In-Vivo vs. Ex-Vivo CRISPR Base Editing Therapies for Sickle-Cell Disease

Introduction

Sickle-cell disease (SCD) is caused by a single-point mutation in the β-globin gene (HBB), leading to abnormal hemoglobin (HbS) that causes red blood cells to sickle. CRISPR-based therapies are emerging as potential cures by fixing this genetic error. Broadly, two approaches are being pursued: **ex vivo** therapies (editing a patient's hematopoietic stem cells outside the body and then returning them) and **in vivo** therapies (delivering gene editors directly into the patient to edit cells **in situ**). This report provides a comprehensive comparison of in-vivo versus ex-vivo **CRISPR base-editing** strategies for SCD, covering their scientific mechanisms, therapeutic application, clinical trial status, efficacy/safety, delivery methods, manufacturing challenges, regulatory outlook, and key players.

Scientific Basis of Base Editors (In Vivo vs. Ex Vivo)

Base Editors: CRISPR base editors are modified Cas enzymes that **directly convert one DNA base into another** without making double-strand breaks. Two main classes exist: **cytosine base editors (CBEs)**, which convert a C·G base pair to T·A, and **adenine base editors (ABEs)**, which convert A·T to G·C . These editors consist of a catalytically impaired Cas9 (nickase) fused to a DNA deaminase enzyme, plus auxiliary domains to guide repair . For example, ABEs use an evolved TadA deaminase to deaminate adenine to inosine, which is read as guanine by the cell's DNA polymerase, effectively installing an A→G substitution . This allows precise single-base **transitions** (purine↔purine or pyrimidine↔pyrimidine changes), avoiding the indels and chromosomal breaks typical of standard CRISPR nucleases . The avoidance of double-strand breaks greatly reduces risks of large deletions, translocations, and p53-mediated DNA damage responses .

Mechanism of Action: Both in-vivo and ex-vivo approaches ultimately rely on the same molecular machinery – a guide RNA directs the Cas9-deaminase to the target HBB gene (or its regulators), and the base editor catalyzes a nucleotide change within a small "editing window" of a few bases . In ex-vivo therapy, patient stem cells are harvested and transfected (often by

electroporation) with base editor mRNA or ribonucleoprotein; the editing occurs in cell culture, after which edited cells are infused back. In in-vivo therapy, the editing components (e.g. mRNA encoding the base editor and a guide RNA) are delivered **directly into the patient**, typically via a vector or nanoparticle, to reach the cells **inside the bone marrow** or target tissue and edit them there. The base-editing chemistry is the same, but in-vivo platforms often use **highly optimized editors** (for potency and reduced size) given the delivery constraints. For instance, in vivo approaches have employed compact, high-efficiency ABEs (like "ABE8e") to achieve sufficient editing levels within a short timeframe **in situ** . Ex-vivo editing can sometimes use larger or multiple editors if needed, since delivery is done in controlled lab conditions.

Adenine vs. Cytosine Editors for SCD: Correcting the SCD mutation (a single A>T transversion in HBB) is not directly achievable with a single CBE or ABE because it requires an A→T (or T→A) change (a transversion). To overcome this, researchers use clever workarounds:

- **Adenine Base Editor (ABE) Strategy:** Convert the sickle allele (GTG, Valine) into a different benign variant. Beam Therapeutics and academic groups developed an ABE that turns the sickle codon GTG into **GCG**, encoding hemoglobin *Makassar*, a naturally occurring normal variant that behaves like wild-type hemoglobin . This is accomplished by an ABE that changes the DNA base on the complementary strand (A→G), which after DNA repair yields the desired T→C change on the coding strand (Valine to Alanine) . Hemoglobin G-Makassar (E6A) has normal function and does not cause SCD . ABEs are also used to edit regulatory regions (as in BEAM-101, discussed below) because many known modifiers of hemoglobin involve A→G changes .
- **Cytosine Base Editor (CBE) Strategy:** Less commonly, CBEs might be used to introduce protective mutations if a C→T change can produce a beneficial effect. For example, certain fetal hemoglobin-promoting mutations (hereditary persistence of fetal hemoglobin, HPFH) are C>T transitions in the HBG promoter. A CBE could reproduce such mutations to derepress fetal hemoglobin. However, in the current SCD base editing programs, ABEs have been favored (because the key HBB correction and at least one major HPFH promoter mutation involve A→G changes).

In summary, **ex vivo and in vivo base editing rely on the same core mechanism**, but in-vivo editing demands more advanced delivery and often uses newer iterations of editors (for higher activity and smaller size), whereas ex-vivo editing can use the base editor in a controlled environment with high efficiency and then select or expand the edited cells if necessary.

Therapeutic Strategies for Correcting SCD Mutations

Both in-vivo and ex-vivo approaches aim to restore effective hemoglobin production, but they differ in how they achieve this:

- **Ex Vivo Base Editing Strategies:** The patient's hematopoietic stem cells (HSCs) are collected (usually from blood or bone marrow), edited in the lab, and then infused back (with the expectation they will engraft and produce healthy red blood cells). Two main strategies have emerged:
    - *1) Reactivating Fetal Hemoglobin (HbF):* Beam Therapeutics' **BEAM-101** exemplifies this approach. BEAM-101 uses an adenine base editor ex vivo to introduce single-base changes in the promoters of the γ-globin genes **HBG1/HBG2**, which disrupt binding of the BCL11A repressor . This mimics benign **HPFH mutations** that derepress fetal hemoglobin production. Edited HSCs then produce high levels of HbF (which is anti-sickling) in red blood cells, compensating for the defective adult β-globin . Notably, BEAM-101 does *not* directly alter the sickle β-globin gene; it leverages a validated strategy also used by other gene therapies (for example, Vertex/CRISPR's nuclease-based **exa-cel** and Editas' Cas12a-edited **EDIT-301** similarly disable BCL11A or its binding site to raise HbF).
    - *2) Directly Correcting the β-globin Mutation:* The ultimate precision cure is to fix the sickle mutation itself. **BEAM-102** is an ex vivo ABE designed to do exactly this by converting the pathogenic HbS (β^S, Glu6Val) codon into the **HbG-Makassar** codon (Glu6Ala) . This single base change (A·T to G·C) eliminates the sickling behavior without introducing any foreign gene sequence. Preclinical studies with BEAM-102's base editor in patient-derived cells showed >70% editing of the sickle allele and effectively eliminated sickling in vitro . While BEAM-102 is not yet in the clinic, it represents the direct correction strategy via base editing.
- **In Vivo Base Editing Strategies:** In vivo approaches deliver the editor directly into the patient's bloodstream or bone marrow to edit HSCs *in situ*, avoiding the need for transplant procedures. This field is nascent but rapidly advancing:
    - *1) Direct Correction In Situ:* A proof-of-concept was recently demonstrated by researchers at University of Pennsylvania/CHOP. They used an in vivo-targeted lipid nanoparticle to deliver mRNA encoding an adenine base editor plus an sgRNA for the sickle mutation . In SCD patient HSCs (in vitro), this achieved an A-to-G edit converting sickle HbS to **HbG-Makassar**, with up to **91.7% of hemoglobin becoming functional (non-sickling) hemoglobin** . Treated cells showed *nearly complete absence of sickled cells* under low oxygen conditions . In a mouse SCD model, earlier studies have likewise shown that base editing can rescue hemoglobin function, with edited bone marrow producing ~43% healthy hemoglobin months after treatment . These results suggest that an in vivo infusion could directly correct a large fraction of a patient's HSCs, potentially curing SCD without an ex vivo transplant .
    - *2) In Vivo HbF Reactivation:* While not yet in human trials, it is conceivable to apply a similar in vivo base-editing approach to knock out repressors or introduce HPFH mutations. For instance, delivering a base editor to the bone marrow to disrupt the BCL11A gene or its enhancer in HSCs could induce fetal hemoglobin

