Appendix B: Additional details of Systematic literature review

A.1 Literature search strategies for non-transfusions SLR

Table 1: Search strategy for non-transfusions search of MEDLINE

#	Searches	Concept
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp length of stay/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	anemia, sickle cell/	Population
9	hemoglobin, sickle/	
10	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	
11	or/8-10	
12	exp antisickling agents/	Interventions
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or L-glutamine or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	meta analysis.pt.	Systematic review and meta-analysis studies
18	((meta adj analys*) or metaanalys or meta-analys*).ti,ab,sh.	
19	(systematic adj5 (review or overview*)).ti,ab,sh.	
20	or/17-19	
21	16 and 20	
22	clinical trial/	RCTs
23	(clinic adj5 trial*).ti,ab,sh.	

#	Searches	Concept
24	single blind method/	
25	double blind method/	
26	random allocation/	
27	placebos/	
28	(placebo or random*).ti,ab,sh.	
29	randomized controlled trial/	
30	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	
31	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	
32	randomi?ed control trial*.tw.	
33	or/22-32	
34	16 and 33	
35	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	Single arm trials
36	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	
37	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
38	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	
39	Clinical Trial, Phase I.pt.	
40	Clinical Trial, Phase II.pt.	
41	Clinical Trial, Phase III.pt.	
42	(registry or registries).ti,ab,kf,hw.	
43	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	
44	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	
45	(nonrandom* or non-random*).ti,ab,kf.	
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	
47	(all adj3 received).ab.	
48	or/35-47	
49	16 and 48	

#	Searches	Concept
50	limit 21 to ed=20170130-20180620	Date limit on rSLR and meta-analysis studies
51	limit 34 to ed=20170130-20180620	Date limit on RCTs
52	limit 49 to ed=20170130-20180620	Date limit on single arm trials

Table 2: Search strategy for non-transfusions search of EMBASE

#	Searches	
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp "length of stay"/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	sickle cell anemia/	Population
9	hemoglobin S/	
10	(sickle cell or sickle h$emoglobin or drepanocyt* or drepanotic or drepanocytemia or h$emoglobin-s or Hb-S or sickle an$emia or meniscocytosis).mp.	
11	or/8-10	
12	antisickling agent/	Intervention
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or L-glutamine or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	randomized controlled trial/	RCTs
18	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	

#	Searches	
19	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or subsitut* or treat*)).ab,kw.	
20	trial.ti.	
21	crossover procedure/	
22	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	
23	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	
24	or/17-23	
25	16 and 24	
26	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross-sectional study/ or case control study/ or population based case control study/	Single-arm trials
27	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	
28	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
29	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	
30	(registry or registries).ti,ab,kw,hw.	
31	(nonrandom* or non-random*).ti,ab,kw.	
32	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	
33	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	
34	(all adj3 received).ab.	
35	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	
36	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	
37	or/26-36	
38	16 and 37	
39	limit 25 to em=201705-201825	Date limit on RCTs
49	limit 38 to em=201705-201825	Date limit on single arm trials

Table 3: Search strategy for non-transfusions search of Cochrane Register of Controlled Trials

#	Searches	
#1	MeSH descriptor: [Pain] explode all trees	Outcomes
#2	(pain or painfull):ti,ab,kw	
#3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	
#4	MeSH descriptor: [Length of Stay] explode all trees	
#5	(hospital near/3 (admission or stay)):ti,ab,kw	
#6	(patient near/3 (admission or stay)):ti,ab,kw	
#7	#1 or #2 or #3 or #4 or #5 or #6	
#8	MeSH descriptor: [Anemia, Sickle Cell] this term only	Population
#9	MeSH descriptor: [Hemoglobin, Sickle] this term only	
#10	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	
#11	#8 or #9 or #10	
#12	MeSH descriptor: [Antisickling Agents] explode all trees	Interventions
#13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or L-glutamine or voxelotor or GBT440):ti,ab,kw	
#14	(#8 or #9 or #10) and prevent vaso-occlusiv*	
#15	#11 or #12 or #13	
#16	#7 and #11 and #14	

Table 6: Search strategy for non-transfusions search of ClinicalTrials.gov*

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Cell trait	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Drug OR Placebo OR Crizanlizumab OR Hydroxyurea OR L-glutamine OR Voxelotor OR GBT440 OR hydroxycarbamide	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR crisis OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

*Advanced Search option without any restrictions except search strings listed.

A.2 Literature search strategies for transfusions SLR

Table 4: Search strategy for transfusions search on CENTRAL database

#	Searches	Results
#1	MeSH descriptor: [Anemia, Sickle Cell] this term only	583
#2	MeSH descriptor: [Hemoglobin, Sickle] this term only	19
#3	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	4790
#4	#1 or #2 or #3	4790
#5	MeSH descriptor: [Blood Transfusion] this term only	1766
#6	MeSH descriptor: [Erythrocyte Transfusion] explode all trees	564
#7	((blood or erythrocyte* or "red cell*" or "red blood cell*" or RBC*) near/5 (transfus* or infus* or unit*))	14775
#8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) near/5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program* or therapy)):ab	30189
#9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)):ti	3612
#10	("allogeneic blood" or (unit* near/2 blood) or "allogenic blood" or (blood near/2 exposure) or "donor blood" or "blood product*" or "blood component*" or "blood support")	3365
#11	hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*	107
#12	(red cell* or erythrocyte* or blood or RBC*) and transfus*:ti	2434
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	41927
#14	MeSH descriptor: [Blood Component Transfusion] this term only	115
#15	MeSH descriptor: [Erythrocytes] this term only	1478
#16	(red cell* or red blood cell* or erythrocyte* or RBC*)	12756
#17	#14 and (#15 or #16)	39
#18	#13 or #17	41927
#19	MeSH descriptor: [Pain] explode all trees	42323
#20	(pain or painfull):ti,ab,kw	124349

#	Searches	Results
#21	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	4404
#22	MeSH descriptor: [Length of Stay] explode all trees	6488
#23	(hospital near/3 (admission or stay)):ti,ab,kw	20854
#24	(patient near/3 (admission or stay)):ti,ab,kw	1779
#25	#19 or #20 or #21 or #22 or #23 or #24	153780
#26	#4 and #18 and #25	332

Table 5: Search strategy for transfusions search on MEDLINE database

#	Searches	Results
1	anemia, sickle cell/	19329
2	hemoglobin, sickle/	3011
3	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	27120
4	1 or 2 or 3	27602
5	Blood Transfusion/	48056
6	Erythrocyte Transfusion/	8033
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	90906
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	47785
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	35184
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	26829
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1217
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	24060
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	183648
14	Blood Component Transfusion/	3477
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	16726

#	Searches	Results
16	14 not 15	3229
17	ERYTHROCYTES/	128578
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	216650
19	17 or 18	258199
20	16 and 19	834
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	13177
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	3326
23	13 or 20 or 21 or 22	188025
24	exp pain/	362648
25	(pain or painfull).tw.	547392
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso - occlusiv* or crisis or crises).tw.	66169
27	exp length of stay/	77857
28	(hospital adj3 (admission or stay)).tw.	104873
29	(patient adj3 (admission or stay)).tw.	6507
30	or/24-29	901074
31	4 and 23 and 30	848
32	clinical trial/	512148
33	(clinic adj5 trial*).ti,ab,sh.	1010
34	single blind method/	25632
35	double blind method/	147368
36	random allocation/	95709
37	placebos/	34063
38	(placebo or random*).ti,ab,sh.	1263924
39	randomized controlled trial/	467730
40	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	786522
41	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	145215
42	randomi?ed control trial*.tw.	6481
43	or/32-42	1565168

#	Searches	Results
44	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	2187051
45	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	1071161
46	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	615678
47	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	340559
48	Clinical Trial, Phase I.pt.	18409
49	Clinical Trial, Phase II.pt.	29604
50	Clinical Trial, Phase III.pt.	14110
51	(registry or registries).ti,ab,kf,hw.	139501
52	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	53439
53	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	114108
54	(nonrandom* or non-random*).ti,ab,kf.	34084
55	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	2644
56	(all adj3 received).ab.	41192
57	or/44-56	3114626
58	31 and 43	120
59	31 and 57	278

Table 6: Search strategy for transfusions search on EMBASE database

#	Searches	Results
1	exp Anemia, Sickle Cell/	32009
2	(h?emoglobin s or h?emoglobin sc or h?emoglobin se or h?emoglobin ss or h?emoglobin c or h?emoglobin d or Hb s or Hb sc or Hb se or Hb ss or Hb c or Hb d or sc disease*).tw.	5794
3	(sickle cell or sicklemia or sickled or sickling or meniscocyt* or drepanocyt*).tw.	29569
4	1 or 2 or 3	38361
5	Blood Transfusion/	108332
6	Erythrocyte Transfusion/	23021
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	135137
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	77239
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	38387
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	43111
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1555
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	28985
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	273982
14	Blood Component Transfusion/	2629
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	19765
16	14 not 15	2279
17	ERYTHROCYTES/	112741
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	256379
19	17 or 18	278120
20	16 and 19	523
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	22304
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	4095
23	13 or 20 or 21 or 22	279695

#	Searches	Results
24	exp pain/	1146280
25	(pain or painfull).tw.	789805
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	82887
27	exp length of stay/	150699
28	(hospital adj3 (admission or stay)).tw.	169748
29	(patient adj3 (admission or stay)).tw.	12514
30	or/24-29	1690290
31	4 and 23 and 30	2325
32	randomized controlled trial/	508600
33	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	1062285
34	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or subsitut* or treat*)).ab,kw.	560662
35	trial.ti.	248694
36	crossover procedure/	56042
37	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	276112
38	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	99658
39	or/32-38	1386841
40	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross - sectional study/ or case control study/ or population based case control study/	1771952
41	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	1282224
42	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	790240
43	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	500633
44	(registry or registries).ti,ab,kw,hw.	183687
45	(nonrandom* or non-random*).ti,ab,kw.	42777
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	3333
47	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	80316
48	(all adj3 received).ab.	75969

#	Searches	Results
49	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	126474
50	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	205403
51	or/40-50	3180246
52	31 and 39	245
53	31 and 51	599

Table 7: Search strategy for transfusions search on clinicaltrials.gov database

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Cell trait	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Transfusion OR blood OR RBC OR hematocrit OR erythrocyte	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR crisis OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

*Advanced Search option without any restrictions except search strings listed.

