, because he predicts the result would've been quite positive, and we'd presume the same given significant improvements to time-in-range and body weight. He raised a question around dapagliflozin's applicability in type 1 diabetes patients with lower baseline A1c, body weight, or total daily insulin dose, suggesting that in these circumstances, further decreases may not be desirable. On the other hand, we imagine ideal candidates for new adjunct treatments like dapagliflozin and sotagliflozin will be those type 1 patients in-need of additional glycemic control and weight loss, so it makes sense for AZ to investigate its SGLT-2 inhibitor in this particular patient population (somewhat elevated baseline A1c of 8.5%). It's true, patients well-controlled and satisfied with their insulin therapy may not see the need for Farxiga to be introduced in pharmacies with a type 1 indication, but this is a small minority of the population - only one in three adults with type 1 diabetes in the US are meeting A1c goal.

- **Dr. Malecki added to Dr. Mathieu's list of what we should look for in an adjunct therapy: Beyond more time-in-range, less weight gain, and less hypoglycemia, he also mentioned CV risk reduction.** The excess risk for mortality in people with type 1 diabetes vs. the background population is almost entirely accounted for by CV death, he explained, arguing that we need better medicines to bring down this risk. DEPICT 1, of course, was not an outcomes trial, and we know it will likely be challenging to get all the funding/resources behind a large CVOT in type 1 diabetes. Dr. Malecki was optimistic, however, about the DECLARE CVOT for dapagliflozin in type 2 diabetes (he cited two positive SGLT-2 CVOTs so far, EMPA-REG OUTCOME and CANVAS). Positive DECLARE results wouldn't support an indication specific to type 1, but at the very least, they would help spread awareness among patients/HCPs about the cardioprotective effects of SGLT-2 inhibitors, and word would certainly spread to the type 1 community as well. DECLARE is expected to complete in the second half of 2018.
- **During Q&A, Dr. Julio Rosenstock cautioned against a possible misinterpretation of DEPICT 1 in context with inTandem 3:** "People need to be extremely careful not to run out of this room and say dapagliflozin is safe and sotagliflozin is not. These are two separate studies, with more MDI in DEPICT 1. People on MDI had less chance of DKA than people on pumps in the inTandem studies." We agree that study design differences make comparisons difficult (and often futile). It is our view that both these phase 3 studies were actually positive.
- **One final word from us on DKA:** The recommendation for no more than 20% insulin dose reduction was the most specific DKA-related study protocol we've heard, and we're curious for more color on the DKA education and risk mitigation strategies in inTandem3. Similar to how the amputation signal in CANVAS highlighted the lack of proper education around foot care in real-world diabetes management, the inTandem program and clinical programs for SGLT-2 inhibitors in type 1 have brought the need for better DKA education to the forefront. As Dr. John Buse remarked in a separate conversation with us, the DKA-related education in inTandem3 was probably far from optimal, which begs the question: what is optimal DKA risk management? And, how can we spread it broadly in the real world? We'd love to collect more insights on this, and we're hoping for some motion toward consensus, in time for sotagliflozin and dapagliflozin to reach the type 1 diabetes market (yes, we're still very hopeful). None of this is to say that these safety concerns of amputations and DKA are trivial - far from it. Rather, it would be a sad story to see clinically-meaningful benefits like time-in-range and weight loss overshadowed by a manageable safety concern, especially when there is such high unmet need in the type 1 population for adjunct therapy.

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