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COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (AA4500) PROTOCOL AUX-CC-871

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF AA4500 FOR THE TREATMENT OF ADHESIVE CAPSULITIS OF THE SHOULDER

Date: 20 September 2013

Sponsor:

Auxilium Pharmaceuticals, Inc.
640 Lee Road
Chesterbrook, PA 19087
USA

1. STUDY SYNOPSIS

Name of Sponsor/Company: Auxilium Pharmaceuticals, Inc.	
Name of Finished Product: XIAFLEX **Study Drug:** AA4500	
Name of Active Ingredient: collagenase clostridium histolyticum	**Study Number:** AUX-CC-871
Title of Study: A randomized, double-blind, placebo-controlled study of the safety and efficacy of AA4500 for the treatment of adhesive capsulitis of the shoulder	
Study Centers: Approximately 35 investigative sites in the United States and Australia	
Subject Study Period: 12 weeks	**Phase of Development:** Phase 2b
Objectives: The objectives of this study are to assess the safety, efficacy, and immunogenicity of AA4500 in the treatment of adhesive capsulitis.	
Methodology/Study Design: This study is a Phase 2b, double-blind, placebo-controlled study of the safety and efficacy of AA4500 for the treatment of adhesive capsulitis of the shoulder. To be eligible for treatment, a subject must have unilateral idiopathic adhesive capsulitis of the shoulder with restricted range of motion in the affected shoulder for at least 3 months but not more than 12 months. Subjects will be screened for study eligibility within 28 days before injection of study drug. Approximately 300 adult women and men are to be enrolled in this study. Following screening and determination of study eligibility, subjects will be randomized 3:1 to receive AA4500 or placebo. Subjects will receive up to 3 injections of study drug. Each injection will be separated by a minimum of 21 days. Subjects will also be instructed in home shoulder exercises after the first injection.	
Number of Subjects Planned: 300 subjects	

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Inclusion Criteria

No subject should be assigned to treatment until all eligibility criteria have been satisfied. To qualify for the study a subject must:

1. Be a male or female and be ≥ 18 years of age
2. If a female of childbearing potential, have a negative urine pregnancy test and be using an effective contraception method (ie, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or barrier control) for at least one menstrual cycle prior to study enrollment and for one menstrual cycle following end of study, or be surgically sterile
3. Have symptoms of unilateral idiopathic adhesive capsulitis for at least 3 months but not more than 12 months before the screening visit and be in Stage 2 (frozen or adhesive stage), as determined by the investigator
4. Have normal range of motion in the contralateral shoulder, as determined by the investigator
5. Have restricted active range of motion (AROM) in the affected shoulder defined as: a deficit of at least 60° in total AROM in the affected shoulder as compared with the total AROM in the contralateral shoulder and a deficit of at least 30° in AROM in at least one of the following planes as compared with the contralateral shoulder:
   - Forward flexion
   - Abduction
   - External rotation
   - Internal rotation
6. Voluntarily sign and date an informed consent agreement approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC). The subject must also sign an authorization form to allow disclosure of his protected health information (PHI). The PHI authorization form and informed consent form may be an integrated form or may be separate forms depending on the institution.

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Exclusion criteria: A subject will be excluded from study participation if he/she:

1. Is a pregnant female or female intending to become pregnant during the study or a female breastfeeding a child
2. Has received treatment for adhesive capsulitis or is planning to receive treatment for adhesive capsulitis at any time during the study including but not limited to:
   - physical therapy or acupuncture within 2 weeks before the first injection of study drug
   - intra-articular or intrabursal injection(s) of lidocaine; suprascapular nerve blocks; corticosteroids, electroanalgesic and/or thermoanalgesic modalities within 1 month before the screening visit
   - intra-articular or intrabursal injection(s) of sodium hyaluronate and/or glenohumeral distension arthrography within 3 months before the screening visit
   - surgical intervention (including shoulder manipulation under anesthesia) at any time
3. Has any of the following conditions, as determined by the investigator to be potentially confounding to the evaluation of safety and efficacy:
   - Adhesive capsulitis as a result of traumatic injury (ie, direct injury to the shoulder such as fracture of the humerus or clavicle immediately preceding the onset of this episode of adhesive capsulitis). Traumatic events in the past that are not temporally related to the onset of this episode of adhesive capsulitis would not necessarily exclude a subject from participating in the study.
   - Active subacromial impingement in the affected shoulder
   - Calcified tendonitis in the affected shoulder
   - Glenohumeral joint arthritis in the affected shoulder
   - Arthrosis of the affected shoulder
   - Chondrolysis of the affected shoulder
   - Subscapularis tendon rupture of the affected shoulder
   - Other rotator cuff injuries of the affected shoulder
   - Uncontrolled hypertension
   - Uncontrolled diabetes
   - Uncontrolled thyroid disease
   - History of thrombosis or post-thrombosis syndrome
   - Physical impairment that would preclude performing the protocol defined exercises
   - Active infection in area to be treated

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- Clinically significant neurological disease
- Bleeding disorder
- Chronic use of anticoagulation medications and the subject cannot be cleared medically to stop taking medication for 7 days prior to each injection. Less than or equal to 150 mg aspirin is allowed during the study.
- Known active hepatitis A, B, or C
- Other significant medical condition (eg, morbid obesity, cervical disc disease), which in the investigator's opinion would make the subject unsuitable for enrollment in the study

4. Is unwilling or unable to cooperate with the requirements of the study including completion of all scheduled study visits.
5. Has received oral or intravenous steroids for any reason within 3 weeks before the screening visit
6. Has received an investigational drug or treatment within 30 days before the first dose of study drug.
7. Has a known allergy to collagenase or any other excipient of AA4500 or any other procedural medication.
8. Has, at any time, received collagenase for the treatment of adhesive capsulitis.
9. Is unable to undergo an x-ray or MRI (contraindication) evaluation of the affected shoulder.
10. Is planning to be treated with commercial XIAFLEX at any time during the study.

Test Product, Dose and Mode of Administration: AA4500: The components of AA4500 are 0.9 mg of collagenase clostridium histolyticum and 0.5 mg of hydrochloric acid, 18.5 mg of sucrose, and 1.1 mg of tromethamine in a lyophilized cake.

Sterile diluent: The components of the sterile diluent are: 0.03% calcium chloride in 0.9% sodium chloride.

AA4500 0.58 mg (volume of 1 mL) will be injected extra-articularly between the bicipital groove and the coracoid process using a Sprotte® 22 gauge 120 mm needle using ultrasound guidance according to the specific dosing instructions outlined in the protocol.

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Reference Therapy, Dose and Mode of Administration: Placebo: The components of placebo for AA4500 are 0.5 mg of hydrochloric acid, 18.5 mg of sucrose, and 1.1 mg of tromethamine in a lyophilized cake.

The components of the sterile diluent are: 0.03% calcium chloride in 0.9% sodium chloride.

1 mL of placebo will be injected extra-articularly between the bicipital groove and the coracoid process using a Sprotte® 22 gauge 120 mm needle using ultrasound guidance according to the specific dosing instructions outlined in the protocol

Dosing: The subject will be supine on the examination table and the affected arm should be passively externally rotated to the subject's level of pain tolerance with the elbow at the side (against the body) and flexed to 90°. **If the affected arm cannot be passively externally rotated to at least the neutral position, the injection cannot be administered**. Pendulous breasts may be retracted.

The bicipital groove and the tip of the coracoid process will serve as the injection site landmarks. These landmarks will be identified by inspection and palpation. Each landmark will be marked with a surgical marker. After the injection site is identified, the area will be prepped with antiseptic antimicrobial skin prep such as ChloraPrep® (chlorhexidine) or Betadine®. Using the 20-gauge, 1 ½ inch needle and 10 cc control syringe, up to 10 ccs of local anesthetic will be administered at the previously marked injection site. The injection of local anesthetic will create the skin puncture site and path for the 22 gauge Sprotte® spinal needle to follow. Study drug will be injected extra-articularly through the local anesthesia needle track using a Sprotte® 22 gauge 120 mm needle under ultrasound guidance to ensure appropriate placement of study drug.

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Statistical Methods

Analyses Population: The intent-to-treat and safety population is defined as all subjects who receive study drug.

Efficacy: The primary endpoint is the change (degrees) from baseline to the Day 95 follow-up in active forward flexion in the affected shoulder.

Secondary endpoints are:

- Change from baseline to Day 95 in ASES function sub-scale
- Change (degrees) from baseline to the Day 95 follow-up in abduction
- Change from baseline to the Day 95 follow-up in pain with movement using a 11-point Visual Analogue Scale (VAS)
- Change (degrees) from baseline to the Day 95 follow-up in internal rotation
- Change from baseline to the Day 95 follow-up in external rotation
- Change from baseline to the Day 95 follow-up in ASES pain sub-scale
- Investigator satisfaction with treatment at the Day 95 follow-up
- Subject satisfaction with treatment at the Day 95 follow-up

Safety: The following variables are safety endpoints:

- Adverse events: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Change in vital signs
- Change in laboratory tests

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Immunogenicity: Immunogenicity variables include anti-AUX-I/anti-AUX-II antibody levels and neutralizing antibodies to AUX-I and AUX-II.

Statistical Analyses
Efficacy: Simultaneous hypothesis tests for all primary and secondary efficacy endpoints will be accomplished with a family-wise 5% significance level by applying a closed hierarchical testing procedure. Under this approach, the first test in the hierarchy that fails to reject its individual hypothesis at the 5% level requires that all hypotheses following the first non-significant hypothesis cannot be tested.

1. For the investigator assessment of improvement with treatment and subject satisfaction with treatment, a Wilcoxon rank sum non-parametric test will be performed to compare active to placebo.
2. Mixed-model analysis of variance (ANOVA) with factors for treatment group and visit will be performed to compare active to placebo for forward flexion, abduction, internal rotation and external rotation, ASES function subscale, and pain with movement.

Safety: Adverse events will be summarized for the active and placebo groups with the proportion of subjects reporting each event.

Actual values and change from baseline in vital signs and laboratory test parameters will be summarized for the active and placebo groups with descriptive statistics at each visit obtained.

Immunogenicity: Anti-AUX-I and anti-AUX-II antibodies levels and neutralizing antibodies to AUX-I and AUX-II will be summarized using descriptive statistics.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or specialist term	Description
AC	Adhesive capsulitis
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AROM	Active range of motion
ASES	American Shoulder and Elbow Surgeons
AST	Aspartate aminotransferase
CRF	Case report form
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
mL	Milliliter
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
IWRS	Interactive Web Response System
kDa	Kilodalton
kg	Kilogram
MedDRA	Medication Dictionary for Regulatory Activities
mg	Milligram
MRI	Magnetic resonance imaging
ng	Nanogram
PHI	Protected Health Information

Abbreviation or specialist term	Description
PROM	Passive range of motion
Qualified designee	Qualified by license, education, and training to perform the study procedure according to local, state, and country requirements.
ROM	Range of motion
SAE	Serious adverse event
SUSARs	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
U	Unit
US	United States
VAS	Visual Analogue Scale

3. INTRODUCTION

3.1. Adhesive Capsulitis

Adhesive capsulitis (AC) is a common, prolonged, painful condition of the shoulder that is associated with loss of range of motion in the glenohumeral joint. AC has been described as a condition of "unknown etiology characterized by gradually progressive, painful restriction of all joint motion with spontaneous restoration of partial or complete motion over months to years"(Grey, 1978).

Primary idiopathic AC is difficult to define, diagnose, and manage. AC affects 2% to 5% of the general population (Grubbs, 1993) and has an incidence of 10% to 20% among patients with diabetes (Pal et al., 1986). AC tends to occur in patients in the sixth decade of life, and onset before the age of 40 is uncommon. AC occurs slightly more often in women than in men (Rizk and Pinals, 1982), and the non-dominant arm is more likely to be involved (Fareed, 1989). Fifteen percent of patients will develop bilateral disease.

The natural history of adhesive capsulitis usually progresses through three overlapping clinical phases (Reeves, 1975): the painful freezing stage; the adhesive or frozen stage; and the resolution or thawing stage.

The painful or freezing stage involves a gradual increase in pain and stiffness around the shoulder that occurs commonly with no history of injury. The painful freezing stage lasts between 3 and 8 months. Commonly, patients notice a decreased ability to reach behind the back when fastening a garment or removing a wallet from a back trouser pocket. The initial discomfort is described by many patients as a generalized shoulder ache. The pain may radiate both proximally and distally and is aggravated by movement and alleviated with rest. The pain is worse at night and sleep may be interrupted if the patient rolls on the affected shoulder.