A.3 Additional results from systematic literature review

Table 8: Cochrane risk of bias assessment of randomized controlled trials included in the feasibility assessment

Trial ID	Random sequence generation	Allocation concealment	Blinding (personnal)	Blinding (outcome assessor)	Incomplete outcome data	Selective reporting	Other bias
Arruda 2013	Low	Low	Unclear	Unclear	Low	Unclear	None
Ataga 2008	Low	Low	Low	Low	Low	Low	Industry funded; Any conflict of interest of authors
Ataga 2011	Low	Low	Low	Low	Low	Low	Industry funded; Any conflict of

Trial ID	Random sequence generation	Allocation concealment	Blinding (personnal)	Blinding (outcome assessor)	Incomplete outcome data	Selective reporting	Other bias
							interest of authors
Ataga 2017	Low	Low	Low	Low	Unclear	Low	Industry funded; Any conflict of interest of authors
Bao 2008	Unclear	Unclear	Low	Low	Low	Low	None
Cabannes 1984	Low	Low	Low	Low	Unclear	Low	Baseline imbalances or not assessed
Deceulaer 1982	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Baseline imbalances or not assessed; Industry funded
Diop 2011	Low	Low	Low	Low	Low	Low	None
Glassberg 2017	Low	Low	Low	Low	Low	Low	None
NCT02482298	Unclear	Unclear	Low	Low	Low	Low	Industry funded
Niihara 2018	Unclear	Unclear	Low	Low	High	Low	Industry funded
Pace 2003	Unclear	Unclear	Low	Low	High	Low	Industry funded
Schlaeger 2017	Low	Low	Low	Low	Low	Low	None
Sins 2017	Low	Low	Low	Low	High	Low	None
Tomer 2001	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Baseline imbalances
Wun 2013	Unclear	Unclear	Unclear	Low	Low	Low	Industry funded
Adegoke 2013	Low	Unclear	High	High	High	Unclear	No placebo used in control group
Alvim 2005	Unclear	Unclear	Unclear	Unclear	Low	Unclear	None
Charnigo 2017	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Subset of a RCT database
Daak 2013	Low	Low	Low	Low	Low	Low	Industry funded
Daak 2018	Unclear	Unclear	Low	Low	Low	Unclear	Baseline imbalances or not assessed
de Abood 1997	High	High	High	High	Unclear	Unclear	Baseline imbalances or not assessed; No placebo used in control group
Eke 2003	Low	Low	High	High	Low	Low	Baseline imbalances or not assessed

Trial ID	Random sequence generation	Allocation concealment	Blinding (personnal)	Blinding (outcome assessor)	Incomplete outcome data	Selective reporting	Other bias
Gail 1982	Low	Low	Low	Low	Low	Unclear	None
Gupta 1995	Low	Unclear	Low	Low	Unclear	Unclear	None
Heeney 2016	Low	Low	Low	Low	Low	Low	Industry funded; Any conflict of interest of authors
Isaacs 1972	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Baseline imbalances or not assessed; Industry funded
Mann 1974	Unclear	Unclear	High	High	Low	Unclear	Risk of carry-over effect in crossover study; No placebo used in control group
Manrique 1987	Unclear	Unclear	Unclear	Unclear	Low	High	None
Oski 1968	Unclear	Unclear	Low	Low	Low	Unclear	Industry funded; Risk of carry-over effect in crossover study
Reid 2014	Unclear	Low	Low	Low	High	Low	Industry funded; Any conflict of interest of authors
Vinchinsky 2010	Unclear	Unclear	High	High	Unclear	Unclear	Industry funded
Wambebe 2001	Low	Low	Low	Unclear	Unclear	Unclear	Risk of carry-over effect in crossover study
Zago 1984	Unclear	Unclear	Unclear	Unclear	High	Unclear	Risk of carry-over effect in crossover study

** Note: Trial bolded were base case studies; Trials shaded in grey were not included in the final network meta-analyses.*

Table 9: Newcastle-Ottawa quality assessment of non-randomized controlled trials included in the feasibility assessment

Al Hashmi 2017	---	★	★	---	★	---	---	---	★	4
Brandalise 2017	---	★	★	---	★	★	★	---	★	6
Bridges 2017	---	★	★	---	---	---	---	---	★	3
Bumma 2017	---	★	★	---	★	---	---	---	---	3
Colombatti 2018	★	★	★	---	★	---	---	★	★	6
Di Maggio 2018	★	★	★	---	★	★	---	★	★	7
Hoppe 2017	★	★	---	---	★		---	---	---	3
Keikhaei 2015	★	★	★	---		---	---	---	★	4
Kwiatkowski 2017	★	★	---	---	---	---	---	★	★	4
LeBlanc 2016	---	★	★	★	---	---	---	★	★	5
Lemonne 2017	---	★	★	---	---	---	★	★	★	5
NCT01476696	---	★	---	---	---	---	---	---	★	2
Quarmyne 2017	★	★	★	---	★	---	---	★	---	5
Rigano 2018	★	★	★	---	★	★	---	★	★	7
Sethy 2018	★	★	★	---	---		---	★	★	5
Styles 2010	---	★	★	★	---	---	---	---	---	3
Youssry 2017	★	★	★	---	★	★	---	★	★	7

Figure 1: Cochrane assessment of randomized controlled trials included in the feasibility assessment

Table 10: Study characteristics of trials included in the feasibility assessment

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
Adegoke 2013	---	Lime juice + Routine oral drugs	Control (Routine oral drugs)	---	---	Open	RCT	6 months	Nigeria
Alvim 2005	---	Piracetam	Placebo	---	---	Double-blind	RCT, crossover	1 year (6 months, then crossover with 2 weeks washout period)	Saudi Arabia
Arruda 2013	---	Placebo	Vitamins C and E	---	---	Double-blind	RCT	180 days	Brazil
Ataga 2008	NCT00040677	Senicapoc (high-dose)	Senicapoc (low-dose)	Placebo	---	Double-blind	RCT	12 week	US
Ataga 2011	NCT00102791	Senicapoc	Placebo	---	---	Double-blind	RCT	52 weeks	United States, Jamaica, Brazil, France, Trinidad and the United Kingdom.
Ataga 2017	NCT01895361	Crizanlizumab (high-dose)	Crizanlizumab (low-dose)	Placebo	---	Double-blind	RCT (Phase 2)	52 weeks	Brazil, Jamaica, USA
Bao 2008	---	Zinc	Placebo	---	---	Double-blind	RCT	3 months	US
Cabannes 1984	---	Ticlopidine	Placebo	---	---	Double-blind	RCT	6 months	Africa
Charnigo 2017	---	PF-04447943	Placebo	---	---	---	RCT (Phase 1b)	29 days	---
Daak 2013	ISRCTN80844630	Omega-3	Placebo	---	---	Double-blind	RCT	1 year	Sudan
Daak 2018	---	AltemiaTM	Placebo	---	---	Double-blind	RCT (Phase 2)	2 months	USA

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
de Abood 1997	---	DMPA	Levonorgestrel + ethinyl estradiol	Surgical sterilized (injectable)	---	Double-blind	RCT	12 months	Spain
Deceulaer 1982	---	Medroxyprogesterone acetate	Placebo	---	---	Double-blind	RCT, crossover	2 years (9 months, then crossover after 6 months washout)	Jamaica
Diop 2011	---	Sulfadoxine-pyrimethamine	Placebo	---	---	Open	RCT	3 months	Senegal
Eke 2003	---	Placebo (Vitamin c)	Proguanil	---	---	Open	RCT (Phase 2)	9 months	Nigeria
Gail 1982	---	Urea	Control	---	---	Double-blind	RCT (Phase 2)	Average: 13.7 months	Ghana
Glassberg 2017	NCT02061202	Mometasone furoate	Placebo	---	---	Triple-blind	RCT	16 weeks	US
Gupta 1995	---	Zinc	Placebo	---	---	Double-blind	RCT (Phase 2)	1.5 years	India
Heeney 2016	NCT01794000	Prasugrel	Placebo	---	---	Double-blind	RCT (Phase 3)	A minimum of 9 months and a maximum of 24 months	Americas, Europe, Asia and Africa
Isaacs 1972	---	Steroid (Testoserone/ Progesterone)	Saline	---	---	---	RCT, crossover (preliminary report before crossover)	4-6 months	Nigeria
Mann 1974	---	Folic acid	Folic acid + Sodium bicarbonate	---	---	---	RCT, crossover	2 years (crossover after 1 year, no washout)	UK
Manrique 1987	---	Pentoxifylline	Placebo	---	---	---	RCT (Phase 2)	6 weeks	Brazil
NCT02482298	NCT02482298	Ticagrelor 45 mg	Ticagrelor 10 mg	Placebo	---	Double-blind	RCT	12 weeks	USA, Egypt, France, Italy,

