Stanford SPARK

PROTOCOL TEMPLATE

**Background and Instructions to User:**

The protocol of a clinical trial plays a key role in study planning, conduct, interpretation, oversight, and external review by detailing the plans from ethics approval to dissemination of results (Chan et al., 2012). A well-written protocol facilitates assessment of the scientific, ethical, and safety issues before a trial begins; consistency and rigor of trial conduct; and full appraisal of the conduct and results after trial completion. The importance of a well-written protocol has been emphasized by journal editors, reviewers, researchers, and public advocates (Chan et al., 2012).

Many publicly available templates of clinical trial protocols are written as outlines that lack much detail. In contrast, complete protocols are increasingly available in appendices of high-impact journals reporting pivotal late-stage phase 3 multinational clinical trial results. Both types of documents are often inadequate as guidance for early-stage SPARK trials, which are investigator-sponsored. This document provides a well-written completed SPARK protocol and adds guidance language, as an instructional template for SPARKees designing a clinical trial. While SPARK trials encompass various phases, designs, and controls, this protocol describes the common SPARK phase 2a parallel-group, placebo-controlled design.

This protocol is consistent with recommendations from both the International Conference on Harmonisation (1996) and the SPIRIT (Standard Protocol Items: Recommendations or Interventional Trials) initiative. The latter was developed in consultation with key stakeholders, including trial investigators, health care professionals, statisticians, journal editors, ethicists, and regulatory agencies to identify key deficiencies in protocol content. The SPIRIT initiative led to a guideline checklist for the minimum content of a clinical trial protocol (Chan et al., 2012).

* + - 1. **Sections highlighted in yellow** contain standard language that in most cases may be copied into your protocol. In some cases, the language in these sections may need to be changed to meet the needs of your protocol.
			2. **All other sections** contain examples of language that should be tailored to your study.
			3. **Italicized text** **(blue)** represents instructional comments at the beginning of some sections.

Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013; 158(3):200-7.

International Conference on Harmonisation (ICH). Guidance for Industry. E6 Good Clinical Practice: Consolidated Guidance. ICH: Geneva, Switzerland. April 1996.

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 2a Study Evaluating the Safety and Efficacy of the Oral Bisphosphonate Alendronate for the Treatment of Patients with Osteonecrosis of the Femoral Head from Sickle Cell Disease

Investigational Drug: Alendronate sodium

Sponsor-Investigator:

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The information contained in this protocol is confidential and is intended for the use of the clinical investigators and their study staff. The information in this document is the property of the sponsor and may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL SYNOPSIS

**Title**: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 2a Study Evaluating the Safety and Preliminary Efficacy of the Oral Bisphosphonate Alendronate in the Treatment of Patients with Osteonecrosis of the Femoral Head from Sickle Cell Disease

**Disease**:

Osteonecrosis of the femoral head from sickle cell disease

**Objectives**:

The primary objective of this study is to assess the safety and preliminary efficacy of alendronate, compared with placebo, administered orally once a week for 24 weeks to patients with osteonecrosis of the femoral head from sickle cell disease.

**Study Design**:

This is a 28-week, randomized, double-blind, placebo-controlled phase 2a study of the oral bisphosphonate alendronate administered to 30 participants with sickle cell disease-related osteonecrosis of the femoral head (SCD+ONFH). Participants will be equally randomized to one of two treatment groups (alendronate vs. placebo). Treatment will be given for 24 weeks and study duration will be 28 weeks.

**Summary of Participant Eligibility Criteria**:

Inclusion Criteria:

1. Age ≥ 12 years.
2. History of diagnosis of sickle cell disease with any of the following hemoglobin genotypes: HbSS, HbSC, or HbSβ-thalassemia).
3. Radiographic diagnosis of stages I-III osteonecrosis of the femoral head (ONFH), as defined by the Association Research Circulation Osseous (ARCO) criteria, within 1 yr before study entry (see Appendix B).
4. A female participant of childbearing potential must have a negative serum pregnancy test at the screening visit and agree to use a medically reliable method of contraception until study completion. Effective contraception methods include total abstinence (when this is in line with the preferred and usual lifestyle of the participant ), female sterilization, barrier methods of contraception (diaphragm or cervical/vault caps with spermicidal foam/gel/film/cream/ vaginal suppository), use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), or placement of an intrauterine device or intrauterine system.
5. Written informed consent from participants ≥ 18 years and parent(s)/guardian(s) of minor participants (< 18 years of age) must be obtained before any study procedure is performed. All participants who are minors must also provide assent.

Exclusion Criteria:

1. Pregnant or nursing.
2. Hypocalcemia (< 8.5 mg/dL).
3. Hospitalization with vaso-occlusive crises, acute chest syndrome, fever, or surgery within 30 days before study entry.
4. Active dental disease or invasive dental procedures within 3 months before study entry.
5. Poorly controlled or symptomatic gastroesophageal reflux disease.
6. Abnormalities of the esophagus which delay emptying such as stricture or achalasia.
7. Inability to stand/sit upright for at least 30 minutes.
8. Severe renal insufficiency, defined as receiving renal dialysis or having a measured or estimated creatinine clearance (CC) < 35 ml/min based on the Cockroft-Gault formula at screening:

CC = [(140 – age) x weight (kg)] / [serum creatinine (mg/dL) x 72] x 0.85 (female) or 1.00 (male)

**Investigational Drug**:

Alendronate sodium (35 mg or 70 mg)

**Study Drug Doses and Route of Administration**:

* Alendronate 70 mg or placebo: a) < 18 years old and weight ≥ 40 kg, and b) ≥ 18 years old.
* Alendronate 35 mg or matched placebo: < 18 years old and weight < 40 kg.

Study drug (alendronate sodium or matched placebo) will be provided as identical flavorless tablets in a bottle. Participants will be instructed to take study drug once weekly with at least 8 oz. of plain water in the morning upon awakening and at least 30 min before taking the first food, drink, or other medicine of the day. Participants will also be instructed to not lie down for at least 30 minutes after taking study drug and until after their first food of the day.

**Procedures**:

* Screening and baseline evaluations will occur within 30 days of initial study drug administration.
* Day 1 is the first day of study drug administration.
* Safety evaluations will consist of vital signs, physical examination, electrocardiogram (ECG), and additional clinical and laboratory data. Clinic visits will occur at screening and/or baseline, and weeks 4, 8, 12, 16, 20, 24, and 28. Telephone interviews to collect adverse event and concomitant medication information will occur on weeks 2, 6, 10, 14, 18, 22, and 26.
* Efficacy will be measured throughout the 24-week treatment period by hip pain, function, and range of motion, using the Children’s Hospital Oakland Hip Evaluation Scale (CHOHES).
* Additional efficacy parameters will include measurement of acute vaso-occlusive crises, markers of bone turnover, and circulating plasma microparticle (MP) levels.
* The planned study duration is 28 weeks. Duration of treatment is 24 weeks, and an additional 4 weeks will occur for safety assessment.

**Primary and Secondary Efficacy Endpoints:**

Primary efficacy endpoint:

* Proportion of patients with major improvement in hip pain, function, and range of motion, defined as ≥ 15 point increase in CHOHES score from baseline to week 24.

Secondary efficacy endpoints:

* Proportion of patients with partial improvement in hip pain, function, and range of motion, defined as ≥ 10-14 point increase in CHOHES score from baseline to week 24.
* Number of acute sickle cell vaso-occlusive crises per patient during the 24-week treatment period.
* Change in markers of bone turnover (urinary C-terminal telopeptides of type I collagen, CTX-1; serum calcium, phosphorus, alkaline phosphatase) from baseline to week 24.

Exploratory endpoints:

* The relationship of circulating plasma microparticle (MP) levels to severity of SCD-ONFH and response to treatment will be evaluated as an exploratory endpoint in participants not receiving chronic blood transfusions. In addition, samples with the highest 10% of total MP levels will be further fractionated to determine their cell of origin.

**Sample Size, Power, and Number of Sites**:

* The planned sample size of 30 participants (15 participants/treatment group) will provide approximately 70% power at an alpha-level (two-sided) of 0.05 to detect a difference between alendronate (45%) and placebo (0%) groups in the proportion of hips with ≥ 15-point increase in CHOHES score from baseline to week 24.
* Three sites: Stanford University Hospital and Clinics, Stanford, CA; Lucile Packard Children’s Hospital, Stanford, CA; and UCSF Benioff Children’s Hospital, Oakland, CA.

**Removal of Participants from Study Drug or Assessment:**

A participant must prematurely discontinue study drug under any of the following circumstances:

* A participant must be withdrawn from the study (and discontinue any study drug) if the participant or, if a minor, their parent(s)/guardian(s) requests such study discontinuation for any reason.
* The investigator wishes the participant to discontinue study drug, especially but not limited to the investigator concluding that further treatment puts the participant at unacceptable risk.
* The participant develops a condition or begins therapy that would have excluded study entry.
* The participant develops evidence of drug allergy such as rash, fever, and signs of anaphylaxis.
* The participant undergoes surgical intervention in the study hip.
* The participant develops an adverse event with a CTCAE (Common Terminology Criteria for Adverse Events) grade 3 or greater toxicity that is related to study drug in the judgment of the investigator.