As the condition progresses, pain becomes more severe and is accompanied by stiffness and decreased range of motion. The stiffening increases to the point where the natural arm swing that accompanies normal gait is lost (Rizk and Pinals, 1982). As the patient tries to compensate for this loss by using other muscle groups and increasing scapular rotation to accomplish various activities, additional strain is placed on these muscle groups and they are left overworked and tender.

Physical examination findings during the painful freezing stage of AC often show muscle spasm and diffuse tenderness around the glenohumeral joint and the deltoid muscle. However, an area of pinpoint tenderness can seldom be found. With disease progression and in patients with long-standing AC, disuse atrophy of the shoulder girdle may occur. Passive and active range of motion in all planes of shoulder movement is lost.

The second stage, the adhesive or frozen stage, involves increasing stiffness with diminution of pain. Pain decreases at night, and discomfort occurs only at the extremes of motion. There is gross reduction of glenohumeral movements with near total obliteration of external rotation. This stage usually lasts 3 to 9 months.

The final stage, called the resolution or thawing stage, takes 12-42 months. This last stage is self-limiting, with a gradual and spontaneous increase in range of motion. Complete recovery, however, is infrequent. The external rotation range of motion improves first, followed by abduction and internal rotation. Short recovery periods may have associated bouts of pain before each phase of improvement. Approximately 7% to 15% of patients permanently lose their full range of motion (Reeves, 1975).

3.2. Pathophysiology

The pathophysiology of AC is not well understood. Neviaser and Neviaser described the histologic findings of perivascular infiltration, capsular fibrosis, and capsular collagen thickening associated with the clinical development of AC (Neviaser and Neviaser, 1987). These findings were previously confirmed by Lundberg, who noted capsular changes including an increase in the density of collagen and a glycosaminoglycan pattern similar to that found in tissue repair (Lundberg, 1969).

AC is thought to be a chronic fibrosing condition of the shoulder joint capsule (DePalma, 1952; Simonds, 1949). Bunker studied biopsies of rotator interval tissue in patients with AC and described a dense matrix of Type III collagen populated predominantly with fibroblasts and myoblasts (Bunker and Anthony, 1995; Hannafin, 1993). The dense Type III collagen matrix within the shoulder joint capsule subsequently contracts and leads to the typical clinical features of pain and stiffness associated with AC. The histology of AC is thought to be very similar to that of Dupuytren's disease and it has been suggested that these two conditions may share a common biochemical pathway that leads to contracture.

3.3. Current Treatments

Methods of treatment of AC are directed at relief of pain and the restoration of motion and function. Non-operative measures encompass pharmacological treatment of the synovitis and inflammatory mediators and other physical modalities to prevent or modify capsular contracture. Oral and intra-articular steroids provide early pain relief but benefit cannot be shown beyond several weeks http://ajs.sagepub.com/. In a study by Dahan et al., there was a 62% improvement in pain in patients who received suprascapular nerve blocks compared with 13% in the control group. However, there was no difference in shoulder function between the groups.

Physical therapy is the most consistently prescribed treatment to prevent capsular contracture and to improve range of motion. Despite its common use, supporting evidence has shown its benefit to be very limited with studies reporting varied patient responses (Harryman et al., 1998). O'Kane et al., (1999) reported that patients treated with home exercise alone improved in a self-assessed shoulder rating system, physical function, and pain after an average of 25 months of follow-up; however 30% to 40% of these patients could not place an 8-pound object on a shelf or carry a 20-pound object at their side.

Surgery can address both the inflammatory component of AC with synovectomy and the capsular contracture through capsular release and/or manipulation under anesthesia. Manipulation under general anesthesia has been used with satisfactory results in both short- and long-term follow-up. However, according to several authors (Hazelman, 1972; Binder et al.,

1984; and Jacobs, 2009), manipulation under anesthesia may provide no additional benefit as compared with steroid injections plus physical therapy or no treatment at all. Additionally, complications from manipulation under anesthesia include humeral fracture, subscapularis rupture, labral tears, and injury to the biceps tendon.

In some patients loss of motion may be refractory to any of these treatments and an operative release may be indicated. Arthroscopic capsulorrhaphy can provide benefit to patients with refractory disease.

3.4. AA4500 (Collagenase Clostridium Histolyticum)

AA4500 is a parenteral lyophilized product comprised of two collagenases in an approximate 1:1 mass ratio, Collagenase I (AUX-I, Clostridial type I collagenase) and Collagenase II (AUX-II; Clostridial type II collagenase). These collagenases are isolated and purified from the fermentation of *Clostridium histolyticum*.

Collagenase AUX-I is a single polypeptide chain containing approximately 1,000 amino acids of known sequence and with a molecular weight of 114 kiloDaltons (kDa). Collagenase AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa. These two collagenases are not immunologically cross-reactive and have different specificities, such that together they become synergistic, providing a very broad hydrolyzing reactivity toward collagen. Clostridial collagenases are proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions.

AA4500 contains purified collagenase clostridium histolyticum, consisting of two microbial collagenases in a defined mass ratio, Collagenase AUX-I and Collagenase AUX-II, which are isolated and purified from the fermentation of *Clostridium histolyticum* bacteria.

Collagenase AUX-I is a single polypeptide chain consisting of approximately 1000 amino acids of known sequence. It has an observed molecular weight of 114 kiloDaltons (kDa). It belongs to the class I *Clostridium histolyticum* collagenases.

Collagenase AUX-II is a single polypeptide chain consisting of approximately 1000 amino acids of deduced sequence. It has an observed molecular weight of 113 kDa. It belongs to the class II *Clostridium histolyticum* collagenases.

AA4500 has been approved as a novel, first-in-class biologic for the treatment of adults with Dupuytren's contracture with a palpable cord in the following geographical regions:

1. 02 February 2010, AA4500 was approved in the United States and is known commercially as XIAFLEX®
2. 28 February 2011, AA4500 was granted marketing authorization by the European Commission and is known commercially as XIAPEX®
3. In July 2011, XIAPEX was approved in Switzerland by Swiss Medic for use in adult patients for the treatment of Dupuytren's contracture with a palpable cord.
4. In July 2012, XIAFLEX was approved by Health Canada for the treatment of adult patients with Dupuytren's contracture with a palpable cord.

5. In 30 July 2013, AA4500 was approved in Australia for the treatment of adult patients with Dupuytren's contracture with a palpable cord.

3.4.1. Findings From the Dupuytren's Contracture Clinical Program and Post-Marketing Use

AA4500 is an acute, intermittent non-systemic treatment that is administered by a qualified healthcare provider in an office setting. In adult subjects with Dupuytren's contracture with a palpable cord, the injection of the AA4500 into the pathologic cord, which is composed predominantly of collagen, followed by a finger extension procedure approximately 24 hours after injection, allows for the local disruption of the cord affecting a metacarpophalangeal (MP) or proximal interphalangeal (PIP) joint. Cord disruption allows correction of the offending contracture and may preclude the resultant morbidity and extensive recovery time and rehabilitation associated with invasive surgical procedures. After successful treatment with AA4500, most subjects should be able to return to most activities of daily living almost immediately, and without the requirement for adjunctive therapy, such as physical therapy of the hand.

Data from two adequate and well-controlled studies independently demonstrate that AA4500 significantly reduces contracture caused by Dupuytren's disease, which may have otherwise required surgical intervention.

AA4500 has a consistent safety profile that has been demonstrated among 1082 Dupuytren's subjects in clinical studies worldwide. Most adverse events following AA4500 injection are local, mild or moderate in severity, confined to the treated extremity, and generally resolve prior to the next injection.

The majority of treatment-related SAEs in the Dupuytren's clinical program were related to events of the hand. Four of these were related to effect of AA4500 on collagen (three tendon ruptures and one ligament injury [pulley injury]).

Data from a definitive Phase 1 single-dose pharmacokinetic study (AUX-CC-855) and from a Phase 3b multidose pharmacokinetic study (AUX-CC-861) confirmed that there is no detectable systemic exposure following a single or two concurrent injection(s) of AA4500 0.58 mg into the cord(s) of the affected finger(s) in subjects with Dupuytren's contracture or following the subsequent procedure to disrupt the cord. These findings are further supported by the results from an earlier single-dose pharmacokinetic study (DUPY-202).

Since the time of product launch February (2010), approximately 54,070 total vials of XIAFLEX were distributed up through 31March 2013. A review of the reports received up through this period reveals that the body systems affected, frequency, and clinical significance of the adverse events reported are consistent with reports received in previous periods, and no new safety concerns were identified. The overall benefit-risk assessment of collagenase clostridium histolyticum remains positive and unchanged.

Because AA4500 is a foreign protein, an antibody response is expected in all subjects following treatment. Serious allergic reaction - possible anaphylaxis has been reported following administration of XIAFLEX for the treatment of Dupuytren's contracture.

3.4.2. Peyronie's Disease

In the clinical studies in subjects with Peyronie's disease, AA4500 was intended to decrease curvature deformity through the injection of collagenase clostridium histolyticum into the pathologic penile plaque, which is composed predominantly of collagen, by disruption of the collagen-rich plaque that causes the curvature deformity.

AA4500 has a consistent safety profile that has been demonstrated among 1044 subjects with Peyronie's disease worldwide. Most adverse events following AA4500 injection were confined locally to the penis or groin and most commonly include penile ecchymosis, penile swelling, and penile pain. Most adverse events following AA4500 injection are mild or moderate in severity and generally resolve prior to the next injection cycle.

In the Peyronie's clinical program, treatment-related SAEs were related to the penis and included corporal rupture (fracture of penis) and penile hematoma.

Data from PK study AUX-CC-805 showed that among evaluable subjects, plasma concentrations for AUX-I and AUX-II were low (ie, maximal concentrations in these subjects: 28.2 ng/mL for AUX-I; 70.8 ng/mL for AUX-II) and transient (ie, detected only through the 0.5 hour post-injection time point) following each injection. No subject had quantifiable plasma levels 15 minutes after modeling of the plaque on Day 3, which suggests that manual modeling of the penis performed 24 hours after the second (Day 2) injection does not result in release of AA4500.

3.5. Adhesive Capsulitis

3.5.1. Proof-of-Concept Study

A previous investigator-initiated, Phase 2 randomized, double-blind, placebo-controlled proof-of-concept study evaluated a single injection of AA4500 0.145 mg (2,500 U; N=16), 0.29 mg (5,000 U; N=15), 0.58 mg (0.58 mg (10,000 U); N=14) each in a volume of 0.5 mL, and placebo (N=15) in a total of 60 subjects with AC. Approximately 30 days after receiving one injection of AA4500, 9 subjects (0.58 mg, 3 subjects; 0.29 mg, 4 subjects; and 0.145 mg, 2 subjects) reached the criteria for successful treatment (ie, active and passive forward flexion 160°; active and passive external rotation 45°; passive internal rotation T10).

Following the double-blind phase, subjects who did not meet the criteria for successful treatment were permitted to receive up to 4 additional injections of AA4500 0.58 mg (10,000 U) in 0.5 mL in the open-label phase of the study (one patient with bilateral disease had one shoulder treated in double-blind phase and the contralateral shoulder treated in the open-label phase). Each injection was to be separated by 30 days.

Of the 46 subjects treated in the open-label phase, 24 were successful after one additional injection of AA4500 0.58 mg, and 20 were successful after two injections. The remaining three subjects received a total of three or four injections and showed some improvement in their condition at the Day 30 evaluation after the last injection.

All 45 subjects who received AA4500 during the double-blind phase reported injection site tenderness and/or bicep ecchymosis, which resolved on average 5.2 and 9.5 days after injection.

Six subjects who received AA4500 had mild injection site edema, which resolved on average 1.4 days after injection. Three serious adverse events were reported. One subject who received a single injection of AA4500 2500 U died 4 months after injection from previously unrecognized cardiac disease. Two subjects who received AA4500 10,000 sustained partial rotator cuff tears as follows: one subject after lifting heavy furniture and a television three weeks after receiving a single injection of AA4500 10,000 U; and one subject sustained a work-related injury to her treated shoulder approximately 5 months after her second injection of AA4500 10,000 U. All three of these SAEs were considered unrelated to study drug by the investigator.