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
									Kenya, Lebanon, UK, Turkey
Niihara 2018	NCT01179217	L-glutamine	Placebo	---	---	Double-blind	RCT (Phase 3)	48 weeks	USA
Oski 1968	---	Promazine hydrochloride	Placebo	---	---	Double-blind	RCT, crossover	3 months	USA
Pace 2003	---	NAC (high-dose)	NAC (mid-dose)	NAC (low-dose)	Placebo	Double-blind	RCT	7 months	USA
Reid 2014	NCT01601340	HQK-1001	Placebo	---	---	Double-blind	RCT	48 weeks	United States, Lebanon, Egypt, Jamaica and Canada
Schlaeger 2017	---	Pregabalin	Placebo	---	---	Double-blind	RCT	3 months	USA
Sins 2017	NCT01849016	NAC	Placebo	---	---	Double-blind	RCT	6 months	Netherlands, Belgium, UK
Styles 2010	---	GMI-1070	---	---	---	---	Single-arm	1 month	USA
Tomer 2001	---	mehaden fish oil	Placebo (olive oil)	---	---	Double-blind	RCT	12 months	US
Vichinsky 2010	---	Transfusion	Standard of care	---	---	---	RCT	---	USA
Wambebe 2001	---	Niprisan	Placebo	---	---	Phase 2	RCT, crossover (Phase 2)	13 months (6 months per treatment, 1-month washout in-between)	Nigeria
Wun 2013	NCT01167023	Prasugrel	Placebo	---	---	Double-blind	RCT (Phase 2)	30 days	United States and Canada
Zago 1984	---	Aspirin	Placebo	---	---	---	RCT, crossover (Phase 2)	10 months (5 months per treatment)	Brazil

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
Al Hashmi 2017	---	Hydroxyurea	---	---	---	---	Single-arm	6 months	Oman
Brandalise 2017	---	Methotrexate	---	---	---	---	Single-arm	12 weeks	Brazil
Bridges 2017	---	GBT440	---	---	---	---	Single-arm	10 weeks	Unclear
Bumma 2017	---	Scheduled outpatient red cell exchange programme	---	---	---	---	Single-arm	1 year	---
Colombatti 2018	NCT02709681	Hydroxyurea	---	---	---	---	Single-arm	1 years	Italy
Di Maggio 2018	---	Hydroxyurea	---	---	---	---	Single-arm	Mean: 6.6 years	Italy
Hoppe 2017	NCT00508027	Simvastatin	---	---	---	---	Single-arm	3 months	USA
Keikhaei 2015	---	Hydroxyurea	---	---	---	---	Single-arm	1 year	Iran
Kwiatkowski 2017	---	Deferiprone	---	---	---	---	Single-arm	1 year	USA
LeBlanc 2016	NCT02709681	Methadone	---	---	---	---	Single-arm	Mean: 2.1 years	USA
Lemonne 2017	---	Hydroxyurea	---	---	---	---	Single-arm	2 years	Guadeloupe
NCT01476696	NCT01476696	Prasugrel	---	---	---	---	Single-arm (Phase 2 part B)	28 days	USA
Quarmyne 2017	---	Hydroxyurea	---	---	---	---	Single-arm	3 months	USA
Rigano 2018	---	Hydroxyurea	---	---	---	---	Single-arm	Median: 7 years	Italy
Sethy 2018	---	Hydroxyurea	---	---	---	---	Single-arm	12 months	India
Youssry 2017	---	Hydroxyurea	---	---	---	---	Single-arm	up to 120 months	Egypt

Note: Trial bolded were base case studies; Trials shaded in grey were not included in the final network meta-analyses.

Table 11: Eligibility criteria of RCTs included in the feasibility assessment

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Adegoke 2013	Lime juice + Routine oral drugs (folic acid, vitamin B complex and proguanil) vs Control (Routine oral drugs (folic acid, vitamin B complex and proguanil))	---	---	Steady state (no painful episode, anemic crisis, or infection on the day of recruitment)	No hydroxyurea treatment	---	Not on any other alternative medicine commonly used by some patients with SCA in Nigeria such as Aloe vera gel, Moringa oleifera, Solamine syrup, and Ciklavit (Cajanus cajal) suspension as well as Discriovite suspension and or Nicosan (Niprisan) capsule
Alvim 2005	Piracetam vs Placebo	5-20 years	---	---	No hydroxyurea treatment	Regular blood transfusion programmes	---
Arruda 2013	Placebo vs Vitamins C and E	≥ 18 years	HbSS or HbSβ^0	---	---	---	Other investigational drugs in the last 12 months

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Ataga 2008	Senicapoc (high-dose) vs Senicapoc (low-dose) vs Placebo	18-60 years	HbSS	≥ 1 nacute sickle-related painful episode that had required hospitalization, but none in the 4 weeks prior to screening	Stable dose for a minimum of 3 months at study enrollment.	Received a transfusion within 30 days of enrollment or undergone an exchange transfusion within 60 days of enrollment	One or more nonallowed medications within 30 days of enrollment (eg, amiodarone, chlorperazine, disopyramide, dofedilide, haloperidol, procainamide, quinidine, risperidone, sotalol, thioridazine, trifluoperazine, warfarin sodium, and erythropoietin)
Ataga 2011	Senicapoc vs Placebo	16-65 years	HbSS, HbSC, $HbS\beta^0$, $HbS\beta^+$	≥ 2 acute sickle-related painful crises in the previous 12 months	Received hydroxyurea for the preceding 12 months and their dose was stabilized for at least 3 months prior to the study	Participated in a chronic transfusion programme	Received previous treatment with senicapoc
Ataga 2017	Crizanlizumab (high-dose) vs Crizanlizumab (low-dose) vs Placebo	16-65 years	HbSS, HbSC, $HbS\beta^0$, $HbS\beta^+$	2-10 SCD-related pain crises in the 12 months before enrollment	---	Undergoing long-term red-cell transfusion therapy	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Bao 2008	Zinc vs Placebo	---	HbSS	---	No hydroxyurea treatment	receiving > 6 transfusions per year	---
Cabannes 1984	Ticlopidine vs Placebo	---	---	---	---	---	Received no antisickling treatment for 2 months before admission
Charnigo 2017	PF-04447943 vs Placebo	---	SCD	---	---	---	---
Daak 2013	Omega-3 vs Placebo	---	---	Steady state, defined as no evidence of fever, infection, or crisis for .4 wk before the start of the study	No hydroxyurea treatment	Prescence of blood transfusion	---
Daak 2018	AltemiaTM vs Placebo	5–17 years	---	2-10 documented sickle cell crises during the 12 months prior to screening	Either not received, or were on a stable regimen of hydroxyurea	---	---
de Abood 1997	DMPA vs Levonorgestrel + ethinyl estradiol vs Surgical sterilized (injectable)	---	---	---	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Deceulaer 1982	Medroxyprogesterone acetate vs Placebo	---	---	---	---	---	---
Diop 2011	Sulfadoxine-pyrimethamine vs Placebo	---	---	---	---	---	---
Eke 2003	Placebo (Vitamin c) vs Proguanil	1-16 years	HbSS	---	---	---	---
Gail 1982	Urea vs Control	---	HbSS	---	---	---	---
Glassberg 2017	Mometasone furoate vs Placebo	≥ 15 years	HbSS or HbSβ^0	< 15 ED visits for SCD pain over the prior 12 months	---	---	---
Gupta 1995	Zinc vs Placebo	> 5 years	HbSS	---	---	---	Patients on drug therapy for some other disease
Heeney 2016	Prasugrel vs Placebo	2-18 years	HbSS, HbSβ^0	≥2 VOC in the year prior to screening	---	History of chronic RBC transfusion for prevention of stroke or current chronic treatment with RBC for any reason.	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Isaacs 1972	Steroid (Testoserone/Progesterone) vs Saline	---	HbSS	Moderately severe pain at least once in 3 months (with little or no fever or exacerbations of jaundice)	---	---	---
Mann 1974	Folic acid vs Folic acid + Sodium bicarbonate	5-17 years	HbSS, HbSC, HbSβ	Previously suffered painful crises	---	---	---
Manrique 1987	Pentoxifylline vs Placebo	---	HbSS	---	---	---	---
NCT02482298 2017	Ticagrelor 45 mg vs Ticagrelor 10 mg vs Placebo	18-30 years	HbSS, HbSβ^0	---	Dose must have been stable for 3 months	Treatment with chronic red blood cell transfusion therapy.	Chronic treatment with anticoagulants or antiplatelet drugs
Niihara 2018	L-glutamine vs Placebo	> 5 years	HbSS, HbSβ^0	≥ 2 pain crises (no upper limit) documented during the previous year	Stable dose within 3 months and continue during the trial	Received any blood products within 3 weeks before screening	Received treatment with l-glutamine within 30 days before the screening
Oski 1968	Promazine hydrochloride vs Placebo	---	---	≥2 painful episodes during	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
				the 2 year period prior to study.			
Pace 2003	NAC (high-dose) vs NAC (mid-dose) vs NAC (low-dose) vs Placebo	> 15 years	HbSS, HbSβ^0	With dense cells greater than 6% and 2 or more VOC episodes per year for the 2 years prior to enrollment	---	Chronic transfusions	Investigational drug therapy
Reid 2014	HQK-1001 vs Placebo	12-60 years	HbSS, HbSβ	≥ 1 acute SCD-related complication or leg ulcers in 12 months	No current (i.e., within 3 months prior to enrolment) hydroxyurea treatment	Regular transfusion program or transfusion in the preceding 3 months unless Hb A had decreased to less than 20%	---
Schlaeger 2017	Pregabalin vs Placebo	18-82 years	---	Pain now score ≥ 4 on a 0-10 scale at registration	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Sins 2017	NAC vs Placebo	≥ 12 years	HbSS, HbSC, HbSβ^0, HbSβ$^+$	≥ 1 VOC per year in the past 3 years	Stable dose for 6 months piror to study	Chronic blood transfusion or transfusion in the preceding 3 months	Use of pain medication for sickle-cell related pains on more than 15 days per month in the past 6 months
Styles 2010	GMI-1070	18-50 years	HbSS and HBSB0thal	---	---	---	---
Tomer 2001	mehaden fish oil vs Placebo (olive oil)	≥ 18 years	---	Frequent pain episodes (≥3 events/year)	Not on hydroxyurea	---	---
Vichinsky 2010	Transfusions vs standard of care	21-55 years	---	---	30% on hydroxyurea on transfusion, 50% on hydroxyurea on standard of care	---	---
Wambebe 2001	Niprisan vs Placebo	2-45 years	HbSS	≥ 3 painful or vaso-occlusive crises in the previous year	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Wun 2013	Prasugrel vs Placebo	18 to 55 years	HbSS, HbSC, HbSβ^0, HbSβ^+	Did not have a diagnosis of acute VOC within 30 days of the study screening visit	Stable dose 30 days prior to randomization	---	---
Zago 1984	Aspirin vs Placebo	---	---	---	---	---	---
Al Hashmi 2017	Hydroxyurea	≥ 18 years	---	> 3 admissions with VOC/year, history of acute chest syndrome, history of priapism, history of splenic sequestration crises	On hydroxyurea 5-10mg/kg/day	Blood transfusion during the study	---
Brandalise 2017	Methotrexate	---	---	> 3 severe VOC episodes/year, that were refractory to opioids for periods longer than 3 weeks duration.	Under chronic hydroxyurea treatment	---	---
Bridges 2017	GBT440	---	SCD and severe anemia, i.e.	---	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
			HB < 6.5 g/dL				
Bumma 2017	Scheduled outpatient red cell exchange programme	---	---	---	---	---	---
Colombatti 2018	Hydroxyurea	---	---	2-3 vaso-occlusive crisis and/or hospitalizations in the last year	---	---	---
Di Maggio 2018	Hydroxyurea	---	---	>3 painful VOC per year and/or >2 Acute Chest Syndrome	New to hydroxyurea treatment	---	---
Hoppe 2017	Simvastatin	>10 years	HbSS or HbSβ^0	≥ 3 vaso-occlusive pain episodes in the preceding year	At a stable dose for ≥ 3 months	Red cell transfusion within the 30 days prior to enrolment	Current treatment with statins, amiodarone or other drugs with known metabolic interactions with statins (e.g. cytochrome P450 3A4 metabolism)
Keikhaei 2015	Hydroxyurea	6-18 years	SCD	---	---	---	Treatment other than hydroxyurea