Following study drug discontinuation due to an adverse event, study drug may be re-initiated at one-half of the previous dose if: the adverse event has resolved, the adverse event was not a drug allergy with CTCAE grade 3 or greater toxicity, and the investigator considers it clinically warranted.

A participant must be withdrawn from the study (and discontinue any study drug) if the participant or their parent(s)/guardian(s) requests such study discontinuation. If possible, the participant should complete the evaluations for study week 24 (Study Termination Visit) *provided that written consent to do so has not been withdrawn*.

**Statistical Analysis**:

Safety and efficacy will be assessed on an intent-to-treat basis for all participants who have received study drug. Data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum and maximum) for continuous variables and frequency and percentages for categorical variables. Tests of significance will be computed to compare the primary and secondary endpoints between the two treatment groups. All p-values will be two-sided. For exploratory endpoints, confidence intervals will be used to summarize treatment group differences.

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# List of Abbreviations

|  |  |
| --- | --- |
| **ABBREVIATION** | **DEFINITION** |
| AE | adverse event |
| ALT | alanine transaminase  |
| ARCO | Association Research Circulation Osseus  |
| AST | aspartate transaminase |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| CHOHES | Children's Hospital Oakland Hip Evaluation Scale  |
| CRF | case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTX-1 | C-terminal telopeptides of type I collagen |
| dL | deciliter |
| ECG | electrocardiogram |
| ESWT | extracorporeal shockwave therapy  |
| Hb | hemoglobin  |
| HbSβ-thalassemia | compound heterozygous sickle cell-beta thalassemia disease |
| HbSC | compound heterozygous sickle cell-hemoglobin C disease |
| HbSS | homozygous sickle cell disease |
| hCG | human chorionic gonadotropin |
| HIPAA | Health Insurance Portability and Accountability Act |
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| kg | kilogram |
| MCV | mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities  |
| mg | milligram |
| MP | microparticles |
| NSAID | nonsteroidal anti-inflammatory drug  |
| OI | osteogenesis imperfecta |
| ONFH | osteonecrosis of the femoral head  |
| SAE | serious adverse event |
| SCD | sickle cell disease  |
| UCSF | University of California, San Francisco  |

# Introduction

## Osteonecrosis of the Femoral Head in Sickle Cell Disease

*(This section should contain a discussion of the target disease state, including any pathophysiology relevant to the potential study drug action. Current treatment approaches for the target disease state should be mentioned, leading to the rationale for why an unmet medical need remains or why an alternative therapeutic approach needs to be tested.)*

Sickle cell disease (SCD) is an inherited red blood cell disorder that arises from a single amino acid substitution on chromosome 11, which alters the structure of the hemoglobin molecule and causes red blood cells to sickle under stressful physiologic conditions. SCD occurs when a person inherits an abnormal copy of the hemoglobin gene from each parent (in an autosomal recessive pattern). The exact prevalence of SCD in the United States is unknown; however, the Centers for Diseases Control and Prevention (2016) estimates that SCD affects approximately 100,000 Americans and occurs among about 1 out of every 365 Black or African-American births. It is estimated that several million Americans are genetic carriers of sickle cell trait.

The morbidity associated with SCD is high and characterized by anemia, severe pain, and potentially life-threatening complications such as sepsis, splenic sequestration, acute chest syndrome, ischemic stroke, and chronic organ damage. The signs and symptoms of SCD are essentially caused by the sickling shape of red blood cells, which cause intermittent episodes of vaso-occlusion from blood vessels that are blocked by the defective red blood cells; this occlusion typically results in tissue injury and organ dysfunction.

Osteonecrosis, or death of bone tissue, is a common complication of SCD - and is believed to occur when sickled red blood cells obstruct blood flow to susceptible articular surfaces, causing bony infarction at the epiphyseal plates and early onset degenerative arthritis (Acurio and Friedman, 1992; Mahadeo et al., 2011; da Silva Junior et al., 2012). The femoral head is the most affected site of osteonecrosis in SCD due to its lack of collateral blood flow (Flouzat-Lachaniete et al., 2009; Poignard et al., 2012). Indeed, SCD-related osteonecrosis of the femoral head (ONFH) affects up to 50% of individuals with homozygous sickle cell disease (HbSS) by age 35 years (Mahadeo et al., 2011). Additional risk factors include co-inheritance of alpha-thalassemia and frequent sickle cell pain crises (Aguilar et al., 2005). Necrosis within the femoral head typically causes severe pain, functional limitations, and compromises quality of life in these patients. The rate of progression to femoral head collapse is higher in patients with SCD than other at-risk groups (Hernigou et al., 2006), and advanced SCD-related ONFH is the most common indication for total hip arthroplasty in young adults (Kamath et al., 2012).

There is no optimal approach for the care of patients with SCD-related ONFH. The National Heart, Lung, and Blood Institute recommends symptomatic management of SCD-related ONFH with pain medications, physical therapy, and early referral to orthopedic surgery (Yawn et al., 2014). Early stages of avascular necrosis of the hip are often managed surgically with core decompression with or without autologous bone grafting. Total hip arthroplasty is the mainstay of treatment of advanced stages of the disease in patients with ONFH who have intractable pain and are medically able to tolerate the procedure. However, this procedure is generally delayed as long as possible in individuals with SCD given the high rate of prosthetic hip failure and ongoing postoperative hip pain (Neumayr et al., 2006). Thus, early detection and effective medical management of SCD-related ONFH are areas of significant unmet need in this highly vulnerable patient population.

## 2.2 Alendronate sodium

[*An investigational agent in a clinical trial may either be a repurposed drug (i.e., approved by the FDA for use in one disease or condition but still considered investigational in other diseases) or a new investigational drug. For a repurposed drug, this section should contain brief information on mechanism of action, approved indications (and relevant unapproved use), and safety profile. For a new investigational agent, the section should include a description of the product and relevant chemical and physical properties, including any pharmacological data. Brief summaries of preclinical information and clinical data typically add value.]*

Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone and can inhibit osteoclast-driven bone resorption. Bisphosphonates are approved in the United States (and other regions) for multiple indications, including treatment and prevention of osteoporosis in post-menopausal women, treatment to increase bone mass in men with osteoporosis, treatment of steroid-induced osteoporosis in men and women on long-term glucocorticoid therapy, treatment of men and women with Paget’s disease of the bone, and treatment of hypercalcemia of malignancy. Bisphosphonates have also been increasingly used off-label with benefit in pediatric patients for the treatment of disorders associated with osteoporosis, resistant hypercalcemia or heterotopic calcifications such as osteogenesis imperfecta (OI), glucocorticoid-induced osteoporosis, malignancy-induced hypercalcemia, osteonecrosis-related chemotherapy, and low bone mass associated with other systemic conditions (Baroncelli and Bertelloni, 2014). In general, the main adverse effects of bisphosphonates treatment in pediatric patients are similar to that of adults.

Alendronate sodium (Fosamax) is an oral bisphosphonate approved in the United States for the indications above, except hypercalcemia of malignancy (Fosamax package insert, 2015). Alendronate does not interfere with osteoclast recruitment or attachment, but instead inhibits osteoclast activity and is a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonate is rapidly taken up and deposited in the skeleton. Concentrations of drug in plasma are too low for analytic detection and there is no evidence that alendronate is metabolized in animals or humans. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting the release of alendronate from the skeleton.

The most common use of bisphosphonates in the pediatric population, including alendronate, is in the treatment of moderate-to-severe OI (Ward et al., 2009). In this population, results of over 30 (mostly uncontrolled) clinical trials showed that patients age 4 months to 18 years receiving long-term therapy had decreased bone pain, decreased bone turnover, increased quality of life, and decreased fracture rate (Bachrach and Ward, 2009). While intravenous bisphosphonates have been more commonly used, alendronate has been studied in pediatric patients with OI at doses of 5 or 10 mg/day (Ward et al., 2009). Nevertheless, there is no agreement on optimal bisphosphonate dosage and duration of therapy in the pediatric population.

One of the largest studies of alendronate in the pediatric population was a randomized, double-blind, placebo-controlled two-year trial of 139 patients, aged 4-19 years, with severe OI (Ward et al., 2011; Fosamax package insert, 2015). One-hundred nine patients were randomized to alendronate daily (5 mg, if weight < 40 kg or 10 mg, if weight ≥ 40 kg) and 30 patients to placebo. Alendronate significantly decreased bone turnover and increased bone mineral density but was not associated with improved fracture outcomes. The oral bioavailability in children was similar to that observed in adults. In general, the overall safety profile of alendronate in OI patients treated for up to 2 years was similar to that of adults with osteoporosis treated with alendronate. However, there was an increased occurrence of vomiting in OI patients treated with alendronate compared to placebo. During the 24-month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with alendronate and 3 of 30 (10%) patients treated with placebo (Fosamax package insert, 2015).

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of Fosamax 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration (Fosamax package insert, 2015). These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with a brief acute-phase response that has been reported in patients receiving bisphosphonates.

