# Efpeglenatide and Heart and Kidney Outcomes in Type 2 Diabetes

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**Figure 1 (facing page). Clinical and Laboratory Data for Patients with VIT and Severe Headache (Pre-VITT Syndrome).**
Shown are the time courses of the manifestation of pre-VITT syndrome (defined by headache onset), hospital admission (including emergency department admission and discharge in Patients 1 and 2), platelet counts, and cerebrovascular complications (in Patients 1, 2, and 3), as well as medical and neurosurgical treatment (decompressive craniectomy). In each graph, the number of days since the onset of headache is shown on the x axis and platelet counts on the y axis. Outcomes were assessed with the modified Rankin scale (mRS); scores on the scale range from 0 to 6, with higher scores indicating greater disability (0 indicates no symptoms, and 6 indicates death). CVST denotes cerebral venous sinus thrombosis, VIT vaccine-induced thrombocytopenia, and VITT vaccine-induced immune thrombotic thrombocytopenia.

should undergo immediate testing for thrombocytopenia and D-dimer levels and, if available, testing for anti–PF4–heparin IgG antibodies. When these antibodies are present at high titers, patients are at imminent risk for CVST, and it is likely that this condition can be prevented with immediate treatment, such as with intravenous immune globulin. The decision to initiate therapeutic-dose anticoagulation is a difficult one; the risk of emerging thrombosis, including CVST, has to be balanced against the risk of intracranial hemorrhage on an individual basis (e.g., with consideration of platelet count and fibrinogen levels).

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# Efpeglenatide and Heart and Kidney Outcomes in Type 2 Diabetes

**TO THE EDITOR:** In the AMPLITUDE-O trial, Gerstein et al. (Sept. 2 issue)[1] found a lower risk of cardiovascular events among participants with type 2 diabetes who received a weekly injection of efpeglenatide than among those who received placebo. This trial confirms the interest in glucagon-like peptide-1 (GLP-1) receptor agonists in terms of cardiovascular protection in patients with type 2 diabetes.[2-5] However, some concerns persist regrading retinal safety, as observed with semaglutide in SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes).[3] Persons with severe retinal disease were excluded from the AMPLITUDE-O trial, and 32.9% of the participants had a history of diabetic retinopathy at baseline. The report of the adverse events shows similar incidences of retinal complications in the efpeglenatide group and the placebo group. However, in the report of serious adverse events, there were eight cases of eye disorders in the efpeglenatide group, as compared with only

one case in the placebo group. The number of retinal serious adverse events seems low in this randomized, controlled trial, but such events can be a concern in a real-world setting, since type 2 diabetes is a very frequent condition. More details regarding the serious adverse events involving eye disorders may be helpful for clinicians.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** The AMPLITUDE-O trial showed that efpeglenatide led to a lower hazard of the composite outcome of a sustained decline in the creatinine-based estimated glomerular filtration rate (eGFR), incident macroalbuminuria, and renal-replacement therapy. The use of creatinine-based eGFR outcomes requires that interventions do not affect creatinine generation from muscle.[1] However, up to 65% of weight loss due to GLP-1 receptor agonists is attributable to reductions in skeletal muscle mass[2] and hence contravenes this requirement. Efpeglenatide-induced decreased production of creatinine will not only spuriously invoke the suggestion of abated deterioration in the creatinine-based eGFR[3] but may also partially conceal the albuminuria-lowering effect of efpeglenatide, because this effect is quantified with the urinary albumin-to-creatinine ratio. Because creatinine production equals excretion under steady-state conditions, regardless of circulating concentrations,[4] decreased excretion (caused by muscle wasting) will inflate the urinary albumin-to-creatinine ratio. Obviously, there are sound reasons for modification of the outcomes of the current or future trials.[5] The AMPLITUDE-O trial could benefit from analyses adjusted for muscle wasting or from the use of alternative GFR-based outcomes[1] or timed urine collections (which enable the assessment of creatinine clearance and albumin excretion).

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** Previous studies have shown a significant association between the use of GLP-1 receptor agonists and increased risks of gallbladder- or biliary-related events.[1] Recent trials have assessed gallbladder-related events as adverse events of special interest and shown more reports of gallbladder-related events with GLP-1 receptor agonists than with placebo.[2,3] Moreover, the product labels of several GLP-1 receptor agonists include warnings about increased risks of gallbladder-related events.[4,5]

Although Gerstein et al. point out the higher risk of severe gastrointestinal events with efpeglenatide than with placebo, we noted a numeric imbalance in hepatobiliary disorders between the efpeglenatide group and the placebo group (24 events in 2717 participants [0.9%] vs. 8 events in 1359 participants [0.6%]). Whether the increased risks of gallbladder- or biliary-related

events were class effects of GLP-1 receptor agonists remains unknown, so it might be necessary to report gallbladder- or biliary-related events as adverse events of special interest in trials of efpeglenatide.

Accordingly, we recommend that the authors provide more detailed information about hepatobiliary disorders and expand the reporting of gallbladder- or biliary-related events with efpeglenatide therapy. We particularly recommend that the authors report and analyze the incidence of cholelithiasis, cholecystitis, and biliary obstruction with efpeglenatide as compared with placebo.

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No potential conflict of interest relevant to this letter was reported.

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**THE AUTHORS REPLY:** The preferred way to assess adverse effects of concern in any large trial is to collect specific data related to these adverse effects and not to rely on spontaneously reported adverse events. Because of the SUSTAIN-6 findings referenced by Borderie et al.,[1] diabetic retinopathy and related complications constituted one such adverse event of interest. Diabetic retinopathy and related complications affected 1.7% of the participants in the efpeglenatide group and 2.0% of those in the placebo group, as noted in Table 3 in our article. A large trial examining the effect of a GLP-1 receptor agonist on the retina is currently ongoing (ClinicalTrials.gov number, NCT03811561).

Groothof et al. raise questions about kidney function in our trial. Although efpeglenatide therapy did reduce body-mass index, the bulk of the effect occurred during the first 3 months of therapy. Conversely, the effect of efpeglenatide therapy on the eGFR clearly extended past that time. Urinary albumin excretion itself is unaffected by body-mass index, and the albumin-to-creatinine ratio mainly serves to account for the degree to which the urine is concentrated.

As noted by He and Zhang, hepatobiliary disorders were not prespecified as adverse events of special interest. Although they occurred with similar frequency in the two trial groups, meta-analyses across trials would be the preferred way to determine the effect of GLP-1 receptor agonists on these events.

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Since publication of their article, the authors report no further potential conflict of interest.

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# Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock

**TO THE EDITOR:** In the Dobutamine Compared with Milrinone (DOREMI) trial, Mathew et al. (Aug. 5 issue)[1] found no significant difference in outcomes among patients with cardiogenic shock (most of whom had stage C or D cardiogenic shock according to the Society for Cardiovascular Angiography and Interventions definitions[2]) who were treated with either dobutamine or milrinone. The authors suggest that the clinical course in the patients was perhaps too advanced for the