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Kwiatkowski 2017	Deferiprone	---	---	---	---	---	---
LeBlanc 2016	Methadone	---	---	> 5 pain events per year	---	---	---
Lemonne 2017	Hydroxyurea	---	---	Absence of acute episodes (infection, VOC, ACS, stroke, priapisrn) at least one month before inclusion into the study.	---	No blood transftisions in the previous three months	---
NCT01476696	Prasugrel	≥2 to <18 years of age and ≥ 12 kg body weigh t	HbSS, HbSβ^0	---	A stable dose for the 60 days prior to enrolment	Treatment with packed RBC or whole blood transfusion therapy within 30 days prior to dosing	Any nonsteroidal anti-inflammatory drug (NSAID) use within 5 days prior to screening or Any aspirin, warfarin, thienopyridine, or other antiplatelet medication use within 10 days prior to dosing or Anticipated use of aspirin, warfarin, thienopyridine, or other antiplatelet medication during the study period

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Quarmyne 2017	Hydroxyurea	---	HbSS, HbSβ^0	---	---	Concurrent chronic transfusion	---
Rigano 2018	Hydroxyurea	---	---	2–3 VOC and/or acute chest syndrome in the year prior	Received hydroxyurea therapy	---	---
Sethy 2018	Hydroxyurea	≥ 18 years	HbSS	> 2 attacks of VOC per year and/or rate of transfusion 1–2 units/month	---	---	---
Youssry 2017	Hydroxyurea	---	---	---	On hydroxyurea ≥3 consecutive months	Chronic blood transfusion protocol	---

** - VOC: vaso-occlusive crisis; SCD: sickle cell disease; ED: emergency department; Note: Trial bolded were base case studies; Trials shaded in grey were not included in the final network meta-analyses.*

A.4 Outcome definitions

Table 12: Definitions of crisis used in 5 RCTs included in adult network

Study	Treatments	Crisis
Ataga 2017	Placebo, High-dose Crizanlizumab, Low-dose Crizanlizumab	Sickle cell–related pain crises were defined as acute episodes of pain, with no medically determined cause other than a vaso-occlusive event, that resulted in a medical facility visit and treatment. with oral or parenteral narcotic agents or with a parenteral nonsteroidal anti-inflammatory drug. The acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events.
Ataga 2011	Placebo, senicapoc	A painful crisis was defined as an episode of acute pain with no cause other than a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral narcotics, or parenteral non-steroidal anti-inflammatory drugs. Included in the definition of painful crisis were acute chest syndrome, hepatic sequestration, splenic sequestration, priapism, stroke and death (with the exception of homicide, suicide, or accidental death). To ensure consistency across sites, all protocol-defined sickle-related painful crises identified by the Investigators that resulted in a visit to a medical facility were adjudicated by an independent, blinded, Crisis Review Committee (CRC).
Ataga 2008	Placebo, senicapoc (low-dose), senicapoc (high-dose)	An independent, blinded crisis review committee adjudicated all sickle cell painful crises and related adverse event data (Document S1). A painful crisis was defined as a period of severe pain (with no explanation other than SCD) lasting 4 or more hours in duration, requiring a visit to a health care facility, and requiring parenteral opiate or other narcotic for relief
Pace 2003	Placebo, NAC (low-dose) 600 mg/day, NAC (mid-dose) 1200mg/day, NAC (high-dose) 2400mg/day	Defined as a visit to a medical facility that lasted more than 4 hr for acute pain related to vaso-occlusion requiring parenteral narcotics. The occurrence of acute chest syndrome, priapism, splenic, or hepatic sequestration was also counted as a VOC episode. Acute chest syndrome included those subjects with chest wall pain and a new infiltrate on chest X ray.
Niihara 2018	Placebo, L-glutamine	A pain crisis was defined as pain leading to treatment with a parenterally administered narcotic or ketorolac in an emergency department (ED) (or outpatient treatment center) or during hospitalization.

A.5 Additional risk of bias results

Overall, the RCTs were considered to have low risk of bias based on assessment using the Cochrane Collaboration's tool. Almost 50% were at unclear risk of bias due to allocation concealment, selective reporting, and random sequence generation. Also, 10-15% were at high risk of bias due to incomplete outcome data, blinding of outcome assessor, and blinding of personnel. Full results are in the appendix.

Overall, the single-arm studies were at high risk of bias due on several domains of the Newcastle-Ottawa scaleFigure 4): 93.7% at high risk of bias due to outcome of interest not being present at start, 87.5% at high risk of bias due to assessment of outcome, and 75% at high risk of bias due to comparability on additional factors. Also, almost 50% were at high risk of bias due to representativeness of exposed cohort, comparability on basic factors, or the follow-up not being long enough. This high risk of bias further discourages use of the single-arm studies for analysis.

Figure 2: Cochrane risk of bias assessment of 9 randomized controlled studies included in network meta-analysis

Figure 3: Cochrane risk of bias assessment across all studies included in review presented as percentages across studies.

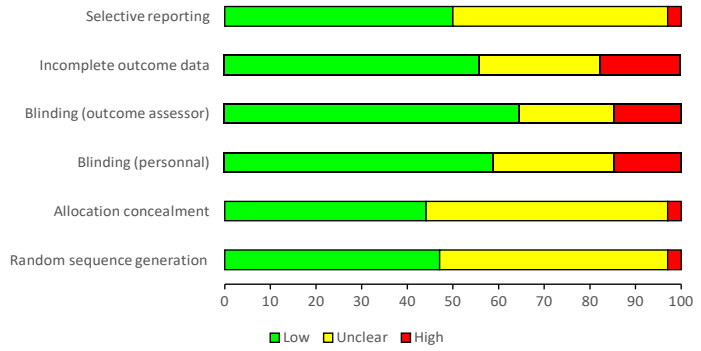
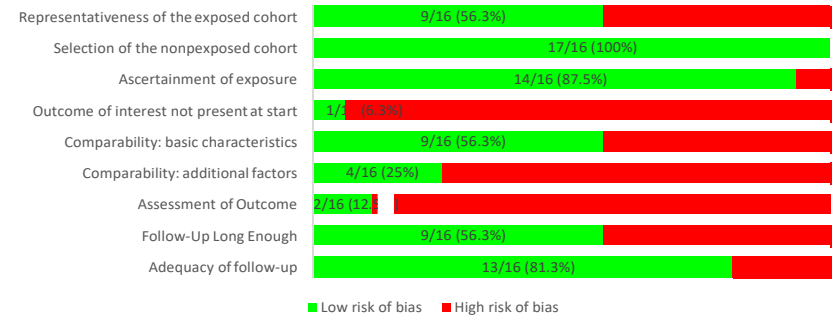


Figure 4: Newcastle-Ottawa quality assessment of non-randomized trials presented as percentages across studies.



