Supplementary Table. Adverse events are tabulated during treatment. All patients who received any treatment and provided toxicity data at each time point are included in the adverse event summary.

	Placebo n = 44		Regadenoson n = 52	
Adverse event grade	**2**	**3**	**2**	**3**
Abdominal pain	-	-	1 (2)	-
Adult respiratory distress syndrome	-	-	1 (2)	-
Anemia	2 (5)	-	1 (2)	-
Arthralgia	-	-	1 (2)	-
Blood and lymphatic system disorders - Other, specify	1 (2)	-	-	-
Chest wall pain	1 (2)	-	-	-
Constipation	3 (7)	-	1 (2)	-
Delirium	-	-	1 (2)	-
Diarrhea	2 (5)	-	-	-
Dry eye	-	-	1 (2)	-
Fever	4 (9)	-	5 (10)	-
Hallucinations	1 (2)	-	-	-
Headache	5 (11)	1 (2)	4 (8)	1 (2)
Hemolysis	-	-	1 (2)	-
Hypertension	1 (2)	-	-	-
Hypoxia	-	-	-	1 (2)
Ileus	-	-	1 (2)	-
Infections and infestations - Other, specify	1 (2)	-	-	-
Infusion site extravasation	1 (2)	-	-	-
Lethargy	2 (5)	-	-	-
Nausea	1 (2)	-	3 (6)	-
Neutrophil count decreased	-	1 (2)	-	-
Non-cardiac chest pain	-	-	1 (2)	-
Pain	-	-	-	1 (2)
Pain in extremity	2 (5)	-	-	1 (2)
Platelet count decreased	1 (2)	-	-	-
Pneumonitis	-	1 (2)	-	-
Pruritus	3 (7)	-	2 (4)	-
Respiratory, thoracic and mediastinal disorders - Other, specify	2 (5)	-	1 (2)	1 (2)
Sinus tachycardia	-	-	2 (4)	-
Skin ulceration	1 (2)	-	-	-
Skin/subcutaneous tissue disorders; Other, specify	1 (2)	-	-	-
Urinary tract infection	1 (2)	-	-	-
Ventricular tachycardia	1 (2)	-	-	-
Vomiting	1 (2)	-	4 (8)	-

Inclusion criteria:

1. Participants must have sickle cell anemia (HbSS or HbSβ-thalassemia^0) confirmed by hemoglobin analysis. Prior hemoglobin analysis measurements may be used to meet study entry criteria.
2. Participants must be admitted to the hospital for or present to the emergency room with pain or acute chest syndrome.

   Definitions: Pain episode: Pain in the extremities, back, abdomen, chest or head for which no other explanation other than SCD can be found, and was not classified as one of the following events: skeletal/joint event, ACS, right upper quadrant pain, dactylitis, neurological event, neurologic events, anemic episodes, febrile illness and priapism.
   Acute chest syndrome: Acute Chest Syndrome is an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray.
   Severe ACS: Severe ACS meets the diagnostic criteria of ACS and one or more of the following: respiratory failure (PaO_2 <60 mmHg or PCO_2 >50 mmHg); mechanical ventilatory support required; transcutaneous oxygen saturation <90% despite maximal supplemental oxygen; segmental or lobar infiltrates that involve 3 or more lobes by chest radiography; requiring transfusion or exchange transfusion of red blood cells to achieve hemoglobin A ≥70%.

3. Ages of assent (10 to 17 years at DFCI/BCH, but different depending on institution) to 70 years.
4. Participants must have the laboratory indices as defined below:

   - Hemoglobin ≥ 5 g/dL
   - Platelets ≥ 100,000/mcL
   - ALT (SGPT) ≤ 3 X institutional upper limit of normal
   - Serum creatinine ≤ 1.5 mg/dL
   - INR ≤2.0, PTT ≤ 48 seconds

5. Participants must have reliable IV access or a plan in place to set the central line, as determined by the study physician.
6. Ability to understand and the willingness to sign a written informed consent document. Please note that per DF/HCC policy, only attending physicians can obtain consent and re-consent on this trial.
7. The effects of regadenoson on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation, including the 30-day follow-up period. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.
8. Female participants must have a negative pregnancy test.

Exclusion Criteria:

1. Participants with a current physician diagnosis of asthma defined by treatment with systemic corticosteroids within the last 12 months and/or predicted or current use of asthma controller medications (inhaled corticosteroids, leukotriene antagonists). Participants prescribed bronchodilators (e.g., albuterol) and participants who have a remote history of asthma will be allowed to participate.
2. Participants with ≥10 hospitalizations for pain in the last 12 months.
3. Participants who are receiving regularly scheduled transfusions (secondary stroke prophylaxis, chronic pain/acute chest syndrome).
4. Participants with severe acute chest syndrome (defined as meeting the diagnostic criteria of acute chest syndrome and one or more of the following: respiratory failure (PaO_2 <60 mmHg or PCO_2 >50 mmHg); mechanical ventilatory support required; transcutaneous oxygen saturation <90% despite maximal supplemental oxygen; segmental or lobar infiltrates that involve 3 or more lobes by chest radiography; requiring transfusion or exchange transfusion of red blood cells to achieve hemoglobin A ≥70%.).
5. Participants with second- or third-degree AV block or sinus node dysfunction.
6. Have a history of a bleeding diathesis.
7. Have a history of clinically overt stroke within three years.
8. Have a history of severe hypertension not adequately controlled with anti-hypertensive medications (SBP ≥ 160 mmHg and/or DBP ≥ 90 mmHg).
9. Participants who are receiving systemic dose anti-coagulation therapy. Participants who receive anti-platelet agents (e.g. aspirin and clopidogrel) and prophylactic dose anti-coagulants are eligible to participate.
10. Participants with a history of metastatic cancer.
11. Participants may not be receiving any other study agents or have received a study agent in the past 30 days. Participants who have participated in the phase I dose seeking study (*Safety of Adenosine 2A agonist Lexiscan in Children and Adults with Sickle Cell Disease,* DFCI IRB 09-308) will be eligible to participate in this study if the prior treatment was greater than 30 days ago. Participants who have ever received an investigational therapy to deplete iNKT cells (monoclonal antibody, NKTT120) will be eligible to participate in this study 60 days after the return of iNKT cells to baseline levels.
12. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris,

cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

13. Pregnant or breastfeeding women are excluded from this study because regadenoson is an investigational agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with regadenoson, we will also exclude nursing women.
14. Participants with known HIV. HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with regadenoson.
15. Participants who have previously enrolled and received the investigational agent as part of this study.
16. Participants who are taking medications that may interact with the investigational agent including dipyridamole, aminophylline, theophylline. Caffeine and theophylline may not be taken within 12 hours of starting the investigational agent. Initiation of study drug may be delayed 12 hours if the participant has taken caffeine or theophylline and otherwise qualifies for the study. Dipyridamole and aminophylline may not be taken within 48 hours of starting the investigational agent.
17. Participants who have undergone an allogeneic transplant. Participants who underwent a hematopoietic stem cell transplant >3 years ago and lost the graft will be eligible to participate. Participants who have any history of solid organ transplant will be excluded.