production *in vivo*. (Notably, a recent in vivo gene-editing study by Liu et al. used prime editing via an adenoviral vector to target the sickle mutation, and they mobilized HSCs with G-CSF to increase editing yield . However, newer targeted delivery methods may achieve sufficient in situ editing without such mobilization.) As of 2025, **direct HBB correction** is the primary focus of in vivo base editing research for SCD, since a one-time precise fix is the most straightforward cure if delivery hurdles can be overcome .

In summary, **ex vivo** base editing strategies for SCD either *modify HSCs to produce fetal hemoglobin* (bypassing the need to fix the mutated gene) or *precisely correct the HBB mutation* in HSCs, after which the cells are transplanted. **In vivo** strategies aim to accomplish the same edits *inside the patient's body* – the emerging data show it's feasible to directly correct the SCD mutation in patient cells with base editors delivered by novel targeted nanoparticles . Each approach has distinct therapeutic implications, as detailed below.

Clinical Trial Landscape (Ongoing & Completed)

Research and development of base-editing therapies for SCD have progressed to clinical trials in the ex vivo realm, while in vivo base editing is just entering first-in-human studies (in other diseases) and preclinical stages for SCD. Below is an up-to-date overview of key trials and programs:

- **BEAM-101 (Ex Vivo Base Editing, SCD):** Beam Therapeutics' BEAM-101 is an autologous HSC therapy using base-edited cells to induce HbF. It is being tested in the Phase 1/2 **BEACON trial** for severe SCD. Initial clinical data from the first patients (reported late 2024) showed remarkable efficacy: in 4 treated SCD patients, **functional fetal hemoglobin rose to >60%** of total hemoglobin within 1–6 months . Their edited red cells showed greatly reduced sickling and improved rheology, and notably **none of these patients experienced vaso-occlusive crises** after treatment . As of late 2024, over 40 patients had been enrolled in BEACON, with Beam expecting to dose at least 30 patients and present further data in 2025 . This trial is the first-ever clinical evaluation of a CRISPR base editor in any disease. Early indications are that base editing is functioning as intended in patients, effectively reprogramming HSCs to alleviate SCD.
- **BEAM-102 (Ex Vivo Base Editing, SCD):** This is Beam's follow-up program aiming to directly correct the sickle mutation (using an ABE to create the HbG-Makassar variant). BEAM-102 was in preclinical development as of 2024. Beam has published preclinical results showing high editing efficiency (~70–80%) in patient-derived cells and normalization of cell properties . An IND filing is expected once BEAM-101 safety is established. (No active clinical trial yet, but this program is a key part of the landscape, indicating where ex vivo base editing is headed next.)

- **Other Ex Vivo Gene-Editing Trials for SCD:** While not base editors, it is important to note the success of related CRISPR and gene therapy trials, as they set the stage for regulatory and clinical expectations. Vertex/CRISPR Therapeutics' ex vivo CRISPR-Cas9 therapy **exa-cel (brand name Casgevy)**, which knocks out a fetal hemoglobin repressor in HSCs, completed Phase 3 and gained FDA approval in Dec 2023 . Similarly, Bluebird Bio's lentiviral gene addition therapy **lovo-cel (Lyfgenia)** was approved at the same time . These are now the first gene therapies for SCD in practice. Additionally, Editas Medicine's **EDIT-301 (a Cas12a-edited cell therapy)** and Intellia's **NTLA-2001** (an in vivo CRISPR for transthyretin amyloidosis) are in trials. These successes demonstrate that genetically modified cell therapies can cure SCD, and they pave a regulatory pathway for base-editing products as well . In fact, Beam's CEO highlighted that the **FDA's clear regulatory pathway**, validated by exa-cel and lovo-cel approvals, provides confidence for BEAM-101's development .
- **VERVE-101 (In Vivo Base Editing, Hypercholesterolemia):** VERVE-101 is not for SCD, but it is the **first in-human trial of in vivo base editing**, and thus highly relevant to the in vivo approach. Developed by Verve Therapeutics, VERVE-101 delivers an mRNA encoding an ABE and an sgRNA via lipid nanoparticles to patients, to inactivate the **PCSK9** gene in liver cells as a one-time treatment for hypercholesterolemia. The Phase 1 **Heart-1** trial dosed its first patients in 2022–2023. Interim data showed substantial gene editing effect: two patients given VERVE-101 had **PCSK9 protein levels drop by ~60–84%** and LDL-cholesterol reduced by ~40–50% on average . Importantly, no serious adverse events were reported, and the FDA—after an initial hold to review safety—lifted the hold in 2023, allowing US expansion of the trial . This trial demonstrates successful **in vivo delivery of a base editor** and provides safety experience (no significant off-target issues so far) in humans . While a different disease, VERVE-101's progress is a proof-of-concept that in vivo base editing can be clinically feasible.
- **Future In Vivo SCD Trials:** Building on the preclinical breakthroughs, we can anticipate an in vivo base-editing trial for SCD in the coming years. Academic consortia and companies are already collaborating – for example, Beam Therapeutics has an initiative (with its **ESCAPE platform**, see below) that could enable in vivo HSC editing. The UPenn/CHOP team's success in targeting HSCs in mice and human cells is likely to move toward animal models of SCD and eventually human trials. As of early 2025, however, **no in vivo HSC editing trial for SCD is yet in clinic** – the field is watching the space closely and gathering safety data from related in vivo gene editors (like Intellia's in vivo CRISPR trials and Verve's base editor trial). It's expected that within a few years, first-in-human in vivo base editing for SCD or β-thalassemia will commence, potentially using targeted LNP delivery to bone marrow.