A.6 Table of characteristics and references for of all studies identified by SLR

Author/Year/Country Ref/Enrolment /NCT registry	Design Total N of PT (N of female); N of arm	Main in/exclusion criteria	Participants					Interventions			Sponsor	Pub type
			Age (years)† Race (n, %)†	Total N of SCD types (n, %)	Total N of HU use (n, %)	Baseline pain/crisis/VOC (n or %) †	Other baseline characteristics (n or %) †	Group	Duration	Other concomitant therapy		
Schlaeger 2017 USA [1]	RCT, double-blind Single centre 22 (16); 2	1. 18-82 years 2. history of SCD pain that was not well controlled (pain now score ≥ 4 on a 0-10 scale at registration) Exclusion: renal impairment	Adults Mean (SD): 33.1 (9.9) African american: 11 (100%)	HbSS: 15 (68%) HbSC: 6 (27%) HbSβ: 1 (5%)	NR	NR	NR	1. Pregabalin 75mg BID oral (n=11) 2. Placebo (n=11)	3 months	NR	NR	JA
Hoppe 2017 USA [2] NCT00508027	Single-arm Single centre 24 (13); 1	1. >10 years 2. history of ≥ 3 vaso-occlusive pain episodes requiring treatment with a prescribed oral or parenteral analgesic in the preceding year 3. Patients receiving treatment with HU at a stable dose for ≥3 months were eligible	Adults and children Overall mean: 18.5 (range 10-34)	HbSS: 17 (89%) HbSβ⁰: 2 (11%)	10 (53%)	NR	NR	Simvastatin (n=19*) OD oral Dose adjusted by weight: 40 mg (weight >60 kg); 30 mg (weight 45–60 kg); 25 mg (weight 35–44 kg)	3 months	NR	DDCF, NHLBI and NCRR	JA
Glassberg 2017 USA [3] Feb 2014 to Oct 2016 NCT02061202	RCT, triple-blind Single centre 54 (23); 2	1. HbSS or HbSβ⁰ 2. ≥15 years 3. self-report of cough or wheeze over the preceding two months Exclusion: Diagnosis of asthma, incareration, pregnancy, ≥15 ED visits for SCD pain over the prior 12 months and discharge from the hospital within the previous 7 days	Adults and adolescents Mean (SD): 30(8.56)	HbSS: 50 (96%) HbSβ⁰: 2 (4%)	34 (65%)	NR	Prior ED Utilization (past 12 months) 0-5 visits: 71% 6-10 visits: 24% 11-15 visits: 6%	1. Mometasone furoate 220mcg OD inhale (n=35*) 2. Placebo (n=17*) In addition to standard SCD care	16 weeks	NR	NHLBI	JA

Ataga 2017 Brazil, Jamaica, USA [4-8] Aug 2013 to Jan 2015 NCT01895361	RCT, double-blind Multicentre 198 (109); 3	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. 16-65 years 3. two to ten SCD-related pain crises in the 12 months before the enrolment Exclusion: long-term red-cell transfusion	Adults and adolescents Median: 26 (range 16-56) Black, or African American: 60 (90%) White: 4 (6%) Other: 3 (4%)	HbSS: 141 (71%) HbSC: 32 (16%) HbSβ^0: 12 (6%) HbSβ$^+$: 10 5%) Other: 3 (2%)	123 (62%)	N of SCD-related pain crises during previous 12 months 2-4: 63% 5-10: 37%	NR	1. High-dose Crizanlizumab 5 mg/kg IV (n=67) 2. Low-dose Crizanlizumab 2.5 mg/kg IV (n=66) 3. Placebo (n=65) Two doses 2 weeks apart (loading dose) and then every 4 weeks. A total of 14 doses for 50 weeks	52 weeks	NR	Selexys Pharmaceuticals, NHLBI and OOPD	JA, JA supp
Lemonne 2017 Guadeloupe **[9]**	Single-arm Single centre 28 (13); 1	1. at the beginning of the HU therapy 2. patients were at steady state, i.e., no blood transfusions in the previous three months and absence of acute episodes (infection, VOC, ACS, stroke, priapisrn) at least one month before inclusion into the study. Exclusion: renal insufficiency, hepatic insufficiency or human immunodeficiency virus infection	Adults Overall mean: 37.0(SD 11.6)	All SCA (50% with α-thalassemia)	N/A	Frequent hospitalized VOC: 14 (50%) N of ACS ≥ 1: 10 (36%)	NR	HU Therapy (n=28)	2 years	NR	Region of Guadeloupe.	JA
Quarmyne 2017 USA **[10]** 2009-2011	Single-arm Retrospective 134 (74); 1	1. HbSS, HbSβ^0 2. started HU in 2009-2011 Exclusion: concurrent chronic transfusion and hydroxyurea therapy, underwent bone marrow transplant, no follow-up data	Adults and Children Overall Median: 7.5 ≤5 years: 39% 6-10 years: 33% 11-15 years: 20% >15 years: 8%	NR	None	NR	NR	HU oral (n=78*) Dose: 20 mg/kg/day (initially), followed by dose escalation every 2 months to 25–30 mg/kg/day or maximum tolerated dose if lower	~3 months	NR	NCATS, NIH and the Abraham J. & Phyllis Katz Foundation.	JA
Daak 2018 USA **[11]**	RCT, double-blind Multicentre 67(NR); 2	1. 5–17 years 2. two and ten (inclusive) documented SCC during the 12 months prior to screening 3. either not received, or were on a stable regimen of hydroxyurea (HU)	Children and Adolescents NR	NR	51 (76%)	NR	NR	1. AltemiaTM (n=50) 2. Placebo (n=17)	2 months	NR	NR	CA
Bridges 2017 Unclear	Single-arm	Patients with SCD and severe anaemia, i.e. Hb < 6.5 g/dL	Adults	HbSS:6 (86%) HbSβ: 1 (14%)	NR	Baseline VOC admission (total n): 15	Baseline transfusions (total n): 24	GBT440 900mg OD (n=7)	10 weeks	NR	NR	CA

[12]	Single centre 7(4); 1		Overall mean: 48.6(SD 15.8)									
Charnigo 2017 Unclear **[13]**	RCT (phase 1b) Retrospective 29 (NR); 2	Stable SCD patients	NR	NR	NR	NR	NR	1. PF-04447943 25mg or 5mg BID oral (n=22) 2. Placebo (n=7)	29 days	NR	Pfizer	CA
Sins 2017 Netherlands, Belgium, UK [14, 15] Apr 2013 to Nov 2015 NCT01849016	RCT, double-blind Multicentre 96 (40); 2	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. ≥ 12 years 3. History of at least 1.0 VOC per year in the past 3 years Exclusion: Chronic blood transfusion or transfusion in the preceding 3 months, VOC in the last 4 weeks, pregnancy, active gastric/duodenal ulcers, HU treatment with unstable dose in the last 3 months or started on HU shorter than 6 months prior to study, use of pain medication for SCD-related pains on more than 15 days per month in the past 6 months, poor compliance	Adults Mean (SD): 28.4(8.9) Latin-America/Caribbean: 17 (43%) Africa :23 (57%)	HbSS/HbSβ^0: 46 (69%) HbSC/HbSβ$^+$:21 (31%)	28 ((42%)	N of VOC over past three years Median: 11 (IQR 6-20)	Number of hospital admission over past three years Median: 3 (IQR 1-6)	1. Placebo (n=40*) 2. NAC 600mg BID oral (n=27*)	6 months	NR	ZonMw, the Academic Medical Centre, JANIVO Stichting, Egbers Stichting,	JA
Niihara 2018 US [16-20] Jun 2010 to Dec 2013 NCT01179217	RCT, double-blind (phase 3) Multicentre 230 (124); 2	1. > 5 years 2. had had at least two pain crises (no upper limit) documented during the previous year 3. HU at stable dose within 3 months and continue during the trial	Adults and children Mean (SD): 21.4(12.42) Black: 144 (95%) Hispanic: 4 (3%) Other: 4 (3%)	SCA: 207 (90%) HbSβ^0: 21 (9%) HbSβ$^+$: 2 (1%)	153 (66.5%)	N of SCD pain crises in the year before trial 0-1: 0.7% 2-5: 84.2% 6-9: 9.9% ≥ 10: 5.3%	NR	1. L-glutamine 0.3 g/kg BID oral (n=152) 2. placebo (n=78) Maximum dose: 30mg	48 weeks	NR	Emmaus Medical	JA
Sethy 2018 India **[21]** 2013 to 2016	Single-arm Single site 142 (46); 1	1. HbSS 2. ≥ 18 years 3. > 2 attacks of VOC per year and/or rate of transfusion 1–2 units/month were included in the study Exclusion: pregnancy, human immunodeficiency virus infection or medications that could potentially enhance HU toxicity, abnormal serum Cr/ALT levels	Adults	All HbSS	N/A	64% presented with repeated VOC, 13% with transfusion dependency and 23% with both the above features	NR	HU 10 mg/kg/day oral (n=128*)	12 months	All the patients were advised to take folic acid (5 mg/day) and ensure adequate fluid intake	NR	JA