3.5.2. Study AUX-CC-870

Study AUX-CC-870 was a Phase 2a open-label dose ranging study. The objectives of this study were to assess the safety, effectiveness, and immunogenicity of AA4500 in the treatment of AC. To be eligible for treatment, a subject must have had unilateral idiopathic AC of the shoulder with restricted ROM in the affected shoulder for at least 3 months but not more than 12 months. Dosing began with Cohort 1 (0.29 mg/1 mL). Dosing for Cohort 2 (0.58 mg/2 mL), Cohort 3 (0.58 mg/1 mL), and Cohort 4 (0.58 mg/0.5 mL) did not begin until the safety of all subjects in Cohort 1 was evaluated. Subjects assigned to Cohorts 1 through 4 could have received up to three injections of AA4500 separated by a minimum of 21 days. Subjects assigned to Cohort 5 received home shoulder exercises only. A total of 50 adult women and men enrolled in this study.

The primary endpoint was the change from baseline to the Day 92 visit in AROM forward flexion of the affected shoulder. Cohorts 2 and 3 had statistically significant mean increases (37.5° and 42.9°, respectively) in AROM forward flexion from baseline to Day 92 compared to Cohort 5 (12.0°).

For the secondary endpoints, Cohort 3 had statistically significant greater mean increases in AROM abduction, PROM forward flexion, PROM abduction, and PROM external rotation compared to Cohort 5. Cohorts 2 and 3 had statistically significant mean increases (41.6 and 35.9, respectively) in ASES composite score from baseline to Day 92 compared to Cohort 5 (9.9). In addition, Cohorts 2 and 3 had statistically significant mean increases in ASES pain (15.5 for each) and function (26.0 and 19.2, respectively) subscale scores from baseline to Day 92 compared to Cohort 5 (1.5 and 8.4, respectively). Cohorts 2 and 3 had the highest satisfaction rates, with 60.0% and 80.0% of subjects, respectively, very satisfied with treatment at Day 92, compared with 50.0% for Cohort 5. Cohorts 2 and 3 had the highest investigator global assessment of improvement, with 50.0% and 70.0%, respectively, very much improved at Day 92, compared with 20.0% for Cohort 5.

AA4500 was well tolerated in all cohorts. Most subjects in cohorts that received AA4500 had TEAEs that were related to study drug. Common (≥2 subjects in any cohort) treatment-related TEAEs were injection site hematoma (all had the verbatim term of bruising), injection site hemorrhage (all had the verbatim term of ecchymosis), injection site pain, injection site swelling, contusion (all had the verbatim term of bruising), musculoskeletal pain, pain in extremity, and ecchymosis. These AEs are expected and consistent with the previous safety profile of AA4500, in which the effects of AA4500 remained localized to the site of injection. No subject died, experienced an SAE, or prematurely discontinued the study or study drug due to AEs. No

clinically meaningful or concerning trends were observed with regard to hematology and chemistry laboratory parameter results, vital sign results, or immunogenicity results.

No clinically significant changes in MRI results from baseline to Day 92 were observed in any cohort. There was no finding suggestive of rotator cuff injury after treatment with AA4500

The efficacy results suggest the clinical effectiveness of AA4500 treatment in Cohort 3 (0.58 mg/1 mL) and Cohort 2 (0.58 mg/2 mL) for the treatment of AC, as shown by statistically significant improvement from baseline to Day 92 in AROM forward flexion compared to Cohort 5 (exercise only). Additionally, subjects in Cohort 3 (0.58 mg/1 mL) had statistically significant improvement from baseline to Day 92 in abduction, external rotation, the ASES pain subscale, the ASES function subscale, and the investigator global assessment of improvement compared with Cohort 5 (exercise only).

Furthermore, the safety results indicate that AA4500 is generally safe and well tolerated, with TEAEs primarily occurring at the site of injection and with a profile consistent with that observed in previous clinical studies with XIAFLEX® in the treatment of Dupuytren's contracture with a palpable cord and Peyronie's disease.

Based on these results, the AA4500 0.58 mg/1 mL dose was selected for further development in the adhesive capsulitis clinical program.

4. STUDY OBJECTIVES

The objectives of this study are to assess the safety, effectiveness, and immunogenicity of AA4500 in the treatment of adhesive capsulitis.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design and Plan: Description

This study is a Phase 2b, double-blind, placebo-controlled study of the safety and efficacy of AA4500 for the treatment of adhesive capsulitis of the shoulder. To be eligible for treatment, a subject must have unilateral idiopathic adhesive capsulitis of the shoulder with restricted range of motion in the affected shoulder for at least 3 months but not more than 12 months. Subjects will be screened for study eligibility within 28 days before injection of study drug.

Approximately 300 adult women and men are to be enrolled in this study. Following screening and determination of study eligibility, eligible subjects will be randomized 3:1 to receive AA4500 0.58 mg/1 mL or placebo. Subjects will receive up to 3 injections of study drug. Each injection will be separated by a minimum of 21 days. Subjects will also be instructed in home shoulder exercises after the first injection.

Table 1: Study AUX-CC-871 Assessments

Procedures	Screening Day -28 to -1	Injection 1 (Day 1)		Day 8 (± 2 days)	Injection 2 (Day 22) and Injection 3 (Day 43) (+7 days)		Day 29 and Day 50 (±2 days)	Follow-up Day 64 (+7 days)	EOS: Day 95 (± 7 days)/ Early Withdrawal
		Pre-injection	Post-Injection		Pre-injection	Post-Injection			
Obtain informed consent	X								
Medical history/AC history	X								
Prior/concomitant medications/procedures	X	X	X	X	X	X	X	X	X
PE with body weight, height, hand dominance	X								
Vital signs	X	X[a]	X[a]	X	X[a]	X[a]	X	X	X
Targeted examination of the affected shoulder:									
•Inspection, signs of instability and impingement	X[b]								
•AROM and PROM	X[b]	X		X	X		X	X	X
•ASES Pain sub-scale	X				X			X	X
•ASES Function sub-scale	X				X			X	X
•Pain with movement	X				X			X	X
12-lead ECG	X								
X-ray of the affected shoulder	X								
MRI of affected shoulder	X								
Clinical laboratories	X								X
Urine pregnancy testing (dipstick)	X	X			X				
Anti-AUX-I/anti-AUX-II antibodies and Nabs	X								X
Randomization		X							
Compliance with home shoulder exercises				X	X		X	X	
Investigator assessment of improvement with treatment									X
Subject satisfaction with treatment									X
Injection site reactions/local tolerability			X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Instructions for home shoulder exercises			X						
Eligible for retreatment (yes/no)					X[c]				

AROM=active range of motion; PROM=passive range of motion; VAS=visual analogue scale

[a] 4 hours before injection and approximately 15, 30 and 45 minutes after injection, and before discharge.

[b] The unaffected shoulder will also be examined at screening.

[c] Subjects may receive up to a total of three injections; each injection separated by a minimum of 21 days.

NOTE: Subjects who are not eligible for Injection 2 and/or Injection 3 (eg, successfully treated or safety concern) will have follow-up visits on Day 43 and Day 64. Subjects who are not eligible for Injection 2 and/or Injection 3 will not be required to have a study visit on Day 29 and/or Day 50, respectively.

Subjects who are not eligible for Injection 2 because of a safety concern may receive Injection 3 at the discretion of the investigator.

All subjects will have a final follow-up visit on Day 95.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1. Subject Inclusion Criteria

No subject should be assigned to treatment until all eligibility criteria have been satisfied. To qualify for the study a subject must:

1. Be a male or female and be ≥ 18 years of age
2. If a female of childbearing potential, have a negative urine pregnancy test and be using an effective contraception method (ie, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or barrier control) for at least one menstrual cycle prior to study enrollment and for one menstrual cycle following end of study, or be surgically sterile
3. Have symptoms of unilateral idiopathic adhesive capsulitis for at least 3 months but not more than 12 months before the screening visit and be in Stage 2 (frozen or adhesive stage), as determined by the investigator
4. Have normal range of motion in the contralateral shoulder, as determined by the investigator
5. Have restricted active range of motion (AROM) in the affected shoulder defined as: a deficit of at least 60° in total AROM in the affected shoulder as compared with the total AROM in the contralateral shoulder and a deficit of at least 30° in AROM in at least one of the following planes as compared with the contralateral shoulder:
   - Forward flexion
   - Abduction
   - External rotation
   - Internal rotation
6. Voluntarily sign and date an informed consent agreement approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC). The subject must also sign an authorization form to allow disclosure of his protected health information (PHI). The PHI authorization form and informed consent form may be an integrated form or may be separate forms depending on the institution.

6.2. Subject Exclusion Criteria

A subject will be excluded from study participation if he/she:

1. Is a pregnant female or female intending to become pregnant during the study or a female breastfeeding a child
2. Has received treatment for adhesive capsulitis or is planning to receive treatment for adhesive capsulitis at any time during the study including but not limited to:
   - physical therapy or acupuncture within 2 weeks before the first injection of study drug
   - intra-articular or intrabursal injection(s) of lidocaine; suprascapular nerve blocks; corticosteroids, electroanalgesic and/or thermoanalgesic modalities within 1 month before the screening visit
   - intra-articular or intrabursal injection(s) of sodium hyaluronate and/or glenohumeral distension arthrography within 3 months before the screening visit
   - surgical intervention (including shoulder manipulation under anesthesia) at any time
3. Has any of the following conditions, as determined by the investigator to be potentially confounding to the evaluation of safety and efficacy:
   - Adhesive capsulitis as a result of traumatic injury (ie, direct injury to the shoulder such as fracture of the humerus or clavicle immediately preceding the onset of this episode of adhesive capsulitis). Traumatic events in the past that are not temporally related to the onset of this episode of adhesive capsulitis would not necessarily exclude a subject from participating in the study.
   - Active subacromial impingement in the affected shoulder
   - Calcified tendonitis in the affected shoulder
   - Glenohumeral joint arthritis in the affected shoulder
   - Arthrosis of the affected shoulder
   - Chondrolysis of the affected shoulder
   - Subscapularis tendon rupture of the affected shoulder
   - Other rotator cuff injuries of the affected shoulder
   - Uncontrolled hypertension
   - Uncontrolled diabetes
   - Uncontrolled thyroid disease
   - History of thrombosis or post-thrombosis syndrome
   - Physical impairment that would preclude performing the protocol defined exercises
   - Active infection in area to be treated
   - Clinically significant neurological disease
   - Bleeding disorder

- Chronic use of anticoagulation medications and the subject cannot be cleared medically to stop taking medication for 7 days prior to each injection. Less than or equal to 150 mg aspirin is allowed during the study.
- Known active hepatitis A, B, or C
- Other significant medical condition (eg, morbid obesity, cervical disc disease), which in the investigator's opinion would make the subject unsuitable for enrollment in the study

4. Is unwilling or unable to cooperate with the requirements of the study including completion of all scheduled study visits.
5. Has received oral or intravenous steroids for any reason within 3 weeks before the screening visit
6. Has received an investigational drug or treatment within 30 days before the first dose of study drug.
7. Has a known allergy to collagenase or any other excipient of AA4500 or any other procedural medication.
8. Has, at any time, received collagenase for the treatment of adhesive capsulitis.
9. Is unable to undergo an x-ray or MRI (contraindication) evaluation of the affected shoulder.
10. Is planning to be treated with commercial XIAFLEX at any time during the study

6.3. Subject Withdrawal Criteria

Each subject has the right to withdraw from the study at any time without prejudice. If a subject withdraws from the study, the reason(s) must be stated in the subject's medical record and recorded onto the case report form (CRF). A final evaluation of the subject should be performed before discharge.

The investigator may discontinue any subject's participation if he or she feels it is necessary for any reason, including any adverse event, clinically significant adverse change in any laboratory test, or failure to comply with the protocol including the use of anticoagulants or inability to comply with the visit schedule.

Subjects who withdraw from the study or who are discontinued for any reason should have a final evaluation performed either before withdrawal or as soon as possible after discontinuation. Please refer to Day 95/Early Withdrawal on Schedule of Assessments for details (Table 1).

Subjects who withdraw from the study will not be replaced unless it is mutually agreed upon in writing by the respective principal investigator and Auxilium Pharmaceuticals, Inc.'s medical monitor.

7. PROCEDURES AND TREATMENTS

7.1. Randomization

Following screening and determination of study eligibility, subjects will be randomized 3:1 to receive AA4500 0.58 mg or placebo. A central randomization scheme will be used with an interactive web response system (IWRS).

