Anchor Point Insights

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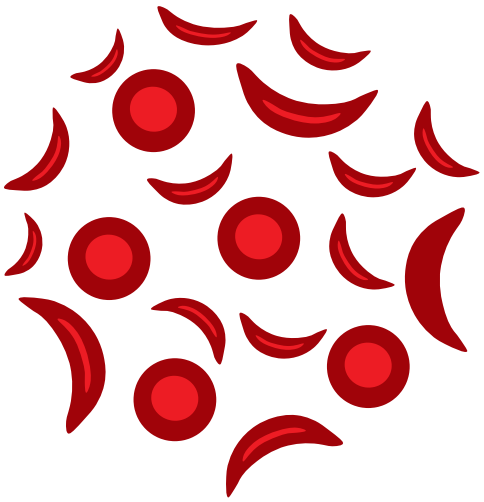

SICKLE CELL DISEASE

ORAL THERAPIES TO REMAIN A MAINSTAY OF SCD TREATMENT EVEN WITH POTENTIALLY CURATIVE OPTIONS NOW A REALITY

ABOUT THE AUTHOR

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ABOUT ANCHOR POINT INSIGHTS

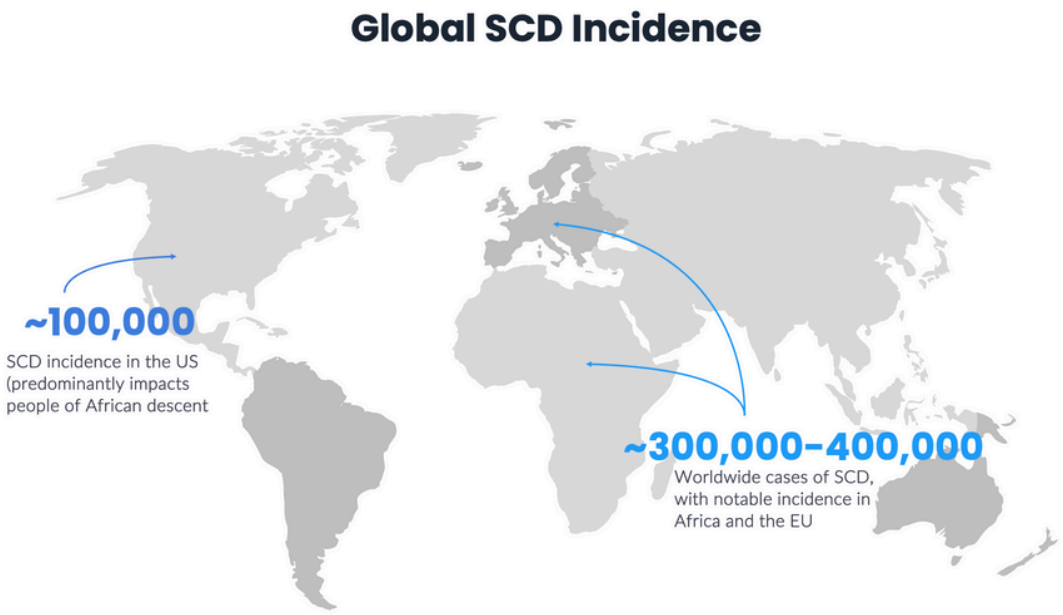
API is a pharmaceutical-focused consultancy that provides clients with customized, evidence-based insights and analysis. We develop bespoke strategies to help our client partners meet challenges in many areas, including therapeutic area assessment and competitor research

Key Takeaway

Currently available SCD therapies are significantly underutilized for reasons ranging from cost and accessibility to lack of patient adherence to limitations of effectiveness and safety concerns. Curative gene therapies may appear to be the answer, but again for reasons of cost, accessibility, and conditioning-related toxicity, may not be available to reach more than 5-15% of patients. Increasing access to current treatment options and development of next-gen treatments with improved efficacy and convenient, oral dosing will be a crucial part of the SCD therapeutic landscape for the foreseeable future.

SCD Intro/Overview

Sickle cell disease (SCD) is a genetic disease caused by a single mutation in the hemoglobin gene resulting in the production of sickle hemoglobin (HbS). Approximately 100,000 people are currently impacted in the US and ~300,000-400,000 worldwide, predominantly of African descent. In a deoxygenated state, HbS polymerizes causing red blood cells (RBCs) to stiffen and form the eponymous “sickle” shape as well as to undergo hemolysis, or RBC destruction. RBCs, platelets, and white blood cells can adhere to the vascular endothelium resulting in vaso-occlusions (VOCs) that can lead to acute pain crises as well as significant end organ damage (stroke, acute chest syndrome, anemia, etc.) resulting in an average life span approximately 20 years shorter than the general population.