The therapeutic equivalence of once-weekly Fosamax 70 mg and Fosamax 10 mg daily has been shown in studies of postmenopausal women with osteoporosis. The current recommended dosage for the treatment of osteoporosis in postmenopausal women or to increase bone mass in men with osteoporosis is one 70 mg tablet once weekly, one bottle of 70 mg oral solution once weekly, or one 10 mg tablet once daily.

The most common adverse reactions (≥3%) observed with Fosamax across multiple approved indications are abdominal pain, acid regurgitation, constipation, diarrhea, dyspepsia, musculoskeletal pain, and nausea (Fosamax package insert, 2015). Severe esophageal adverse experiences, hypocalcemia, musculoskeletal pain, osteonecrosis of the jaw, and diaphyseal femoral fractures have been infrequently described in adults. In the pediatric population, transient hypocalcemia, acute-phase reactions, uveitis, iatrogenic osteopetrosis, and the possibility of delayed fracture healing have been described (Ward et al., 2009). No case of osteonecrosis of the jaw has been reported in the pediatric population (Ward et al., 2009).

## Use of Bisphosphonates for Osteonecrosis of the Femoral Head from Sickle Cell Disease

*(Summarize the available preclinical and clinical data relevant to the relationship of the investigational agent to the target disease to be studied. Include an introductory statement indicating if no published clinical study data is available with the investigational drug in the targeted disease state or study population.)*

There is no published study that has evaluated the use of bisphosphonate for ONFH that is SCD-related or in adolescents. Dalle Carbonare et al (2015) showed that the bisphosphonate zoledronic acid used before recurrent vaso-occlusive events prevented bone impairment and promoted osteogenic activity in a mouse model of sickle cell disease. In addition, there is accumulating evidence, however, that use of bisphosphonates (specifically alendronate) may improve nontraumatic ONFH in adults. Lai et al (2005) conducted a randomized, double-blind, placebo-controlled trial that evaluated 40 adults with stage II or III nontraumatic ONFH and a necrotic area of >30% (class C). Participants were randomly divided into alendronate 70 mg and control groups and received treatment once weekly for 25 weeks. During a 2-year study period, 2 of 29 femoral heads in the alendronate group collapsed compared to 9 of 25 femoral heads in the control group. One hip in the alendronate group underwent total hip arthroplasty, whereas 16 hips in the control group underwent total hip arthroplasty.

Luo et al (2014) reviewed eight studies involving the use of alendronate to treat 788 hips in adults with ONFH. Despite methodological limitations that included observational non-controlled designs and small sample sizes, most studies suggested a benefit of alendronate for nontraumatic ONFH. None of the studies reported serious adverse events and the most common adverse events (gastric dyspepsia and dizziness) were known side effects of the drug that resolved while on study.

Hong et al. (2014) reviewed five randomized controlled trials that evaluated use of alendronate in 305 hips of 230 adults with stage I-III (ARCO) disease. Three studies investigated alendronate versus placebo or control, and the other two compared combined alendronate plus extracorporeal shockwave therapy (ESWT) with ESWT alone. Data suggested that patients treated with alendronate had less collapse of their ONFH compared with patients treated with placebo. An exception was a randomized, double-blinded, controlled study that showed no significant difference in radiographic and MRI data for ONFH between 64 patients treated with alendronate versus placebo for 2 years (Chen et al., 2012). In addition, Hong et al. (2014) noted that some patients in different studies treated with alendronate still did not preserve their femoral head and required total hip replacement, suggesting that femoral head failure could ultimately occur even in patients with slower progression of disease due to alendronate.

The rate of progression to femoral head collapse is higher in patients with SCD than in other at-risk groups (Hernigou et al. 2006) and advanced SCD-related ONFH is the most common indication for total hip arthroplasty in young adults (Kamath et al., 2012). The present study will evaluate the safety and preliminary efficacy of alendronate for the treatment of patients with SCD-related ONFH.

## Risk/Benefit

There is currently no approved bisphosphonate for ONFH that is SCD-related or in adolescents. Anticipated risk is low based on the mechanism of action and known clinical safety data. The benefit of alendronate sodium for ONFH that is SCD-related is unknown. However, the benefit-risk balance for this study is considered favorable given the overall risks to participants compared with the potential benefits of alendronate sodium for the treatment of ONFH from SCD, which remains a serious unmet medical need.

# Objectives

*[Objectives are distinct from endpoints and should reflect the more global purpose of the study. The endpoints (or outcomes), determined for each study participant, are the quantitative measurements required to address the objective.]*

The primary objective of this study is to assess the safety and preliminary efficacy of alendronate, compared with placebo, administered orally once weekly for 24 weeks, in the treatment of patients with SCD-related ONFH.

Safety will be evaluated using adverse event, physical examination (including vital signs), electrocardiogram (ECG), and clinical laboratory data.

Efficacy will be evaluated by Children's Hospital Oakland Hip Evaluation Scale (CHOHES) score, acute sickle cell vaso-occlusive crises, markers of bone turnover, and plasma microparticle levels by the following endpoints:

 Primary efficacy endpoint:

* Proportion of participants with major improvement in hip pain, function, and range of motion, defined as ≥ 15 point increase in CHOHES score from baseline to week 24.

Secondary efficacy endpoints:

* Proportion of participants with partial improvement in hip pain, function, and range of motion, defined as ≥ 10-14 point increase in CHOHES score from baseline to week 24.
* Number of acute sickle cell vaso-occlusive crises per patient during the 24-week treatment period.
* Change in markers of bone turnover (urinary CTX-1; serum calcium, phosphorus, alkaline phosphatase) from baseline to week 24.

Exploratory endpoints:

* The relationship of circulating plasma microparticle (MP) levels to severity of SCD-ONFH and response to treatment will be evaluated as an exploratory endpoint in participants not receiving chronic blood transfusions. In addition, samples with the highest 10% of total MP levels will be further fractionated to determine their cell of origin.

# Investigational Plan

*[This section should include the type/design of the study (e.g., phase, randomized, double-blind, parallel group), number and location of study sites, expected duration of treatment and participation, description of the sequence of assessments, and a schematic diagram of the trial design and duration.]*

## Summary of Study Design

This is a 28-week, randomized, double-blind, placebo-controlled phase 2a study to evaluate the safety and preliminary efficacy of alendronate in 30 participants with SCD-related ONFH. Thirty participants will be equally randomized to one of two treatment groups (15, alendronate; 15, placebo). Stratification to treatment assignment will be performed to balance representation of patients with bilateral (vs. unilateral) hip disease. Alendronate 70 mg (or placebo) will be given to participants < 18 years old weighing ≥ 40 kg, and participants ≥ 18 years old. Alendronate 35 mg (or placebo) will be given to participants < 18 years old weighing < 40 kg. Treatment will be given for 24 weeks and study duration will be for 28 weeks. Three sites are planned to participate: Stanford University Hospital and Clinics and Lucile Packard Children’s Hospital, Stanford, CA, and University of California, San Francisco (UCSF) Benioff Children’s Hospital, Oakland, CA.

Clinic visits will occur at screening and/or baseline, and weeks 4, 8, 12, 16, 20, 24, and 28. Telephone interviews to collect adverse event and concomitant medication information will occur on weeks 2, 6, 10, 14, 18, 22, and 26. Adverse events will be collected through week 28.

Safety evaluations will consist of adverse event, physical examination (including vital signs), ECG, and laboratory data. Efficacy will be evaluated by Children's Hospital Oakland Hip Evaluation Scale (CHOHES) score, acute sickle cell vaso-occlusive crises, markers of bone turnover, and plasma microparticle levels.

The study design is illustrated below.

Figure 1. Illustration of Study Design

**Study Period**

**alendronate 35 mg or 70 mg once weekly**

**Therapy Period**

**Day -30**

 **0**

****

**28**

**Weeks**

**4**

****

 **12**

 **16**

**screening**

**placebo once weekly**

 **20**















**N=15**

**N=15**

## Outline of Visit Schedule

*[This section summarizes the evaluations by visits. Visits may also be described by number (Visit 3) but should always include a date (e.g. Week 6). Screening evaluations refer solely to those assessments that are required to determine study eligibility (i.e. entry criteria). If data from screening evaluations are desired to also be used for baseline assessments (e.g., change from baseline analyses), they do not need to be repeated at Baseline Evaluations if you believe that the values will not change between the initial period of Screening and the final period of Baseline (30 days in the example below). In the example below, serum calcium is required as a screening assessment for the entry criterion of hypocalcemia but the same value (and other values from the metabolic panel) will also be used for a change from baseline analysis and will not be collected again at Baseline Evaluations.]*

### Screening and Baseline Evaluations

#### Screening Evaluations (Day –30 to 0)

The following screening assessments must be done to determine participant eligibility. Written consent (and assent, when applicable) will be obtained before conducting any study procedures.

* Screen for inclusion/exclusion criteria (see Section 5).
* Medical history.
* Metabolic panel [serum concentrations of sodium, potassium, chloride, total bilirubin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, uric acid, phosphorous, calcium, glucose, total protein, albumin, cholesterol].
* Serum 25-hydroxyvitamin D level.
* Serum beta hCG pregnancy test on females of childbearing potential.