7.2. Blinding

This will be a double-blind study in which the investigator, study subject, and other study personnel involved in the evaluation of the subject efficacy or safety are blinded to study drug treatment. All precautions will be taken to ensure that the blinding of AA4500 and placebo is maintained throughout the study period. Unblinding will not be permitted by the study site unless it is deemed necessary for appropriate treatment of a medical emergency. The study site will have the ability to immediately determine treatment identification in the event of an emergency by swiping the label portion of the drug kit with an alcohol pad; however, the medical monitor at Auxilium must be notified immediately.

7.3. Reconstitution of Study Drug

Before reconstitution, designated study personnel will visually inspect the study drug vials to determine the integrity and acceptability of the lyophilized drug product and sterile diluent(s) for reconstitution. The vial containing lyophilized drug product is to be reconstituted with 1.55 mL sterile diluent. The written procedures for inspection of the study drug vials and reconstitution of study drug will be provided in the Pharmacy Manual.

Designated study personnel will maintain a record of the date and time of reconstitution and dispensation of the assigned treatment. The reconstituted A4500 solution can be kept at room temperature (20° to 25°C/68° to 77°F) for up to one hour or refrigerated at 2° to 8°C (36° to 46°F) for up to 4 hours prior to administration.

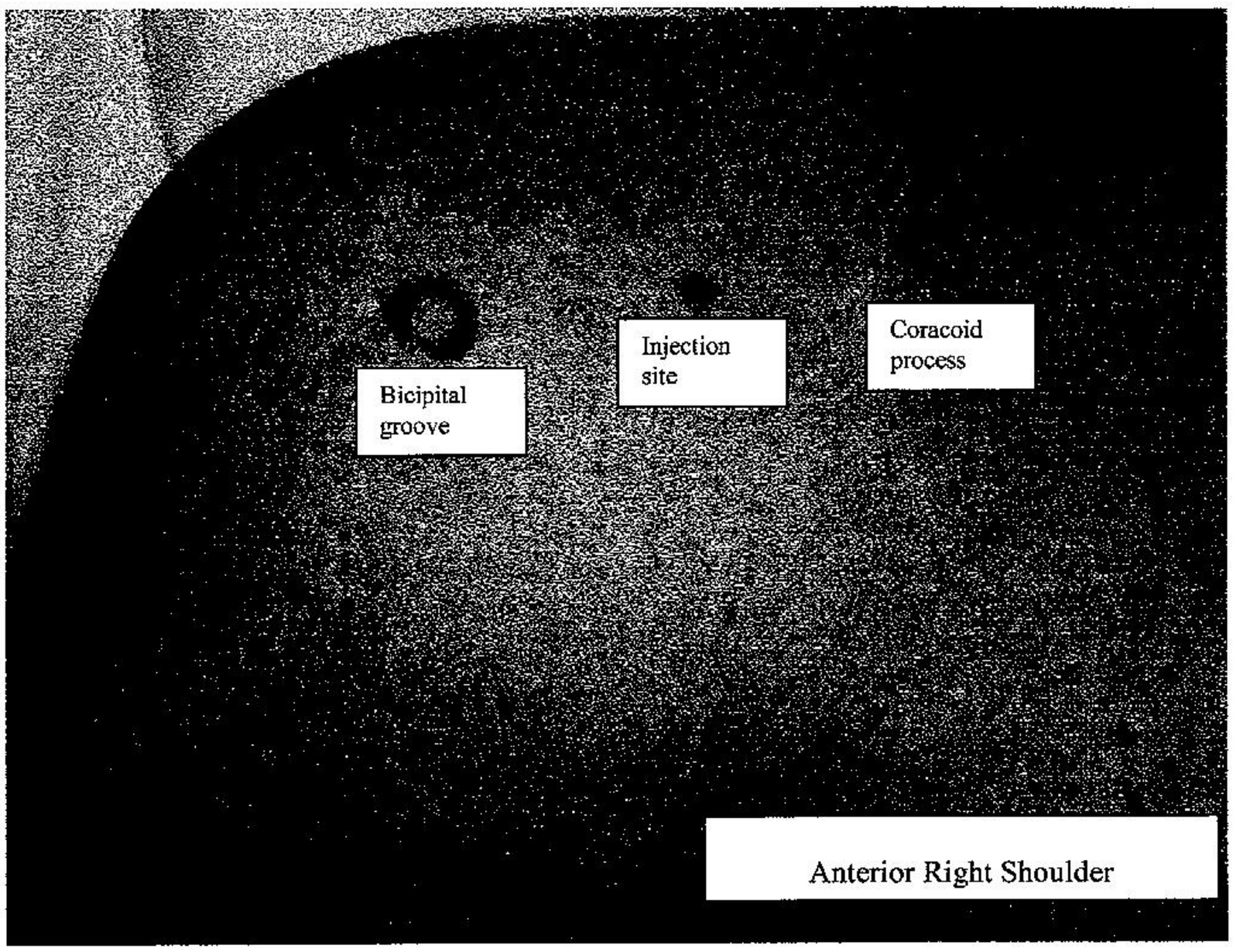
7.4. Location of Injection Site

The subject will be supine on the examination table and the affected arm should be passively externally rotated to the subject's level of pain tolerance with the elbow at the side (against the body) and flexed to 90°. **If the affected arm cannot be passively externally rotated to at least the neutral position, the injection cannot be administered.** Pendulous breasts may be retracted.

The bicipital groove and the tip of the coracoid process will serve as the injection site landmarks. These landmarks should be identified by inspection and palpation. Each landmark is marked with a surgical marker. Internal and external rotation of the shoulder can aid in identifying the approximate location of the bicipital groove. In subjects with pendulous breasts, the breasts may be retracted medially to aid in identifying the injection site.

The injection site, which is located in the coronal plane midway between the bicipital groove and the tip of the coracoid process, will be marked with a surgical marker as shown in Figure 1. The middle marking will serve as the location of the injection site.

Figure 1: Injection Site



Badalamente MA and Wang ED

7.5. Administration of Local Anesthesia

The affected arm should be passively externally rotated to the subject's level of pain tolerance with the elbow at the side (against the body) and flexed to 90°. **If the affected arm cannot be passively externally rotated to at least the neutral position, the injection cannot be administered**. Pendulous breasts may be retracted.

1. After the injection site is identified as described in Section 7.4, the area should be prepped with antiseptic antimicrobial skin prep such as ChloraPrep® (chlorhexidine) or Betadine®.
2. The local anesthetic should be administered at the previously marked injection site. Using the 20-gauge, 1 ½ inch needle and 10 cc control syringe, administer up to 10 ccs of local anesthetic. The injection of local anesthetic will create the skin puncture site and path for the 22-gauge Sprotte® spinal needle to follow. The Sprotte® spinal needle will be used to inject study drug.

The local anesthetic should be administered as follows:

3. First, numb the skin at the injection site by injecting approximately 1/3 of the local anesthetic. Then, inject the remaining local anesthetic, as necessary, along the needle path extending directly towards the anterior shoulder capsule. Be sure to withdraw on the plunger of the syringe prior to injection of the local anesthetic to ensure that you are not injecting intravascularly. This injection should be perpendicular to the subject's skin at the injection site. Do not penetrate the shoulder capsule with the needle.
4. Be sure to allow a minimum of 10 minutes to elapse between the injection of the local anesthetic and the administration of study drug. Do not allow more than 30 minutes to elapse, as the anesthetic effect may wane.

7.6. Ultrasound-Guided Injection of Study Drug

AA4500 0.58 mg and placebo will be administered in a volume of 1 mL after reconstitution with sterile diluent (0.9% sodium chloride containing 0.03% calcium chloride) according to the instructions in the Pharmacy Manual.

Prior to the injection procedure, the investigator, the assistant, ultrasound machine, and all necessary supplies should be prepared and in place. The subject should be in the supine position. The ultrasound machine should be placed at the head of the subject. The sterile ultrasound probe cover should be placed on the ultrasound probe. The sterile ultrasound transducer gel should be easily accessible.

- Once the anesthetic effect has been achieved, the injection site area should once more be prepped with an appropriate antiseptic such as ChloraPrep® (chlorhexidine) or Betadine®. The injection site of the local anesthetic should be visible.

- The affected arm should be passively externally rotated to the subject's level of pain tolerance with the elbow at the side (against the body) and flexed to 90°. **If the affected arm cannot be passively externally rotated to at least the neutral position, the injection cannot be administered.** Pendulous breasts may be retracted.

- The assistant should apply sterile ultrasound transducer gel and place the sterile ultrasound probe 2 cm to 5 cm cephalad to the previously marked injection site. The affected shoulder joint and anterior capsule should be visible on the ultrasound screen. These anatomic landmarks should be identified. The ultrasound image of the affected shoulder joint and the anterior capsule should be visible to the investigator throughout the entire injection procedure.

- The investigator will handle the metal shaft of the spinal needle with one hand ("needle" hand) and the syringe containing reconstituted study drug with the other hand ("syringe" hand). Sterile gloves will be needed to allow the "needle" hand to remain sterile throughout the injection procedure. The "needle" hand will be the hand guiding the needle tip into the same skin puncture hole previously made by the anesthetic needle.

- With his/her "syringe" hand, the investigator should pick up the previously prepared syringe of the reconstituted study drug with the attached 22-gauge spinal needle. The assistant should then carefully remove the protective plastic covering of the spinal needle.

- With his/her "needle" hand, the investigator should help guide the spinal needle as needed through the puncture site that was created by the 20-gauge local anesthetic needle. This step should be performed slowly and with care under ultrasound guidance.

- When the investigator feels the resistance of the pathologically thickened shoulder joint capsule, a bending or flexing of the spinal needle will usually be appreciated. He or she should stop further advancement of the needle. At this time, the location of the needle tip should be confirmed by ultrasound as being extra-articular. The tip of the spinal needle should stay outside of the anterior shoulder joint capsule. Do not allow the spinal needle to penetrate the anterior shoulder capsule or joint. If it is suspected that the spinal needle has penetrated the anterior shoulder joint capsule, do not inject study drug. Reposition the spinal needle tip.

- When the proper position of the spinal needle is confirmed, inject the entire dose of study drug. After study drug is injected, remove the spinal needle. Place an adhesive bandage on the injection site. All needles and sharps in this clinical trial should be handled using appropriate guidelines and in accordance with the investigator's institution.

- Following the injection of study drug, the subject should remain supine and be directly observed for 20 minutes. Thereafter the subject should be observed in accordance with the instructions as outlined in Section 7.14.7.

7.7. Care Procedures After Injection

To evaluate the subject for possible immediate immunological adverse events, the subject will remain in direct observation of medical personnel who are skilled in the management of acute allergic reactions for the first 20 minutes after receiving an injection of study drug (see Section 7.6). A subject may be discharged from the study unit after a 45-minute observation period provided:

- The subject exhibits no sign of an immunological or other clinically significant systemic or local adverse event

- The subject's vital signs have remained stable throughout the 45-minute observation period (see Section 7.14.7)

Before discharge, the subject will be instructed to limit movement of his/her treated shoulder for 10 to 12 hours after injection of study drug. The investigator or qualified designee will apply a sling to the treated shoulder within 4 hours after injection. The sling will serve as a reminder to the subject to limit movement of the treated shoulder. Subjects will be instructed to remove the sling before sleeping and to inspect the treated shoulder for edema, sensation, and movement. The subject will be instructed to contact the investigator immediately if any problems are noticed.

Additionally, subjects will be instructed **NOT** to lift or carry any heavy objects for at least 8 weeks after each injection of study drug.

7.8. Identity of Investigational Product

The components of AA4500 are 0.9 mg of collagenase clostridium histolyticum and 0.5 mg of hydrochloric acid, 18.5 mg of sucrose, and 1.1 mg of tromethamine in a lyophilized cake.

The components of placebo for AA4500 are 0.5 mg of hydrochloric acid, 18.5 mg of sucrose, and 1.1 mg of tromethamine in a lyophilized cake.

The components of the sterile diluent are: 0.03% calcium chloride in 0.9% sodium chloride. Only sterile diluent supplied by Auxilium Pharmaceuticals, Inc. will be used.

7.9. Packaging and Labeling

Sterile vials of lyophilized study drug and sterile diluent will be provided to the investigator by Auxilium Pharmaceuticals, Inc. Each kit will contain 1 vial of lyophilized study drug and 1 vial of sterile diluent.

