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TO THE EDITOR: We would like to highlight a few features of tirzepatide from the pharmacologic perspective. Tirzepatide has dual agonism with differential affinity toward the glucose-dependent insulinotropic polypeptide (GIP) receptor and the glucagon-like peptide-1 (GLP-1) receptor.[1] Tirzepatide binds the GIP receptor with equal affinity to native GIP, although the affinity of the drug for the GLP-1 receptor is approximately one fifth as weak as for native GLP-1. Apart from the differential affinity toward GIP and GLP-1, tirzepatide shows biased agonism toward the GLP-1 receptor.[2] This deliberate imbalance is a crucial innovation, given that selective GLP-1 receptor agonism can be limited by gastrointestinal side effects such as nausea and vomiting, whereas GIP receptor agonism is not limited by such side effects. By favoring selective agonistic action toward the GIP receptor, higher doses of tirzepatide than of semaglutide can be taken without an unacceptable level of side effects, which maximizes the therapeutic benefits of tirzepatide as compared with semaglutide.[3] Tirzepatide incorporates a C20 unsaturated di-acid acyl chain that enhances albumin binding, which ensures prolonged circulation and enables once-weekly administration. We agree with Farzam and Patel[4] that this extended half-life will not only enhance treatment adherence but also contribute to greater clinical efficacy.

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

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THE AUTHORS REPLY: Our trial showed that 176 weeks of tirzepatide treatment led to an apparent 93% lower risk of type 2 diabetes than placebo. We agree with Birkenfeld and colleagues that during the 17-week off-treatment follow-up period, the effects on body weight and the glycated hemoglobin level began to reverse; these findings were expected, given that medications for most chronic diseases generally need to be continued to maintain efficacy.[1,2] The follow-up period was of sufficient duration to allow drug washout (i.e., five times the half-life of tirzepatide [25 days total] plus 30 days) and account for erythrocyte turnover (>90 days). As such, the occurrence of new cases of type 2 diabetes during the follow-up period may have been due to a combination of losing the direct effects of the drug on glycemia and on centrally mediated regulation of body weight and appetite, with the latter leading to a mean weight regain of approximately 7%, as stated in the article.

We therefore advise caution in using the 17-week follow-up period to evaluate the important question of prediabetes disease modification, because such an assessment would be confounded by the rapid and dynamic physiological effects of recent drug withdrawal. To ascertain the potential disease-modifying effects of 3 years of tirzepatide treatment more accurately, further studies are warranted in which participants would be followed for a longer period after the end of treatment to assess weight regain and stabiliza-

tion, compare the incidence of type 2 diabetes with that in the control group, and determine whether the natural trajectory of the disease was altered. We agree that prevention strategies for any chronic disease, including diabetes and obesity, are important. We also agree that more work is needed with regard to investigations in persons with obesity who are older, with an emphasis on body composition and function in this population as well as across the life span.

Shukla and Bhavya highlight some of the key differentiating characteristics of tirzepatide as a GIP and GLP-1 receptor agonist. We agree that studies in animals suggest that GIP receptor agonism may potentially mitigate some of the common gastrointestinal side effects that are observed with nutrient-stimulated hormone-receptor modulators[3,4]; additional studies are warranted. We also agree that chemical factors that allow for weekly administration provide patients with more convenient therapeutic options and enable greater adherence than subcutaneous medications with a shorter half-life.

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

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Incidence of Scrub Typhus in Rural South India

TO THE EDITOR: The study by Devamani et al. (March 12 issue)[1] of the incidence of scrub typhus in rural South India presents several methodologic considerations that warrant careful attention. First, the reliance on participant-reported febrile illness may result in underreporting (particularly in the context of the ongoing Covid-19 pandemic), potentially leading to biased incidence estimates. Second, the study design included extended intervals between follow-up visits (6 to 8 weeks), which present a risk of missing acute febrile episodes and possibly contribute to incomplete data. Furthermore, although the use of the enzyme-linked immunosorbent assay for IgM detection is acknowledged for its sensitivity, it also carries the potential for cross-reactivity with other pathogens. The limited precision associated with standard diagnostic tests must be acknowledged when evaluating patients presenting with acute undifferentiated fever in India.[2]

In addition, the adjustments made for IgM seropositivity among asymptomatic controls are predicated on the basis of assumptions that might not adequately encompass the complexities of asymptomatic infections and cross-reactivity. Finally, the generalizability of the findings is constrained by the focus of the study, which was conducted in a region where scrub typhus is highly endemic and may not accurately reflect the epidemiologic patterns of scrub typhus in other geographic regions.

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

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THE AUTHORS REPLY: Mohapatra and colleagues make valid points that relate mainly to the estimation of the incidence of symptomatic infection independent of severity. We discussed these limitations in our article and carried out sensitivity analyses to explore plausible incidence values. We acknowledge the debate over the limitations