



## Comment on “Cost Effectiveness of Vericiguat for the Treatment of Chronic Heart Failure with Reduced Ejection Fraction Following a Worsening Heart Failure Event from a US Medicare Perspective”

Afschin Gandjour<sup>1</sup>

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A recent publication in *Pharmacoeconomics* presents a decision model evaluating the “[c]ost effectiveness of vericiguat for the treatment of chronic heart failure with reduced ejection fraction following a worsening heart failure event from a US Medicare perspective” [1]. The model shows that the probability of vericiguat being cost effective was 88% at a willingness-to-pay (WTP) threshold of US\$150,000 per quality-adjusted life year (QALY) gained.

The model was informed by clinical data from VICTORIA, a phase III, randomized, double-blinded trial comparing vericiguat with placebo in addition to guideline-based medical therapy [2]. Vericiguat had a significant effect on a composite of death from any cause or hospitalization for heart failure. However, this result was driven primarily by the significant impact on hospitalization for heart failure. The impact of vericiguat on overall and cardiovascular mortality was not statistically significant. For death from any cause, the hazard ratio (HR) was 0.95 (95% confidence interval [CI] 0.84–1.07).

While the cost-effectiveness model extrapolates the survival benefit of vericiguat from VICTORIA, the paper fails to mention the statistical insignificance of the survival benefit. This is a relevant omission as shown in the following. Considering that vericiguat therapy is continuous, total drug spending is US\$4786 per patient over VICTORIA’s follow-up period of 10.8 months. Total hospitalizations for heart failure were reduced by 4.1% (= 42.4–38.3%) in

VICTORIA, yielding savings of US\$427 per patient.<sup>1</sup> Considering that the cost of background therapy is the same in both arms and thus cancels out (disregarding an uncertain period of extended survival), vericiguat does not lead to a net saving. It can be safely assumed that extending vericiguat treatment and its effect beyond the trial period does not change this conclusion, that is, the total drug acquisition cost is projected to remain higher than savings from averted hospitalizations. To stay below the willingness-to-pay (WTP) threshold of US\$150,000 per QALY gained, the QALY gain thus needs to be at least 0.03 [(4786–427)/150,000]. The modelled disutility of a heart failure hospitalization is 0.077 but lasts only for a maximum of 30 days [1]. Therefore, vericiguat cannot be considered a cost-effective treatment based on its impact on hospitalizations for heart failure alone. Hence, a survival benefit of vericiguat is a necessary condition for demonstrating cost effectiveness. However, based on the finding that the 95% CI of the HR crosses one and the upper limit of the CI is at 1.07, the probability of a mortality increase is 20%.<sup>2,3</sup> Therefore, the probability that vericiguat is not cost effective at any WTP threshold is at least 20%. Considering the size of a survival benefit conditional on the presence of a survival benefit is unlikely to change the conclusion substantially because even a small-size benefit such as the 5% HR reduction shown in VICTORIA can be

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✉ Afschin Gandjour  
a.gandjour@fs.de

<sup>1</sup> Frankfurt School of Finance and Management, Adickesallee 32-34, 60322 Frankfurt, Germany

<sup>1</sup> I did not include follow-up costs after hospitalization discharge (US\$337 per month) but this is unlikely to change the conclusion.

<sup>2</sup> Given that the 95% CI of the HR of survival in VICTORIA is symmetrical about the HR estimate, it is possible to calculate a standard error and z score assuming a normal distribution. The z score allows calculating the probability that the HR is >1.

<sup>3</sup> It is unclear from Supplementary Table 2 whether the cost-effectiveness model accounts for a potential mortality increase. Figure 2, which shows the results of univariate sensitivity analyses, yields negative cost-effectiveness ratios when varying the risk of cardiovascular death; however, the paper does not state whether this finding is caused by a mortality increase.

sufficient for demonstrating cost effectiveness. Assuming an exponential survival distribution and a remaining life expectancy of 5 years for a 70-year-old patient with heart failure with reduced ejection fraction (Tromp et al. 2022)<sup>4</sup> [3], a back-of-the-envelope calculation multiplying the increase in survival probability by the remaining life expectancy yields an expected life expectancy gain of 0.08 years. This gain increases assuming continuation of vericiguat therapy and its effects beyond the trial period.

As an unrelated point, the authors report that they “did not model any numeric differences in adverse events, given that the VICTORIA trial did not show statistically significant differences in the safety profiles of the vericiguat plus PSoCT [prior standard-of-care therapies—author's note] and placebo plus PSoCT arms” [1]. However, this conclusion seems inconsistent with the approach of incorporating an insignificant survival benefit.

In summary, my analysis reaches a conclusion about the cost effectiveness of vericiguat that is not substantially different than the authors'. However, the approach is quite different and, in my opinion, much more transparent. Acknowledging the insignificance of the survival benefit simplifies the cost-effectiveness analysis. For clinical trial results such as those reported in VICTORIA, a simplified version of a cost-effectiveness analysis can be reasonably accurate and perhaps more compelling to payers and pricing and reimbursement agencies. Furthermore, the analysis emphasizes the need to demonstrate a significant survival benefit in jurisdictions where cost effectiveness matters but an insignificant survival benefit is not accepted as an outcome. Future trial planning and selection of primary endpoints in this and similar clinical scenarios (e.g., encountered by other pharmaceutical companies) may consider such requirements if trials are to be tailored towards the pricing and reimbursement policies in these jurisdictions.

## Declarations

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<sup>4</sup> As the authors highlight, participants in VICTORIA were sicker than patients enrolled in previous trials on heart failure with reduced ejection fraction. Hence, their remaining life expectancy is expected to be “slightly lower”.