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BRIEF REPORT

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Effect of empagliflozin on cardiorenal outcomes and mortality according to body mass index: A subgroup analysis of the EMPA-REG OUTCOME trial with a focus on Asia

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Abstract

Aim: To investigate whether the cardiorenal benefits of the sodium-glucose co-transporter-2 inhibitor empagliflozin are affected by body mass index (BMI) in type 2 diabetes patients with established cardiovascular (CV) disease, including Asians.

Methods: In this exploratory analysis of the EMPA-REG OUTCOME trial, we used Cox regression to evaluate the effects of empagliflozin on all-cause mortality, hospitalization for heart failure (HHF) or CV death, and incident or worsening nephropathy by baseline BMI category.

Results: Of the 7020 participants (1517 Asians [21.6%]), 934 (13.3%), 2465 (35.1%) and 3621 (51.6%) had a BMI of less than 25, 25 to less than 30, and 30 kg/m^2 or higher, respectively. Overall, hazard ratios for empagliflozin versus placebo for all-cause mortality, HHF or CV death, and incident or worsening nephropathy were 0.68 (95% CI 0.57, 0.82), 0.66 (0.55, 0.79) and 0.61 (0.53, 0.70), respectively, and were consistent across BMI categories (*P* values for interaction between treatment and BMI were .6772, .3087 and .6265, respectively).

Results were similar in Asians using these BMI categories and categories of less than 24, 24 to less than 28, and 28 kg/m^2 or higher.

Conclusion: Empagliflozin reduced cardiorenal and mortality risk regardless of BMI at baseline, including in Asians with a lower BMI.

KEYWORDS
cardiovascular disease, clinical trial, diabetic nephropathy, empagliflozin, weight control

1 | INTRODUCTION

Obesity is one of the main factors fuelling the type 2 diabetes (T2D) pandemic. Epidemiology studies show a J- or U-shaped relationship between body mass index (BMI) and mortality, whereby individuals at the lower end of the BMI distribution, as well as those who are overweight/obese, have an increased risk of mortality.[1,2] Although BMI-based cut-off points for overweight and obesity differ between Caucasian and Asian populations (as Asians tend to have a more adverse cardiometabolic adipose profile at any given BMI than Caucasians[3,4]), this relationship is also observed in Asians.[5]

Because of the relationship of obesity to T2D incidence and outcomes, the effect of glucose-lowering drugs on body weight is an important consideration for selecting treatment to manage hyperglycaemia. Sodium-glucose co-transporter-2 (SGLT2) inhibitors are one of the few classes of oral glucose-lowering drugs that have been shown to consistently reduce body weight. They were also the first class of glucose-lowering drugs found to reduce the risk of cardiovascular (CV) events and mortality. In the EMPA-REG OUTCOME trial in T2D patients, the SGLT2 inhibitor empagliflozin reduced the risk of CV death by 38%, hospitalization for heart failure (HHF) by 35%, three-point major adverse CV events (CV death, non-fatal myocardial infarction, or non-fatal stroke) by 14%, and all-cause mortality by 32%.[6] Empagliflozin also reduced the risk of incident or worsening nephropathy by 39%.[7] However, it has not been extensively studied if the beneficial effect of empagliflozin on clinical outcomes is modified by BMI, in particular when extending to the lower and higher ranges.

Consequently, we explored the potential association between BMI and cardiorenal outcomes and mortality with empagliflozin in EMPA-REG OUTCOME. In addition to the analysis of the overall trial population, we also investigated the subgroup of Asian participants using both international and Asian-specific BMI cut-off points.