Comparison Table – Key Therapies and Trials: The table below summarizes notable therapies for SCD and related base-editing trials:

Therapy (Approach)	In Vivo or Ex Vivo?	Mechanism	Clinical Status (2025)	Developer/Institution
BEAM-101 (Base-edited HSC)	Ex vivo (Autologous)	ABE edits HBG1/2 promoter to ↑HbF	Phase 1/2 ongoing (BEACON)	Beam Therapeutics / Boston Children's
BEAM-102 (Base-edited HSC)	Ex vivo (Autologous)	ABE edits HBB E6V -> E6A (Makassar)	Preclinical (IND-enabling)	Beam Therapeutics / Broad Institute
Exa-cel (Casgevy)	Ex vivo (Autologous)	CRISPR-Cas9 nuclease knocks out BCL11A enhancer (↑HbF)	**Approved 2023** (FDA/EMA)	Vertex & CRISPR Therapeutics
Lovo-cel (Lyfgenia)	Ex vivo (Autologous)	Lentiviral addition of anti-sickling β-globin gene	**Approved 2023** (FDA)	bluebird bio
EDIT-301 (Reni-cel)	Ex vivo (Autologous)	CRISPR-Cas12a edits HBG1/2 promoter (↑HbF)	Phase 1/2 ongoing (RUBY)	Editas Medicine
VERVE-101 (In vivo ABE)	In vivo (Systemic LNP)	ABE mRNA in LNP knocks out PCSK9 in liver	Phase 1 ongoing (Heart-1)	Verve Therapeutics
UPenn/CHOP HSC-ABE	In vivo (Targeted LNP)	ABE mRNA + anti-CD117 LNP edits HBB E6V->E6A	Preclinical (mice, in vitro)	Univ. of Pennsylvania & CHOP
Prime Editing (HDAd)	In vivo (HD Adenovirus)	Prime editor corrects HBB E6V precisely	Preclinical (mouse model)	Broad Institute (David Liu et al.)

(Table abbreviations: ABE = adenine base editor; LNP = lipid nanoparticle; HDAd = helper-dependent adenovirus; ↑HbF = increased fetal hemoglobin expression.)

Efficacy and Safety Data

Therapeutic Efficacy: Early data suggest both ex vivo and in vivo base-editing approaches can achieve functionally curative outcomes in SCD, but most clinical evidence to date comes from ex vivo trials:

- **Ex Vivo (BEAM-101):** Patients treated with base-edited HSCs have shown dramatic increases in healthy hemoglobin. In BEAM-101's efficacy cohort, HbF comprised over 60% of total hemoglobin within months , exceeding the ~40% HbF levels seen at 2 years

with prior gene therapies . Even at this early stage, such levels were sufficient to **eliminate vaso-occlusive crises and red-cell sickling** in those patients . Engraftment of edited cells has been robust and rapid, with only short periods of low blood counts post-transplant . These results indicate that base-edited cells are competitively repopulating the marrow and producing high levels of anti-sickling hemoglobin. For direct HBB correction (BEAM-102), preclinical efficacy was very high – edited cells from SCD patients produced >79% Makassar β-globin in vivo in mice, with a **3-fold reduction in sickling under stress** . Taken together, ex vivo base editing appears capable of **fully reversing the cellular hallmarks of SCD**, given sufficient editing rates.

- **In Vivo:** In humans, we are extrapolating from related indications. Verve's in vivo base editing (targeting the liver) achieved **potent, lasting gene silencing** (>80% protein reduction) with a single infusion , which bodes well for hitting therapeutic thresholds in other organs. In animal models for SCD, in vivo base editor delivery has led to significant correction: one study achieved ~44% editing of HSCs in mice, enough to raise healthy hemoglobin and improve red cell shape over 4 months . Another approach using in vivo prime editing fully corrected the sickle mutation in a mouse model, though with lower HSC targeting efficiency, requiring HSC mobilization to boost it . The Penn/CHOP team's targeted LNP-base editor showed that **>90% of erythroid cells derived from treated human HSCs were healthy** (with near-zero sickled cells) in vitro – a remarkable efficacy that, if replicated in patients, would essentially cure SCD. Thus, while human efficacy data for in vivo editing of HSCs are not yet available, the preclinical evidence suggests it can rival ex vivo methods in outcome.

Durability: A major advantage of gene editing (base editing included) is that the genetic correction should be permanent in the edited stem cells, leading to long-term benefits. For ex vivo therapies, patients from earlier trials (CRISPR Cas9 and lentiviral) have remained essentially sickle-free for **2–3+ years** post-treatment, with stable engraftment of edited cells producing fetal or modified hemoglobin. Base-edited cells would be expected to behave similarly. The BEAM-101 trial is still in early follow-up, but no decay in fetal hemoglobin production has been reported in the first year – if anything, levels tend to increase in the months after transplant as edited cells fully engraft . In vivo base editing's durability will depend on whether long-lived HSCs are edited. Data from Verve's trial indicates the edits in liver are persisting (since LDL levels remain low months after dosing, consistent with permanent gene knockout) . In an SCD context, once an HSC is successfully base-edited, all of its progeny should carry the correction, making the effect lasting. A key question for in vivo will be achieving a high enough fraction of HSCs edited in one treatment to ensure the patient's blood largely consists of corrected cells long-term. Encouragingly, strategies like targeted delivery and mild selective pressure on edited cells (see conditioning below) could help maximize durable engraftment of corrected cells in vivo.