#### Baseline Evaluations (Day –30 to 0)

Screening and baseline evaluations may be conducted on the same day. However, screening tests (e.g., select laboratories) must be available before the participant receives study drug.

Once screening is completed and the participant meets all eligibility criteria, the participant will obtain baseline evaluations. Certain tests obtained at screening will be used as the baseline values. Participant randomization to study drug assignment may occur after completion of all baseline procedures.

* Physical examination, including weight and vital signs (blood pressure, respiratory rate, heart rate, and temperature).
* Children’s Hospital Oakland Hip Evaluation Scale (see Appendix B).
* Complete blood count with differential, including reticulocyte count.
* Coagulation panel.
* Urinalysis.
* Total plasma circulating microparticle level.
* Urinary C-terminal telopeptides of type I collagen (CTX-1) level.
* Electrocardiogram (ECG).
* Collect concomitant medication information.

### Drug Administration and Additional Study Evaluations

#### Day 1 (First Dose of Study Drug)

Following completion of screening and baseline procedures, eligible participants will be randomized to study drug assignment and receive a bottle of study drug (4-week supply) from the study site pharmacist. *The first dose of study drug is to be taken the following morning* (Day 1) by the participant upon awakening with at least 8 oz. of plain water and at least 30 min before taking the first food, drink, or other medicine of the day. Participants will also be instructed to not lie down for at least 30 minutes after taking study drug and not until after their first food of the day.

#### Week 2 (and Weeks 6, 10, 14, 18, 22, and 26) Visits (± 3 days) http://consultation-medium-auditive.wifeo.com/images/1/119/11949848961789922052telephone_sauvetage_yves_01_svg_hi.png

There will be no clinic visits on these study dates. Confirmation that study drug is being taken and information on adverse events and concomitant medications will be obtained by telephone on these study dates.

* Confirm that study drug is being taken.
* Collect adverse event information
* Collect concomitant medication information

#### Week 4 Visit (± 3 days)

* Physical examination, including vital signs.
* Children’s Hospital Oakland Hip Evaluation Scale (Appendix B).
* Complete blood count with differential, including reticulocyte count.
* Metabolic panel.
* Coagulation panel.
* Collect adverse event information.
* Collect concomitant medication information.
* Collect unused study drug
* Dispense study drug supply (4-week supply)

#### Weeks 8, 12, 16, and 20 Visits (± 3 days)

* Physical examination, including vital signs
* Children’s Hospital Oakland Hip Evaluation Scale (Appendix B).
* Complete blood count with differential, including reticulocyte count
* Metabolic panel
* Coagulation panel
* Total plasma circulating microparticle level (week 12 only)
* Collect adverse event information
* Collect concomitant medication information
* Collect unused study drug
* Dispense study drug supply (30-day supply)

#### Week 24 Visit (± 3 days)

* Physical examination, including vital signs.
* Children’s Hospital Oakland Hip Evaluation Scale (Appendix B)
* Complete blood count with differential, including reticulocyte count
* Metabolic panel
* Coagulation panel
* Serum beta hCG pregnancy test on females of childbearing potential
* Total plasma circulating microparticle levels
* Urinalysis
* Urinary C-terminal telopeptides of type I collagen (CTX-1) level
* Electrocardiogram (ECG)
* Collect adverse event information
* Collect concomitant medication information
* Collect unused study drug

#### Week 28 Visit (± 3 days)

* Physical examination, including vital signs
* Collect adverse event information
* Collect concomitant medication information

### Early Termination Visit

For participants who terminate study drug prematurely, continued assessments should occur if consent to do so has not been withdrawn. For participants who terminate the study early, assessments identical to study week 24 should occur, if possible.

# Discussion of Design

*(This section typically summarizes the rationale for study dosage, control, endpoints, and length of assessment).*

This is a 28-week randomized, double-blinded, placebo-controlled Phase 2a study of oral bisphosphonate alendronate administered to 30 participants with SCD-related ONFH. Participants will be equally randomized to one of two treatment groups (alendronate vs. placebo). Treatment will be given for 24 weeks and study duration will be for an additional 4 weeks to collect safety information (total of 28 weeks). This design allows the most direct assessment of the safety and preliminary efficacy of alendronate in this patient population.

Dose: The dosage of alendronate to be used in the present study (70 mg oral tablet once weekly) for participants 18 years of age and older is the dosage recommended for the treatment of osteoporosis in men and postmenopausal women (Fosamax package insert, 2015). In the pediatric population, bisphosphonates have also been used off-label with benefit in pediatric patients for the treatment of disorders associated with osteoporosis, resistant hypercalcemia or heterotopic calcifications such as OI, glucocorticoid-induced osteoporosis, malignancy-induced hypercalcemia, osteonecrosis-related chemotherapy, and low bone mass associated with other systemic conditions (Baroncelli and Bertelloni, 2014). There is no consensus on optimal bisphosphonate dosage and duration of therapy in the pediatric population. However, the largest body of safety and efficacy data on use of alendronate in both uncontrolled and controlled trials in the pediatric population involves the treatment of patients with OI (Bachrach and Ward, 2009; Ward et al., 2009; Ward et al., 2011; Fosamax package insert, 2015). In this population, weight-based dosing for up to 2 years involving 5 mg/day (equivalent to 35 mg once weekly) for those weighing < 40 kg and 10 mg/day (equivalent to 70 mg once weekly) for those weighing ≥ 40 kg resulted in a safety profile similar to that of adults with osteoporosis treated with alendronate (Fosamax package insert, 2015).

Safety Endpoints: The safety assessments used in this trial are standard assessments for Phase 2a studies evaluating the safety of repeated dosing.

Efficacy Endpoints: The CHOHES is an easy-to-use, valid, and reliable tool for the evaluation of hip pain, function, and range of motion (Aguilar et al., 2005). In particular, the CHOHES score reflects clinically meaningful changes in ONFH status and is important for the evaluation of patients with SCD-related ONFH (Aguilar et al., 2005; Neumayr et al., 2006). A 15-point increase in CHOHES score is considered a major improvement between three stages of ONFH based on a radiographic scale similar to ARCO (Aguilar et al., 2005). Acute SCD-related vaso-occlusive disease is a significantly morbid event. Bone turnover markers, in general, have not predicted the occurrence of ONFH but have also not been well studied as a function of response to drug treatment. The relationship of circulating plasma MP levels to severity of SCD-ONFH and response to treatment will be evaluated as an exploratory endpoint in participants not receiving chronic blood transfusions, which can confound results. In addition, samples with the highest 10% of total MP levels will be further fractionated to determine their cell of origin (e.g. erythrocyte-, leukocyte-, megakaryocyte-, endothelial cell-derived MP).

Length of Assessment: Efficacy assessments will be evaluated through 28 weeks (1 month following completion of the last dose). This period is considered relevant to show clinically meaningful changes of alendronate on ONFH status in this patient population. In adult patients with nontraumatic ONFH, alendronate has resulted in improvement following periods of up to 24 weeks of treatment (Luo et al., 2014).

# Study Population

*[The investigator is responsible for ensuring that informed consent is obtained from each participant before that participant participates in the clinical trial (i.e. before any study procedure is performed). If a child or minor is to be enrolled in a clinical investigation, the parent(s) or guardian must provide permission, with assent of the child or minor when capable of doing so.]*

The investigators participating in this study have expertise in the diagnosis and management of patients with SCD-related ONFH. Participating centers include Stanford University Hospital and Clinics and Lucile Packard Children’s Hospital, both at Stanford University, Stanford, CA; and UCSF Benioff Children’s Hospital, Oakland, CA. Participants will be recruited from investigator and subinvestigator clinical practices and referring physicians.

Investigators in the department of adult and pediatric hematology will diagnose participants with SCD-related ONFH based on history, physical examination, and imaging studies. Inclusion criteria for this study include patients (age ≥ 12 years) with SCD (HbSS, HbSβ thalassemia, HbSC) and stages I-III ONFH by ARCO (1992) criteria.

Participation in this study is voluntary. The nature of the study will be fully explained to each participant and their parent(s)/guardian(s), if applicable, during the informed consent (and when applicable, assent) process. The participants and/or their parent(s)/guardian(s) will have the opportunity to ask questions. An informed consent document will then be signed by the participant or the participant’s parent(s)/guardian(s) and the person performing the consent discussion, and retained by the investigator according to Good Clinical Practice. Informed assent will occur with participants < 18 years old. All documents will be retained by the investigator according to Good Clinical Practice. A copy of the signed informed consent (and any signed assent) document will be given to the participant or their parent(s)/guardian(s), or both.

Enrollment eligibility will be based on the results of screening for the following inclusion and exclusion criteria.

## Inclusion Criteria

Patients may be included in the study only if they meet **all** of the following criteria:

[1] Age ≥ 12 years.

[2] History of diagnosis of sickle cell disease with any of the following hemoglobin genotypes: HbSS, HbSC, or HbSβ-thalassemia).

