

SUPPLEMENTARY NOTE 1

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SPONSORS OF THE TRIAL

The sponsors of the trial were Boehringer Ingelheim and Eli Lilly and Company. Boehringer Ingelheim had the organizational oversight over the EMPULSE trial, which included trial conduct, supervision and monitoring of the enrolling study centers, data collection and storage as well as data storage and data analysis. The trial design was developed by the academic members of the executive Committee in co-

operation with representatives from Boehringer Ingelheim, who were also represented in the executive committee of the trial.

The executive committee developed and amended the protocol, case report forms, and statistical analysis plan; oversaw the recruitment of patients and the quality of follow-up; supervised the analysis of data; and the academic members provided an independent interpretation of the results. Jonathan Blatchford is the statistician who coordinated all analyses. The corresponding authors, who had unrestricted access to the data, prepared the drafts of the manuscript, which were then reviewed and edited by all authors, including representatives of Boehringer Ingelheim.

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KEY INCLUSION AND EXCLUSION CRITERIA

Key Inclusion criteria

1. ≥ 18 years currently hospitalized for the primary diagnosis of acute HF
2. Currently hospitalized for the primary diagnosis of acute heart failure (de novo or decompensated chronic HF), regardless of EF. Patients with a diagnosis of hospitalized heart failure must have the following HF signs and symptoms at the time of hospital admission:
 - Dyspnoea (exertional or at rest) and at least two of the following signs of fluid overload:
 - i. Congestion on chest X-ray
 - ii. Rales on chest auscultation
 - iii. Clinically relevant oedema (e.g. $\geq 1+$ on a 0 to 3+ scale)
 - iv. Elevated jugular venous pressure
3. Evidence of left ventricular ejection fraction (LVEF, either reduced or preserved EF) as per local reading preferably measured during current hospitalization or in the 12 months prior to randomization
4. Patients must be randomized after at least 24 hours and no later than 5 days after admission, as early as possible after stabilization and while still in hospital
5. Patients must fulfil the following stabilization criteria (while in the hospital):
 - SBP ≥ 100 mmHg and no symptoms of hypotension in the preceding 6 h
 - No increase in i.v. diuretic dose for 6 h prior to randomization
 - No i.v. vasodilators including nitrates within the last 6 h prior to randomization
 - No i.v. inotropic drugs for 24 h prior to randomization
6. Elevated NT-proBNP ≥ 1600 pg/mL or BNP ≥ 400 pg/mL (50% more for patients with AF) measured during index hospitalization, or in the 72 h prior to hospital admission. For patients treated with an angiotensin receptor neprilysin inhibitor (ARNI) in the previous 4 weeks prior to randomization, only NT-proBNP values should be used
7. HF episode leading to hospitalisation must have been treated with a minimum single dose of 40 mg of i.v. furosemide (or equivalent i.v. loop diuretic defined as 20 mg of torasemide or 1 mg of bumetanide)

Key Exclusion criteria

1. Cardiogenic shock
2. Current hospitalization for acute HF primarily triggered by pulmonary embolism, cerebrovascular accident, or acute myocardial infarction
3. Current hospitalization for acute heart failure not caused primarily by intravascular volume overload.
4. Interventions in the past 30 days prior to randomization or planned during the study:
 - Major cardiac surgery, or TAVI, or PCI, or MitraClip
 - All other surgeries that are considered major according to investigator judgement
 - Implantation of cardiac resynchronization therapy device
 - Cardiac mechanical support implantation
 - Carotid artery disease revascularization
5. Acute coronary syndrome/myocardial infarction, stroke or transient ischemic attack in the past 90 days prior to randomization