2 | METHODS

The randomized, double-blind EMPA-REG OUTCOME trial was conducted in 42 countries including the following 11 in Asia: Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan and Thailand (ClinicalTrials.gov, NCT01131676).[6] In brief, 7020 people aged 18 years or older with T2D, established CV disease, HbA1c levels of 7.0%-10.0%, BMI of 45 kg/m^2 or less, and an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m^2 or higher (as per the Modification of Diet in Renal Disease [MDRD] formula) received empagliflozin (10 or 25 mg) or placebo once-daily. Investigators were encouraged to adjust background glucose-lowering therapy if necessary to meet local standards of care (except during the initial 12 weeks), and to meet local standards of care for other CV risk factors. This event-driven trial was designed to continue until 691 or more patients had experienced three-point major adverse CV events. The other prespecified clinical outcomes included all-cause mortality, the composite of HHF or CV death (excluding fatal stroke), and incident or worsening nephropathy (a composite of progression to macroalbuminuria, doubling of serum creatinine level accompanied by eGFR ≤ 45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease). Macroalbuminuria was defined as an urinary albumin-to-creatinine ratio of more than 300 mg/g. All CV events and deaths were adjudicated by independent committees. At trial completion, participants had been followed for a median of 3.1 years.

In this post hoc analysis, we categorized participants by their BMI at baseline using the World Health Organization (WHO) categories of less than 25, 25 to less than 30 (overweight), and 30 kg/m^2 or higher (obese).[8] We used Cox regression models to analyse the effects of empagliflozin versus placebo on all-cause mortality, HHF or CV death (excluding fatal stroke), and incident or worsening nephropathy across these baseline BMI categories in the treated set (all randomized patients who received ≥1 dose of study drug). The Cox models included terms for age, sex, baseline HbA1c category, baseline eGFR category, geographical region, treatment, baseline BMI category and treatment-by-baseline-BMI-category interaction. In addition, we evaluated the same clinical outcomes in the subgroup of Asian participants using BMI categories of less than 24, 24 to less than 28 (overweight), and 28 kg/m^2 or higher (obese), as these cut-off points are used in some Asian countries.[9–12] Separate analyses were conducted for participants who self-identified as being of Asian race and those living in the Asian region. The Cox models for these analyses included the same terms as for the main models except that analyses were restricted to Asian participants (once for Asians by race, once for Asian by region) and the analyses by Asian region lacked the term for geographical region.

We also evaluated changes in body weight, systolic blood pressure (SBP) and HbA1c according to baseline BMI using mixed models for repeated measures (MMRM), as described in the supporting information (Appendix S1).

All analyses were post hoc and exploratory with a nominal two-sided significance level of .05 without adjustment for multiple comparisons. Adverse events were analysed descriptively.

3 | RESULTS

3.1 | Baseline characteristics

At baseline, 934 (13.3%) of the 7020 participants had a BMI of less than 25 kg/m^2, 2465 (35.1%) had a BMI of 25 to less than 30 kg/m^2, and 3621 (51.6%) had a BMI of 30 kg/m^2 or higher. A total of 1517 participants (21.6%) were of Asian race while 1347 (19.2%) resided in Asian countries.

Baseline characteristics by WHO BMI categories in all participants are shown in Table S1. Those with a BMI of less than 25 kg/m^2 were slightly older, more commonly from Asia, and had a longer duration of diabetes than those with a BMI of 25 to less than 30, or of 30 kg/m^2 or higher. More participants with a BMI of less than 25 kg/m^2 had a history of stroke compared with those with a BMI of 30 kg/m^2 or higher, but fewer had a history of myocardial infarction. More participants with a BMI of 30 kg/m^2 or higher had received a coronary artery bypass graft compared with those with lower BMI, and the prevalence of heart failure was also greatest in the highest BMI category. Similar trends were observed in participants of Asian race by both WHO BMI categories (Table S2) and Asia-specific categories (Table S3).

3.2 | Cardiometabolic risk factors

Compared with placebo, empagliflozin consistently reduced HbA1c, SBP and body weight in all participants, including in those of Asian race, regardless of baseline WHO BMI category (Figures S1–S6). However, empagliflozin-elicited reductions in body weight seemed to be more pronounced in participants with a higher baseline BMI.

3.3 | Clinical outcomes

In the overall trial population, empagliflozin reduced all-cause mortality, HHF or CV death (excluding fatal stroke), and incident/worsening nephropathy in participants across WHO BMI categories, with benefits being consistent between those with a BMI of less than 25 kg/m^2, 25 to less than 30 kg/m^2, or 30 kg/m^2 or higher ($P > .05$ for interaction between treatment effect and baseline BMI category; Figure 1). Similar, consistent risk reductions for all-cause mortality, HHF or CV death, and incident/worsening nephropathy, occurred with empagliflozin versus placebo in the subgroup of participants of Asian race (Figure 1).