[3] Radiographic diagnosis of stages I-III osteonecrosis of the femoral head (ONFH), as defined by the Association Research Circulation Osseous (ARCO) criteria, within 1 yr before study entry (see Appendix B).

[4] A female participant of childbearing potential must have a negative serum pregnancy test at the screening visit and agree to use a medically reliable method of contraception until study completion. Effective contraception methods include total abstinence (when this is in line with the preferred and usual lifestyle of the participant), female sterilization, barrier methods of contraception (diaphragm or cervical/vault caps with spermicidal foam/gel/film/cream/vaginal suppository), use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), or placement of an intrauterine device or intrauterine system.

[5] Written informed consent from participants ≥ 18 years and parent(s)/guardian(s) of minor participants (< 18 years of age) must be obtained before any study procedure is performed. All participants who are minors must also provide assent.

## Exclusion Criteria

*(For a repurposed drug, attention to the package insert can guide some of the appropriate exclusion criteria.)*

Patients meeting any of the following criteria will not be eligible to participate in the study:

[6] Pregnant or nursing.

[7] Hypocalcemia (< 8.5 mg/dL).

[8] Hospitalization with vaso-occlusive crises, acute chest syndrome, fever, or surgery within 30 days before study entry.

[9] Active dental disease or invasive dental procedures within 3 months before study entry.

[10] Poorly controlled or symptomatic gastroesophageal reflux disease.

[11] Abnormalities of the esophagus which delay emptying such as stricture or achalasia.

[12] Inability to stand/sit upright for at least 30 minutes.

[13] Severe renal insufficiency, defined as receiving renal dialysis or having a measured or estimated creatinine clearance (CC) < 35 ml/min based on the Cockroft-Gault formula at screening:

CC = [(140 – age) x weight (kg)] / [serum creatinine (mg/dL) x 72] x 0.85 (female) or 1.00 (male)

## Removal of Participants from Study Drug or Assessment

*(A distinction is made between a participant’s early discontinuation of study drug and withdrawal from the study. In many situations, it is advantageous for the integrity of the final data analysis for a participant with early discontinuation of study drug to complete remaining scheduled visits and procedures, provided consent to do so has not been withdrawn. Continued follow-up also aids safety assessment – e.g., helps determine if an adverse event resolves following discontinuation of study drug).*

### Early Discontinuation of Study Drug

A participant must prematurely discontinue study drug under any of the following circumstances:

• The participant or, if a minor, their parent(s)/guardian(s) wishes study drug to be discontinued for any reason.

• The investigator wishes the participant to discontinue study drug, especially but not limited to the investigator concluding that further treatment puts the participant at unacceptable risk.

• The participant develops a condition or begins a therapy that would have excluded entry into the study.

• The participant has evidence of drug allergy such as rash, fever, and signs of anaphylaxis.

* Surgical intervention on study hip.
* An adverse event with a CTCAE (Common Terminology Criteria for Adverse Events) grade 3 or greater toxicity that is related to study drug in the judgment of the investigator.

Following study drug discontinuation due to an adverse event, study drug may be re-initiated at one-half of the previous dose if: the adverse event has resolved, the adverse event was not a drug allergy with CTCAE grade 3 or greater toxicity, and the investigator considers it clinically warranted.

A participant has the right to discontinue study drug treatment at any time for any reason without prejudice to future medical care by the investigator or other physician at the institution. A participant who discontinues study drug should complete all scheduled study visits *provided that written consent to do so has not been withdrawn*.

### Participant Withdrawal from the Study

A participant must be withdrawn from the study (and discontinue any study drug) if the participant or their parent(s)/guardian(s) requests such study discontinuation.

The reason for withdrawal must be recorded in the participant’s case report form (CRF). If possible, the participant should complete the evaluations for study week 24 (Study Termination Visit) *provided that written consent to do so has not been withdrawn*. Participants who withdraw from the study will not be replaced.

### Participant Replacement

Replacement patients may be enrolled. An exception is a participant withdrawn due to an adverse event judged to be related to alendronate, who will be considered evaluable but not replaced.

# Treatments

## Participant Assignment

After signing the informed consent documents, participants who meet all eligibility criteria will be assigned to study drug assignment.

## Method of Assignment to Treatment

Participants who have met all the inclusion criteria for enrollment and none of the exclusion criteria will be equally randomized into one of two possible groups: alendronate or placebo. Stratification will be performed to balance representation of patients with bilateral (vs. unilateral) hip disease in each treatment group because the responses may differ among these groups for the primary endpoint. Computer-generated random numbers will be used by the study statistician to generate the randomization allocation sequence. The investigator (or designee) will call an interactive voice response system to receive a randomization number assigned to the participant, which will be used to link the participant to a treatment and unique medication number for the first bottle of study drug to be dispensed to the participant.

## Materials and Supplies

### Formulation, Packaging, and Labeling

Study drug (alendronate or placebo) will be provided to the participant (or parent(s)/guardian(s)) in bottles from the investigator through the participating hospital’s outpatient pharmacy every month (day of randomization, weeks 4, 8, 12, 16, and 20) during the study period. Alendronate tablets were initially manufactured by Merck and Co., Inc. under the brand name Fosamax and are now available in generic form from other manufacturers. Generic alendronate sodium will be used in this study. Each alendronate and matched placebo tablet is identical in size and appearance.

Table 7.1 Study Drug Treatment and Packaging

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment** | **Study Drug** | **Frequency** | **Packaging** |
| 35 mg alendronate | One alendronate (35 mg) tablet | Once weekly | Bottle |
| 70 mg alendronate | One alendronate (70 mg) tablet | Once weekly | Bottle |
| Placebo | One placebo tablet | Once weekly | Bottle |

Study drug bottle will contain the following information:

* A precautionary statement that the investigational product is for limited use.
* Lot number.
* Storage conditions.
* Statement regarding date for reanalysis or retest.

### Storage and Handling

The study drug will be provided to participants in bottles. The study drug is stable at room temperature (59-86 ºF). No other special handling is required. Participants [and their parent(s)/guardian(s)] will be instructed to return empty bottles and any unused study drug to the investigator at specified study visits.

### Final Disposition of Clinical Supplies

At the end of the study, study drug supply and accountability records will be reconciled as to drug shipped, drug consumed, and drug remaining. Any discrepancies noted will be documented.

Participant accountability for study drug (or placebo) will be ensured through participant or parent(s)/guardian(s) interviews (during visits or by telephone) and study drug reconciliation at selected visits before dispensing drug supplies for the next visit interval. At clinic visits on study weeks 4, 8, 12, 16, 20, and 24, participants will be asked to return any unused study drug to the study site. Final drug accountability reconciliation will be performed at the participant visit occurring at the end of therapy (study week 24) or early discontinuation. Unused study drug will be destroyed.

## Dosage Administration

The investigator will distribute a 4-week (4 tablets) supply of study drug to participants beginning on the day of randomization *to begin the first dose on the following morning upon awakening* (day 1). Participants will receive an additional 4-week supply of study drug from the investigator at clinic visits on weeks 4, 8, 12, 16, and 20. Participants will be instructed to take study drug at similar times each day.

Each participant or their parent(s)/guardian(s) will be instructed to have the participant take one tablet with at least 8 oz. of plain water once weekly in the morning throughout the treatment period at least 30 minutes before the first food, drink, or other medication of the day. Participants will be instructed to do not lie down for at least 30 minutes after taking study drug and not until after their first food of the day.

The investigator is responsible for explaining the correct use of the study drug to the participant, verifying that instructions are followed properly, maintaining accurate records of study drug dispensing, and collection of all unused study drug, including empty drug packaging.

Participants (or parent(s)/guardian(s)) will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug or drug delivery system so that the situation can be assessed.

## Blinding

This is a randomized, double-blind, placebo-controlled study. Neither the participants nor the study personnel with direct contact with the participant will know which study drug (alendronate vs. placebo) is being administered during the treatment period. Placebo and active drug tablets will be similar in appearance and taste, and the number of tablets will be the same for each treatment group. To preserve the blinding of the study, a minimum number of study personnel who do not have direct interactions with the participant’s study procedures will see the randomization table before the study is complete.

Emergency unblinding for adverse events will be performed through the study pharmacist. Emergency unblinding for adverse events may be used only if a participant’s medical care requires knowledge of the participant’s treatment assignment. The investigator should make every effort to contact the sponsor-investigator before unblinding a participant’s treatment assignment. If a participant’s treatment assignment is unblinded, the sponsor-investigator must be immediately notified by telephone.

