Poster Number: POSB22

Indirect Treatment Comparisons of Empagliflozin versus Sacubitril/ Valsartan for Patients with Heart Failure with Reduced Ejection Fraction

EMPEROR
Heart failure studies

Sarah Smith[1], Hollie Pilkington[1], Neil Roskell[1], Stephan Linden[2], Leana Bellanca[3]
[1]BresMed Health Solutions Ltd, Manchester, UK; [2]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [3]Boehringer Ingelheim Ltd, Bracknell, United Kingdom.

OBJECTIVES

- Heart failure with reduced ejection fraction (HFrEF) is a complex clinical syndrome characterized by structural and/or functional impairment of the left ventricle of the heart
  - This results in a decrease in heart pump function (left ventricular ejection fraction [LVEF] ≤ 40%) and an insufficient amount of oxygenated blood being delivered to the body's tissues and organs
- This research aimed to investigate the relative efficacy of empagliflozin (a highly selective, sodium–glucose cotransporter 2 [SGLT2] inhibitor) compared with sacubitril/valsartan (a standard therapy) in treating HFrEF
- Given the lack of head-to-head data, an indirect treatment comparison (ITC) methodology was used

METHODS

Evidence base:

- Empagliflozin was investigated as an add-on to standard of care (SoC) in patients with HFrEF in EMPEROR-REDUCED (NCT03057977), a Phase III, randomized, double-blind, placebo-controlled trial[1]
- Sacubitril/valsartan for the treatment of HFrEF was investigated in PARADIGM-HF, a Phase III, randomized, double-blind, enalapril-controlled trial[2]

ITC methodology:

- We primarily used Bucher ITC methodology for comparisons. This methodology assumes that treatment effects within each trial are homogeneous across the variables that differ between trials[3]
  - To investigate this assumption, we conducted anchored matching-adjusted indirect comparisons (MAICs), which adjust for treatment effect modifiers to ensure balance across trials[4, 5]
- We assumed that the placebo + SoC arm in EMPEROR-REDUCED was comparable to the enalapril + SoC arm in PARADIGM-HF
- The variables used in the matching were based on those identified as important treatment effect modifiers through exploratory subgroup analyses of the empagliflozin patient-level data but were limited to those reported in the comparator evidence
- Endpoints compared were time to first event of adjudicated cardiovascular (CV) death or adjudicated hospitalization for heart failure (HHF), time to adjudicated HHF, time to adjudicated CV death, and time to all-cause mortality
- As patients in EMPEROR-REDUCED could receive sacubitril/valsartan (an angiotensin receptor-neprilysin inhibitor [ARNI]), the subgroup of EMPEROR-REDUCED patients who did not receive an ARNI at baseline were used in the primary analyses
  - EMPEROR-REDUCED was not stratified for this subgroup
  - Therefore, analyses were also performed using the EMPEROR-REDUCED intention-to-treat (ITT) population, which retained randomization, as a sensitivity analysis

RESULTS

Matching variables:

The treatment effect modifiers identified and used in the MAIC analyses, and available in EMPEROR-REDUCED and PARADIGM-HF studies, were:

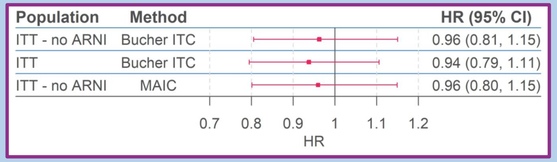
- Race (white versus non-white)
- New York Heart Association (NYHA) Class (II versus III/IV)
- N-terminal prohormone brain natriuretic peptide (NT-proBNP; ≤ median in PARADIGM-HF versus > median in PARADIGM-HF)
- Left ventricular ejection fraction (LVEF; ≤ median in PARADIGM-HF versus > median in PARADIGM-HF)
- Estimated glomerular filtration rate (eGFR; < 60, ≥ 60 ml/min/1.73 m^2)

The identified treatment effect modifiers and the associated matching categories were deemed clinically meaningful based on an external expert opinion (i.e. a cardiologist).

Time to first event of adjudicated CV death or adjudicated HHF results:

- For the composite primary endpoint, the Bucher ITC, which compared the subset of the EMPEROR-REDUCED patients who were not receiving sacubitril/valsartan at baseline with the PARADIGM-HF ITT population, showed a similar efficacy between the two treatments (see Figure 1)
- Using the full ITT population from EMPEROR-REDUCED gave a consistent result
- The MAIC produced a similar result to the Bucher ITC, justifying the assumption required for a Bucher ITC to be the primary analysis

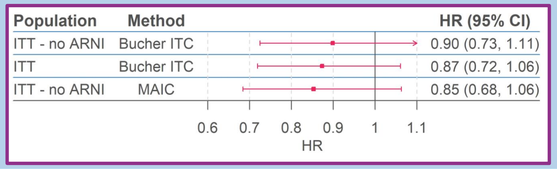
Figure 1: Forest plots to show time to first event of adjudicated CV death or adjudicated HHF results



Time to adjudicated HHF results:

- For time to HHF, the primary analysis resulted in a hazard ratio (HR) (95% confidence interval [CI]) of 0.90 (0.73, 1.11). Again, this suggests comparable efficacy between empagliflozin and sacubitril/valsartan (see Figure 2)

Figure 2: Forest plots to show time to adjudicated HHF results

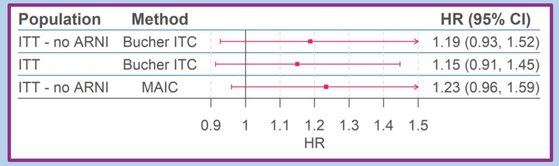


RESULTS

Time to adjudicated CV death results:

- For time to CV death, the primary analysis resulted in an HR (95% CI) of 1.19 (0.93, 1.52)

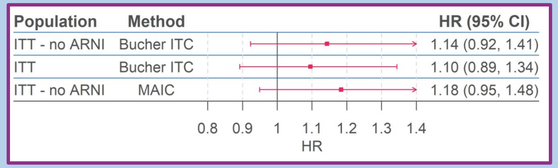
Figure 3: Forest plots to show time to adjudicated CV death results



Time to all-cause mortality results:

- For time to all-cause mortality, the primary analyses resulted in an HR (95% CI) of 1.14 (0.92, 1.41)

Figure 4: Forest plots to show time to all-cause mortality results



Overall:

- Across the four endpoints compared, the results suggested comparable efficacy between empagliflozin and sacubitril/valsartan (HRs were close to 1 and all CIs contained 1)
- Sensitivity analyses were performed and supported the results

CONCLUSIONS

- This research, based on Bucher ITCs and anchored MAICs, suggests patients with HFrEF, who are treated with empagliflozin, have similar efficacy, across key outcomes in heart failure, when compared with patients, treated with sacubitril/valsartan

REFERENCES

References: 1. Packer et al. New Engl J Med. 2020; 383(15):1413–24. **2.** McMurray et al. New Engl J Med. 2014; 371(11): 993–1004. **3.** Bucher et al. J Clin Epidemiol. 1997; 50(6) :683–91. **4.** Signorovitch et al. Value Health. 2012; 940–47. **5.** Phillippo et al. 2016. http://nicedsu.org.uk/wp-content/uploads/2018/08/Population-adjustment-TSD-FINAL-ref-rerun.pdf. Accessed: 23 September 2021.

Key: ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; SGLT2, sodium–glucose cotransporter 2; SoC, standard of care.

Boehringer Ingelheim

Presented at Virtual ISPOR 2021, November 30-December 3

EMPOWER