Current Treatments

Until recently, hydroxurea was the only available therapy for SCD, but within the last 5-6 years the SCD therapeutic space has seen a dramatic uptick in activity with multiple approved agents and more therapies advancing through development.

1998

Hydroxyurea

Hydroxyurea, a chemotherapy compound, was approved in 1998 for SCD and is known to address both RBC-mediated and vascular-mediated complications of SCD. Hydroxyurea induces fetal hemoglobin (HbF) expression, thereby inhibiting HbS polymerization while also increasing nitric oxide, a vasodilator, and decreasing RBC adhesion. While hydroxyurea is considered standard-of-care (SOC) and recommended for all SCD patients beginning at 9 months of age, adoption is low (~28% in pediatric patients and ~23% in adults with >3 VOCs/year), likely related to access and concerns with side effects.

2017

L-glutamine

Emmaus' Endari (L-glutamine) is an oral amino acid supplement that was approved in 2017 based on its ability to reduce pain crises and hospitalizations in SCD patients. While the MOA of L-glutamine is unclear, it is thought that an increase in nicotinamide adenine dinucleotide (NAD+), reducing oxidative stress, which is known to contribute to the pathophysiology of SCD. Issues have persisted since its approval with both uptake and patient adherence.

2019

Crizanlizumab

Novartis' Adakveo (crizanlizumab) was approved in 2019. A P-selectin targeted mAb delivered via IV infusion, crizanlizumab functions by preventing cellular adhesion between platelets, RBC's, and the vascular endothelium. A Phase 2 trial demonstrated significant reduction in vaso-occlusive crises and median hospitalization rate. The subsequent confirmatory Phase 3 STAND trials failed to show a benefit, and the CHMP recommended its conditional marketing authorization (CMA) be revoked in the EU. While its fate in the US is still unclear, uptake has been severely limited due to cost and dosing concerns.

2019

Voxelotor

Oxbryta (voxelotor) inhibits HbS polymerization by stabilizing hemoglobin in its oxygenated state. Granted accelerated approval for patients ≥4 years of age with significant anemia in 2019, Global Blood Therapeutics originally launch Oxbryta before being acquired by Pfizer in 2022 for $5.4B. Voxelotor was approved using the surrogate endpoint of increase in Hb based on a 24-week Phase 3 trial. In addition, voxelotor improved anemia and markers of hemolysis. Unfortunately, in September 2024, Pfizer has reported that it will withdraw Oxbryta from all markets after data review showed an "imbalance" of fatalities and complications related to SCD.

2023

Ex-vivo cell therapies

Led by Vertex/CRISPR Therapeutics (Casgevy, exa-cel) and bluebird bio (Lyfgenia, lovo-cel), both of which recently received FDA approval for SCD (12/8/23), gene therapy is now a reality for patients. Both treatments have shown remarkable efficacy in reducing pain crises to near-zero while also improving anemia and markers of hemolysis. Some safety concerns have arisen, with bluebird's Lyfgenia experiencing several partial clinical holds from the FDA due to concerns over oncogenic risk.

Novel Agents

The majority of novel therapies typically target 1) RBC pathways (HbS stabilization, PKR activation, HbF induction via epigenetic modification, SYK inhibition, etc.), 2) reduction in vascular adhesion or inflammation (selectin inhibitors, complement pathway inhibition, etc.) or are 3) potentially curative therapies attempting to modify patient cells to induce HbF production or to express novel anti-sickling Hb's.

RBC-targeted therapies

As part of it's GBT acquisition, Pfizer is also developing GBT021601 (a next-gen HbS polymerization inhibitor currently in Phase 2/3 studies) which has been shown to increase Hb levels as much as 3X that of voxelotor. Both Agios (mitapivat and next-gen AG-946) and Novo Nordisk via acquisition of Forma Therapeutics (etavopivat) are developing pyruvate kinase activators thought to increase energy availability and oxygen-carrying capacity in RBCs which could reduce sickling. Multiple companies (AkiraBio, Fulcrum Therapeutics, GSK, Novo Nordisk, Secura Bio) are testing various epigenetic modifiers to induce HbF expression.