7.10. Storage and Disposition of Study Drug Supplies

Study drug and sterile diluent must be kept in a refrigerator (2°-8°C) with locked access. The reconstituted solution can be kept at room temperature (20° to 25°C/68° to 77°F) for up to one hour or refrigerated at 2° to 8°C (36° to 46°F) for up to 4 hours prior to administration.

All unused clinical supplies will be stored at controlled, refrigerated temperature, in an appropriate, secure place until used or returned to Auxilium Pharmaceuticals, Inc. The investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. Upon termination of the study, all used and unused study drug and remaining materials supplied by Auxilium will be returned for destruction as instructed by the clinical monitor.

7.11. Treatment

Subjects may receive up to a maximum of 3 injections of study drug. Each injection will be separated by a minimum of 21 days.

Subjects will receive Injection 1 on Day 1 of the study. Administration of subsequent injections (ie, Injection 2, Injection 3) will be determined by the guidelines outlined in Table 2:

- Do not retreat: Subjects who meet all criteria for 'do not retreat' after Injection 1 or Injection 2 **will not** receive subsequent injection(s).
- Retreat: Subjects who meet **all** the criteria for 'retreat' after Injection 1 or Injection 2 will be eligible to receive subsequent injection(s) provided there are no safety issues (eg, adverse events; allergic reaction), as determined by the investigator.
- Investigator-Discretion: Subjects who do not meet the criteria for 'do not retreat' or 'retreat' after Injection 1 or Injection 2, will receive additional treatment at the discretion of investigator.

Table 2: Guidelines for Retreatment of Affected Shoulder

	Do Not Retreat[a]	Retreat[b]
Forward flexion:		
Active (sitting)	≥160°	<140°
Passive (supine)	≥160°	< 140°
Abduction:		
Active (sitting)	≥160°	<140°
Passive (supine)	≥160°	< 140°
External rotation with the elbow up to 90° abduction:		
Active (sitting)	≥45°	<30°
Passive (supine)	≥45°	< 30°
Internal rotation with the elbow up to 90° abduction:		
Active (sitting)	≥45°	<30°
Passive (supine)	≥45°	< 30°

[a] Do not retreat if all measurements criteria are met.
[b] Retreat if all measurement criteria are met and if the investigator determines there are no safety issues (eg, ongoing adverse events).

IF NEITHER THE CRITERIA FOR 'DO NOT RETREAT' OR 'RETREAT' ARE MET AFTER INJECTION 1 OR INJECTION 2, THEN ADDITIONAL TREATMENT WILL BE AT THE DISCRETION OF INVESTIGATOR.

7.11.1. Subjects Not Eligible for Injection 2 and/or Injection 3

Subjects who are not eligible for Injection 2 and/or Injection 3 (eg, successfully treated or ongoing adverse events) will have follow-up visits on Day 43 (Section 7.13.5) and Day 64 (Section 7.13.7). Subjects who are not eligible for Injection 2 and/or Injection 3 will not be required to have a study visit on Day 29 and/or Day 50, respectively. Subjects who are not eligible for Injection 2 because of ongoing adverse events may receive Injection 3 at the discretion of the investigator.

All subjects will have a final follow-up visit on Day 95.

7.12. Drug Accountability

Auxilium or its agent will maintain a master log of kits dispensed to the investigative sites. A drug inventory form must be kept current by the study designated reconstitution person and must be made available to the clinical monitor, Auxilium employees, IRB/IEC, and regulatory agencies for routine inspection and accountability during monitoring visits. When instructed by Auxilium Pharmaceuticals, Inc., the investigator agrees to return all original containers of unused study drug to Auxilium Pharmaceuticals, Inc. or their designee.

7.13. Assessments by Visit

7.13.1. Informed Consent

Signed and dated informed consent will be obtained from each subject before any study procedures are undertaken. Details about how the informed consent will be obtained and documented are provided in Section 11.3, Subject Information and Consent.

7.13.2. Screening Period (Day -28 to Day -1)

Subjects meeting the relevant eligibility criteria listed in Section 6 may be enrolled in the study after the nature and purpose of the protocol have been explained and written informed consent to participate has been voluntarily provided by the subject. All subjects will have a screening evaluation within 28 days before their initial injection. The following procedures will be performed and documented during the screening period:

1. Obtain written informed consent, if subject not already consented
2. Medical history including adhesive capsulitis (AC) history (Section 7.14)
3. Record prior and concomitant medications/procedures (Section 7.14.2)
4. Physical examination (Section 7.14.3)
5. Vital sign measurements (Section 7.14.7)
6. Targeted examination of the shoulders including:
   - Inspection, signs of instability, signs of impingement (affected and unaffected shoulders)
   - AROM and PROM (affected and unaffected shoulders) (Section 7.14.4.2)
   - ASES function sub-scale (affected shoulder) (Section 7.14.4.3)
   - ASES pain sub-scale (affected shoulder) (Section 7.14.4.3)
   - Pain on movement (affected shoulder) (Section 7.14.5)
7. 12-lead electrocardiogram (ECG) (Section 7.14.8)
8. X-ray of affected shoulder (Section 7.14.9)

9. Magnetic resonance imaging (MRI) of the affected shoulder (Section 7.14.9)
10. Collection of samples for:
    a. Clinical laboratory testing (Section 7.14.10.1)
    b. Urine pregnancy testing
    c. Anti-AUX-I and anti-AUX-II antibody testing and neutralizing antibodies to AUX-I and AUX-II (Section 7.14.10.2)
11. Adverse events (Section 8)

7.13.3. Injection 1 (Day 1)

7.13.3.1. Before Injection

1. Record concomitant medications/procedures (Section 7.14.2)
2. Vital sign measurements (Section 7.14.7)
3. Targeted examination of the affected shoulder including:
    - AROM and PROM (Section 7.14.4.2)
4. Urine pregnancy testing
5. Randomization
6. Adverse events (Section 8)

Subjects will receive study drug under ultrasound guidance after administration of local anesthesia (Section 7.6).

7.13.3.2. After Injection

1. Record concomitant medications/procedures (Section 7.14.2)
2. Vital sign measurements (Section 7.14.7)
3. Examination of the affected shoulder for injection site reactions and local tolerability
4. Adverse events (Section 8)

Before discharge, subjects will be given instructions for home shoulder exercises (Section 7.14.6).

7.13.4. Day 8

The following procedures will be performed on Day 8:

1. Record concomitant medications/procedures (Section 7.14.2)
2. Vital sign measurements (Section 7.14.7)

3. Examination of affected shoulder including:
    - AROM and PROM (Section 7.14.4.2)
4. Compliance with home shoulder exercises
5. Injection site reactions and local tolerability
6. Adverse events (Section 8)

7.13.5. Injection 2 (Day 22) and Injection 3 (Day 43)

7.13.5.1. Before Each Injection

1. Record concomitant medications/procedures (Section 7.14.2)
2. Vital sign measurements (Section 7.14.7)
3. Targeted examination of the affected shoulder including:
    - AROM and PROM (Section 7.14.4.2)
    - ASES function sub-scale (Section 7.14.4.3)
    - ASES pain sub-scale (Section 7.14.4.3)
    - Pain on movement (Section 7.14.5)
4. Urine pregnancy testing
5. Compliance with home exercises
6. Injection site reactions and local tolerability
7. Adverse events (Section 8)

Subjects who are deemed eligible for re-treatment by the investigator will receive study drug under ultrasound guidance after administration of local anesthesia (Section 7.6)

7.13.5.2. After Each Injection

1. Record concomitant medications/procedures (Section 7.14.2)
2. Vital sign measurements (Section 7.14.7)
3. Injection site reactions and local tolerability
4. Adverse events (Section 8)

7.13.6. Day 29 and Day 50 (7 Days After Injection 2 and Injection 3)

The following procedures will be performed on Days 29 and 50:

1. Record concomitant medications/procedures (Section 7.14.2)

2. Vital sign measurements (Section 7.14.7)
3. Examination of affected shoulder including:
    - AROM and PROM (Section 7.14.4.2)
    - ASES function sub-scale (Section 7.14.4.3)
    - ASES pain sub-scale (Section 7.14.4.3)
    - Pain with movement (Section 7.14.5)
4. Compliance with home shoulder exercises
5. Injection site reactions and local tolerability
6. Adverse events (Section 8)

7.13.7. Follow-up Day 64

The following procedures will be performed on Day 64:

1. Record concomitant medications/procedures (Section 7.14.2)
2. Vital sign measurements (Section 7.14.7)
3. Examination of the affected shoulder including:
    - AROM and PROM (Section 7.14.4.2)
    - ASES function sub-scale (Section 7.14.4.3)
    - ASES pain sub-scale (Section 7.14.4.3)
    - Pain with movement (Section 7.14.5)
4. Compliance with home shoulder exercises
5. Injection site reactions and local tolerability
6. Adverse events (Section 8)

7.13.8. Follow-up Day 95 (End of Study)

The following procedures will be performed on Day 95:

1. Record concomitant medications/procedures (Section 7.14.2)
2. Vital sign measurements (Section 7.14.7)
3. Examination of the affected shoulder including:
    - AROM and PROM (Section 7.14.4.2)
    - ASES function sub-scale (Section 7.14.4.3)
    - ASES pain sub-scale (Section 7.14.4.3)
    - Pain with movement (Section 7.14.5)

4. Collection of samples for:
    a. Clinical laboratory testing (Section 7.14.10.1)
    b. Anti-AUX-I and anti-AUX-II antibody testing and neutralizing antibodies to AUX-I and AUX-II (Section 7.14.10.2)
5. Subject satisfaction with treatment (Section 7.14.11)
6. Investigator assessment of improvement with treatment (Section 7.14.12)
7. Injection site reactions and local tolerability
8. Adverse events (Section 8)
9. Discharge from study

7.14. Demographic, Efficacy, and Safety Assessments

7.14.1. Medical History

During the screening period, the investigator or qualified designee will obtain a medical history from each subject that includes relevant diagnoses including past episodes of adhesive capsulitis and procedures/therapies with onset/resolutions dates.

Medical histories should also include history of the current episode of AC including the affected shoulder (right or left), onset date of symptoms, and determination of idiopathic or traumatic AC.

History of tobacco and alcohol use (never, current, former) should also be included.

7.14.2. Prior/Concomitant Medications and Procedures

All prior medications taken within 90 days before randomization will be recorded. All medications (including over-the-counter medications) taken by the subject on Day 1 through the end of the study must be recorded.

Additionally, any diagnostic, therapeutic or surgical procedures performed during the study period should be recorded including the date, indication for and description of the procedure.

7.14.3. Physical Examination

During the screening period, the investigator or qualified designee will perform a physical examination (by body system) on each subject. Height and body weight will be measured and recorded. Hand dominance will be recorded.

7.14.4. Targeted Examination of the Shoulder

7.14.4.1. Inspection

During the screening visit, each subject will have an examination of the affected and unaffected shoulders that will include:

- inspection for swelling and bruising, scars suggestive of old trauma, deformity, and asymmetry
- signs of shoulder instability
- signs of shoulder impingement

7.14.4.2. Active and Passive Range of Motion

During the screening visit, the investigator or qualified designee will measure AROM (performed by the patient), and PROM (performed by the investigator or qualified designee without assistance from the subject), in the affected shoulder and the unaffected shoulder of each subject. AROM will be performed with the subject seated (Appendix A). PROM will be performed with the subject in the supine position (Appendix B). AROM should be performed before PROM. The unaffected arm will be measured with the goniometer first; then the affected arm will be measured with the goniometer second.

Follow-up AROM and PROM measurements of the affected shoulder will be recorded as follows:

- Before each injection, Days 8, 29, 50, 64, and at the Day 95 follow-up visit.

At each time point, the measurement should be repeated a total of three times. For forward flexion, abduction, external rotation, and internal rotation, if the measurements are within 10 degrees of each other, record the highest of the three measurements. If any of the three measurements are greater than 10 degrees of another, the sequence of measurements should be repeated.

The person (ie, investigator or qualified designee) who performs the screening AROM and PROM measurements should, when possible, perform all follow-up measurements for that subject.

7.14.4.3. American Shoulder and Elbow Surgeons (ASES) Patient Self-Evaluation

7.14.4.3.1. Function Sub-Scale

During the screening visit; before injection on Days 22 and 43; and at the Days 64 and 95 follow-up visits, each subject will indicate his/her ability to perform each of the activities listed in Table 3 using the affected shoulder/arm as follows:

'Circle the number in the box that indicates your ability to do the following activities with your affected shoulder/arm'. Please answer **all** questions.