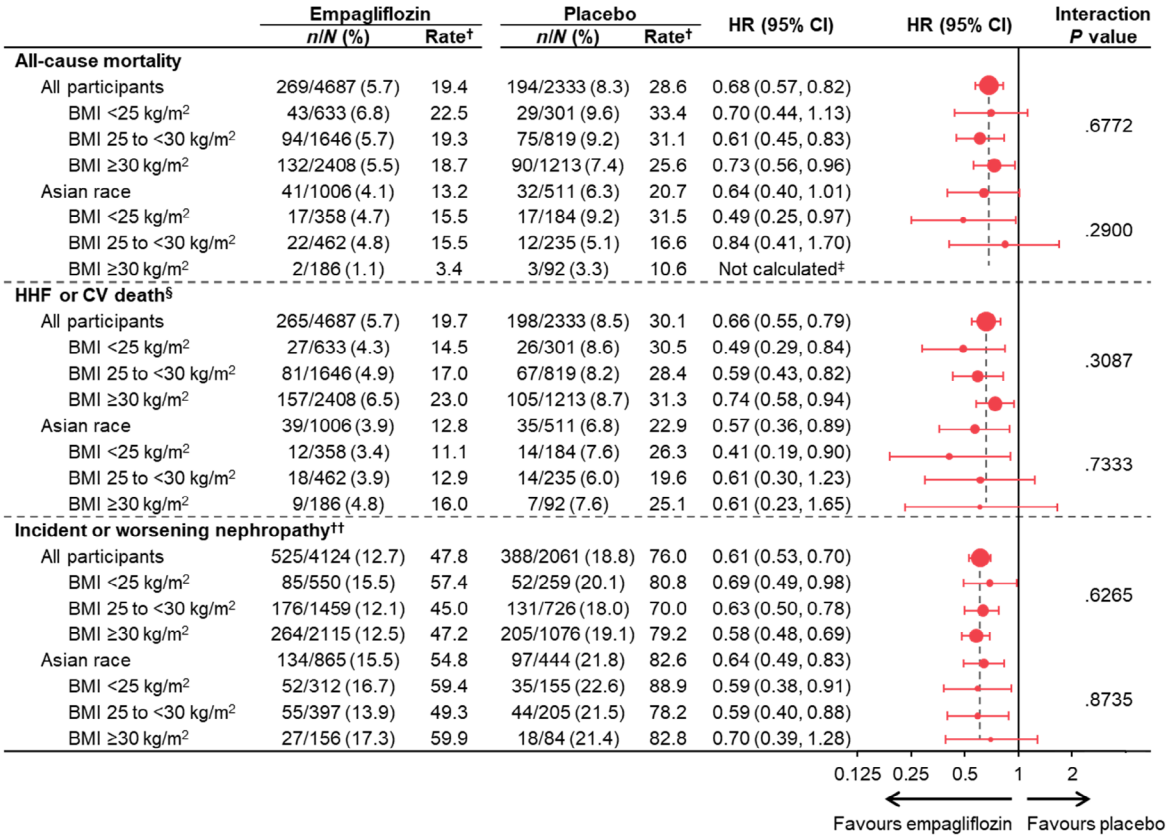

FIGURE 1 Effect of empagliflozin on all-cause mortality, HHF or CV death, and incident/worsening nephropathy by baseline BMI category (WHO) in all participants and participants of Asian race. Data from Cox regression models as described in the Methods section. BMI, body mass index; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; WHO, World Health Organization. †Incidence rate per 1000 patient-years. ‡HR not calculated as <14 events. §Excluding fatal stroke. ††Progression to macroalbuminuria, doubling of serum creatinine accompanied by eGFR ≤ 45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease

Among participants of Asian race or in those resident in Asia, empagliflozin also reduced the risk of all-cause mortality, HHF or CV death (excluding fatal stroke), and incident/worsening nephropathy consistently across Asia-specific BMI categories of less than 24, 24 to less than 28, or of 28 kg/m^2 or higher (Figure 2).

