

Emerging disease-modifying therapies for sickle cell disease

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Table 1 (Supplementary). Recently completed and ongoing drug trials for targets intrinsic to the RBC, with a goal of disease modification

Target	Study title	Clinical trials identifier/status (phase)	Study drug	Mechanism of action
Hemoglobin F induction	Hydroxyurea optimization through precision study (HOPS)	NCT03789591 Recruiting (3)	Hydroxyurea	Ribonucleotidereductase inhibitor (plus other intervention)
	Hydroxyurea and transfusion	NCT03644953 Recruiting (2)		
	Enhancing use of hydroxyurea in SCD using patient navigators (SHiP HU)	NCT02197845 (N/A)		
	Study of decitabine and THU in patients with SCD	NCT01685515 Ongoing (1)	Decitabine and THU	Hypomethylating agent
	Decitabine for high-risk SCD	NCT01375608 Completed (2)	Decitabine	
	Phase 1/2 study to evaluate the safety, tolerability and pharmacokinetics of HQK-1001 administered daily in patients with SCD	NCT00842088 Completed (1/2)	Dimethyl butyrate (HQB-1001)	Unknown (Possible histone deacetylase inhibitor)
	A study of HQK1001 in patients with SCD	NCT01322269 Completed (2)		
	Effects of HQK1001 in patients with SCD	NCT01601340 Terminated (2)		

	A study to evaluate safety, pharmacokinetic, and biological activity of INCB059872 in subjects with SCD	NCT03132324 Terminated (1)	INCB059872	LSD1 inhibitor (Hypomethylating agent)
	Fetal hemoglobin induction treatment	NCT02981329 Recruiting (1)	Metformin	FOXO3 induction
	A study of panobinostat (LBH589) in patients with SCD	NCT01245179 Active, not recruiting (1)	Panobinostat	Histone deacetylase inhibitor
	Study to determine the maximum tolerated dose, safety and effectiveness of pomalidomide for patients with SCD	NCT01522547 Completed (1)	Pomalidomide	Histone deacetylase inhibitor

Other anti-sickling agents	A single dose study of the safety, blood levels and biological effects of Aes-103 compared with placebo in subjects with SCD	NCT01597401 Completed (1)	Aes-103	Binds to α -globin subunit in HbS, increasing oxygen affinity and favoring the relaxed state
	Evaluation of a different dose regimens of Aes103 given for 28 days to subjects with stable SCD	NCT01987908 Terminated (2)		
	Dipyridamole/ Magnesium to improve sickle cell hydration	NCT00276146 Withdrawn (2)	Dipyridamole/ Magnesium	Inhibits sRBC cation transport through sickle-induced passive leak pathway

	Intravenous magnesium for sickle cell VOC (MAGiC)	NCT01197417 Completed (2/3)	Magnesium	Improves vascular tone
	Study of SANGUINATE™ Vs. hydroxyurea in SCD patients	NCT01848925 Completed (1)	Sanguinate	Carbon monoxide releasing/oxygen transfer agent
	Study of SANGUINATE™ in the treatment of SCD patients with VOC	NCT02411708 Completed (2)		
	Dose-escalation study of SCD101 in SCD	NCT02380079 Ongoing (1)	SCD-101	Unknown mechanism
	A study of the efficacy and safety of ICA17043 (with or without hydroxyurea) in patients with sickle cell anemia	NCT00040677 Completed (2)	Senicapoc (ICA-17043)	Gardos channel blocker (KCNN4), inhibits sickle red cell dehydration
	A stratified sickle event randomized trial (ASSERT)	NCT00102791 Terminated (3)		
	A study evaluating the long-term safety of ICA-17043 in SCD patients with or without hydroxyurea therapy	NCT00294541 Terminated (3)		
Antioxidant therapy	A phase III safety and efficacy study of Lglutamine to treat SCD or sickle-β0 thalassemia	NCT01179217 Completed (3, FDA approved)	L-Glutamine (Endari™)	Increases production of NADPH within the sRBC

	N-acetylcysteine in patients with SCD (NAC)	NCT01849016 Completed (3)	N-acetylcysteine	Increases production of glutathione and reduces sRBC oxidative stress, reduction of vonWillebrand factor activity
	A pilot study of N-acetylcysteine in patients with SCD (NACinSCD)	NCT01800526 Recruiting (1/2)		