Table 3: ASES Function Sub-Scale

	Affected Shoulder/Arm			
	0=Unable to do	**1=Very** difficult to do	**2=Somewhat** difficult	**3=Not** difficult
1. Put on coat	0	1	2	3
2. Sleep on your painful or affected side	0	1	2	3
3. Wash back/do-up bra in back	0	1	2	3
4. Manage toileting	0	1	2	3
5. Comb hair	0	1	2	3
6. Reach a high shelf	0	1	2	3
7. Lift 10 lbs (4.5 kg) above shoulder	0	1	2	3
8. Throw a ball overhand	0	1	2	3
9. Do usual work – List:	0	1	2	3
10. Do usual sport – List:	0	1	2	3

Adapted from the American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form, Patient Self-Evaluation

7.14.4.3.2. Pain Sub-Scale

During the screening visit; before injection on Days 22 and 43; and at the Days 64 and 95 follow-up visits, each subject will circle a number on the 11-point pain visual analogue scale (VAS) that corresponds to his/her response to the following question: 'How bad is the pain in your affected shoulder today'.

0	1	2	3	4	5	6	7	8	9	10
No pain at all										Pain as bad as it can be

Adapted from the American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form, Patient Self-Evaluation

7.14.5. Pain With Movement

During the screening visit; before injection on Days 22 and 43; and at the Days 64 and 95 follow-up visits, each subject will circle a number on the 11-point pain visual analogue scale (VAS) that corresponds to his/her response to 'How bad is the pain upon movement of your affected shoulder at its worst in the last 24 hours'.

0	1	2	3	4	5	6	7	8	9	10
No pain at all										Pain as bad as it can be

7.14.6. Home Shoulder Exercises

Home shoulder exercises as described in Appendix C should be performed by each subject a minimum of three times a day. Home shoulder exercises will begin one day after Injection 1 and will end on Day 64. Each subject will be provided with a pulley for home exercise use.

7.14.7. Vital Signs

During the screening period, each subject will have blood pressure (systolic/diastolic), respiratory rate, and radial pulse assessed after he/she has been seated upright for at least 5 minutes. Body temperature will also be recorded.

On each injection day, vital signs will be assessed after the subject has been seated upright for at least 5 minutes as shown in Table 4.

Table 4: Vital Signs Measurements – Injection Days

Time point Relative to Injection	Blood Pressure, Respiratory Rate, Radial Pulse	Body Temperature
Up to 4 hours before	X	X
Approximately 15 minutes after	X	
Approximately 30 minutes after	X	
Approximately 45 minutes after	X	
Before discharge from the unit	X	X

Follow-up vital sign measurements, including blood pressure (systolic/diastolic), respiratory rate, and radial pulse, will be assessed after the subject has been seated upright for at least 5 minutes on Days 8, 29, 50, 64, and at the Day 95 follow-up visit.

NOTE: blood pressure should be taken on the non-treated arm.

7.14.8. 12-Lead Electrocardiogram

During the screening period, subjects will have a resting 12-lead electrocardiogram (ECG). A qualified physician will interpret, sign, and date the ECGs. Electrocardiogram assessments must be 'within normal limits' or interpreted as 'abnormal, not clinically significant' for the subject to be included in the study. ECG findings will be documented as normal; abnormal, clinically significant; or abnormal, not clinically significant. The investigator or qualified designee must sign and date the ECG, thereby acknowledging review of ECG results.

7.14.9. X-Ray and Magnetic Resonance Imaging (MRI) of the Affected Shoulder

During the screening period, subjects will have an x-ray of their affected shoulder to assist in ruling out other clinically significant conditions and clinically significant pathology (eg, glenohumeral arthritis, fracture). Magnetic resonance imaging (MRI) without contrast will be performed during the screening period to assist in ruling out other conditions (eg, subscapularis tendon rupture, rotator cuff injuries). MRI findings at screening will be assessed by the investigator or qualified designee and documented as normal; abnormal, clinically significant;

or abnormal, not clinically significant. Note: Clinically significant MRI findings refer to significant pathological conditions that are distinct from adhesive capsulitis.

X-rays or MRIs of the affected shoulder that were performed within 3 months of the screening visit may be used provided the subject has not experienced a worsening of symptoms during this time period.

Copies of both X-rays and MRIs will be collected as part of the study data. All image data must be de-identified prior to submission to the Sponsor or designee.

7.14.10. Clinical Laboratory and Immunogenicity Testing

Blood (~15 mL) and urine samples will be collected for testing of the following clinical laboratory and immunogenicity parameters.

7.14.10.1. Clinical Laboratory Testing

Clinical laboratory testing as shown in Table 5 will be done at the following time points:

- Screening
- Follow-up (Day 95)

Table 5: Clinical Laboratory Parameters

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	Blood urea nitrogen	Specific gravity
Hemoglobin	Creatinine	Ketones
Red blood cell count	Total bilirubin	pH
Red blood cell morphology	Alanine aminotransferase (ALT)	Protein
White blood cell count	Aspartate aminotransferase (AST)	Blood
Neutrophils	Alkaline phosphatase	Glucose
Lymphocytes	Sodium	
Monocytes	Potassium	
Basophils	Calcium	
Eosinophils	Chloride	NOTE: Women of
Platelets	Phosphate	childbearing potential
	Serum bicarbonate	(including but not limited to all
	Uric acid	women ≤55 years of age) will
	Total cholesterol	have urine pregnancy testing
	Total protein	(dipstick) at screening and
	Thyroid stimulating hormone	before each dose of study drug.
	Glucose	
	Triglycerides	
	Albumin	

A sponsor-selected central clinical laboratory will process specimens and provide results for each subject. The investigator or qualified designee will evaluate each laboratory value for

clinical significance. If a laboratory value is outside the reference range for the subject, and the investigator determines it represents a clinically significant change from the baseline or previously assessed value(s), the investigator will make an assessment of drug relatedness and record as an adverse event as appropriate. A subject with a clinically significant laboratory value should be followed until there is a satisfactory resolution of the abnormality, or until the subject's condition has stabilized. Details regarding blood and urine sample collection, processing, and shipping will be provided in a separate Laboratory Manual. The investigator or qualified designee must note clinical significance for abnormal values and sign and date laboratory reports acknowledging review of laboratory results.

7.14.10.2. Anti-AUX-I and Anti-AUX-II Antibodies and Neutralizing Antibodies to AUX-I and AUX-II

Serum samples for the determination of anti-AUX-I and anti-AUX-II antibody testing and neutralizing antibodies to AUX-I and AUX-II will be collected during the screening visit and at the Day 95 follow-up visit.

The serum samples obtained will be stored at -20°C and then shipped on dry ice to the designated clinical laboratory before forwarding to Auxilium Pharmaceuticals, Inc.'s appointed laboratory for the determination of anti-AUX-I and anti-AUX-II antibodies.

Neutralizing antibody plasma samples collected in this study will be stored until the end of the study, at which time a decision for longer term storage will be made. These samples may be analyzed in the future, if needed.

7.14.11. Subject Satisfaction With Treatment

At the Day 95 follow-up visit, each subject will be asked to rate his/her satisfaction with treatment as follows:

1. Very Satisfied
2. Quite Satisfied
3. Neither Satisfied nor Dissatisfied
4. Quite Dissatisfied
5. Very Dissatisfied

7.14.12. Investigator Assessment of Improvement With Treatment

At the Day 95 follow-up visit, the investigator will determine the degree of improvement in the severity of the subject's treated shoulder compared with screening as follows:

1. Very Much Improved
2. Much improved

3. Minimally Improved
4. No Change
5. Minimally Worse
6. Much Worse
7. Very Much Worse

7.14.13. End of Study

The end of study is when the last subject completes the Day 95 follow-up visit.

8. ADVERSE EVENTS

Throughout the study, the investigator will monitor each subject for evidence of drug intolerance and for the development of clinical and/or laboratory evidence of an AE. An AE assessment will be made by the investigator on a routine basis throughout the study.

All AEs that occur during the course of the study must be reported in detail on the subject's chart (source document), appropriate CRFs, and on any other report form required by national law.

8.1. Definitions

8.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product. Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be clinically significant AEs.

A treatment-emergent AE is defined as any AE with onset or worsening reported by a subject from the time that the first dose of study drug is administered until completion of or discharge from the study (see Section 6.3 for details regarding premature discontinuation).

8.1.2. Serious Adverse Event

Any AE that results in 1 or more of the following is considered a serious adverse event (SAE):

1. Death - Includes death of a fetus due to miscarriage/spontaneous abortion and elective abortion in the subject's partner.
2. Life Threatening Situation - The subject was at immediate risk of death at the time of the event. It does not refer to the hypothetical risk of death if the AE was more severe or was to progress.
3. Inpatient Hospitalization - This includes any new hospital admission during the study or prolongation of an existing hospitalization. The following are not considered serious due to inpatient hospitalization:
   a. Trips to the ER that do not include a hospital admission

b. Optional admission not associated with a precipitating medical AE (eg, cosmetic surgery)

c. Admission for treatment of a pre-existing condition that has not worsened or had an increase in severity or frequency (eg, cataract surgery)

d. Pre-planned treatments or surgical procedures noted in the baseline source documentation

4. Persistent or Significant Disability/Incapacity - Any AE having an outcome that is associated with a substantial disruption of the ability to carry out normal life functions. This includes the inability to work. This is not intended to include transient, interruptions of daily activities.

5. Congenital Anomaly/Birth Defect in a child of the subject's partner.

6. Other Medically Important Events - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon medical judgment, they may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in 1 through 5 above.

If any serious, life-threatening, or fatal adverse event occurs whether related to study drug or not, the investigator must notify Auxilium within 24 hours by entry into the CRF as an SAE and/or telephone, facsimile, email (see Section 8.5).

8.2. Adverse Event Severity

The severity of the adverse event will be graded using the following definitions:

- Mild - The adverse event is transient and easily tolerated by the subject.
- Moderate - The adverse event causes the subject discomfort and interrupts the subject's usual activities.
- Severe - The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

8.3. Relationship to Study Drug

The investigator must record the causal relationship of each adverse event in the CRF, and on the serious adverse reporting form (if applicable). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an adverse event.

- Related: There is evidence to suggest a causal relationship between the drug and the adverse event.
- Not related: An adverse event is due to underlying or concurrent illness or effect of another drug or event and is not related to the study drug (eg, has a more likely

alternate etiology and / or a temporal relationship does not suggest a causal relationship).

8.4. Adverse Event Collection Period

All (serious and non-serious) adverse events, whether elicited during study visits or spontaneously reported by the subject, that occur from the time the subject signs the study-specific informed consent form until completion of or discharge from the study will be collected.

Subjects with clinically significant AEs will be followed until the condition resolves or stabilizes, as determined by the investigator.

8.5. Serious Adverse Event Reporting

In the event of an SAE, whether related to study drug or not, the investigator will notify Auxilium within 24 hours of being made aware of the SAE:

Telephone: +1 877-663-0412
Fax: +1 866-837-7293
Email: ae@auxilium.com

8.6. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including reporting of suspected unexpected serious adverse reactions (SUSARs), will be carried out in accordance with applicable local regulations.

8.7. Exposure During Pregnancy

An exposure during pregnancy (also referred to as exposure in-utero [EIU]) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to study drug (maternal exposure).
2. A male has been exposed, either due to treatment or environmental, to study drug prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study subject is found to be pregnant during the study the investigator must submit EIU information to Auxilium within 24 hours of awareness of the pregnancy, irrespective of whether an adverse event has occurred.

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. Auxilium will follow the pregnancy until completion or until pregnancy termination (eg, induced abortion).

9. PROTOCOL DEVIATIONS

When a variation from the protocol is deemed necessary for an individual subject, the investigator or qualified designee in attendance must contact the Auxilium Pharmaceuticals, Inc. designee listed below:

For non-medical issues contact:

Diane McCaul
Associate Director, Global Clinical Operations
Telephone: 484-321.- 068 (cell: 484-843-4329)
Fax: 484-321-2019

For medical issues contact:

Gregory J. Kaufman, MD (or qualified designee)
Executive Director, Global R & D and Safety
Telephone: 484-321-5920 (cell: 610-757-5539)
Fax: 610-239-7398

Such contact with the Auxilium designee must be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study. The deviation from the protocol will be authorized only for that subject and will be documented in writing by both parties.

10. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

10.1. Statistical and Analytical Plans

10.1.1. Analysis Populations

The intent-to-treat and safety population is defined as all subjects who receive study drug.