## Concomitant Therapy

*(This section summarizes what concomitant medications may be allowed or prohibited during the study. Prohibited medications typically include but are not limited to those mentioned in the entry exclusion criteria. The present protocol has no medications whose use at time of study entry precludes study eligibility. In addition, this section can also provide guidance on medications that are allowed during the study period and have potential interactions with the investigational drug.)*

* Calcium Supplements/Antacids: Co-administration of alendronate and calcium, antacids, or oral medications containing multivalent cations will interfere with absorption of alendronate. Therefore, participants must wait at least 30 minutes after taking alendronate before taking any other oral medications.
* Aspirin: In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of alendronate greater than 10 mg and aspirin-containing products.
* Nonsteroidal anti-inflammatory drugs (NSAIDs): Alendronate may be administered to participants taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking alendronate 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.
* Vitamin D: Participants with inadequate screening Vitamin D [25(OH)D] levels, based on the reference range of the local laboratory, will receive oral supplementation with Vitamin D 400 IU daily during the study period.
* Participants were advised to meet the age-related dietary reference intake for calcium and vitamin D; the addition of supplemental calcium and vitamin D is left to the judgment of the investigator if the participant’s dietary intake is considered inadequate.

## Dental Hygiene

Participants should be encouraged to practice optimal dental hygiene during the study period. Osteonecrosis of the jaw, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including alendronate. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).

## Extension Study

Following completion of this study, participants receiving alendronate may be eligible to enter a long-term open-label extension study to evaluate ONFH-related surgical intervention or clinical progression. This extension study is currently in the planning stage.

# Adverse Event Reporting

## Definition of Adverse Event

For purposes of this trial, an adverse event (AE) will be defined as **any** new unfavorable or unintended sign, symptom, or disease or change of an existing condition, which occurs during or after treatment, whether or not considered treatment-related. If a clinically significant laboratory value is considered clinically significant, the diagnosis should be reported as an adverse event. Lack of drug effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish drug effect.

Before enrollment, study site personnel will note the occurrence and nature of each participant’s medical condition(s) in the appropriate section of the CRF. During the remainder of the study, site personnel will again note any change in the condition(s) and the occurrence and nature of any adverse events.

If a participant experiences an adverse event after the informed consent document is signed (entry) but the participant is never assigned to treatment (enrollment), the event will only be reported if the investigator believes that the event may have been caused by a protocol procedure.

All adverse events occurring after the participant has entered the study (that is, after the informed consent document is signed) must be recorded in the case report form. If the study drug is discontinued for a participant, study site personnel must report and clearly document the circumstances and data leading to any such discontinuation, using designated case report forms. For adverse events, the participant should be followed until the event resolves or stabilizes, with frequency of follow-up at the discretion of the investigator.

In cases where the investigator notices an unanticipated benefit to the participant, study site personnel should enter “unexpected benefit” with the actual event term (for example, the complete actual term would be “unexpected benefit—sleeping longer”).

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported for tracking purposes. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

### Reporting Procedures for All Adverse Events

Investigators are responsible for monitoring the safety of participants who have entered this study and noting any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant. The investigator is responsible for appropriate medical care of participants during the study.

The investigator remains responsible for following, through an appropriate health care option, adverse events that are serious or that caused the participant to discontinue the study. The participant should be followed until the event is resolved or explained. Frequency of follow-up is left to the discretion of the investigator.

Adverse event information will be collected through study week 28. Participants who discontinue study drug at any time will have adverse events collected through approximately 28 weeks following their randomization, provided consent to continue in the study has not been withdrawn.

The investigator is responsible for assessing and recording all adverse experiences. Each adverse experience will be recorded and classified for intensity, seriousness, and causality. All adverse events either observed by the investigator or reported by the participant will be recorded regardless of causality. The investigator will follow the participant until an adverse event resolves or stabilizes.

### Adverse Event Severity

 *(Scales may be used in place of investigator judgment to grade the severity of an adverse event. For non-oncology studies, use the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. For oncology studies, use the Common Terminology Criteria for Adverse Events scale. The term “severity” as used here refers to intensity of an adverse event.)*

*For non-oncology studies*, the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events version 2.0 (November 2014) should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the experience is not covered in the DAIDS criteria, the following guidelines should be used to grade severity:

* Mild (grade 1): Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
* Moderate (grade 2): Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicate.
* Severe (grade 3): Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
* Life-threatening (grade 4): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

*For oncology studies*, the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (June 14, 2010) should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the experience is not covered in the CTCAE criteria, the following guidelines should be used to grade severity:

* Mild (grade 1): Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The participant may be aware of the sign or symptom but tolerates it reasonably well.
* Moderate (grade 2): Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
* Severe (grade 3): Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
* Life-threatening (grade 4): The participant is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

The term “severe” is a measure of intensity and a severe AE is not necessarily serious.

### Adverse Event Relationship to Study Drug

The relationship of an AE to the study drug should be based on the judgment of the investigator and assessed using the following guidelines:

* Definitely: Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
* Probably: An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the participant’s clinical state or by other interventions.
* Possibly: An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
* Unrelated: An event that can be determined with certainty to have no relationship to the study drug.

### Serious Adverse Event Definition and Reporting Procedures

Any AE that meets the definition of serious noted below and occurs in a participant during the course of the study must be reported to the sponsor by telephone within 24 hours of the investigator becoming aware of the event. In addition, a serious adverse event form (SAE) must be completed by the investigator and faxed to the study sponsor within 24 hours of the investigator becoming aware of the event. In addition, the site investigator must report SAEs to their local Institutional Review Board (IRB) in accordance with the IRB’s standard operating procedures and policies.

An SAE is defined as an adverse event that suggests a significant hazard or side effect, regardless of the relationship to study drug. An SAE includes, but may not be limited to, any event that:

* Results in death.
* Is life-threatening. This definition implies that the participant, in the view of the investigator, is at immediate risk of death from the event. It does not include an event that, had it occurred in a more serious form, might have caused death.
* Requires inpatient hospitalization or prolongs existing hospitalization.
* Results in persistent or significant disability/incapacity.
* Results in a congenital anomaly or birth defect. This serious criterion applies if a participant exposed to an investigational product gives birth to a child with a congenital anomaly or birth defect.

Medical and scientific judgment will be exercised in deciding whether classification of an adverse event as serious is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or require intervention to prevent one of the outcomes listed in the definition above. These should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependence or abuse.

Serious adverse events occurring after a participant is discontinued from the study will only be reported if the investigator believes that the event may have been caused by the study drug or a protocol procedure.

For the purpose of expedited reporting to regulatory agencies, an investigator will be responsible for identifying any adverse event that is serious, unexpected, and believed to be related to study drug. An adverse event or suspected adverse reaction is considered “unexpected” if it is not consistent with the risk information described in the general investigational plan or elsewhere in the current investigational new drug application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure or investigational drug application referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure or investigational drug application listed only “cerebral vascular accidents.

### Laboratory Tests

Clinical laboratory tests will be performed at the times specified in the Study Schedule (see Appendix A). All clinical laboratory assessments will be analyzed at the participating site’s local laboratory.

Laboratory values that fall outside a clinically accepted reference range or values that differ significantly from previous values must be further evaluated by the investigator. Investigators must document their review of each laboratory report by signing or initialing and dating each report.

Clinically significant laboratory abnormalities will be reported as AEs.

### Safety Monitoring

The sponsor-investigator or designees will monitor blinded safety data throughout the course of the study. The sponsor-investigator will review SAEs within time frames mandated by regulatory requirements and will review trends, laboratory analytes, and adverse events at periodic intervals.

# Quality Control and Quality Assurance

The investigator agrees to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standard of Good Clinical Practice; and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The investigator must allow study-related monitoring, audits, and inspection by the IRB, sponsor (or designee), government regulatory agencies, and, if applicable, University compliance and quality assurance groups of all trial-related documents and procedures.

The investigator shall prepare and maintain accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations.

# Data Analysis Methods

## Determination of Sample Size

*(The statistical power of a study is the probability that a significance test will detect an effect that truly exists. A common error is estimating treatment effects as unrealistically favorable to justify both a small number of evaluable patients and a desire for 80% power. This may complicate the ability to interpret clinically important but statistically nonsignificant results.)*

The planned sample size of 30 participants (15 participants/treatment group) will provide approximately 70% power at an alpha-level (two-sided) of 0.05 to detect a difference between alendronate (45%) and placebo (0%) groups in the proportion of hips with ≥ 15-point increase in CHOHES score from baseline to week 24. This was calculated based on a 2-arm binomial test. The estimate of the placebo response rate is based on observational data obtained from clinical experience in this patient population.

## Efficacy Variables

###  Children’s Hospital Hip Evaluation Scale (CHOHES)

The CHOHES is an instrument designed to measure hip pain, function, and range of motion (Aguilar et al., 2005). The total score for each hip ranges from 0 to 100 points, and includes 27 items. The CHOHES consists of three subscales (pain, function, and physical examination). Higher scores indicate less severe disease; for example, a score of 100 would be achieved if a participant had no pain or functional limitations, and a normal physical examination

* Pain (0-40). The pain scale consists of a rating of pain over the past 4 weeks for each hip as “none” (40 points), “mild” (30 points), “moderate” (20 points), “severe” (10 points), or “incapacitating” (0 points).
* Function (0-32). The functional assessment domain consists of 5 questions about dressing, sitting, walking, gait aid use, and stair climbing. This portion of the scale is scored from 0 to 32 and includes a demonstration by the patient of functional ring sitting, step height, and ambulation. Scores derived from this subscale are the same for both hips.
* Physical exam (0-28). The physical examination portion consists of goniometric measurements to evaluate range of motion. The range of scores for each hip on this section of the CHOHES is 0 to 28.

