

**Supplementary Table 1 The characteristics of each sodium glucose transporter 2 inhibitor - particularly their pharmacological properties and structural features**

<b>PARAMETERS</b>	<b>Empagliflozin</b>	<b>Dapagliflozin</b>	<b>Ertugliflozin</b>	<b>Canagliflozin</b>
Formula	C <sub>23</sub> H <sub>27</sub> ClO <sub>7</sub>	C <sub>21</sub> H <sub>25</sub> ClO <sub>6</sub>	C <sub>22</sub> H <sub>25</sub> ClO <sub>7</sub>	C <sub>24</sub> H <sub>25</sub> FO <sub>5</sub> S
Molecular weight	450.91 g/mol	408.87 g/mol	436.90 g/mol	444.52 g/mol
Substituents	Tetrahydrofuran (THF) ring	Ethylphenyl moiety	ether Dioxo-bicyclo [3.2.1] octane	Thiophene ring & Fluorine
SGLT2 selectivity (Fold vs SGLT1)	> 2500	> 1200	~ 2000	~ 250-400
Lipophilicity (Log <i>Pow</i> (approximately))	~ 2.3	~ 2.7	~ 2.5	~ 3.4
SGLT1 effect (Inhibition potential)	Negligible	Negligible	Negligible	Moderate (Intestinal)
Daily dose	10-25 mg	5-10 mg	5-15 mg	100-300 mg
t <sub>1/2</sub>	12.4 h	12.9 h	11-17 h	10-13 h

**Supplementary Table 2 The key characteristics of the major clinical trials evaluating sodium glucose transporter 2 inhibitors in heart failure**

<b>Trial name</b>	<b>DAPA-HF</b>	<b>EMPEROR- Reduced</b>	<b>EMPEROR-Preserved</b>	<b>DELIVER</b>
Drug	Dapagliflozin 10 mg once daily	Empagliflozin 10 mg once daily	Empagliflozin 10 mg once daily	Dapagliflozin 10 mg once daily
Publication Year	2019	2020	2021	2022
Clinical trials ID	NCT03036124	NCT03057977	NCT03057951	NCT03619213
Study design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
Sample size (total)	4,744	3,730	5,988	6,263
Median follow-up (months)	18.2	16.0	26.2	27.6
Patient population	HFrEF	HFrEF	HFpEF	HFmrEF/HFpEF
NYHA functional class	NYHA Class II (67.7%), III (31.5%), IV (0.8%)	NYHA Class II (75.1%), III (24.4%), IV (0.5%)	NYHA Class I (0.1%), II (81.1%), III (18.4%), IV (0.3%)	NYHA Class II (73.9-76.6%), III (23.1-25.8%), IV (0.3%)
LVEF	LVEF =<40%	LVEF =<40%	LVEF >40%	LVEF >40%

Mean/Median LVEF (%)	31.2 ± 6.7	27.7 ± 6.0	54.3 ± 8.8	54.0 ± 8.6
Diabetes mellitus (%)	41.8% (with type 2 diabetes)	49.8% (with diabetes)	48.9% (with diabetes)	44.7% (with type 2 diabetes)
Mean eGFR (ml/min/1.73 m <sup>2</sup> )	66.0 ± 19.6	61.8 ± 21.7	60.6 ± 19.8	61 ± 19
Median NT-proBNP (pg/ml)	1,428 (857-2,655)	1,887 (1,077-3,429)	994 (501-1,740)	994 (501-1,740) [estimated]
Hospitalization for HF within 12 months (%)	47.4%	31.0%	23.3%	Recent hospitalization allowed
Primary outcome	Composite of worsening HF or CD	Composite of CD or hospitalization for HF	Composite of CD or hospitalization for HF	Composite of worsening HF or CD
Primary endpoint definition	Worsening HF: hospitalization or urgent IV therapy for HF CD: adjudicated CD	CD or first hospitalization for HF (adjudicated)	CD or first hospitalization for HF (adjudicated)	Worsening HF: hospitalization or urgent visit for HF CD: adjudicated CD
Key results	Primary outcome results	Primary outcome results	Primary outcome results	Primary outcome results
Primary outcome event rate -	16.3% (386/2,373)	19.4% (361/1,863)	13.8% (415/2,997)	16.4% (512/3,131)

drug group (%)					
Primary outcome event rate -	21.2% (502/2,371)	24.7% (462/1,867)	17.1% (511/2,991)		19.5% (610/3,132)
placebo group (%)					
HR (95% CI)	0.74 (0.65-0.85)	0.75 (0.65-0.86)	0.79 (0.69-0.90)		0.82 (0.73-0.92)
p value	<0.001	<0.001	<0.001		<0.001
Number needed to treat (95% CI)	21 (15-38)	19 (13-37)	31 (20-69)		Approximately 32 patients
Secondary outcomes	Secondary efficacy results	Secondary efficacy results	Secondary efficacy results		Secondary efficacy results
First HF hospitalization - HR (95% CI)	0.70 (0.59-0.83)	0.69 (0.59-0.81)	0.71 (0.60-0.83)		0.79 (0.69-0.91)
Total (first + recurrent) HF hospitalizations - HR/RR (95% CI)	0.75 (0.65-0.88)	0.70 (0.58-0.85)	0.73 (0.61-0.88)		0.77 (0.67-0.89)
CD - HR (95% CI)	0.82 (0.69-0.98)	0.92 (0.75-1.12)	0.91 (0.76-1.09)		0.88 (0.74-1.05)
All-cause mortality - HR (95% CI)	0.83 (0.71-0.97)	0.92 (0.77-1.10)	1.00 (0.87-1.15)		0.94 (0.83-1.07)
Key safety findings	Safety Profile	Safety Profile	Safety Profile		Safety Profile

Serious adverse events (%)	Dapa: 43.5% Placebo: 45.5%	vs	Empa: 47.9% Placebo: 51.6%	vs	Empa: 47.9% Placebo: 51.6%	vs	Dapa: 43.5% Placebo: 45.5%
Discontinuation due to adverse events (%)	Dapa: 4.7% Placebo: 4.9%	vs	Empa: 19.1% Placebo: 18.4%	vs	Empa: 19.1% Placebo: 18.4%	vs	Dapa: 5.8% Placebo: 5.8%
Volume depletion (%)	Dapa: 7.5% Placebo: 6.8%	vs	Similar between groups		More common with empagliflozin		Dapa: 1.3% Placebo: 1.0%
Renal adverse events (%)	Dapa: 6.5% Placebo: 7.2%	vs	Similar between groups		Similar between groups		Dapa: 2.3% Placebo: 2.5%
Genital tract infections	More common with dapagliflozin		More common with empagliflozin		Genital and urinary tract infections more common		Similar between groups
Diabetic ketoacidosis	3 cases (0.1%) vs 0 in placebo		Rare cases reported		Rare cases: 2 (0.1%) in empagliflozin		Rare: 2 cases (0.1%) vs 0
Major hypoglycemia	Rare: 4 cases (0.2%) in each group		Similar between groups		Similar between groups		Similar: 6 (0.2%) vs 7 (0.2%)

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