Di Maggio 2018 Italy **[22]** January 2000 to April 2014	Single-arm Retrospective 140 (71); 1	1. start HU treatment 2. >3 painful vaso-occlusive crises per year and/or >2 Acute Chest Syndrome	Adults and children Median(range): 35 (0.4-61)	HbSS: 25 (18%) HbSβ⁰: 54 (39%) HbSβ⁺ : 56 (40%) HbSα-β: 4 (3%) HbSLepore: 1 (0.7%)	90 (64%)	NR	NR	HU oral (n=140) Starting dose: 10 mg/kg daily Titration: increased at a rate of 5 mg/kg/week	Mean follow-up: 6.6 years	NR	NR	JA, JA supp
Youssry 2017 Egypt **[23]**	Single-arm Retrospective 60 (37); 1	Patients who were on HU therapy for at least 3 consecutive months Exclusion: Chronic blood transfusion, chronic disabling hepatic/renal disease	Adults and children Mean: 12.8 (SD 5.5) (range 4 to 24)	HbSS: 27 (45%) HbSβ: 33 (55%)	N/A	NR	NR	HU 15-30mg/kg/day oral (n=60)	Up to 120 months	NR	NR	JA
Bumma 2017 USA **[24]** 1/1/2000 to 1/15/2016	Single-arm Retrospective 104 (60); 1	NR	Adults and Adolescents Median (range): 24(15-62)	HbSS: 89 (86%)	13%	NR	NR	Scheduled outpatient red cell exchange (n=104)	1 year	NR	NR	CA
Kwiatkowski 2017 USA **[25]**	Single-arm Registry data 291 (166); 0	Inclusion on a patient registry has been maintained for all US patients who receive deferiprone	Adults and children Mean: 29.5 (SD15.7) ≤ 18years: 79	NR	NR	NR	NR	Deferiprone oral (n=291)	Mean: 1.3 years (range 0-4.1)	NR	NR	CA
Rigano 2018 Italy **[26]**	Single-arm Retrospective cohort 652 (302); 1	1. On HU therapy 2. The indication for HU initiation was 2–3 vaso-occlusive crisis and/or acute chest syndrome in the year prior	Adults and children Mean: 24.5 (SD 15) Median: 24 (range 1-67) Caucasian: 400/621 Africa: 221/621	HbSS: 277 (47%) HbSβ⁰: 167 (28%) HbSβ⁺: 131 (20%) Other: 19 (3%) Total N: 594	N/A	NR	NR	HU oral (n=628*) 10 mg/kg/day, and adjusted or escalated according to tolerance	Median duration: 7 years (range <1-29)	Folic acid was concomitantly used in 71.3% of patients (n/N = 388/448).	NR	JA

Al Hashmi 2017 Oman **[27]**	Single-arm Single centre 18 (6); 1	1. Aged ≥ 18 years 2. on HU 5-10mg/kg/day 3. history of more than three admissions with vaso-occlusive crises /year, history of acute chest syndrome, history of priapism, history of splenic sequestration crises Exclusion: pregnancy, blood transfusion during the study, follow-up of < 6 months	Adults	NR	N/A	NR	NR	HU 5-10mg/kg/day oral (n=18)	At least 6 months	NR	NR	CA
Colombatti 2018 Italy **[28]**	Single arm Multicentre 204 (20); 1	1. On HU therapy	Children and adolescents Overall mean: 7.68 (range 11-221 months) Nigeria: 65 (32%) Ghana: 32 (16%) Senegal: 12 (6%) Italy and Albania: 37 (18%) Central America and India: 10 (5%) Unknown: 10 (5%)	HbSS:172 (84%) HbSβ^0: 22 (11%) HbSC: 8 (4%) HbSβ$^+$: 3 (1.5%) Other: 1 (0.5%)	N/A	NR	NR	HU therapy (varied by centre) (n=204)	1 year	NR	NR	JA
Brandalise 2017 Brazil **[29]** RBR-2s9xvn	Single arm Single centre 14 (5); 1	1. Under chronic hydroxyurea treatment 2. >3 severe VOC episodes/year, that were refractory to opioids for periods longer than 3 weeks duration Exclusion: pregnancy, concomitant infection	Adults Overall median: 23.5 (range 18-32)	HbSS:11(79%) HbSC:3 (11%)	14 (100%)	Previous VOC/month: 3.3 (95% CI 2.0-5.0) (excluding one PT with 19.3 VOC/month)	Avascular necrosis: 7	MTX 10mg weekly IM (n=14)	12 weeks	NR	Boldrini Children's Center and UNIEM Institute.	JA
Keikhaei 2015 Iran Cohort **[30]** 2013 to 2014	Single-arm Single centre 48 (24); 1	1. admitted to Shafa Hospital, Ahvaz, Iran, from 2013 to 2014 2. aged 6-18	Children and adolescents Overall mean 13.7 (range 6 to 18)	NR	NR	NR	NR	HU 10 mg/kg/day oral (n=48)	1 year	NR	Ahvaz Jundishapur University of Medical Sciences	JA

LeBlanc 2016 USA **[31]** NCT02709681	Single-arm Retrospective cohort study 16 (6); 1	More than 5 pain events per year	Adults and adolescents Mean: 15.5 (SD 2.8)	HbSS: 14 (88%) HbSβ⁰: 1 (6%) HbSC: 1 (6%)	NR	NR	ED visit/month: Mean 0.31 (SD 0.27) Hospitalization/month: 0.19 Chronic transfusions: 10	Methadone oral (n=16) Flexible dose	Mean: 2.1 years	NR	NR	CA
Heeney 2016 Americas, Europe, Asia and Africa **[32, 33]** May 2013 to Jun 2015 NCT01794000	RCT, double-blind (phase 3) Multicentre 341 (173); 2	1. HbSS, HbSβ⁰ 2. At least 2 VOC in the year prior to screening 3. TCD within the last year for patients ≤16 years of age 4. Children aged 2 to <18 years 5. Body weight ≥12 kg Exclusion: abnormal/conditional TCD, chronic transfusion, hepatic/renal dysfunction, history of transient ischemic attach or haemorrha, severe head traumatic stroke, chronic treatment with NSAID, use of anticoagulants or other antiplatelet drugs	Children and adolescents Mean:10.6 (SD 4.3) White: 58/169 Black: 109/169 Multiple: 2/169	NR	153 (45%)	N of VOCs in previous year: Mean 4.0 (SD 7.9)	NR	1. Placebo (n=170) 2. Prasugrel oral (n=171) Individual dose-adjustment strategy: Initial dose: 0.08 mg/kg; maintenance: 0.04-0.12 mg/kg (maximum 10mg) by a targeted level of platelet reactivity	9 to 24 months	No anticoagulants or antiplatelet drugs during the study No NSAID drugs	Daiichi Sankyo and Eli Lilly	JA
Reid 2014 United States, Lebanon, Egypt, Jamaica and Canada **[34]** Aug 2012 to May 2013 NCT01601340	RCT, double-blind (phase 2, terminated early) Multicentre 76 (49); 2	1. HbSS or HbSβ 2. Aged 12-60 years 3. at least one acute SCD-related complication or leg ulcers in 12 months prior to enrolment 4. no current (i.e., within 3 months prior to enrolment) HU treatment Exclusion: regular transfusion, an acute vaso-occlusive event within 3 weeks, pulmonary hypertension requiring oxygen therapy, symptomatic untreated peptic ulcer or gastroesophageal reflux disease, history of pancreatitis, abnormal ALT/AST levels, HIV infection	Adults and children Mean: 27.8 (range 12-55) Black or African-American: 24 (63%) White :14 (37%)	HbSS: 60 (79%) HbSβ⁰: 16 (21%)	N/A	N of pain crises in the 12 months before enrolment 0-1: 13 >2: 25	NR	1. HQK-1001 15 mg/kg BID oral (n=38) 2. placebo (n=38)	48 weeks	Folic acid daily	HemaQuest Pharmaceuticals	JA