CHOHES will be assessed at baseline or screening and weeks 4, 8, 12, 16, 20, and 24 visits.

###  Acute Sickle Cell Vaso-occlusive Crises

The number of acute SCD-related vaso-occlusive crises per patient is a highly morbid and clinically relevant event that will be assessed as a secondary efficacy endpoint throughout the 24-week treatment period.

### Markers of Bone Turnover

Urinary C-terminal telopeptides of type I collagen (CTX-1) and serum calcium, phosphorus, and alkaline phosphatase are well-established markers of bone formation or resorption. Change in these markers of bone turnover will be evaluated from baseline to week 24.

### Total Circulating Plasma Microparticles

Microparticles (MPs) are small, membrane-derived vesicles believed to be released by cells in response to activation or injury. In SCD, MPs derived from erythrocytes, platelets, monocytes, and endothelial cells are elevated in both crises and steady state (Shet et al., 2003). Circulating platelet MPs have been elevated, compared with controls, in patients with nontraumatic ONFH and may contribute to their hypercoagulability (Kang et al, 2008). Because of this independent relationship of MPs to both SCD and ONFH, Marsh et al (2015) evaluated the association between circulating MPs and SCD-ONFH in 10 patients with SCD-ONFH, 10 patients with SCD (without ONFH), and 10 healthy controls. MPs were 2.3-fold higher in patients with ONFH compared with SCD patients without ONFH, and 2.5-fold higher than in healthy controls. The present study will evaluate the relationship of circulating plasma MP levels to severity of SCD-ONFH and response to treatment as an exploratory endpoint in participants not receiving chronic blood transfusions. In addition, samples with the highest 10% of total MP levels will be further fractionated to determine their cell of origin (e.g. erythrocyte-, leukocyte-, megakaryocyte-, endothelial cell-derived MP).

## Safety Variables

Safety evaluations will include collection of adverse event, physical examination, vital sign, ECG, and clinical laboratory data. Laboratory data will include evaluation of:

* Hematology: hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume (MCV), segmented neutrophils, juvenile neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, cell morphology, reticulocyte count.
* Metabolic panel: Serum concentrations of sodium, potassium, chloride, total bilirubin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, uric acid, phosphorous, calcium, glucose, total protein, albumin, cholesterol.
* Coagulation: prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR).
* Serum beta hCG pregnancy test on females of childbearing potential.
* Urinalysis: specific gravity, pH, protein, glucose, blood, leukocyte esterase.

## Statistical and Analytical Plans

### General Considerations

Efficacy analyses will be done on an intent-to-treat (ITT) basis using the full analysis population. The full analysis population will include all randomly assigned participants who have received study drug. The analysis of safety variables will also include all participants who receive study drug.

All variables will be summarized by descriptive statistics for each treatment group. The statistics for continuous variables will include mean, median, standard deviation, and number of observations. Categorical variables will be tabulated using frequencies and percentages. Tests of significance will be computed to compare the primary and secondary endpoints between the two treatment groups. The analyses of multiple endpoints will not be adjusted for multiple comparisons. All p-values will be two-sided. For exploratory endpoints, confidence intervals will be used to summarize treatment group differences. Where confidence intervals are presented, they will be two-sided 95% confidence intervals.

### Handling of Missing Data

Missing data will not be imputed for safety analyses. For efficacy analyses, missing values may be imputed using the last observation carried forward method.

### Participant Disposition

Study participant disposition will be summarized by treatment group. Participants who discontinued study drug prematurely or withdrew from the study will be summarized and listed, with reason for early termination/withdrawal.

### Participant Characteristics

Demographic and other baseline characteristics will be summarized by treatment group.

### Treatment Compliance

Treatment compliance will be evaluated by visits and phone interviews. This will include the date the study drug was dispensed, the number of tablets dispensed, and the number of tablets returned.

### Efficacy Analyses

#### Efficacy Analyses

Data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum and maximum) for continuous variables and frequency and percentages of categorical variables.

Tests of significance for the primary efficacy endpoint (proportion of participants with major improvement in hip pain, function, and range of motion, defined as ≥ 15 point increase in CHOHES score from baseline to week 24) will be performed using Fisher's exact test.

Tests of significance for the categorical secondary efficacy endpoint (proportion of participants with major improvement in hip pain, function, and range of motion, defined as ≥ 10-14 point increase in CHOHES score from baseline to week 24) will also be performed using Fisher's exact test.

Tests of significance for the following secondary endpoints with continuous variables will be performed using a t-test:

* Number of acute sickle cell vaso-occlusive crises per patient during the 24-week treatment period.
* Change in markers of bone turnover (urinary CTX-1; serum calcium, phosphorus, alkaline phosphatase) from baseline to week 24.

Exploratory endpoints of relationship of circulating MP levels to severity of SCD-ONFH and response to treatment, and fractionated samples, will be assessed using descriptive statistics and confidence intervals.

### Safety Analyses

Treatment-emergent adverse events are defined as adverse events occurring after the first dose of study drug until 28 days after the last dose of study drug.

Duration of treatment will be summarized by treatment group.

The incidence of all reported AEs and treatment-related AEs will be tabulated by treatment group. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be listed and summarized by treatment group, MedDRA preferred term, severity, seriousness, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one participant, the AE will be counted once as the worst occurrence. The incidence of AEs will be tabulated by system organ class and treatment group. AEs leading to premature discontinuation of study drug or withdrawal from the study will be summarized and listed in the same manner.

Summary statistics for actual values and change from baseline will be summarized for laboratory results by treatment group and scheduled visit. Participants with laboratory values outside of the normal reference range at any postbaseline assessment will be identified.

For vital signs, descriptive statistics will be used to summarize the mean absolute values and change from baseline for each treatment group. Physical examination findings and changes from baseline will be summarized for each patient in data listings only.

### Interim Analyses

No interim analyses are planned for this study.

# Administrative, Ethical, and Regulatory Considerations

The investigator is responsible for presenting the risks and benefits of study participation to the participant in simple terms using the informed consent document. The investigator will ensure that written informed consent is obtained from each participant or legally authorized representative by obtaining the appropriate signatures and dates on the informed consent document before the performance of protocol evaluations or procedures. In addition, the investigator will ensure that assent is obtained from any child or minor participant, when applicable.

## Ethical Review

The sponsor-investigator will obtain documentation of the IRB approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing IRB are provided in the investigator file.

The sponsor-investigator will supply the following to the investigative site’s IRB:

* Protocol and amendments.
* Informed consent document and updates.
* Investigational New Drug Application.
* Relevant curricula vitae, if required.
* Required safety and SAE reports.
* Any additional submissions required by the site’s IRB.

The sponsor-investigator will retain the following documentation, if applicable:

* The IRB periodic (e.g., quarterly, annual) re-approval of the protocol.
* The IRB approvals of any amendments to the protocol or revisions to the informed consent document.
* The IRB receipt of safety and SAE reports, as appropriate.

## Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the 2013 version of the Declaration of Helsinki or the applicable guidelines on Good Clinical Practice, and all applicable federal, state, and local laws, rules, and regulations.

All data recorded in the CRF for participants participating in this study will be transcribed from medical records. After reading the protocol, the investigator will sign the protocol signature page and return it to the sponsor-investigator or designee.

### Investigator Information

The contact information and qualifications of the principal investigator (sponsor- investigator for the purposes of this trial) and subinvestigators, and name and address of the research facilities are included in the investigator file.

### Protocol Amendments and Study Termination

The sponsor-investigator will initiate changes to the protocol as necessary (except for changes to eliminate an immediate hazard to a study participant) and seek approval by the IRB before implementing. The investigator is responsible for enrolling participants who have met protocol eligibility criteria. Protocol violations must be reported to the local IRB following IRB policies.

The sponsor-investigator may terminate the study at any time. The IRB must be advised in writing of study completion or early termination.

### Study Documentation, Privacy, and Records Retention

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the investigator for a minimum of 5 years (or longer if required by the local IRB).

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and participant medical records in the participant files as original source documents for the study. If requested, the investigator will provide the applicable regulatory agencies and applicable IRB with direct access to original source documents.

Records containing participant medical information must be handled following the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and consistent with the terms of the participant authorization contained in the informed consent document for the study. Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the informed consent document. Furthermore, CRFs and other documents should be completed in strict accordance with the instructions provided by the sponsor-investigator, including the instructions regarding the coding of participant identities.

## Study Finances

This study is financed through grants from the SPARK Translational Research Program and the Child Health Research Institute (both at Stanford University).

## Publications

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study. The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this trial will be either submitted for publication or posted in a publicly accessible database of clinical trial results.

