Inadequate Evidence of Safety Regarding Exagamglogene Autotemcel Gene Therapy for Sickle Cell Disease (BLA# 125787/0, Vertex Pharmaceuticals)

Testimony before the Food and Drug Administration's Cellular, Tissue, and Gene Therapies Advisory Committee

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I'm Michael Abrams with Public Citizen's Health Research Group. We have no financial conflicts of interest on this matter.

The exagamglogene autotemcel (exa-cel) gene-editing therapy to reduce the frequency of vaso-occlusive crises in patients with sickle cell disease has demonstrated apparent efficacy in 29 of 30 subjects who have received this therapy.[1] This therapy involves stem cell extraction, CRISPR/cas9 gene-editing aimed at re-igniting the expression of fetal hemoglobin, and autologous reinfusion of the re-engineered stem cells. Chemotherapy (including with busulfan) is used to prepare patients for the auto-transplant.

The Food and Drug Administration's (FDA) scientific review has concluded that these results, although limited to small single-arm studies, are overall "strongly positive." This review also notes that if this therapy is approved, a 15-year follow-up study— the design of which is pending— has been proposed to fully evaluate safety outcomes including the possibility that aberrant gene-editing may lead to plausible adverse effects, such as malignant cancers, blood diseases, organ damage, transplantation-related illnesses, and early death.

The focus of this meeting is, accordingly, not on the efficacy of exa-cel, but on its safety. Specifically, there is considerable uncertainty about off-target gene-editing, that is, unintended editing of other genes besides those which 'turn-on' the expression of fetal hemoglobin.

Per the FDA's review, the sponsor has thus far assessed the probability of off-target gene editing in two ways. First, by using algorithmic reviews of existing genome databases, and second, by using more direct biochemical assays of cells that are modified with the exa-cel therapy. Unfortunately, both of those evaluations have insufficient scope. The algorithmic (silico) analysis, relies on a limited amount of sequencing data that may not capture all the variants that

[1] FDA briefing document. BLA# 125787/0. Drug name: exagamglogene autotemcel. Applicant: Vertex Pharmaceuticals Inc. Cellular, Tissue and Gene Therapies Advisory Committee Meeting. October 31, 2023. https://www.fda.gov/media/173414/download. Accessed October 30, 2023.

are vulnerable to off-target editing. For example, the review notes that only 61 whole genome maps of individuals of African descent from the southwest US were used to consider whether tens of millions of genetic variants might be at-risk for off-target editing. Moreover, the review notes that one recent silico study published in *Nature Genetics*,[2] did not identify the same variants of concern that were identified by the sponsor's study under consideration today— a discrepant finding that may underscore the sampling concerns.

Finally, the cellular assay data was limited to 9 subjects: 3 healthy, 3 with thalassemia, and 3 with sickle cell disease. As stated by the FDA: "It is unclear whether this limited sample size will provide for an adequate understanding of the potential risk of off-target editing." Sickle cell disease, is known to alter chromatic structure and stem cell function; such alterations could plausibly effect the risks of off-target editing.

Public Citizen's Health Research Group strongly believes that more study is needed to determine if off-target gene editing is a near- or long-term concern for patients receiving exa-cel therapy. We thus encourage this advisory committee and the FDA to require that such comprehensive studies be completed before exa-cel is approved for wide-spread use.

Thank you.

[2] Cancellieri S, Zeng J, Lin LY et al. 2023, Human genetic diversity alters off-target outcomes of therapeutic gene editing, *Nat Genet*. 2023. 55(1):34-43.