6. Heart transplant recipient, or listed for heart transplant with expectation to receive a transplant during the course of this trial (according to investigator judgement), or planned for palliative care for HF, or currently using left ventricular assist device (LVAD) or intra-aortic balloon pump (IABP) or any other type of mechanical circulatory support, or patients on mechanical ventilation, or patients with planned inotropic support in an outpatient setting
7. Haemodynamically severe uncorrected primary cardiac valvular disease planned for surgery or intervention during the course of the study
8. eGFR <20 mL/min/1.73m² during hospitalization (latest local lab measurement before randomization) or patients requiring dialysis
9. Type 1 diabetes mellitus
10. History of ketoacidosis, including diabetic ketoacidosis

MAJOR PROTOCOL-SPECIFIED EFFICACY ENDPOINTS

Primary endpoint

The primary endpoint was clinical benefit at 90 days, defined as a hierarchical composite outcome of time to all-cause death, the number of HF events (HFE), time to first HFE and a ≥ 5 -point difference in change from baseline in KCCQ total symptom score (KCCQ-TSS) after 90 days of treatment.

An HFE was:

- A hospitalization/ER visit OR
- An urgent care visit OR
- An Outpatient visit

With all of the following:

- The question “Was visit related to the primary diagnosis or worsening of heart failure in the opinion of the treating physician?” is answered yes
- At least one symptom of:
 - o dyspnea
 - o decreased exercise tolerance
 - o fatigue
 - o edema
 - o other symptoms of worsened end-organ perfusion or volume overload
- At least two physical examination findings OR (one physical examination finding and at least one laboratory criterion).
 - o Physical examinations are:
 - peripheral edema,
 - increased abdominal distention or ascites,
 - pulmonary rates/crackles/crepitations,
 - Increased jugular venous pressure and/or hepatojugular reflux,
 - S3 gallop,
 - Clinically significant or rapid weight gain thought to be related to fluid distention,
 - other
 - o Laboratory criteria are:
 - Increased BNP or NT-proBNP,
 - radiological *or ultrasonographic* evidence of pulmonary congestions,
 - non-invasive diagnostic evidence of clinically significant elevated ventr. filling pressure or low cardiac output
 - invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure ≥ 18 mmHg, central venous pressure ≥ 12 mmHg or cardiac index < 2.2 L/min/m²
 - Other
- Intensification of therapy (significant augmentation of oral diuretics, IV diuretics, vasoactive agent, or mechanical or surgical intervention)

Exploratory endpoints (pre-specified)

All other endpoints other than primary endpoint are considered exploratory and included an improvement in KCCQ-TSS of ≥ 10 points after 90 days of treatment, Change from baseline in KCCQ-TSS after 90 days of treatment, change from baseline in log-transformed NT-proBNP AUC over 30 days, time to first occurrence of CV death or HFE, occurrence of HHF until 30 days after initial hospital discharge, days alive and out of

hospital from study drug initiation until 30 days after initial hospital discharge, days alive and out of hospital from study drug initiation until 90 days after randomization, and diuretic response during follow up (defined as kg of weight loss per daily unit of furosemide) after 15 days and 30 days. Safety parameters included markers of volume depletion, hypotension, and Occurrence of chronic dialysis or renal transplant or sustained reduction of $\geq 40\%$ estimated glomerular filtration rate (eGFR) Chronic Kidney Disease Epidemiology Collaboration Equation ((CKD-EPI)cr), or o sustained eGFR (CKD-EPI)cr.

METHODOLOGY USED FOR THE PRIMARY ENDPOINT (WIN RATIO)

The primary endpoint was assessed using a stratified win ratio approach. The statistical model was a non-parametric generalized pairwise comparison within HF status strata.