Safety Profile and Off-Target Effects: Thus far, base editing has shown a generally favorable safety profile, but certain risks and challenges are unique to each approach:

- **Ex Vivo:** The primary risks come not from the gene editor itself, but from the transplant procedure (myeloablative conditioning) and the infusion. In BEAM-101, there have been no toxicities definitively attributed to the base editor. Notably, one trial patient died, but this was caused by complications of **busulfan chemotherapy (conditioning)**, not the editing – the patient's lungs suffered toxicity consistent with known busulfan effects, and **no sickling was observed even under that stress**, confirming the edit's beneficial effect . Overall, patients have tolerated the BEAM-101 edited cell infusion similarly to other autologous transplants. Off-target DNA edits are a concern in theory, but base editors are designed for high specificity. Beam reported **no significant off-target mutations** with their improved "inlaid base editor" design in preclinical studies (guide-independent off-target editing was greatly reduced) . Unlike nuclease editing, base editors cause almost no indels or chromosomal breaks, so risks of oncogenic chromosomal rearrangements are lower . Nonetheless, ex vivo products undergo thorough genomic QC – so far, no concerning off-target events have been reported publicly for BEAM-101. Immune reactions to the edited cells have not been an issue (the cells are the patient's own), and since the editing machinery is not present during infusion (it's used in the lab and washed out), there's little risk of immune response to Cas9 or the deaminase in the patient.
- **In Vivo:** Safety here must consider the delivery vehicle, the base editor effects in the body, and potential immune responses. From Verve-101's initial human data, **no serious adverse events** were seen at effective doses . Mild infusion reactions (e.g. due to LNPs) can occur but have been manageable. Importantly, regulatory scrutiny has focused on off-target edits – for example, the FDA initially paused Verve's IND because an off-target site was observed in animal studies (an edit in a gene *LRRK1* in monkeys). Verve optimized their approach and presented data suggesting this off-target editing was mitigated or had no adverse consequence . Indeed, the **clinical hold was lifted after safety data from overseas trials assuaged these concerns** . Off-target editing in vivo is monitored by sequencing blood or tissue samples; so far in the PCSK9 trial, no deleterious off-target mutations have been reported. Immune response is another consideration: many people have pre-existing antibodies to Cas9 proteins (from common bacteria), and introducing a Cas9-based editor in vivo could, in theory, trigger immune clearance or inflammation. In practice, delivering mRNA encoding the editor (as opposed to a viral vector continuously expressing it) limits the window of Cas9 presence, reducing the chance for the adaptive immune system to mount a response. Moreover, modified mRNA chemistry (pseudouridine, etc.) helps evade innate immune sensors . Verve's approach did not require immunosuppression, and no neutralizing antibody issues have been noted publicly. Still, with any in vivo gene therapy, there's a risk of immune reaction to the delivery vehicle (e.g., antibodies to AAV capsids, or infusion reactions to LNP). Those need to be managed (for instance, patients with high titers against a viral vector might be excluded or given steroids). Another safety aspect for in vivo HSC editing is **on-target cell effects**: editing HSCs in place could theoretically trigger p53 or DNA damage responses in some cells. However, base editors cause single-base changes which most cells tolerate well, and studies have not shown obvious toxicity to HSCs from base editing – edited HSCs in mice and human cell assays continued to thrive and differentiate normally . In Penn's work, *no impairment of HSC viability or proliferation* was observed after in vivo base editing of the sickle mutation .

Unique Considerations – Conditioning and Engraftment: A safety and efficacy factor common to both approaches is how to ensure the edited HSCs populate the bone marrow effectively:

- **Ex Vivo:** Patients receive high-dose chemotherapy (e.g. busulfan) to destroy a portion of their marrow, creating "space" for the infused edited HSCs to engraft. This is effective but carries significant toxicity (infection risk, organ damage, infertility, etc.). Beam and others are working on gentler alternatives. One innovation is Beam's **ESCAPE** platform, which involves base-editing the HSCs to make them resistant to a certain antibody, and then using that antibody in vivo to selectively purge native (unedited) HSCs – **conditioning without chemotherapy** . In preclinical models (non-human primates), this approach enabled successful engraftment of base-edited cells and **durable high levels of HbF** production, without needing toxic chemo . This strategy is still experimental but could greatly improve ex vivo therapy safety if translated clinically.
- **In Vivo:** The patient's existing HSCs are being edited directly, so in theory no transplantation is needed. However, if only a subset of HSCs gets corrected, they must outcompete the diseased cells to cure the patient. There's ongoing research into **in vivo selection** methods. The Penn study explored a two-step approach: first, deliver base editor to correct HSCs, then deliver an apoptotic protein (PUMA) via targeted LNP to **specifically kill off remaining diseased HSCs**, allowing the corrected cells to fill the marrow without chemo . In mouse experiments, this antibody-LNP mediated conditioning achieved engraftment levels high enough to cure immunodeficiency disorders without traditional conditioning . Such a tandem in vivo edit-and-select strategy could potentially be applied to SCD: patients might receive one injection to edit a large fraction of HSCs, and another injection to deplete the unrepaired ones, resulting in a marrow largely composed of corrected HSCs. This is an area of active investigation and will be crucial for in vivo approaches to ensure long-term cure without retreatment.

In summary, **ex vivo base editing has so far demonstrated impressive efficacy in SCD patients with an acceptable safety profile, aside from the known risks of bone marrow transplant procedures . In vivo base editing is showing strong efficacy in models and early trials (in a different disease) with encouraging safety, but it remains early-stage for SCD.** Ongoing trials will further illuminate off-target profiles and any immune issues, but current data give reason to be optimistic about the risk-benefit balance of both approaches.

Delivery Technologies

A critical difference between in-vivo and ex-vivo base editing lies in **how the editing tools are delivered to cells**:

- **In Vivo Delivery:** The challenge is to package the editor (Cas9-deaminase and guide RNA) into a delivery system that can be administered like a drug, survive in the bloodstream, and specifically transfect the target cells (HSCs in bone marrow, in the case of SCD). Several delivery technologies are in development:
    - *Lipid Nanoparticles (LNPs):* These are tiny fat-based droplets that can encapsulate nucleic acids (e.g. mRNA and sgRNA). LNPs have been used successfully for liver-targeted delivery (e.g., VERVE-101 uses an LNP that naturally accumulates in the liver to deliver ABE mRNA to hepatocytes). For HSC targeting, LNPs are being engineered with surface modifications. A breakthrough study decorated LNPs with an antibody against **CD117 (c-Kit)**, a marker on HSCs . This CD117-targeted LNP achieved efficient uptake by HSCs in bone marrow after IV injection . Using such targeted LNPs, researchers delivered base editor mRNA to HSCs and achieved high editing rates of the sickle mutation in vitro . LNPs have the advantage of being **non-viral and transient** – the mRNA produces the editor for a short period, then degrades. They can also be re-dosed if needed. The LNP formulations used include standard lipid components (like those in mRNA vaccines) and often incorporate chemically modified mRNAs to reduce innate immune activation .
    - *Viral Vectors:* Viral gene therapy vectors can deliver DNA encoding base editors. **Adeno-associated virus (AAV)** has been explored – researchers have created **compact base editors** small enough to fit in AAV's cargo limit (by truncating Cas9 or using smaller Cas proteins) . A single AAV carrying both ABE and sgRNA has shown efficient base editing in mice . However, for HSC editing, AAV has hurdles: it tends to target liver/muscle more than bone marrow, many people have pre-existing anti-AAV immunity, and AAV DNA may persist (though using a transient editor is possible). Another approach was using a **helper-dependent adenovirus (HDAd)** to deliver a prime editor for SCD in a mouse model . The HDAd could carry the large prime editing machinery and achieved gene correction, but it required mobilizing HSCs into blood (with G-CSF) to infect them . Viral vectors thus *can* deliver editors in vivo, but issues of targeting specificity and immunogenicity mean they are currently not the frontrunners for SCD base editing.
    - *Other Novel Vehicles:* Early research is examining exosomes and cell-penetrating protein fusions as well. For example, one could imagine an approach where the base editor protein is fused to an antibody or ligand that binds HSCs, so that injecting the protein:guide complex could directly shuttle into HSCs. This is still speculative, and no such therapy is in trials yet. In summary, the leading in vivo delivery method for base editors appears to be **systemic LNPs**, potentially with cell-specific targeting ligands, due to their tunability and non-integrating, transient nature .
- **Ex Vivo Delivery:** Delivering editors ex vivo is comparatively straightforward because it occurs in a controlled laboratory setting:

- The most common method is **electroporation (nucleofection)** of the patient's harvested HSCs with either an **RNP (ribonucleoprotein)** complex (purified Cas9 nickase protein pre-loaded with sgRNA) or with **mRNA** encoding the base editor plus a synthetic sgRNA. Electroporation creates temporary pores in the cell membrane, allowing these molecules to enter the cells. This technique has been successfully used for ex vivo CRISPR editing by several groups (e.g., CRISPR Therapeutics' exa-cel uses Cas9 RNP via electroporation). Beam has likely employed a similar approach for BEAM-101, using either an ABE mRNA or protein. The high editing rates reported (>60% of alleles) suggest an efficient transfection process. Electroporation is virus-free and the editor is only present transiently, which limits off-target activity to a short window.
- Another ex vivo method is to use a **viral vector to transduce the cells** with the editor components. For instance, a lentiviral or Sendai virus vector (non-integrating, if engineered) could deliver the base editor gene to HSCs. However, this is less common in clinical programs due to regulatory complexity (if DNA integrates, it raises additional safety questions). Beam's base editors are likely delivered as mRNA or protein, not via integrating vectors. Non-integrating lentiviral or adenoviral vectors could be an option to transiently express base editors in HSCs ex vivo, but electroporation of RNP/mRNA is generally preferred for precision editing.
- **Selection and culture:** After editing, HSCs may be cultured briefly to assess editing efficiency or to allow them to recover. In some experimental protocols, cells can be flow-sorted (FACS) to enrich for successfully edited cells if there's a selectable marker or phenotypic change, but in clinical protocols like BEAM-101 no additional genetic marker is used – all cells are returned to the patient without selection, relying on high initial editing rates and the in vivo advantage of corrected cells. The ex vivo process also includes quality control steps: checking that the HSCs are viable, pluripotent, and have the intended edit (often a sample of cells is deep sequenced to confirm on-target editing frequency and to screen for top off-target edits, before releasing the product for infusion).

Comparison: In essence, **in vivo delivery** must solve the problem of targeting HSCs inside the patient (LNP with antibody targeting being a promising solution), whereas **ex vivo delivery** must efficiently introduce the editor to cells in a dish (electroporation is standard). In vivo approaches avoid the need to remove and handle cells, but require sophisticated delivery vehicles to find the cells in the body; ex vivo approaches simplify delivery by direct manipulation of cells, but then those cells must be successfully returned and engrafted.

Manufacturing and Scalability

The logistics and scalability of these approaches are vastly different, which impacts cost, access, and deployment:

- **Ex Vivo (Autologous Cell Therapy) Manufacturing:** Each patient's cells are essentially a bespoke product. The process involves harvesting HSCs (often by stem cell mobilization with drugs and apheresis collection), shipping them to a manufacturing site, editing them, performing quality checks, and cryopreserving or transporting the product back for infusion. This labor-intensive process must be done under strict Good Manufacturing Practice (GMP) conditions and can take several weeks. The need for individualized manufacturing drives **very high costs (estimated $1–2 million or more per treatment)** and limits scalability . Indeed, current ex vivo gene therapies for SCD are expected to be in the seven-figure price range due to the complex cell processing. Moreover, the requirement for specialized cell-processing facilities and transplant infrastructure means access is largely restricted to major medical centers. As noted, ex vivo gene therapies are **expensive (on the order of 2–3 million dollars per patient) and involve arduous procedures like chemotherapy** . This model is feasible in developed healthcare systems (with payer support) but would struggle in low-resource settings where SCD is most prevalent. Manufacturing improvements like automation of cell handling, or allogeneic "off-the-shelf" donor cells (not applicable for SCD due to rejection issues), are being considered to streamline ex vivo therapy. But fundamentally, ex vivo base editing will likely follow the paradigm of current cell therapies: high-cost, centralized manufacturing with limited throughput.
- **In Vivo (Pharmaceutical) Manufacturing:** In vivo base editing treatments would be manufactured more like a conventional **drug product**. For example, production of an LNP-encapsulated mRNA is a scalable process – it can be done in bulk, purified, and vialed in doses, rather than one patient at a time. This opens the possibility of **economies of scale**. A single batch could produce hundreds or thousands of doses to be distributed worldwide, dramatically lowering per-patient cost once development costs are amortized. In vivo therapies also simplify logistics: a finished vial can be shipped to a hospital pharmacy and administered to the patient, **eliminating the need for specialized cell-processing facilities**. Turnaround time is essentially just the scheduling of an infusion. This could hugely expand access – potentially any clinic that can handle an IV infusion and monitor the patient could administer the therapy, as opposed to requiring a transplant unit and months of coordination. Especially for SCD, which affects tens of thousands in sub-Saharan Africa and South Asia, an in vivo therapy is seen as the more **globally scalable solution** in the long run .