Table 2A (Supplementary). Recently completed and ongoing drug trials for targets extrinsic to the RBC (*cellular adhesion and vascular health*), with a goal of disease management

Target	Study title	Clinical trials identifier/status (phase)	Study drug	Mechanism of action
Endothelial adhesion	Study of GMI-1070 for the treatment of sickle cell pain crisis	NCT01119833 Completed (2)	GMI-1070 (Rivipansel)	Pan-selectin antagonist, increased activity against E-selectin
	Efficacy and safety of Rivipansel (GMI1070) in the treatment of VOC in hospitalized subjects with SCD	NCT02187003 Recruiting (3)		
	Intravenous gammaglobulin for sickle cell pain crises	NCT01757418 Recruiting (1/2)	IVIg	Inhibits neutrophil activation and adhesion, disrupts neutrophil-mediated sRBC capture
	Phase III randomized study of poloxamer 188 for VOC of SCD	NCT00004408 Completed (3)	Poloxamer 188	Surfactant and copolymer that reduces adhesion through multiple mechanisms
	Evaluation of purified poloxamer 188 in VOC of SCD (EPIC)	NCT01737814 Completed (3)		
	Study of propranolol as antiadhesive therapy in SCD	NCT01077921 Completed (2)	Propranolol	Inhibits sRBC adhesion to endothelium
	Study to assess safety and impact of SelG1 with or without hydroxyurea therapy in SCD patients with pain crises (SUSTAIN)	NCT01895361 Completed (2)	SEG101 (Crizanlizumab, formerly SelG1)	Monoclonal antibody against P-selectin

	Pharmacokinetics and pharmacodynamics study of SEG101 (Crizanlizumab) in SCD patients with VOC	NCT03264989 Recruiting (2)	SEG101 (Crizanlizumab)	
	Sevuparin infusion for the Management of acute VOC in people with SCD	NCT02515838 Recruiting (2)	Sevuparin	Heparinoid with antiP-selectin, anti-L-selectin, and anti-VCAM-1 activity

Vascular tone	The role of endothelin-1 in SCD	NCT02712346 Recruiting (1)	Ambrisentan	Endothelin type-A receptor antagonist
	Arginine therapy in SCD-VOC clinical trial	NCT01796678 Completed (2)	Arginine	Substrate for nitric oxide (NO)
	Arginine therapy for SCD pain	NCT02536170 Recruiting (2)		
	Arginine therapy for the treatment of pain in children with SCD	NCT02447874 Recruiting (1/2)		
	Phase II randomized trial: arginine butyrate plus standard local therapy in patients with refractory sickle cell ulcers	NCT00004412 Completed (2)		
	A dose escalation study of intravenous Lcitrulline in steadystate SCD	NCT02314689 Completed (1)	Citrulline	Amino acid precursor to arginine
	A phase I study of continuous intravenous Lcitrulline during sickle cell pain crisis or acute chest syndrome	NCT02697240 Unknown (1)		

	A study of IMR-687 in adult patients with sickle cell anemia (homozygous HbSS or sickle- β 0 thalassemia)	NCT03401112 Recruiting (2)	IMR-687	PDE9 inhibitor
	A study of the effect of IW-1701, a stimulator of sGC, on patients with SCD	NCT03285178 Recruiting (2)	IW-1707	Stimulates sGC
	A multi-center study of riociguat in patients with SCD	NCT02633397 Recruiting (2)	Riociguat	Stimulates sGC
	Topical sodium nitrite in SCD and leg ulcers	NCT02863068 Recruiting (2)	Sodium nitrite	Local donor of NO
	Effect of atorvastatin on endothelial dysfunction and albuminuria in SCD (ENDO)	NCT01732718 Completed (2)	Statins (Atorvastatin)	Activates endothelial NO synthase and other mechanisms
	Effect of simvastatin treatment on vasoocclusive pain in SCD	NCT01702246 Completed (1/2)	(Simvastatin)	
	Simvastatin (Zocor) therapy in SCD	NCT00508027 Completed (1/2)	(Simvastatin)	
	Central nervous system vascular changes in adult SCD and the effect of treatment with simvastatin	NCT03599609 Recruiting (1/2)	(Simvastatin)	