3.4 | Adverse events

Overall, the incidence of adverse events was generally no greater in participants with a BMI of less than 25 kg/m^2 compared with those with a BMI of 25 to less than 30, or of 30 kg/m^2 or higher. Moreover, the proportion of participants with adverse events was generally similar between empagliflozin and placebo across WHO BMI categories for serious events, hypoglycaemia (including severe episodes), urinary tract infections and volume depletion. However, genital infections were consistently more frequent with empagliflozin compared with placebo (Table S4). Similar trends were observed for participants of Asian race (Table S5).

4 | DISCUSSION

This subgroup analysis of EMPA-REG OUTCOME suggests that neither the beneficial effects of empagliflozin on clinical outcomes nor its safety profile were affected by higher or lower categories of BMI, either in the overall trial cohort or in the Asian subgroup.

Because of the J- or U-shaped association between BMI and mortality, it was of interest to explore the effects of empagliflozin on cardiorenal outcomes and mortality in participants with low (<25 kg/m^2) and high BMI (≥30 kg/m^2). In particular, high BMI in T2D patients is associated with poor metabolic health, as well as sodium/fluid retention and heart failure, all of which are alleviated by SGLT2 inhibition.[13] On the other hand, there may be some concern for patients with low BMI receiving a weight-reducing drug, albeit one with only mild-to-moderate weight-loss effects. Despite these theoretical considerations, empagliflozin consistently, and with a similar magnitude of effect, reduced the risk of all-cause mortality, HHF or CV death, and new or worsening nephropathy regardless of BMI category at baseline in the EMPA-REG OUTCOME trial cohort. Almost half of these