10.1.2. Efficacy

For ROM, baseline is before injection on Day 1. Baseline for all other efficacy parameters is the screening visit.

The primary endpoint is the change (degrees) from baseline to the Day 95 follow-up in active forward flexion in the affected shoulder.

Secondary endpoints are:

1. Change from baseline to Day 95 in ASES function sub-scale
2. Change (degrees) from baseline to the Day 95 follow-up in abduction
3. Change from baseline to the Day 95 follow-up in pain with movement using a 11-point VAS
4. Change (degrees) from baseline to the Day 95 follow-up in internal rotation
5. Change from baseline to the Day 95 follow-up in external rotation
6. Change from baseline to the Day 95 follow-up in ASES pain sub-scale
7. Investigator satisfaction with treatment at the Day 95 follow-up
8. Subject satisfaction with treatment at the Day 95 follow-up

10.1.3. Safety

The following variables are safety endpoints.

1. Adverse events: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
2. Change from screening visit in vital signs
3. Change from screening visit in laboratory tests

10.1.4. Immunogenicity

Immunogenicity variables include anti-AUX-I/anti-AUX-II antibody levels.

10.2. Statistical Methodology

10.2.1. Efficacy

Simultaneous hypothesis tests for all primary and secondary efficacy endpoints will be accomplished with a family-wise 5% significance level by applying a closed hierarchical testing procedure. Under this approach, the first test in the hierarchy that fails to reject its individual hypothesis at the 5% level requires that all hypotheses following the first non-significant hypothesis cannot be tested.

1. For the investigator assessment of improvement with treatment and subject satisfaction with treatment, a Wilcoxon rank sum non-parametric test will be performed to compare active to placebo.
2. Mixed-model ANOVA with factors for treatment group and visit will be performed to compare active to placebo for forward flexion, abduction, internal rotation, and external rotation, ASES function subscale, and pain with movement.

10.2.2. Safety

Adverse events will be summarized for the active and placebo groups with the proportion of subjects reporting each event.

Actual values and change from baseline in vital signs and laboratory test parameters will be summarized for the active and placebo groups with descriptive statistics at each visit obtained.

10.2.3. Immunogenicity

Anti-AUX-I and anti-AUX-II antibodies levels and neutralizing antibodies to AUX-I and AUX-II will be summarized using descriptive statistics.

10.3. Determination of Sample Size

A sample size of 240 subjects with a 3:1 allocation ratio is sufficient to detect the following deltas between active and placebo for the following primary and secondary parameters with power ≥90%, based on results observed in Study AUXCC-870:

Endpoint (Change from Baseline)	Delta=AA4500-Placebo
Forward Flexion(SD=30 degrees)	15 degrees
Abduction(SD=30 degrees)	15 degrees
External Rotation(SD=25 degrees)	15 degrees
Internal Rotation(SD=20 degrees)	10 degrees
Function (SD=15 points)	10 points
Pain(SD=15 points)	10 points

Assuming a dropout rate of 20%, then planned sample size is 300 subjects (225 AA4500 and 75 Placebo) is sufficient to insure each of the primary and secondary endpoints have sufficient power to detect meaningful differences.

11. ETHICS

11.1. Independent Ethics Committee or Institutional Review Board

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent, and all other forms of subject information related to the study (eg, advertisements used to recruit subjects) and any other necessary documents be reviewed by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB). IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site. Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design.

11.2. Ethical Conduct of the Study

The study will be conducted in accordance with GCP guidelines and the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/17c.pdf). At appropriate intervals, the clinical monitor will visit the site during the clinical study and assure that the investigator's obligations are being fulfilled.

Trial documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated-marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. For Phase 4 studies in countries in the ICH regions and for countries not in ICH Regions, trial documents should be retained for the length of time local GCP guidelines or law require. If there are no local laws, the site should retain the file for 5 years after completion of the study. Records include the Confidential Follow-up Forms and other documents such as informed consents, lab reports and other source documents, drug accountability forms, Ethics Committee approvals, protocols, and CRFs.

11.3. Subject Information and Consent

For all investigators participating in the study, the study protocol and consent form must be approved by the investigator's Institutional Review Board/Independent Ethics Committee and a copy of the approved consent form must be supplied to Auxilium Pharmaceuticals, Inc. The subject will be asked to read the consent form or have the form read to him/her. If the subject decides to participate in the study, the subject will be asked to sign and date the form as evidence of consent. Each subject must voluntarily sign and date a consent form before participating in this study. A designated and legally authorized representative may also sign and date the informed consent form when necessary. It is the obligation of the investigator or his representative to explain the nature of the study to the subject. The investigator must

document in the subject's medical chart that the subject has signed a consent form to participate in an investigational trial, a copy of the signed and dated consent form should be given to the subject or his/her representative, and the original should be retained with the subject's study records. The subjects may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

The ICF will provide the new requirement as per 21CFR50.25(c) and will include the specific statement that refers to the trial's description on www.clinicaltrials.gov.

For investigators in the United States, the privacy protection of individually identifiable health information (Protected Health Information [PHI]) became a requirement under the Privacy Rules of the Health Insurance Portability and Accountability Act (HIPAA) effective April 14, 2003. Protected Health Information (eg, results of tests, exams and medical records etc.) generated during clinical studies may be communicated amongst several parties in generating final study reports. Accordingly, prior to a subject participating in a clinical study he must authorize the use and disclosure of his PHI by signing an authorization form.

PHI authorization must be approved by the investigator's Institutional Review Board or Privacy Board and a copy of the authorization form must be supplied to Auxilium Pharmaceuticals, Inc. The subject will be asked to read the PHI authorization form or have the forms read to him/her. If the subject decides to participate in the study, the subject will be asked to sign and date the form as evidence of consent. Each subject must voluntarily sign and date a PHI authorization before participating in this study. A designated and legally authorized representative may also sign and date the PHI authorization when necessary. The investigator will document in the subject's medical chart that the subject has signed a PHI authorization form to participate in an investigational trial, a copy of the PHI authorization, if not contained in the informed consent, will be given to the subject or his representative, and the original will be retained with the subject's study records.

12. SOURCE DOCUMENTS AND CASE REPORT FORMS COMPLETION

12.1. Source Documents and Access to Source Data/Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of Auxilium's study, each site will permit authorized representatives of the sponsor's, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source documents are all information, original records of clinical findings, observations, or other activity in a clinical trial necessary for reconstruction and evaluation of the trial. Examples of these original documents and data records include, but not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, x-rays, and subject files and records kept at the pharmacy , at the laboratories involved in the clinical trial.

All source documents and laboratory reports must be reviewed by qualified individuals at each participating site, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality and reviewed by the site Principal Investigator or designee.

12.2. Electronic Case Report Forms (eCRFs)

Auxilium will provide an Electronic Data Capture (EDC) system for this study. This system will be used to transmit the information collected in the performance of this study to Auxilium Pharmaceuticals, Inc. and to governmental agencies. eCRF data should be completed by qualified individuals at each participating site and be available for review by Auxilium Pharmaceuticals, Inc. personnel or representative within a reasonable period of time after completion of each study visit.

Data entries will be corrected by changing the entry in the EDC system. Any changes or corrections to eCRF data will be electronically tracked and will include the reason for correction, who made the correction and the date/time stamp when the correction was made within the audit trail of the EDC system. The investigator will review the eCRFs for completeness and accuracy and electronically sign and date the eCRF data where indicated. Auxilium Pharmaceuticals, Inc. personnel or representatives will review eCRFs

periodically for completeness and acceptability. The investigator will be provided with complete electronic copies of the data for his/her files at the conclusion of the study.

13. QUALITY CONTROL AND COMPLIANCE

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Reports will be submitted to Auxilium on monitoring activities.

The investigators will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Data management will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the sites(s) for clarification/resolution.

13.1. Investigator Documentation

Prior to beginning the study, the principal investigator will provide the essential documentation in compliance with ICH E6 8.2 and relevant parts of Title 21 of the CFR.

14. USE OF INFORMATION

All information concerning AUX-CC-871 and Auxilium Pharmaceuticals, Inc. operations, such as Auxilium Pharmaceuticals, Inc. patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Auxilium Pharmaceuticals, Inc. and not previously published, is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Auxilium Pharmaceuticals, Inc. in connection with the development of AA4500. This information may be disclosed as deemed necessary by Auxilium Pharmaceuticals, Inc. To allow the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Auxilium Pharmaceuticals, Inc. with complete test results and all data developed in this study.

This confidential information shall remain the sole property of Auxilium Pharmaceuticals, Inc., shall not be disclosed to others without the written consent of Auxilium Pharmaceuticals, Inc., and shall not be used except in the performance of this study.

15. COMPLETION OF THE STUDY

The investigator will complete this study in satisfactory compliance with the protocol within the timeframe allotted in the financial contract. Delays in the completion and/or reporting of the study beyond this time must be mutually agreed upon in writing by both the investigator and Auxilium Pharmaceuticals, Inc. It is agreed that, for reasonable cause, Auxilium Pharmaceuticals, Inc. may terminate this study prematurely, or the investigator may terminate participation in the study, provided that written notice is submitted at a reasonable time in advance of the intended termination.

16. INVESTIGATOR'S AGREEMENT

I have read the AUX-CC-871 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____ _____

Signature of Investigator Date

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APPENDICES

APPENDIX A ACTIVE RANGE OF MOTION

APPENDIX B PASSIVE RANGE OF MOTION

APPENDIX C HOME EXERCISES

APPENDIX A ACTIVE RANGE OF MOTION (AROM)

AROM in both the affected and unaffected shoulder will be measured with goniometry while the subject is seated comfortably, without assistance of others. Forward flexion, abduction, internal rotation with the elbow up to 90° abduction, and external rotation will be measured as shown in the following depictions.

Active Forward Flexion (Range: 0-180°)

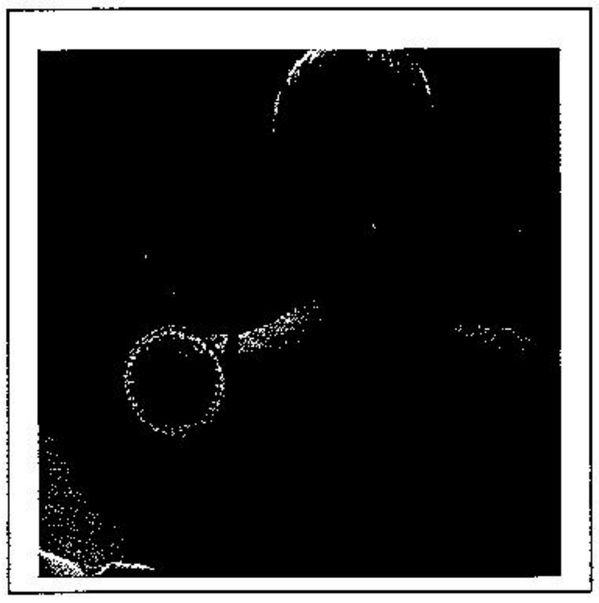
1. To evaluate flexion, have the subject sit comfortably in a chair. Ask the subject to place his/her arm at their side, with the palm facing the hip. Stabilize the scapula and clavicle by cupping the superior aspect of the shoulder. This stabilization will also help keep the subject in an upright position and prevent the subject from leaning backwards.
2. The axis or center of the goniometer is placed at the lateral aspect of the center of the humeral head, just inferior to the lateral aspect of the acromion process. The stationary arm of the goniometer is parallel to the midline of the trunk (**Picture 1**).
3. Ask the subject to keep his/her palm medial and to slowly lift the arm in an anterior and upward direction to the limit of motion in elevation. Keep the stationary arm of the goniometer in midline of the trunk and the moveable arm of the goniometer pointed towards the olecranon process (**Picture 2**). Ask the subject to stop with the onset of shoulder pain.
4. The measurement should be repeated a total of three times. If the measurements are within 10 degrees of each other, please record the highest of the three measurements. If any of the measurements are greater than 10 degrees of each other, the sequence should be repeated. The unaffected arm should be measured first, followed by the affected arm.