For any two patients, a patient would win, i.e. achieve a better clinical outcome, as determined by assessing the following criteria sequentially, and stopping when an advantage for either patient was shown:

1. Death within common follow-up time
 - death is worse than no death
 - earlier death is worse
 - tied, if not possible to determine
2. Number of HFEs within common follow-up time
 - more HFEs is worse
 - tied, if same number of HFEs
3. Time to first HFE within common follow-up time
 - earlier HFE is worse
 - tied, if not possible to determine
4. KCCQ-TSS change from baseline at Day 90
 - more positive change from baseline is better
 - the threshold for the difference is ≥ 5 for a win
 - tied, if difference < 5

Note, priority was therefore given to death over HFE, and both of these over changes in KCCQ-TSS. Below are some examples:

1. Death, e.g.:
 - Patient A dies 30 days after randomization (loses)
 - Patient B dies 40 days after randomization (wins)
2. If no winner based on death, number of HFEs within common follow-up time, e.g.:
 - Patient A had two HFEs (loses)
 - Patient B had one HFE (wins)
3. If no winner based on number of HFEs, time to first HFE, e.g.:
 - Patient A had an HFE 30 days after randomization (loses)
 - Patient B had an HFE 50 days after randomization (wins)
4. If no winner based on time to first HFE, KCCQ-TSS change from baseline at Day 90, e.g.:

- Patient A: KCCQ-TSS change from baseline at Day 90 is 5 (loses)
- Patient B: KCCQ-TSS change from baseline at Day 90 is 11 (wins)

The implemented generalized pairwise comparisons approach compared all patients in one treatment group to all other patients within their strata in the other treatment group.

Applying weights that are analogous to a Mantel-Haenszel approach (1), the stratified win ratio is:

$$WR = \frac{\sum_{m=1}^2 n_e^{(m)} / N^{(m)}}{\sum_{m=1}^2 n_p^{(m)} / N^{(m)}}$$

where m is the stratum number ($m = 1, 2$), $n_e^{(m)}$ is the number of wins in the empagliflozin group in the m^{th} stratum, $n_p^{(m)}$ is the number of wins in the placebo group in the m^{th} stratum and $N^{(m)}$ is the total number of patients in the m^{th} stratum.

The variance was calculated by the asymptotic normal U statistics approach (2)

Missing data for the KCCQ-TSS (as part of the stratified win ratio) was estimated using multiple imputation (MI), according to whether patients were on-treatment or off-treatment.

In brief: The intention was to impute missing data using available data. We intended to do so separately for on-treatment data and use the placebo course to impute off-treatment data (this is called a “jump-to-placebo” approach). In addition, baseline and previous KCCQ data, as well as HF status (de-novo vs chronic HF) was used.

In detail: Values measured after premature discontinuation of study drug were included in the analyses. All available on- and off-treatment data up to the planned measurement at Day 90 was included.

Different types of missing data were considered for the imputation as follows:

Missing data imputation (Assumption of missingness)	Non-monotone	Monotone
On-treatment data	MCMC-MI ¹ (MAR ³)	SLR-MI ² (MAR)
Off-treatment ⁴ data	Jump-to-Placebo (MNAR ⁵)	Jump-to-Placebo (MNAR)

¹ Markov Chain Monte Carlo – Multiple imputation (MCMC-MI)

² Sequential linear regression – Multiple imputation (SLR-MI)

³ Missing at random (MAR)

⁴ Any instance of a patient discontinuing treatment will lead to all future measurements being considered as off-treatment.

⁵ Missing not at random (MNAR)

As the first step, non-monotone on-treatment missing data was imputed using Markov Chain Monte Carlo (MCMC) simulation and standard techniques; MI was performed separately by treatment with baseline value as a continuous variable and HF status as a binary variable. One hundred imputations were performed to ensure adequate efficiency and stability of the estimation for missing data.

For the monotone missing on-treatment data, a sequential linear regression MI (SLR-MI) approach was used. The MI was performed on a data set only including on-treatment data and once per imputation from the previous step. This procedure imputed values for all missing time points both on- and off-treatment, so imputations for off-treatment values were then deleted. The regression models were fitted separately by treatment and included the baseline value as a continuous covariate, HF status as a class covariate and the values at previous time points as separate continuous covariates.