Adegoke 2013 Nigeria **[35]** Jul to Dec 2011	RCT, open Multicentre 113 (56); 2	Steady state (no painful episode, anemic crisis, or infection on the day of recruitment) Exclusion: alternative medicine (Aloe vera gel, Moringa oleifera, Solamine syrup, and Ciklavit (Cajanus cajal) suspension), hydroxyurea, Discriovite suspension, Niprisan	Children and adolescents Mean: 4.55 (SD 3.57)	NR	NR	N of previous significant painful episodes Mean: 3.27 (SD 3.93)	N of previous Transfusion Mean: 1.29 (SD 0.77) N of Previous hospitalization Mean: 2.12 (SD 2.67)	1. Lime juice + Routine oral drugs (folic acid, vitamin B complex and proguanil) BID oral (n=58) 2. Control (Routine oral drugs (folic acid, vitamin B complex and proguanil)) BID (n=55) Adjusted by body weight: ≤10kg: 5 ml; 11-20 kg: 10 ml; ≥20 kg: 15 mg	6 months	NR	NR	JA
Arruda 2013 Brazil **[36]** Sep to Dec 2010	RCT, double-blind Single centre 83 (53); 2	1. HbSS or HbSβ^0 Exclusion: hospitalized patients, pregancy, untreated iron overload, other investigational drugs in the last 12 months or contraindications to Vitamin C/E	Adults Overall median: 27 (range 18-68)	HbSS: 73 (88%)	NR	NR	Chronic use of NSAIDs: 52 Chronic use of opioids: 16 Transfused patients (past 12 months): 18	1. Placebo (n=39) 2. Vitamins C 1400 mg/day and E 800 mg/day oral (n=44)	6 months	NR	FAPESP and CNPq	JA
Wun 2013 United States and Canada **[37-39]** 26 Aug 2010 to 13 Jun 2011 NCT01167023	RCT, double-blind (phase 2) Multicentre 62 (30); 2	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. aged 18 to 55 years 3. did not have a diagnosis of acute VOC within 30 days of the study screening visit 4. NSAIDs for treatment of pain were not permitted in the 5 days prior to randomization or for ≥5 consecutive days during the study period. 5. HU was permitted in patients already on a stable dose 30 days prior to randomization Exclusion: hepatic/renal dysfunction, HCt < 18%, risk of excessive bleeding, history of bleeding disorders, haemorrhagic or ischemic stroke, retinal haemorrhage, TIA or intracranial haemorrhage	Adults Mean:31.5	HbSS: 37 (61%) HbSC: 15 (25%) HbSβ^0: 3 (5%) HbSβ þ+: 6 (8%)	NR	Vaso-occlusive crisis: 61% Pain intensity: Mean: 1.8 vs 2.4	Acute chest syndrome: 22.0% (prasugrel) vs 9.5% (placebo) Pulmonary hypertension: 17.1% (prasugrel) vs 9.5% (placebo)	1. Prasugrel 5 mg/day oral (n=41) 2. placebo (n=19*)	30 days	NR	Daiichi Sankyo Co., Ltd. and Eli Lilly and Company.	JA
Daak 2013 Sudan **[40]** Apr 2009 to May 2010	RCT, double-blind Single centre 140 (61); 2	Steady state, defined as no evidence of fever, infection, or crisis for >4 week before the start of the study Exclusion: other chronic diseases, transfusion within 4 months,	Children and adolescents Mean (SD): 7.8(5.5)	All HbSS	NR	NR	Crisis-induced hospitalization (N/year) No. admission: 9.8%	1. Placebo (n=61*) 2. Omega-3 (n=67*)	1 year	All of the patients were receiving regular folate supplementation, and those ,5	Marie Curie Transfer of Knowledge Programme, Efamol, and the Kitchner	JA

ISRCTN80844 630		hydroxyurea treatment, history of overt stroke, pregnancy					1-2: 43.7% 3-5: 24.1% > 5: 22.4%			y of age were receiving standard oral prophylactic penicillin.	Memorial Trust Fund and University of Khartoum	
Ataga 2011 United **States, Jamaica, Brazil, France, Trinidad and the United** **Kingdom.** **[41]** **Feb 2005 to Apr 2007** **NCT00102791**	RCT, double-blind (phase 3, terminated early) Multicentre 297 (160); 2	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. aged 16-65 years 3. at least two acute sickle-related painful crises in the previous 12 months 4. Patients were permitted to receive concomitant therapy with HU if they had received HU for the preceding 12 months and their dose was stabilized for at least 3 months prior to the study Exclusion: unstable cardiovascular, neurological, endocrine, hepatic, or renal disorders, Hb < 40 or > 110 g/L, chronic transfusion, cancer diagnosis within 5 years, or hepatitis B/C or HIV infection	Adults and adolescents Mean: 28.5(SD 9.9) Black: 134 (92%) Multiracial: 6 (4%) Caucasian: 3 (2%) Other: 2 (2%)	HbSS: 245 (85%) HbSC: 16 (6%) HbSβ^0: 21(7%) HbSβ$^+$: 4 (1%) Other: 3 (1%)	163 (56%)	SCD crises history in past 12 months (%) 2-4: 59% >5: 41%	NR	1. Senicapoc 20mg/d BID (loading) and then 10mg/dOD oral (n=145*) 2. placebo (n=144*)	52 weeks	NR	Icagen (Research Triangle Park)	JA
Diop 2011 Senegal **[42, 43]** Sep 2007 to Feb 2008	RCT, open Single centre 60 (31); 2	1. Follow-up at least 2 years before in the clinic with records of standardized clinical and laboratory Exclusion: allergic to sulfonamide	Adults and adolescents Mean: 23.2 (SD 6.9)	All SCA	NR	N of VOC/year: Mean 0.8 (SD 1.25)	N of SCD with chronic complications: 8	1. Sulfadoxine-pyrimethamine (S: 25 mg/kg/P: 1.25 mg/kg) OD oral (n=30) 2. Placebo (n=30) The treatment was given once during the following months: September, October, and November	3 months	1. Folic acid, paracetamol during pains 2. Artemisinin-based combination therapy or injectable quinine for malaria attacks	NR	JA

Alvim 2005 Saudi Arabia **[44, 45]** Sep 1998 to Dec 1999	RCT, crossover, double-blind 73 (40); 2	Exclusion: renal, hepatic, cardiac or coagulation disorders secondary or not to SCD, regular transfusion, hydroxyurea use, age > 20 or < 5 years, cognitive dysfunction	Adults and children Median: 12.1 (range 5 to 20)	HbSS: 42 (58%) HbSC: 26 (36%) HbSβ⁰: 5 (7%)	NR	NR	History of transfusion: once: 13; 2-5 times: 19; More than 5: 18 Splenectomy: 5 Cholecystectomy: 5 Osteomyelitis: 11 Acute splenic sequestration: 12 Aplastic crisis: 1 Avascular necrosis of femoral head: 4	1. Piracetam 4.8 g/m^2/day QID (n=73*) 2. Placebo (n=73*)	6 months, then crossover with 2 weeks washout period	NR	FAPEMIG, CNPq	JA
Bao 2008 US **[46]**	RCT, double-blind Single centre 36 (14); 2	Exclusion: non-ambulatory, receiving more than 6 transfusions per year or taking hydroxyurea, history of substance abuse, neurological or psychiatric deficits that could affect compliance, use of immunosuppressive drugs, HIV and hepatitis B	Adults Overall mean: 32.9 (SD 9.7) (range 18-47) All black	HbSS: 32 (89%) HbSC: 3 (8%) HbSβ: 1 (3%)	None	N of sickle pain episode 3-month prior to the study: 5 (placebo); 3 (zinc)	NR	1. Placebo (n=18) 2. Zinc 25mg TID (n=18)	3 months	NR	NR	JA
Ataga 2008 **US** **[47]** **Feb 2002 and Jan 2004** **NCT00040677**	RCT, double-blind (phase 2) Multicentre 90 (45); 3	1. HbSS 2. Aged 18-60 years 3. at least one prior acute sickle-related painful episode (commonly referred to as painful crisis) that had required hospitalization, but none in the 4 weeks prior to screening Exclusion: Hb< 40 g/L or > 100 g/L, received a transfusion within 30 days or underwent an exchange transfusion within 60 days, hepatitis B, HIV, cancer diagnosis within 5 years, mediations (eg, amiodarone, chlorperazine, disopyramide, dofedilide, haloperidol, procainamide, quinidine, risperidone, sotalol, thioridazine, trifluoperazine, warfarin sodium, and erythropoietin)	Adults Mean: 33.6(range 19-55)	All HbSS	24 (27%)	Hospitalizations due to painful episodes in previous 12 months: None: 12 (39%) 1: 6 (19%) 2-3: 6 (19%) ≥3: 7 (23%)	NR	1. Placebo (n=30) 2. Senicapoc (low-dose): 100 mg (loading dose); 6 mg/d (maintenance) oral OD (n=29) 3. Senicapoc (high-dose): 150 mg (loading dose); 10 mg/d (maintenance) oral OD (n=31)	12 weeks	NR	Icagen (Research Triangle Park, NC)	JA

Eke 2003 Nigeria **[48]**	RCT, open (phase 2) Single centre 101 (48); 3	1. HbSS 2. Aged 1-16 years 3. Stable condition Exclusion: loss to 2 consecutive follow-up, pregnancy	Children and Adolescents Mean: 8.1 (SD 4.3) (Range 2-16)	HbSS: 101 (100%)	NR	NR	Total N of malarial parasites: 20 (equally distributed)	1. Pyrimethamine 0.5 mg/kg once weekly oral (n=36*) 2. Proguanil 1.5 mg/kg OD oral (n=32*) 3. Placebo (Vitamin c 7 mg/kg) OD oral (n=29*)	9 months	NR	Combating Childhood Communicable Diseases (Atlanta, Georgia)	JA
Pace 2003 US **[49]**	RCT, double-blind Single centre 21 (10); 4	1. HbSS or HbSβ^0 2. Aged above 15 years 3. With dense cells greater than 6% and 2 or more VOC episodes per year for the 2 years prior to enrollment. Exclusion: pregnancy, narcotic addition, chronic transfusions, history of stroke, HIV, investigational drug	Adults and Adolescents Mean:17.9 (SD1.2)	NR	NR	N of VOC episodes Mean: 5 (SD 2)	NR	1. Placebo (n=5) 2. NAC (low-dose) 600 mg/day (n=5) 3. NAC (mid-dose) 1200mg/day (n=5) 4. NAC (high-dose) 2400mg/day (n=6) All doses were divided by 3 to be taken	7 months	NR	Zambon Corp.	JA
Wambebe 2001 Nigeria **[50, 65]**	RCT, cross-over, double-blind (Phase 2) 82 (46); 2	1. HbSS 2. Aged 2-45 years 3. at least 3 painful or vaso-occlusive crises in the previous year Exclusion: HIV, hepatitis, pregnancy	Adults and children Overall (years) < 9: 1 (1%) 10-19: 67 (82%) 20-29: 11 (13%) 30-39: 3 (4%)	All HbSS	NR	Mild to Moderate Pains (Mean): 18.38 Severe Pains: 12.67	NR	1. Niprisan 12 mg/kg OD (n= 70*) 2. Placebo (n=70*)	6 months, then crossover without washout	NR	NR	JA
Tomer 2001 US **[51, 52]**	RCT, double-blind Single centre 13 (NR); 2	1. Frequent pain episodes (≥3 events/year) 2. Not on HU	Adults NR	NR	None	Frequency of pain episodes in 12 months: 7.8	NR	1. Mehaden fish oil: 0.25 g/kg/day OD oral daily (n=5*) 2. Placebo (n=5*)	12 months	NR	NR	JA
de Abood 1997 Spain **[53]**	RCT, double-blind Single centre 43 (43); 3	1. HbSS 2. history of at least one painful crisis per month were included	Adults Overall range: 17-39	All HbSS	NR	NR	NR	1. DMPA 150mg per month for first three months, then usual dose of 150mg every 3 months oral (n=13) 2. levonorgestrel/ethinyl estradiol (0.15/0.03 mg) OD oral (n=14) 3. Surgically sterilized (n=16) [not eligible]	12 months	NR	Special Programme of Human Reproduction of WHO	JA