Table 2B (Supplementary). Recently completed and ongoing drug trials for targets extrinsic to the RBC (<i>coagulation or platelet activation</i>), with a goal of disease management				
Target	Study title	Clinical trials identifier/status (phase)	Study drug	Mechanism of action
Agents inhibiting platelet activation	Abciximab (ReoPro) as a therapeutic intervention for sickle cell vasoocclusive pain crisis	NCT01932554 Withdrawn (2)	Abciximab	Monoclonal antibody against GPIIb/IIIa
	A phase I/II randomized, double-blind, placebocontrolled study to evaluate the safety of eptifibatide as treatment of acute pain episodes in SCD	NCT00834899 Terminated (1/2)	Eptifibatide	Reversible inhibition of platelet aggregation through GPIIb/IIIa
	An assessment of prasugrel on healthy adults and sickle cell adults	NCT01178099 Completed (1)	Prasugrel	Irreversible inhibition of platelet aggregation through P2Y12 class of ADP receptors
	Prasugrel versus placebo in adult SCD	NCT01167023 Completed (2)		
	A study to assess the effect of ticagrelor in reducing the number of days with pain in patients with SCD (HESTIA2)	NCT02482298 Completed (2)	Ticagrelor	P2Y12 receptor antagonist
Agents targeting coagulation	Apixaban in patients with SCD	NCT02179177 Recruiting (3)	Apixaban	Novel direct factor Xa inhibitor

	Treatment of sickle cell patients hospitalized in pain crisis with prophylactic doses of low molecular weight heparin (LMWH) vs. Placebo	NCT01419977 Completed (2)	Dalteparin	Anticoagulant effect
	Defibrotide in SCD-related acute chest syndrome	NCT03805581 Recruiting (2)	Defibrotide	Sodium salt of a singlestranded polydeoxyribonucleotide with anti-thrombotic and anti-inflammatory properties
	The effect of rivaroxaban in SCD	NCT02072668 Completed (2)	Rivaroxaban	Novel direct factor Xa inhibitor
	Therapeutic anticoagulation strategy for acute chest syndrome (TASC)	NCT02580773 Recruiting (3)	Tinzaparin	Anticoagulant effect
	Feasibility study of unfractionated heparin in acute chest syndrome	NCT02098993 Terminated (2)	Unfractionated heparin	Anticoagulant effect
	Anticoagulation for pulmonary hypertension in SCD	NCT01036802 Terminated (2)	Warfarin	Vitamin K antagonist

Table 2C (Supplementary). Recently completed and ongoing drug trials for targets extrinsic to the RBC (*inflammation*), with a goal of disease management

Target	Study title	Clinical trials identifier/status (phase)	Study drug	Mechanism of action
Leukocytes	Inhaled mometasone to reduce painful episodes in patients with SCD (IMPROVE)	NCT02061202 Recruiting (2)	Mometasone	Inhaled corticosteroid
	Inhaled mometasone to promote reduction in vasoocclusive events 2 (IMPROVE2)	NCT03758950 Recruiting (2)		
	Safety, pharmacokinetic, and pharmacodynamic study of NKTT120 in adult patients with stable SCD	NCT01783691 Completed (1)	NKTT120	Humanized monoclonal antibody that depletes iNKT cells
	Adenosine 2A agonist lexiscan in children and adults with SCD	NCT01085201 Completed (1)	Regadenoson	Adenosine A2A receptor agonist on iNKT cells
	A phase II trial of regadenoson in sickle cell anemia	NCT01788631 Completed (2)		
Other	Study of efficacy, safety, and tolerability of ACZ885 (Canakinumab) in pediatric and young adult patients with sickle cell anemia	NCT02961218 Recruiting (2)	ACZ885 (Canakinumab)	Monoclonal antibody against IL-1 β
	Trial of zileuton CR in children and adults with SCD	NCT01136941 Completed (1)	Zileuton	Inhibition of 5lipoxygenase

	Phase 2 study of montelukast for the treatment of sickle cell anemia	NCT01960413 Completed (2)	Montelukast	Blocks leukotriene D4 activity on CysLT1 receptor
	Omega-3 fatty acids in SCD	NCT02947100	Omega-3 fatty acids	Antioxidant, impacts endothelium and sRBCs
		Terminated (1/2)		
	Prevention of vaso-occlusive pain crisis by using omega-3 fatty acid supplements (OM3FA)	NCT02525107 Not yet recruiting (3)		
	Rifaximin to modify the disease course in SCD	NCT03719729 Recruiting (2)	Rifaximin	Microbiome modification ('gut decontamination')

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