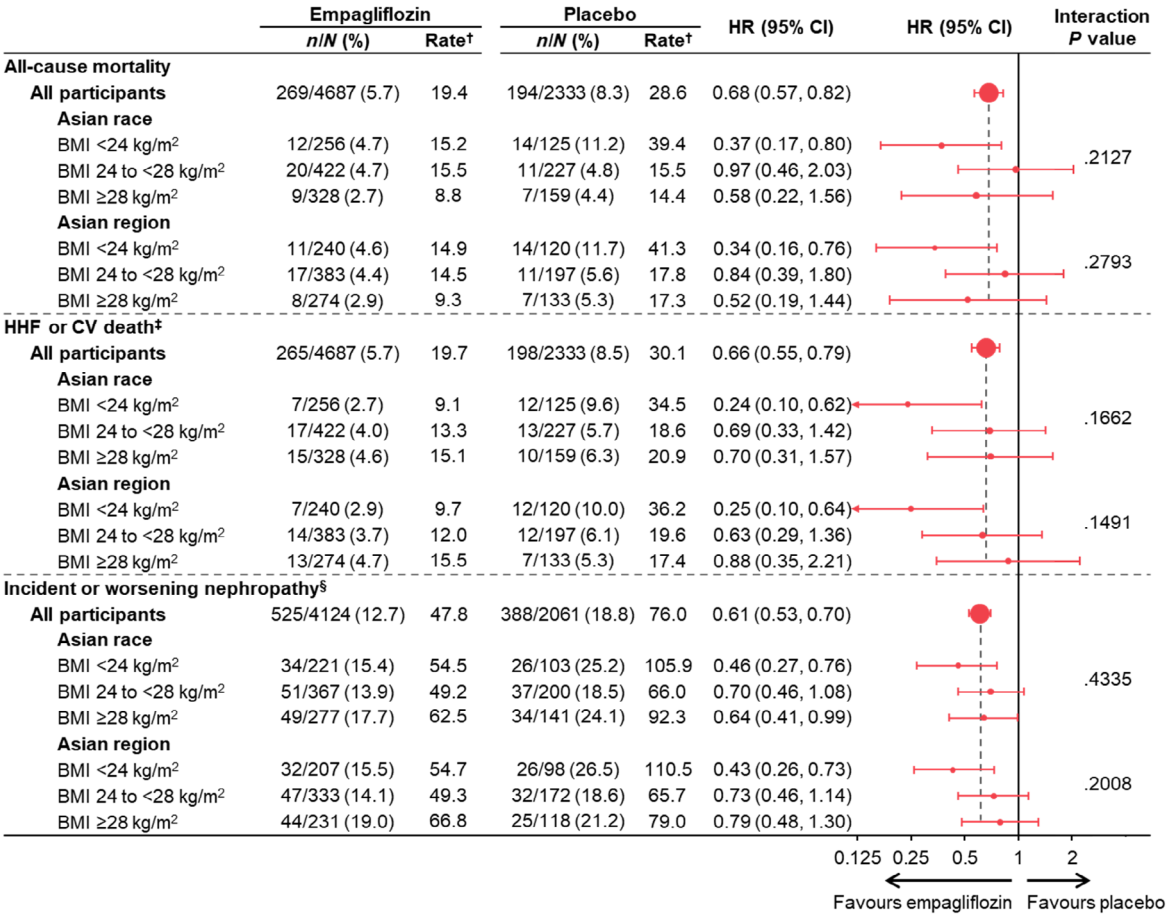

FIGURE 2 Effect of empagliflozin on all-cause mortality, HHF or CV death, and incident/worsening nephropathy in Asian participants by baseline BMI category <24, 24 to <28, or ≥28 kg/m^2. Data from Cox regression models as described in the Methods section. BMI, body mass index; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio. †Incidence rate per 1000 patient-years. ‡Excluding fatal stroke. §Progression to macroalbuminuria, doubling of serum creatinine accompanied by eGFR ≤ 45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease

participants had a BMI of less than 30 kg/m^2, and risk reductions also occurred in participants with low BMI, despite additional weight loss.

BMI-independent risk reduction for cardiorenal events and mortality with empagliflozin also occurred in Asian participants in EMPA-REG OUTCOME, regardless of whether BMI was classified using WHO- or Asia-specific categories. The latter analyses showed that approximately two-thirds of participants of Asian race had a BMI of less than 28 kg/m^2. These observations have high clinical relevance, as Asian T2D patients generally have lower BMI than their Western counterparts, which probably reflects differences in adiposity phenotype and other pathophysiological variables.[3,14,15]

The consistent effect of empagliflozin across BMI categories suggests that the mechanism by which this SGLT2 inhibitor reduces cardiorenal events and mortality involves BMI-independent factors. Empagliflozin also reduced HbA1c, SBP and body weight across BMI categories, although weight reductions were greater in participants with high baseline BMI, consistent with its effects in other reports.[16,17]

The incidence of adverse events overall was generally no greater in participants with low BMI (<25 kg/m^2) than in those in the higher BMI categories, and the expected pattern associated with empagliflozin and other SGLT2 inhibitors—in particular, an increased incidence of genital infections—was observed in both the overall trial cohort and the Asian subgroup.

The strength of this analysis is that its findings are derived from rigorously adjudicated clinical outcomes in a large, robustly conducted, modern CV outcomes trial that included 934 participants with a BMI of less than 25 kg/m^2 and 1517 patients of Asian race. It is, however, subject to the usual limitations of subgroup analyses, notably the possibility of type 1 error arising from many statistical comparisons without adjustment for multiplicity, as well as type 2 errors resulting from reduced statistical power. That said, the subgroup analyses were consistent with the overall findings, and the results are also consistent with a post hoc analysis of the CANVAS trial that found that the cardiorenal risk reduction with the SGLT2 inhibitor canagliflozin was unaffected by BMI.[18] Additional limitations included the paucity of Asians with a BMI of less than 20 kg/m^2, and the lack of delineation of South, East and Southeast Asians, who are heterogenous groups.

In conclusion, risk reductions for cardiorenal events and mortality with empagliflozin were not modified by BMI in the large trial cohort from EMPA-REG OUTCOME, including in the subgroup of Asian participants. These findings should be informative for physicians managing cardiorenal risk in T2D patients, particularly those with low BMI, which is more common in Asia than in Western countries.