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*[The format below was recommended by the International Committee of Medical Journal Editors in 1978 as a uniform requirement for bibliographic references in manuscripts to be submitted to their journals (see Iverson C, Christiansen S, Flanagin A, et al. AMA Manual of Style: A Guide for Authors and Editors. 10th ed. New York, NY: Oxford University Press; 2007. http://www.amamanualofstyle.com). Most importantly, whatever reference style is followed, consistency and accuracy are critical.]*

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**APPENDIX A:**

**SCHEDULE OF EVENTS**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Activity | Screening(D-30 to 0) | Baseline(D-30 to 0) | D1 | Wk2 | Wk4 | Wk6 | Wk8 | Wk10 | Wk12 | Wk14 | Wk16 | Wk18 | Wk20 | Wk22 | Wk24 | Wk26 | Wk28 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Recruitment/Informed Consent | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Metabolic panel a | X |  |  |  | X |  | X |  | X |  | X |  | X |  | X |  |  |
| Serum (25-OH) Vitamin D level | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serum hCG pregnancy test b | X |  |  |  |  |  |  |  |  |  |  |  |  |  | X |  |  |
| Physical examination |  | X |  |   | X |  | X |  | X |  | X |  | X |  | X |  | X |
| Vital signs c |  | X |  |  | X |  | X |  | X |  | X |  | X |  | X |  | X |
| Administer CHOHES |  | X |  |   | X |  | X |  | X |  | X |  | X |  | X |  |  |
| Complete blood count (w/ retic count) d |   | X |  |  | X |  | X |  | X |  | X |  | X |  | X |  |  |
| Coagulation panel e |   | X |  |  | X |  | X |  | X |  | X |  | X |  | X |  |  |
| Urinalysis f |   | X |  |  |  |  |  |  |  |  |  |  |  |  | X |  |  |
| Total + fractionated plasma MP levels |  | X |  |  |  |  |  |  | X |  |  |  |  |  | X |  |  |
| Urinary CTX-1 level |  | X |  |  |  |  |  |  |  |  |  |  |  |  | X |  |  |
| Electrocardiogram |  | X |  |  |  |  |  |  |  |  |  |  |  |  | X |  |  |
| Collect concomitant medication info  |  | X |  | Xh | X | Xh | X | Xh | X | Xh | X | Xh | X | Xh | X | Xh | X |
| Collect adverse event info  |  |  |  | Xh | X | Xh | X | Xh | X | Xh | X | Xh | X | Xh | X | Xh | X |
| Confirm study drug use |  |  |  | Xh |  | Xh |  | Xh |  | Xh |  | Xh |  | Xh |  | Xh |  |
| Dispense study drug g |  |   | X |  | X |  | X |  | X |  | X |  | X |  |  |  |  |
| Collect unused study drug |  |  |  |  | X |  | X |  | X |  | X |  | X |  | X |  |  |

a. Metabolic panel: Serum concentrations of sodium, potassium, chloride, total bilirubin, alkaline phosphatase, alanine transaminase, aspartate transaminase, blood urea nitrogen, creatinine, uric acid, phosphorous, calcium, glucose, total protein, albumin, cholesterol.

b. Females of childbearing potential defined as anatomically and physiologically capable of becoming pregnant *and* will be, or could possibly be, engaging in sexual activity with males during the study period.

c. Vitals signs: blood pressure, respiratory rate, heart rate, and temperature. Weight will also be taken at all visits specified for vital signs.

d. Complete blood count and reticulocyte count: hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume (MCV), segmented neutrophils, juvenile neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, cell morphology.

e. Coagulation panel: aPTT, PT/INR

f. Urinalysis: specific gravity, pH, protein, glucose, blood, leukocyte esterase.

g. Following completion of screening and baseline procedures, the participant can be randomized to study drug assignment and receive a bottle of study drug (4-week supply) from the study site pharmacist. The first dose of study drug is to be *taken the following morning* (Day 1) by the participant upon awakening with at least 8 oz. of plain water and at least 30 min before taking the first food, drink, or other medicine of the day. Participants will also be instructed to not lie down for at least 30 minutes after taking study drug and not until after their first food of the day.

h. Confirm study drug use, adverse event, and concomitant medication information over the telephone.

**APPENDIX B:**

**ASSOCIATION OF RESEARCH CIRCULATION OSSEOUS (ARCO) STAGING SYSTEM, AVASCULAR NECROSIS**

(ARCO 1992)

| **Stage** | **Radiological findings** | **Subclassification** |
| --- | --- | --- |
| 0 | positive: histology negative/normal: Radiograph/CT/MRI/scintigraphy | – |
| I | positive: MRI and/or bone scintigraphy negative/normal: radiograph/ CT | +′ (a) |
| II | Radiograph: sclerotic, cystic, or osteoporotic changes of femoral head | +′ (a) |
| III | Radiograph: subchondral fracture (“crescent sign”) | +′ (a) |
| IV | Radiograph: flattening of femoral head | ++′ (b) |
| V | Radiograph: flattening of femoral head and osteoarthrotic changes: decreased joint space and acetabular changes | ++′ (b) |
| VI | Complete joint destruction | – |

(a) *Location of femoral head necrosis:* 1) medial third, 2) median third, 3) lateral third. *Size of femoral head necrosis:* A) <15%, B) 15–30%, C) >30%

(b) *Intrusion degree of femoral head contour:* A) <2 mm, B) 2–4 mm, C) >4 mm

**APPENDIX C:**

**CHILDREN'S HOSPITAL OAKLAND HIP EVALUATION SCALE (CHOHES)**

 (Aguilar et al., 2005)

|  |
| --- |
| **Pain** |
| Degree of hip pain |
|  ∘ Incapacitating (0) |
|  ∘ Severe (10) |
|  ∘ Moderate (20) |
|  ∘ Mild (30) |
|  ∘ None (40) |
| **Function** |
| Dressing: pain, discomfort, or difficulty with putting on or taking off socks or shoes |
|  ∘ Most of the time (0) |
|  ∘ Occasionally (2) |
|  ∘ Never (4) |
| Gait aid: used in past few weeks |
|  ∘ None (8) |
|  ∘ Cane, crutches, walker, wheelchair (0) |
| With gait aid: comfortable walking distance without stopping |
|  ∘ Unlimited (8) |
|  ∘ Long distances but limited (7) |
|  ∘ Short distances (5) |
|  ∘ Household only (3) |
|  ∘ Transfers only; requires wheelchair (0) |
| Without gait aid: comfortable walking distance without stopping |
|  ∘ Unlimited (11) |
|  ∘ Long distances but limited (7) |
|  ∘ Short distances (5) |
|  ∘ Household only (3) |
|  ∘ Transfers only; requires wheelchair (0) |
| Sitting: |
|  ∘ Can sit comfortably in ANY position (5) |
|  ∘ Can sit comfortably at a table or movies but can’t tolerate other sitting position (3) |
|  ∘ Unable to sit comfortably for more than a few minutes without changing positions (0) |
| Stair climbing: |
|  ∘ Foot over foot without a railing (4) |
|  ∘ Foot over foot with a railing (2) |
|  ∘ Foot to foot stair climbing with or without railing (1) |
|  ∘ Unable to climb stairs or only with great difficulty (0) |
| **Physical examination** |
| Passive range of motion: |
|  ∘ Hip internal rotation, sitting, knee 90° (<16°=0, 16°–29°=1, 30°–39°=2, >39°=3) |
|  ∘ Hip external rotation, sitting, knee 90° (<16°=0, 16°–29°=1, 30°–39°=2, >39°=3) |
|  ∘ Hip flexion, supine (<90°=0, 90°–100°=1, 101°–114° =2, >114°=3) |
|  ∘ Hip abduction, supine (<20°=0, 20°–29°=1, 30°–39°=2, >39°=3) |
| Thomas test: |
|  ∘ Hip flexion contracture present (0) |
|  ∘ Hip flexion contracture not present (1) |
| Manual muscle testing: (Score each as follows: trace, no movement, or less than anti-gravity resistance=0, anti-gravity=1, anti-gravity with resistance=2, tolerates normal resistance=2) |
|  ∘ Hip flexion ( ) |
|  ∘ Hip extension ( ) |
|  ∘ Hip abduction ( ) |
|  ∘ Hip adduction ( ) |
| Best step height performance: |
|  ∘ Unable (0) |
|  ∘ 15–20 cm (2) |
|  ∘ >50 cm/transportation (6) |
| Limp: |
|  ∘ No limp; no gait aid (1) |
|  ∘ No limp; with gait aid (0) |
|  ∘ Limp; no gait aid (0) |
|  ∘ Limp; with gait aid (0) |
| Total score for each hip: ( ) |

**APPENDIX D**

**PROTOCOL SIGNATURE PAGE**

By signing this protocol, the investigator agrees to conduct the study in accordance with the protocol, generally accepted standards of good clinical practice, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study. In addition, the investigator agrees to provide the sponsor-investigator with accurate financial information to allow the sponsor-investigator to submit complete and accurate certification and disclosure statements as required by FDA regulations.

By signing this protocol, the sponsor-investigator agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written procedures to ensure that the trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of good clinical practice, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the study.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
| Investigator’s Signature |  | Print Name |  | Date |
| Investigator’s Signature |  | Print Name |  | Date |
|  |  |  |  |  |
| Site Address and Telephone |  |  |  |  |
|  |  |  |  |  |
| Sponsor-Investigator’s Signature |  |  |  | Date |