Evaluate Vantage

January 06, 2023

Will Graphite's blow-up add to FDA caution over gene editing?

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The FDA was already treading very carefully with gene editing, and the Graphite Bio blow-up suggests that this stance will not shift any time soon. The company has paused the Cedar study of nulabeglogene autogedtemcel for sickle cell disease because the first patient to be dosed, in August last year, has developed pancytopenia. The condition, prolonged low blood cell count, has not improved as expected and the patient is still receiving transfusion and growth factor support. As Graphite describes it, nula-cel uses homology-directed repair Crispr-based gene editing to correct permanently the beta-globin gene mutation, a novel approach even for this nascent space. Anaemia was always considered a risk, according to some investors. To make matters worse for Graphite, figuring out what went wrong will take time, with several potential hypotheses on the table, according to SVB analysts. These include the quality of the patients' underlying bone marrow, the HDR platform itself, the gene correction approach and use of an AAV6 vector. While this issue is likely to be specific to this company's technology, other gene-editing groups awaiting FDA approval to commence clinical studies cannot rule out even closer scrutiny.

Status of selected gene-edited projects

Project	Company	Description	Status
Nulabeglogene autogedtemcel (GPH101)	Graphite Bio	Homology-directed repair Crispr-based gene editing project for SCD	Ph1/2 Cedar trial put on "voluntary pause" in Jan 2023 on safety concerns
VERVE-101	Verve	In vivo base-editing project targeting PCSK9 for high cholesterol	Ph1 Heart-1 enrolling in NZ & UK; US IND put on clinical hold in Dec 2022
BEAM-201	Beam	Ex vivo base edited Car-T for leukaemia/ lymphoma	Clinical hold on US IND lifted, IND cleared in Dec 2022; next steps awaited
NTLA-2001	Intellia/ Regeneron	In vivo Crispr editing project targeting TTR for amyloidosis	Ph1 enrolling in NZ, Sweden, UK; US IND to be submitted mid-2023 (early ex-US data reported)
NTLA-2002	Intellia	In vivo Crispr editing project targeting KLKB1 for HAE	Ph1/2 enrolling in Netherlands, NZ, UK; US IND to be sumitted H1'23 (early ex-US data reported)

Source: Evaluate Pharma, clinicaltrials.gov & company statements.

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