To impute the missing off-treatment data, a residual-based approach was used to enact the 'jump-to-placebo'. Throughout this imputation, all observed off-treatment data was temporarily removed and added back at the end. A covariate-adjusted difference between the relevant treatment arm and placebo (i.e. 0 for those in the placebo arm) was calculated at each visit using ANCOVA (with HF status and treatment as categorical covariates and baseline value as a continuous covariate). Next, the relevant estimated treatment difference was deducted from all observed data in the active treatment group. Note that the adjustments were for the duration of the imputation only and the original values for the observed data were in the final imputed data set.

SLR-MI was then performed once per imputation upon this modified data but only including patients either with missing values and/or those in the placebo arm, ensuring imputations were performed using the placebo distribution. The models included baseline value as a continuous covariate, HF status as a class covariate and the values at previous time points as separate continuous covariates. All missing data therefore followed the distribution of the placebo arm, jumping from one arm's distribution to the placebo's arm at the point of missingness, while still accounting for past within-treatment performance (the residuals). After this imputation, all the original observed values (i.e. off-treatment values) were restored.

The practical implementation proceeded as follows:

1. Off-treatment data was removed from dataset
2. Non-monotone missing data was imputed under MAR to create a monotone pattern
 - a. 100 imputations were performed by MCMC-MI, stratified by treatment, with the following parameters:
 - i. Baseline value included as a continuous variable, HF status as a binary variable (de novo or decompensated chronic HF)
 - ii. Multiple chains with 200 burn-in iterations per chain
 - iii. Jeffrey's prior
3. SLR-MI was used to impute missing monotone on-treatment data:
 - a. All data was imputed using SLR-MI, separately by treatment, with the following parameters:
 - i. Baseline (continuous), HF status (de novo or decompensated HF) included as covariates
 - b. All imputed data for patients at an off-treatment time point was deleted
4. On-treatment group means were calculated for each imputation at each visit
 - a. ANCOVA used to calculate adjusted means with the following parameters:
 - i. Baseline (continuous), HF status (de novo or decompensated chronic HF), and treatment included as covariates
 - ii. Restricted Maximum Likelihood and Kenward-Rogers methods
 - iii. Least Square Means used
5. Placebo group on-treatment means at each visit were subtracted from all group on-treatment means at the same visit, to give treatment differences
 - a. Note that these were 0 for the placebo group

6. Individual data was 'temporarily saved' at this point, excluding available off-treatment data
7. Treatment differences were subtracted from the respective (by visit and treatment) data values
 - a. Results were the 'residuals' after removal of treatment effect(s)
 - b. This was referred to as the residual data
8. A subset of the residual data was created with all patients in the placebo group and all patients with missing values at first visit requiring imputation. Note that these missing values were all off-treatment.
9. Multiple imputation was performed on the first visit requiring imputation
 - a. Linear regression models were used to derive the distributional parameters;
 - i. One imputation per existing imputation
 - ii. Residual subset used
 - iii. Baseline (continuous), HF status (de novo or decompensated chronic HF), all previous visits (continuous) included as model covariates
10. Imputed off-treatment values from subset merged with residual data sets.
11. If visits that required imputation remained, step 8 was repeated, else it proceeded to the next step
12. Original data set, saved data sets and residual data sets were merged so that all missing values in the saved data set were filled with observed off-treatment measurements, where available, otherwise the values from corresponding residual data sets were used.
13. The stratified win ratio was calculated using these imputed data sets, by combining with the non-imputed death and HFE data. Then logs of the stratified win ratios were taken.
14. Estimates and variances were combined using Rubin's rules to give a single estimate and variance for each parameter of interest across all imputations.

References for the Win-ratio

1. Dong G, Qiu J, Wang D, Vandemeulebroecke M. The stratified win ratio. *Journal of Biopharmaceutical Statistics* 2018;28:778–96
2. Dong G, Li D, Ballerstedt S, Vandemeulebroecke M. A generalized analytic solution to the win ratio to analyze a composite endpoint considering the clinical importance order among components. *Pharm Stat.* 2016. 15: 430-437