Gupta 1995 India **[54]**	RCT, double-blind Phase 2 145 (34); 0	1. > 5 years 2. HbSS Exclusion: chronic persistent infection or exposed to extremes of temperature variation frequently, on drug therapy for some other disease, evidence of organ failure	Adults and children Mean: 16.4 (range12-27)	All HbSS	NR	NR	NR	1. Zinc: 220 mg TID oral (n=65*) 2. Placebo (n=65*)	1.5 years	NR	NR	JA
Manrique 1987 Brazil **[55]**	RCT Phase 2 60 (23); 2	HbSS Exclusion: acute infections	Adults and children Range: 7-34	All HbSS	NR	Overall pain events (n) None: 11 < 5 times: 7 < 10 times: 15 > 10 times: 11 Persistent: 14 Not clear: 2 Overall pain duration (days) None: 11 < 5 days: 12 < 10 days: 17 > 10 days: 4 Persistent: 14 Not clear: 2 All in 6 months observation period		1. Placebo (n=29*) 2. Pentoxifylline :(Adults: 1200mg; children: 400-600 mg, depending on body weight) oral (n=28*)	6 weeks	NR	NR	JA
Zago 1984 Brazil **[56]**	RCT, crossover 42 (NR); 2	NR	Adults and children Median: 12 (range 4 - 31)	HbSS: 25 (86%) HbSβ⁰: 4 (14%)	NR	NR	NR	1. Aspirin 17-45 mg/kg OD (n=29*) 2. Placebo (n=29*)	5 months, then crossover without washout	NR	NR	JA
Cabannes 1984 Africa **[57]**	RCT, double-blind Multicentre 140 (NR); 2	No antisickling treatment for two months before admission to the study Exclusion: other than HbSS; uncontrolled parasitic disease; malnutrition; a history of drug abuse; glaucoma, prostatis hypertrophy, urinary retention, hypersensitivity to ticlopidine or anticholingeric drugs, acute cerebro-vascular accidents, severe intercurrent infection, pulmonary oedema or renal failure	Adults and adolescents Overall range 15-45	All HbSS	NR	N of crises in 6 months before study: 223	NR	1. Ticlopidine 250mg BID if body weight <45kg; 250mg TID if body weight >45kg oral (n=70) 2. Placebo (n=70)	6 months	Acute crises treatment varied depends on regions but including transfusions, analgesic, antibiotics and anticoagulants	NR	JA

Gail 1982 Ghana **[58]** Sep 1976 to Sep 1978	RCT, double-blind Phase 2 79 (39); 2	HbSS Exclusion: other major illnesses	Adults and children Overall: < 5 years: 21 5-14 years: 28 > 14 years: 30	All HbSS	NR	Number of crises in the previous year 0-2: 18 > 2: 21	NR	1. Control (n=39) 2. Urea: 0.266 g/kg Low-dose: twice a week; High-dose: daily (n=40)	Average: 13.7 months	1. Folic acid (1 mg) and multivitamins daily 2.Chloroquine was given with urea or sucrose placebo	International Sickle Cell Anemia Research Institute and CSRPM	JA
Deceulaer 1982 Jamaica **[59]**	RCT, crossover, double-blind Single centre 25 (25); 2	HbSS	Adults Overall age range: 20-41	All HbSS	NR	NR	NR	1. placebo (n=10*) 2. medroxyprogesterone acetate 150mg every 3-month IM (n=13*)	2 years (9 months, then crossover after 6 months washout)	NR	NR	JA
Mann 1974 UK **[60]**	RCT, crossover Single centre 18 (12); 2	1. HbSS, HbSC, HbSβ 2. 5-17 years 3. Previously suffered painful crises	Children and adolescents Overall mean 8.4 (SD 3.2)	HbSS: 15 (83%) HbSC: 2 (11%) HbSβ: 1 (6%)	NR	NR	NR	1. Folic acid 5 mg daily oral (n=25) 2. Folic acid 5mg + Sodium bicarbonate 0.06-0.2 gm/kg/day initially, then 0.1-0.4 mg/kg/day oral (n=25)	2 years (1 year than crossover without washout	NR	United Birmingham Hospitals and Endowment Research Fund	JA
Isaacs 1972 Nigeria **[61]**	RCT, crossover (preliminary report before crossover) 44 (28); 2	1. HbSS 2. Moderately severe pain at least once in three months (with little or no fever or exacerbations of jaundice)	Adults and children Overall range 2-35	All HbSS	NR	NR	NR	1. Saline IM (n=44*) 2. Steroid (Testoserone/Progesterone) Male: testosterone 10 mg; Female: progesterone 10 mg every week IM (n=44*)	4-6 months	All patients were on regular folates and had high or normal serum-iron values	Glaxo Allenburys of Nigeria	Journal article
Oski 1968 USA **[62]**	RCT, crossover, double-blind 14 (5); 2	At least 2 painful episodes during the 2 year period prior to study	Adults and children NR	HbSS: 10 (71%) HbSC: 4 (29%)	NR	NR	NR	1. Promazine hydrochloride oral (n=14*) Based on weight: 2 tablets a day: 40-80 pounds; 3 tablets a day: 80-120 pounds; 4 tablets a day: > 120 pounds 2. Placebo (n=14*)	3 months	NR	NR	JA

NCT02482298 USA, Egypt, France, Italy, Kenya, Lebanon, UK, Turkey [63] Jul 2015 to Nov 2016	RCT, double-blind Multicentre 87 (47); 3	1. HbSS, HbSβ^0 2. Aged 18-30 3. If treated with hydroxyurea, the dose must have been stable for 3 months	Adults Mean: 21.6 (SD 3.42) Black Or African American: 17 (57%) White: 13 (43%)	NR	NR	NR	NR	1. Placebo (n =30) 2. Ticagrelor 10MG BID oral (n=27) 3. Ticagrelor 45mg BID oral (n=30)	12 weeks	NR	AstraZenec a	CT
NCT01476696 USA [64] Feb 2014 to Oct 2016 NCT01476696	Single-arm Phase 2 (Part B) 18 (NR); 1	1. HbSS, HbSβ 2. ≥2 to <18 years of age and ≥ 12 kg body weight 3. Participants on hydroxyurea must be on a stable dose for the 60 days prior to enrolment without signs of hematologic toxicity at screening	Children and adolescents NR (only reported overall, part A+B)	NR	NR	NR	NR	Prasugrel 0.06-0.12 mg/kg depending on their steady-state PD response oral (n=18)	14 ± 4 days	NR	Eli Lilly and Company	CT
Vichinsky 2010 [66]	RCT 36 (NR)	1. HbSS 2. Normal neurological exam, WAIS III PIQ score ≤ 90, hemoglobin ≤ 9 g/dL 3. Aged 21-55	Adults Mean: 29	All HbSS	HU: 14 (39%)	NR	Transfusion group had average of 5.6 transfusions (which differ from standard care group) ACS: 35%	1. Chronic transfusion (n = 20) maintaining a hemoglobin of 2 g/dL rise over baseline with matched red cells for D, C/c, E/e, and Kell antigens 2. Standard care (n = 16)	4 weeks	NR	NR	CT
Styles USA [67]	Single-arm Open-label ½ study Three centers 15 (0); 1	NR	Adults Mean: 32 (range 18-50) All African-American	HbSS: 13 HbSβ^0: 2	HU: 4 (26.7%)	VOC: 6 (past year)	ACS: 2 (past year) Transfusion: 2 (past year) Priapism: 1 (past year)	GMI-1070 20mg/kg (first dose) and 10 mg/kg after 10 hours	28 days	NR	NR	CT

†If not stated, only one arm data were shown as representative

*final number used for analysis or crossover design

ACS: Acute chest syndrome; ALT: Alanine transaminase; CA: Conference abstract; Cr: creatinine; CSRPM: Center for Scientific Research into Plant Medicine; CT: Clinical trial registry; DDCF: Doris Duke Charitable Foundation; ED: emergency department; HbSS: Homozygous sickle haemoglobin (HbS); HbSC: sickle haemoglobin S and haemoglobin C; HbSβ: sickle beta thalassemia, type '0' or '+'; HU: hydroxyurea; JA: Journal article; MTX: Methotrexate; NAD: N-acetylcysteine ;NCATS: National Center for Advancing Translational Sciences; NCRR: National Center for Research Resources; NHLBI: National Heart Lung and Blood Institute; NSAID: Nonsteroidal anti-inflammatory drugs; NR: Not reported; OOPD: FDA's Office of Orphan Products Development; PT: patient; SCD: sickle cell disease; TCD: transcranial Doppler; ZonMw: The Netherlands Organisation for Health Research and Development

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