  That said, in vivo manufacturing has its own complexities. High-tech nanoparticles or viral vectors require advanced production and strict quality controls (for purity, potency, sterility, etc.). There may be limited facilities globally that can produce gene therapy products at scale currently, but capacity is increasing. Another consideration is **supply chain for components**: for instance, the lipid components of LNPs or the Cas9 protein source. These need to be consistent, safe (e.g., no immunogenic impurities), and abundant. Companies are investing in manufacturing platforms for mRNA and LNP (benefiting from the mRNA vaccine experience). If an in vivo base editor becomes approved, manufacturing enough doses for broad use will be a challenge, but one that is

surmountable with industrial processing (unlike the inherently one-by-one nature of autologous cell prep). Cost-wise, while initial gene therapies have been extremely expensive, an in vivo therapy could trend down in cost over time – perhaps into the several hundred thousand dollar range or less – if competition and production efficiency improve. Moreover, without the need for hospitalization for transplant and chemotherapy, the **total cost of care** for an in vivo treatment could be much lower than for ex vivo (which involves ICU-level care during transplant).

- **Time-to-Patient:** Ex vivo therapy usually has a lead time of several weeks (for mobilization, cell engineering, and recovery post-transplant). This isn't a big issue for a chronic disease like SCD (patients can wait a bit for a curative therapy), but it means a lot of coordination. In vivo therapy could be more or less "on-demand" – a patient could be evaluated and receive the treatment within days potentially, if no individualized manufacturing is needed. This could be crucial in scenarios like acute crises or in regions where maintaining a patient in care for a prolonged process is difficult.
- **Feasibility in Different Settings:** In wealthy countries, both ex vivo and in vivo could be feasible (though ex vivo will be done only at centers of excellence). In poorer regions, ex vivo gene therapy for SCD is almost impractical currently – it requires too much infrastructure (blood stem cell harvest, labs, isolation rooms, etc.). In vivo therapy, if it becomes as simple as an injection that reverts SCD, could in theory be deployed in broader healthcare settings, dramatically increasing the number of patients who can be treated. Researchers and global health advocates often mention that **making SCD gene therapy in vivo is key to reaching the majority of SCD patients worldwide**, who currently have limited access to even basic care .

In summary, ex vivo base editing involves complex, patient-specific manufacturing with high costs and logistical demands, while in vivo base editing would be produced like a standard biologic therapy, offering greater scalability and easier distribution. The trade-off is that in vivo is currently more scientifically challenging (delivery-wise), but if solved, it could democratize SCD cures far beyond what ex vivo methods can achieve.

Regulatory Status and Approvals

Ex Vivo Therapies: The regulatory environment for genome-edited cell therapies has matured quickly. In late 2023, the FDA and EMA approved the first two autologous gene therapies for SCD – **Casgevy** (exa-cel, CRISPR-edited HSCs) and **Lyfgenia** (lovo-cel, lentiviral gene addition) . These approvals indicate that regulators are amenable to genetic cures for SCD, provided efficacy and safety are demonstrated. BEAM-101, as a first-in-class base editing therapy, is currently in Phase 1/2; it will likely require Phase 3 data before seeking approval. However, Beam might benefit from regulatory designations (SCD therapies often get Orphan

Drug, Fast Track, or Breakthrough Therapy designations if they show extraordinary promise). The **clear pathway established by exa-cel's approval** is encouraging – for example, showing that end-points like increases in fetal hemoglobin and reduction in crises can support approval . Beam has suggested a "validated regulatory pathway" now exists . One can expect BEAM-101 (or a subsequent iteration) to follow on the heels of exa-cel if outcomes remain positive. Similarly, Editas' EDIT-301 is in clinical trials and could be another ex vivo gene-editing therapy reaching the market in a few years (though it uses a nuclease, not a base editor). In terms of **regulatory considerations for base editors**: agencies will examine off-target profiles carefully. They will likely require extensive genomic analysis of edited cell products (for ex vivo) to ensure no unintended risky mutations. The fact base editors make specific single nucleotide changes – many of which mimic natural benign variants (like HbF promoter mutations or Hb Makassar) – could be a point in their favor. Still, long-term follow-up (on the order of 15 years) will be mandated to watch for any delayed adverse effects (e.g., hematologic cancers) in patients who receive these edited cells, as is standard for gene therapy trials.

In Vivo Therapies: No in vivo CRISPR-based therapy (base editor or nuclease) is approved yet as of 2025. Regulatory agencies have been cautious but supportive in allowing first-in-human trials to proceed. The FDA's initial clinical hold on VERVE-101, followed by lifting the hold upon additional data , exemplifies this cautious approach: regulators wanted more evidence of safety (especially regarding off-target editing in germline or other tissues) before green-lighting trials on U.S. soil. Verve had to provide comprehensive animal data and even early human data from overseas to address those concerns . Once satisfied, the FDA did permit the trial, and even granted Fast Track designation to Verve's follow-on candidate VERVE-102 , showing that they recognize the potential of this modality. For SCD, an in vivo base editing trial would likely be given similar scrutiny. Key regulatory issues will include: ensuring the editing is restricted to somatic HSCs (no unintended germline editing if patients are of childbearing potential), minimizing off-target changes, and managing immunological risks. The field of in vivo gene therapy has some precedents (many AAV gene therapies are approved for other diseases), but none involve genome editing in HSCs yet. That means an in vivo HSC edit will be breaking new ground – agencies may initially recommend starting in very controlled settings (perhaps starting with adult patients only, requiring contraception, etc., as was done with ex vivo gene therapies too). If early trials show safety and efficacy, regulatory momentum could build quickly, given the transformative potential. It's conceivable that in vivo editing could receive **Breakthrough Therapy** designation if it shows a curative effect without transplant, as that would be a huge advance.

Ethical and Oversight Aspects: Both approaches involve permanent DNA changes, so regulators also consider ethical aspects and patient consent. However, since these are targeting somatic cells to cure a serious disease, there has been broad ethical acceptance. Community engagement has been strong in SCD, ensuring patients and advocates are on board with gene-editing trials. Regulatory agencies in the US (FDA) and Europe (EMA) have set up guidelines for gene editing trials, and these programs are following those frameworks closely.

In summary, **ex vivo base-edited therapies for SCD are on a path to follow recent approvals, likely reaching the market in the next few years if trials confirm safety and efficacy. In vivo therapies are still in an earlier phase of regulatory navigation** – the first approvals for in vivo base editors will probably be in non-SCD indications (e.g., cardiovascular), but the knowledge gained will directly feed into SCD applications. Both FDA and EMA have shown openness to these innovations, granting special designations to expedite development when warranted.