Adhesion/Inflammation

Pfizer again is notable here via its GBT acquisition, with inclacumab (a P-selectin inhibitor) in Phase 3 development. Both Roche (crovalimab) and Alexion (ALXN1820) have therapies targeted at disrupting the complement cascade and reducing inflammation that can worsen pain crises, while CSL Behring is developing CSL889 (hemopexin) targeted at removing hemolysis byproducts to prevent inflammation from occurring.

Gene Therapy

Multiple competitors are advancing alternative gene therapies for SCD including Editas Medicine's EDIT-301 (novel Cas12a enzyme-based gene editing), Aruvant's ARU-1801 (alternative lentiviral based therapy), and Beam Therapeutics' BEAM-101 (CRISPR-based gene editing).

Selected Treatments in Development for SCD

Company	Asset	Class	MOA
Academic	Arginine	Adhesion/ Inflammation	Supplement
Addmedica	SIKLOS	Adhesion/ Inflammation	Hydroxycarbomide
Affimmune	Epeleuton	Adhesion/ Inflammation	Novel synthetic fatty acid
Alexion	ALXN1820	Adhesion/ Inflammation	Complement activation inhibitor
Asklepion Pharmaceuticals	L-citrulline	Adhesion/ Inflammation	Supplement
CSL Behring	CSL889	Adhesion/ Inflammation	Plasma-derived hemopexin
CSL/Vifor (International) Inc.	VIT-2763 (Vamifeport)	Adhesion/ Inflammation	Ferroportin inhibitor
Invenux	SCD-101	Adhesion/ Inflammation	Traditional medicine
Novartis	Crizanlizumab	Adhesion/ Inflammation	P-selectin inhibitor
Pfizer/GBT	Inclacumab	Adhesion/ Inflammation	P-selectin inhibitor
Roche	Crovalimab	Adhesion/ Inflammation	Complement inhibitor (C5)
Academic	Several	Potentially Curative	Gene Therapy
Academic/Aruvant	ARU-1801	Potentially Curative	Gene Therapy (γ-globinG16D Insertion)
Beam Therapeutics	BEAM-101	Potentially Curative	Base Editing (HGB1, HGB2 activation)
Beam Therapeutics	BEAM-102	Potentially Curative	Base Editing (β-globin correction)
Bluebird bio	Lentiglobin	Potentially Curative	Gene Therapy (βA-T87Q Insertion)
Editas	EDIT-301	Potentially Curative	CRISPR/Cas12a (HGB1, HGB2 activation)
Novartis/Intellia	OTQ923	Potentially Curative	CRISPR/Cas9 (BCL11A disruption)
Sangamo	BIVV003	Potentially Curative	Zinc Finger Nuclease (BCL11A disruption)
Vertex/CRISPR	Exa-cel (CTX-001)	Potentially Curative	CRISPR/Cas9 (BCL11A disruption)
Agios	Mitapivat (AG-946)	RBC-targeted	Pyruvate kinase inhibitor
AkiraBio	AB1	RBC-targeted	HbF Inducer (hypomethylation)
Fulcrum Therapeutics	Pociredir (FTX-6058)	RBC-targeted	HbF inducer (EED inhibitor)
GSK	GSK4172239D (GSK4172239)	RBC-targeted	HbF inducer (DNMT1 inhibitor)
Novo Nordisk	NDec - oral decitabine-tetrahydrouridine	RBC-targeted	HbF inducer (hypomethylation)
Novo Nordisk/Forma Therapeutics	Etavopivat	RBC-targeted	Pyruvate kinase inhibitor
Pfizer/GBT	GBT021601	RBC-targeted	HbS polymerization inhibitor
Pfizer/GBT	Voxelotor	RBC-targeted	HbS polymerization inhibitor
Rigel	Fostamatinib	RBC-targeted	SYK inhibitor
Secura Bio	Panobinostat	RBC-targeted	HbF inducer (HDAC inhibitor)

Future directions

Potential future advancements for SCD include in vivo gene-editing approaches as well as novel conditioning regimens to improve safety and broaden the potential reach of ex vivo cell therapies. Without these advancements, curative approaches will remain limited to only the most severely impacted SCD patients (currently expected to be only 10-15% of SCD patients) with access to healthcare that can cover the significant costs associated with these one-time therapies ($2.2M for Casgevy and $3.1M for Lyfgenia). Improving access and adherence to current therapies and development of next-gen molecules for already approved targets (HbS polymerization, P-selectin, etc.) are likely to be a mainstay of patient care for the foreseeable future.

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