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Safety Update on Dapagliflozin (DAPA) Across the Phase 2b/3 Clinical Trial Program

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Abstract:
Safety/tolerability of sodium-glucose cotransporter-2 inhibitors (SGLT2i) are of interest. DAPA is a highly selective SGLT2i for the treatment of type 2 diabetes. Data were pooled from 13 placebo (PBO)-controlled trials (**Table**). To detect rare adverse events (AEs), larger PBO/comparator-controlled pools of 21 trials (≤208 week [wk]; DAPA, n=5936; Control, n=3403) and 30 trials (≥12 wk; DAPA, n=9195; Control, n=4629) assessed diabetic ketoacidosis (DKA) and lower-limb amputations, respectively. Over 24 wks, AE and serious AE rates were similar for DAPA vs PBO; 60 vs 56% and 5 vs 5%, respectively. Rates of hypoglycemia, volume depletion AEs and urinary tract infection were balanced between groups (**Table**). Genital infections were more frequent with DAPA vs PBO (6 vs 1%), fractures were balanced between groups (0.3 vs 0.7%) and renal function AEs occurred in 3 vs 2% of patients (most common was decreased creatinine clearance; 1.1 vs 0.7%). In the 21-study pool, 1 serious event of DKA and 3 events of ketonuria/metabolic acidosis occurred with DAPA; estimated incidence for any of these events was 0.03 (95% CI: 0.010, 0.089). In the 30-study pool, lower-limb amputation occurred in 8 (0.1%) DAPA vs 7 (0.2%) Control patients. In summary, DAPA was well tolerated across the clinical trial program. AE rates were generally balanced for DAPA vs PBO/Control, including special interest AEs such as hypoglycemia, fractures, amputations and DKA.

Adverse events of special interest in the dapagliflozin Phase 2b/3 clinical trial program

PBO/comparator-controlled 30-study pool			**PBO/comparator-controlled 21-study pool**		
Amputation	**DAPA total (N=9195)**	**Control (N=4629)**	**DKA**	**DAPA total (N=5936)**	**Control (N=3403)**
Pts with lower-limb amputation, n (%)	8 (0.1)	7 (0.2)	SAE of DKA, n AE ketonuria, n AE metabolic acidosis, n Incidence DKA* % (95% CI) . Incidence DKA/metabolic acidosis*, % (95% CI) .	1 2 1 0.02 (0.004, 0.059) . 0.03 (0.010, 0.089) .	0 0 0 0 . . 0 . .

Patients with events, n (%)	**ST PBO-controlled 13-study pool**	
	DAPA 10 mg (N=2360) 998 p-y	**PBO (N=2295) 958 p-y**

Fractures	8 (0.3)	17 (0.7)
Hypoglycemia	324 (14)	284 (12)
Major event	3 (0.1)	2 (0.1)
AE → discon.	1 (<0.1)	0
Renal function†	76 (3)	42 (2)
Volume depletion§	27 (1)	17 (1)
UTI	110 (5)	81 (4)
Females	85 (4)	64 (3)
Genital infection	130 (6)	14 (1)
Females	84 (4)	11 (<1)

Adverse events are based on a predefined list of preferred terms; Includes data after rescue; *Estimated incidence; †Includes renal failure or impairment, creatinine renal clearance decreased/increased/abnormal, blood creatinine increased/decreased, glomerular filtration rate decreased/increased/abnormal, cystatin C increased, renal function test abnormal, urine flow or output decreased/increased/abnormal, anuria. §Hypotension/hypovolemia/dehydration. DAPA total includes DAPA 2.5, 5, 10, 20 and 50 mg groups combined. Control includes placebo with/without background medications or active control including benchmark treatments. AE=adverse event; DAPA=dapagliflozin; discon.=discontinuation; LT=long term; PBO=placebo; p-y=patient-years; SAE=serious adverse event; ST=short term; UTI=urinary tract infection; wks=weeks

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Author Disclosure Information:

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