Key Players and Institutions

The development of in vivo and ex vivo base-editing therapies for SCD involves a broad collaboration between biotech companies, academic institutions, and clinical centers. Here are some of the notable players driving progress:

- **Beam Therapeutics:** A pioneer in base editing, co-founded by base-editing inventor Dr. David Liu. Beam is leading ex vivo base editing for blood disorders. It has developed BEAM-101 and BEAM-102 for SCD, and is also researching base editing for other diseases (like BEAM-201 for immuno-oncology). Beam collaborates with academic centers such as Boston Children's Hospital (where the BEACON trial is being conducted) . They are also innovating solutions to improve HSC editing and transplant (the ESCAPE conditioning platform) . Beam's work is at the forefront of proving base editing's clinical value in ex vivo settings.
- **Verve Therapeutics:** Co-founded by Dr. Sekar Kathiresan and Dr. Kiran Musunuru, Verve is focused on in vivo base editing for cardiovascular conditions. While not directly working on SCD, Verve's progress with VERVE-101 (PCSK9) and VERVE-102 (another liver-targeted base editor, possibly for ANGPTL3) is blazing the trail for in vivo base editing in humans. They have partnered with pharma (e.g., a collaboration with Lilly) and are setting up a roadmap that others (including for SCD) can follow for in vivo delivery and regulatory clearance.
- **Intellia Therapeutics:** An adjacent player, Intellia has achieved success with in vivo CRISPR *nuclease* editing (not base editing) for transthyretin amyloidosis (NTLA-2001) and hereditary angioedema (NTLA-2002) using LNPs. Their work, though using a cutting strategy, demonstrates that LNP delivery of gene editors to organs (liver in their case) can be effective in humans. Intellia's platform and know-how in LNP design, mRNA chemistry, and clinical trial execution for in vivo editing provide a foundation that base-editing efforts can leverage. (They have also expressed interest in base editing or prime editing applications in the future.)
- **Editas Medicine:** Editas has its own SCD program (EDIT-301) which is an ex vivo gene-edited cell therapy using a different CRISPR system (AsCas12a) to knock out a repressor in HBG. While not base editing, Editas is a competitor in the race to cure SCD with gene editing. Their progress in the RUBY trial (early data show patients achieving

near-normal total hemoglobin with increased HbF) adds to the momentum in this field. Editas and Beam are effectively racing with different editing technologies; successes and learnings from one will benefit the other in terms of validation and regulatory acceptance.

- **CRISPR Therapeutics & Vertex Pharmaceuticals:** These companies developed exa-cel (Casgevy), the first approved CRISPR therapy for SCD. Though exa-cel uses nuclease editing, many of the trial investigators, clinical sites, and manufacturing techniques overlap with what base editing programs will use. For instance, the network of sickle cell centers that participated in exa-cel trials (in the US, Europe, and elsewhere) are likely also engaged or interested in trials like BEAM-101. These companies also continue to innovate (e.g., looking into in vivo delivery themselves, and next-gen editors). Their commercial rollout of exa-cel will also influence how future base-edited products are implemented in healthcare (e.g., infrastructure for delivering gene therapies).
- **Academic Institutions:** Academia has been crucial, especially for in vivo approaches:
    - *University of Pennsylvania and Children's Hospital of Philadelphia (CHOP):* Teams here (led by Dr. Stefano Rivella, Dr. Laura Breda, Dr. Hamideh Parhiz, and others) published the recent Science paper demonstrating in vivo HSC base editing with CD117-targeted LNP . CHOP and Penn are long-time leaders in gene therapy (having pioneered CAR-T and AAV gene therapies), so their involvement lends significant credibility. They are likely to continue developing this approach toward clinical translation, possibly in partnership with biotech (or via internal efforts).
    - *Broad Institute of MIT/Harvard:* The Broad, where base editing was invented, continues to contribute through research by Dr. David Liu's lab and others. For example, the prime editing approach for SCD (using adenoviral delivery) had Broad researchers involved . The Broad/Harvard group also works on improved base editors (e.g., novel deaminases, reducing off-target RNA edits, etc.) which will feed into safer/more effective therapeutics.
    - *Stanford University and others:* Several academic centers have programs for gentler conditioning and in vivo editing. For instance, Stanford researchers have explored anti-CD117 antibody-based conditioning in transplant (Magenta Therapeutics spun out of this work), and others are exploring gene editing to confer drug resistance to HSCs (similar to Beam's ESCAPE concept). These innovations often come from academia and then are adopted by companies.
- **Clinical Trial Sites & Hospitals:** High-profile hospitals are running these trials: **Boston Children's Hospital/Dana-Farber** (Beam's trial) , **NIH** (the NIH's own trial with CRISPR Cas9 editing of BCL11A), **Oxford University** (UK sites for exa-cel and likely for base editor trials in the future), and many sickle cell centers globally. These institutions contribute patients, expertise in SCD care, and long-term follow-up.
- **Funding and Consortia:** Organizations like the **Bill & Melinda Gates Foundation** and NIH have invested in gene editing cures for sickle cell, especially with the goal of an in vivo (in vivo is seen as more accessible globally). The Gates Foundation, for example, partnered with Novartis a few years ago to look into in vivo gene therapies for sickle cell. While specific companies weren't mentioned there, such funding could accelerate platform technologies and eventual trials in lower-resource settings.

Key Companies by Approach: In summary, *ex vivo base editing for SCD* is being spearheaded by **Beam Therapeutics** (with potential competition from companies using other editing tech like Editas, CRISPR Therapeutics). The ecosystem involves partnerships with academic hospitals for trial execution. *In vivo base editing* for SCD is still preclinical, but **Verve Therapeutics** is proving the concept in humans (albeit in liver), and academic teams at **Penn/CHOP** and the **Broad Institute** are driving the HSC-targeted research. It's likely that either Beam or another biotech will eventually license or collaborate on the Penn approach to bring it to trials, or a new startup might emerge around in vivo HSC editing for hemoglobinopathies. Given the complexity, a collaboration between experienced gene therapy academics and industry seems probable for the first in vivo SCD base-editing trial.

Conclusion

Both in-vivo and ex-vivo CRISPR base-editing therapies hold the promise of a one-time cure for sickle-cell disease by fixing the root cause – but they represent different routes with unique advantages and challenges. Ex vivo base editing has already entered the clinic and shown that it can **safely produce curative outcomes** , essentially combining the efficacy of a bone marrow transplant with precision gene correction. However, it remains a complex, resource-intensive treatment. In vivo base editing, while a step behind in development, aspires to make SCD treatment as simple as an injection that genetically repairs a patient's own stem cells **inside their body**, potentially broadening access to a cure .

The scientific foundations – from the clever engineering of ABEs/CBEs to target specific mutations, to novel delivery systems – are rapidly maturing. The **clinical trial landscape** is expanding with multiple base editor trials (e.g. BEAM-101 in SCD, VERVE-101 in vivo) and more on the horizon, reflecting a healthy pipeline of innovation. Early **efficacy data** are very encouraging (patients with >60% fetal Hb and no crises; animals with corrected disease phenotypes) , and the **safety profile** so far suggests that base editing can avoid many of the pitfalls of earlier gene therapies (fewer off-target issues than nucleases, and no viral integration) .