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CONFLICT OF INTEREST

Q.J. has received travel support as an advisory board member from Merck & Co., Inc. for the STRATEGY study, has attended advisory boards and been a speaker of Eli Lilly, Novo Nordisk, Merck Sharp & Dohme China, Sanofi Aventis, Huadong Pharmaceuticals Company, and Medtronic, and has received research grants from Novo Nordisk, Merck Sharp & Dohme China, and AstraZeneca. L.J. has nothing to declare. Y.M. has received lecture fees from Novo Nordisk, Eli Lilly and Boehringer Ingelheim. J.Z. has nothing to declare. B.Z. has received research grants awarded to his institution from Boehringer Ingelheim, AstraZeneca and Novo Nordisk, and honoraria from Janssen, Sanofi, Eli Lilly and Company, Boehringer Ingelheim, Novo Nordisk and Merck Sharp & Dohme. C.W. has received fees for advisory services to Boehringer Ingelheim and MSD as well as honoraria for lecturing from AstraZeneca, Eli Lilly and Sanofi. I.Z. is an employee of Boehringer Ingelheim. K.U. has received lecture fees from Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Kissei, Kowa, Kyowa Kirin, Mitsubishi Tanabe, MSD, Novartis, Novo Nordisk, Ono, Sanofi, Sanwa Kagaku, Shionogi, Sumitomo Dainippon, Taisho Toyama and Takeda; and grants from Astellas, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Kyowa Kirin, Mitsubishi Tanabe, MSD, Novartis, Novo Nordisk, Ono, Sanofi, Sumitomo Dainippon, Taisho Toyama, and Takeda. K.Y. has received honoraria (e.g. lecture fees) from MSD, Mitsubishi-Tanabe, Novonordisk, Kowa, Takeda, Astellas, Dainippon-Sumitomo, Ono, Astra-Zeneca, Novartis, Nippon Boehringer-Ingelheim, Nippon Eli-Lilly, Taisho, Sanofi, Jansen, Astellas-Amgen, Daiichi-Sankyo, Kyowa-Kirin and Pfizer; clinical research funding from Taisho and Astellas; scholarship grants from Takeda, Shionogi, Dainippon-Sumitomo, Nippon Boehringer-Ingelheim, Bayer, Astellas, Teijin, Mitsubishi-Tanabe, Ono, Novonordisk, Daiichi-Sankyo, MSD, Pfizer, Taisho, Japan Eli-Lilly, Teijin and Kowa; and courses endowed by MSD. W.O. has received endowment, research funding and honorarium from Astellas Pharma, Abbott Japan and Mitsubishi Tanabe Pharma Corporation; endowment and honorarium from Nippon Boehringer Ingelheim Co., Novartis Pharma, MSD, Sanofi K.K, Sumitomo Dainippon Pharma Co. and Takeda Pharmaceutical Co.; endowment and grants from Eli Lilly Japan; endowment from Novo Nordisk Pharma Ltd., Ono Pharmaceutical Co. and Daiichi Sankyo Co.; and research funding from Kyorin Pharmaceutical Co., AstraZeneca and Boehringer Ingelheim Pharma GmbH & Co. KG. J.T.G. and O.E.J. were employees of Boehringer Ingelheim at the time of this study.

AUTHOR CONTRIBUTIONS

B.Z., C.W. and O.E.J. participated in the design of the study, conduct of the study, acquisition and interpretation of data, and preparation of the manuscript. Q.J., L.J., Y.M., J.Z., J.T.G., K.U., K.Y. and W.O. participated in interpretation of data and preparation of the manuscript. I.Z. participated in design of the study, statistical analysis and interpretation of data, and preparation of the manuscript. O.E.J. wrote the first draft of the manuscript. Q.J. and L.J. are co-first authors. W.O. and O.E.J. are co-senior authors. All the authors were fully responsible for all content and editorial decisions, were involved

at all stages of manuscript development, have approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14415.

DATA AVAILABILITY STATEMENT

The sponsor of the clinical trials (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. Researchers are invited to submit inquiries via the following website (https://trials.boehringer-ingelheim.com/).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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