Comparative Outlook: The table below summarizes key differences between in-vivo and ex-vivo base-editing approaches for SCD:

Aspect	In Vivo Base Editing	Ex Vivo Base Editing
Mechanism of Action	Delivers editor (e.g. ABE mRNA + sgRNA) **inside patient** to directly edit HSCs in bone marrow *in situ*. No cell	Delivers editor to HSCs **outside body** (in a lab dish). Patient's HSCs are

Aspect	In Vivo Base Editing	Ex Vivo Base Editing
	removal; editing occurs within the body.	harvested, edited with base editor (ABE/CBE), then returned to patient.
Therapeutic Strategy	Usually aims for **direct gene correction in vivo** (e.g. convert sickle β-globin to a normal variant) . Could also target regulatory genes (e.g. edit BCL11A or HBG promoter to induce HbF) if that proves efficient in vivo. One-shot treatment intended to permanently edit a portion of the patient's own stem cells.	Can pursue **gene correction or HbF induction** in the harvested cells. For SCD, one strategy is editing HBG promoters to boost fetal Hb (BEAM-101) ; another is correcting the HBB mutation to Hb Makassar (BEAM-102) . The edited cells are then transplanted back, aiming for lifelong engraftment.
Delivery Method	**Non-viral nanoparticles** (e.g. LNPs) or viral vectors injected IV. For HSC targeting, may use *cell-specific targeting* (e.g. anti-CD117-LNP to home to HSCs) . Editor is typically delivered as **mRNA and guide RNA** (transient expression). No surgical procedures – just IV infusions (possibly multiple for editing + conditioning).	**Electroporation or transduction** of HSCs ex vivo. Commonly uses **Cas9-deaminase RNP or mRNA** introduced into cells via electroporation (high efficiency). No viral vector needed for editor in most cases (to avoid integration); sometimes a viral vector if a gene insert was required, but not for base edits. Requires apheresis to collect cells and IV infusion to return them.
Efficacy (so far)	Preclinical results show high potential: *e.g.* ~90% conversion to healthy hemoglobin in vitro with targeted LNP delivery ; significant disease amelioration in SCD mouse models . First-in-human data (from non-SCD use) showed ~40–60% clinical efficacy (LDL reduction in VERVE-101) with durable effect . Goal is to edit enough HSCs in vivo to alleviate SCD – modeling suggests even ~20% corrected HSCs could be curative if they have a fitness advantage.	Achieved ex-cellulo and in patients: BEAM-101 patients >60% HbF and no crises . Other gene-edited cell therapies show stable engraftment and >40% fetal or modified Hb at 2 years . Base editing ex vivo can reach very high on-target edit rates (>70–80% in HSCs) , making curative outcomes likely. Early clinical data validate that the edited cells produce functional hemoglobin and reduce sickling dramatically .
Safety Considerations	Avoids transplant risks but introduces **systemic exposure to editor**. Key concerns: off-target edits in the genome (need precise guides and high-fidelity editor) and immune reactions (to Cas9 protein or vector) . Thus far, in vivo ABE has been well tolerated in humans . No conditioning chemo required *if* enough HSCs are	Avoids exposing the body to gene-editing machinery (editing done in lab), so no risk of widespread off-target editing in vivo. The main risks are those of **autologous transplant**: chemotherapy side effects (infection, organ toxicity – e.g. busulfan lung injury), and infusion risks. Thus far, base-edited products haven't shown

Aspect	In Vivo Base Editing	Ex Vivo Base Editing
	edited, but new conditioning methods (antibody or apoptosis-based) might be used to enhance engraftment . Critical to prevent germline editing (e.g. avoid editing reproductive cells). Overall, one less step of risk (no infusion reaction to cell product or graft failure risk), but new risks in delivering a gene editor internally.	any cell-intrinsic adverse effects (no abnormal clonal growth or mutations observed). Off-target edits are checked in the cell product; base editors show low off-target profile . Immune rejection is minimal since cells are the patient's own. Requires heavy immune-suppressive conditioning, which is a major safety and recovery hurdle (research ongoing to replace chemo with safer methods).
Manufacturing & Access	**Scalable drug-like manufacturing.** A single process to produce the LNPs or viral vectors can serve all patients. Easier distribution (vials to hospitals). **Lower marginal cost per patient** once developed – potentially enabling use in low-resource settings. However, upfront R&D is high, and initial therapies could be very expensive. Logistical ease: no need for specialized cell labs on patient-by-patient basis, meaning a broader range of hospitals could administer therapy if approved.	**Custom manufacturing per patient.** Complex supply chain: harvesting cells, processing in GMP facility, product release testing, etc. High cost and infrastructure requirements, limiting to specialized centers. Turnaround time of weeks and significant labor per patient. Scaling up means building more cell therapy facilities – a slower, costly expansion. Likely to be limited to developed healthcare systems and specialized transplant centers, at least in near term .
Regulatory Status	*Early-stage.* No approvals yet for in vivo base editing. First trial (VERVE-101) in Phase 1; fast track designations granted for related programs . Regulators cautious but permitting trials with careful monitoring. For SCD, in vivo approach will likely enter trials in the next couple of years, with stringent oversight (due to it being first-in-human for HSC editing). Approval timeline will depend on trial results, but optimistically could be later this decade if a program shows clear curative benefit and safety.	*Advancing in clinic.* Base-edited cell therapy is in Phase 1/2 (BEAM-101) with encouraging interim results. Comparator gene-edited cell therapies have already been **approved in 2023** , which sets a precedent. BEAM-101 could follow a similar path if Phase 2/3 outcomes are strong, possibly aiming for approval by mid/late-decade. Regulatory agencies have frameworks in place for these autologous gene therapies, and base editing doesn't introduce radically new regulatory questions beyond what nuclease-edited products did. Long-term patient registry follow-up will be required post-approval.

As seen above, **ex vivo and in vivo base editing each have strengths**: ex vivo is currently more proven and controlled, whereas in vivo offers greater scalability and patient convenience. In the coming years, we may see these approaches converge – for instance, transient in vivo editing might be combined with targeted conditioning to yield transplant-like outcomes without the transplant. It's an exciting era where technologies such as base editors, advanced delivery systems, and improved conditioning agents are converging to finally bring a cure for sickle-cell disease within reach.

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