Picture 1

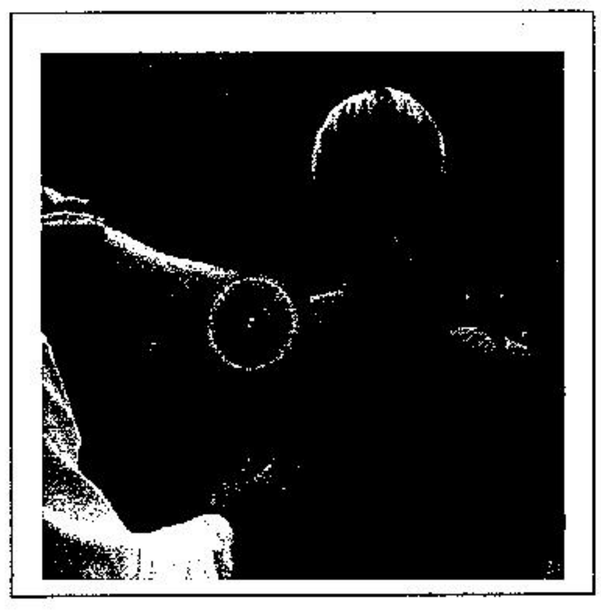
Picture 2

Active Shoulder Abduction (Range: 0-180°)

1. To evaluate abduction, have the subject sit comfortably in a chair. Next have the subject place his/her arm at the side, with the palm facing the hip. No stabilization will be necessary while testing abduction.
2. The axis or center of the goniometer will be placed at the midpoint of the posterior aspect of the glenohumeral joint. The stationary arm of the goniometer will be lined up parallel to the sternum and the midline of the trunk (**Picture 1**).
3. Ask the subject to slowly move their arm out to the side and upward with the palm rotating towards the front of their body. Have the arm continue to rotate upward until the limit of abduction. While the subject is elevating the arm keep the stationary arm of the goniometer in line with the trunk and the movable arm of the goniometer parallel to the humerus (**Picture 2**). Ask the subject to stop with the onset of shoulder pain.
4. The measurement should be repeated a total of three times. If the measurements are within 10 degrees of each other, please record the highest of the three measurements. If any of the measurements are greater than 10 degrees of each other, the sequence should be repeated. The unaffected arm should be measured first, followed by the affected arm.



Picture 1



Picture 2

Active External Rotation With the Elbow up to 90° Abduction (Range: 0-90°)

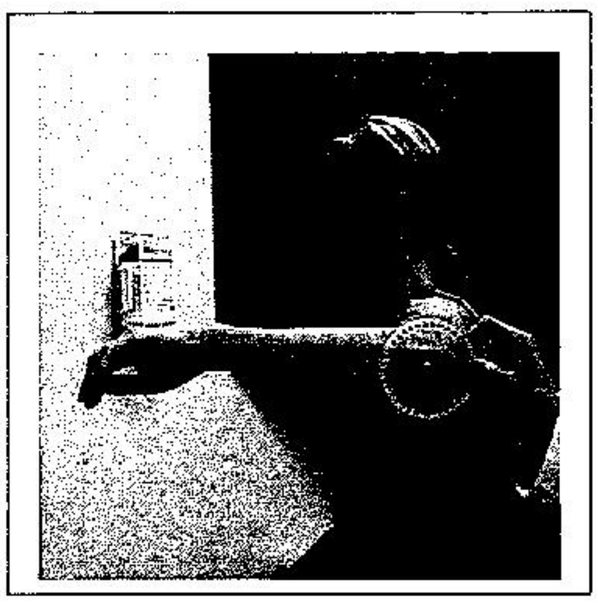
1. To evaluate external rotation, have the subject sit comfortably in a chair and have him/her raise their arm as far as possible up to 90 degrees of abduction. Next ask the subject to bend the elbow to 90 degrees with the forearm parallel to the floor. No stabilization will be necessary while completing active external rotation.
2. The axis or center of the goniometer is placed over the olecranon with the arms parallel to the shaft of the ulna. The stationary arm of the goniometer will remain parallel to the floor. The moveable arm of the goniometer will remain along the longitudinal axis of the ulna (**Picture 1**).
3. Ask the subject to slowly move their arm upward. The arm will continue to move upward with the palm beginning to face anterior. Have the subject continue to the limit of external rotation or until the shoulder and body begins to move back. The stationary arm of the goniometer will remain parallel to the floor and the moveable arm of the goniometer will remain in line with the ulna (**Picture 2**). Ask the subject to stop with the onset of any shoulder pain.
4. The measurement should be repeated a total of three times. If the measurements are within 10 degrees of each other, please record the highest of the three measurements. If any of the measurements are greater than 10 degrees of each other, the sequence should be repeated. The unaffected arm should be measured first, followed by the affected arm.

Picture 1

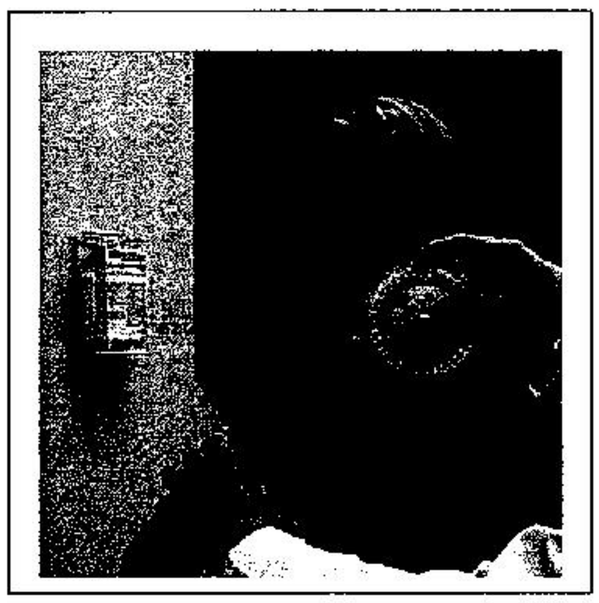
Picture 2

Active Internal Rotation With the Elbow up to 90° Abduction (Range: 0-90°)

- To evaluate internal rotation, have the subject sit comfortably in a chair and have him/her raise their arm as far as possible up to 90 degrees of abduction. Next ask the subject to bend the elbow to 90 degrees with the forearm parallel to the floor. No stabilization will be necessary while completing active internal rotation.
- The axis center of the goniometer is placed over the olecranon process with the arms parallel to the shaft of the ulna. The stationary arm of the goniometer will remain parallel to the floor. The moveable arm of the goniometer will remain along the longitudinal axis of the ulna (**Picture 1**).
- Ask the subject to slowly move their arm downward. The arm will continue to move downward with the palm beginning to face posterior. Have the subject continue to the limit of internal rotation or until the shoulder and body begins to move forward. The stationary arm of the goniometer will remain parallel to the floor and the moveable arm of the goniometer will remain in line with the ulna (**Picture 2**). Ask the subject to stop with the onset of any shoulder pain.
- The measurement should be repeated a total of three times. If the measurements are within 10 degrees of each other, please record the highest of the three measurements. If any of the measurements are greater than 10 degrees of each other, the sequence should be repeated. The unaffected arm should be measured first, followed by the affected arm.



Picture 1



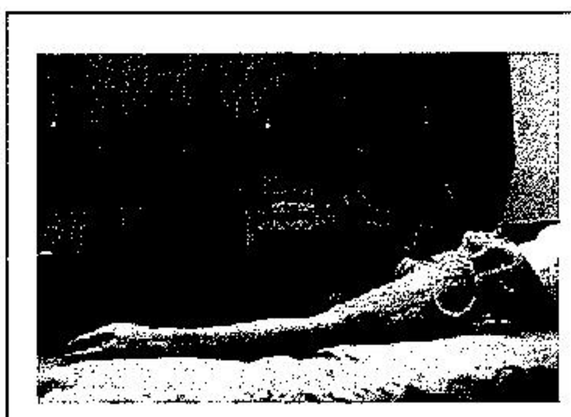
Picture 2

APPENDIX B PASSIVE RANGE OF MOTION (PROM)

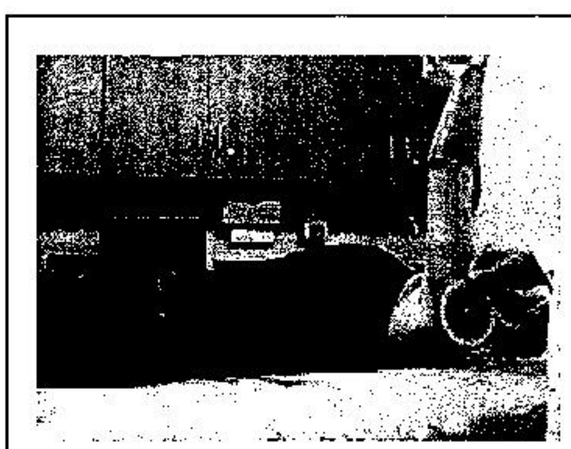
PROM in both the affected and unaffected shoulder will be measured with goniometry while the subject is in the supine position with the knees bent. Forward flexion, abduction, external rotation with the elbow up to 90° abduction, and internal rotation with the elbow up to 90° abduction will be measured as shown in the following depictions.

Passive Forward Flexion (Range: 0-180°)

1. To evaluate passive flexion, the subject should be lying in a supine position with the knees bent. The subject's arm is at their side with the palm facing medially. In order to obtain true glenohumeral flexion, the scapula needs to be stabilized. This stabilization can be done by placing one hand on the side of the scapula while the other hand grasps the distal humerus.
2. The axis or center of the goniometer is placed at the lateral aspect of the center of the humeral head. This location will be just inferior to the lateral aspect of the acromion process. The stationary arm of the goniometer is parallel to the lateral midline of the trunk. This arm of the goniometer can be held while stabilizing the scapula (**Picture 1**).
3. The movable arm of the goniometer will run parallel to the longitudinal axis of the humerus. This arm of the goniometer will be held in the same hand as the hand moving the humerus and will move along with the humerus.
4. Grasp the elbow and move the arm away from the subject's side and up over the head. During this examination, the scapula requires observation. When scapula movement is observed, the PROM measurement should be taken. Advise the subject that you will move the arm until a good stretch is felt and that you will stop as soon as any pain develops (**Picture 2**).
5. The measurement should be repeated a total of three times. If the measurements are within 10 degrees of each other, please record the highest of the three measurements. If any of the measurements are greater than 10 degrees of each other, the sequence should be repeated. The unaffected arm should be measured first, followed by the affected arm.



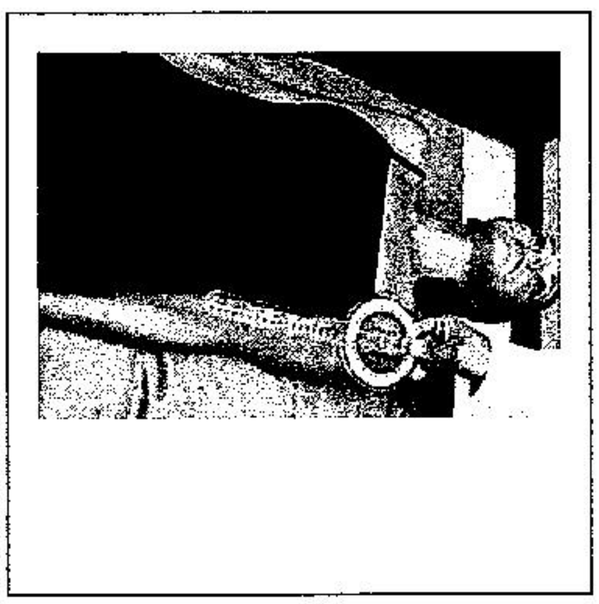
Picture 1



Picture 2

Passive Shoulder Abduction (Range 0-180°)

1. To evaluate passive abduction, the subject should be lying in a supine position with the knees bent. The subject's arm is at the side with the palm facing up or anteriorly. This position will not require stabilization of the subject; the weight of the trunk will provide the necessary stability to the scapula.
2. The axis or center of the goniometer is placed at the midpoint of the anterior aspect of the glenohumeral joint. This will be over the acromion process. The stationary arm of the goniometer will be aligned with the anterior midline of the humerus. The stationary arm will remain still and run parallel with the sternum running along the thorax (**Picture 1**).
3. The movable arm of the goniometer should remain over the anterior aspect of the humerus and will be moving in conjunction with the arm during the stretch.
4. Move the humerus in a lateral and upward motion. Place one hand on the shoulder joint to hold the goniometer and stabilize the shoulder. The other hand will support the forearm and move the palm outward from the side. Advise the subject that you will move the arm until a good stretch is felt and that you will stop as soon as any pain develops (**Picture 2**).
5. The measurement should be repeated a total of three times. If the measurements are within 10 degrees of each other, please record the highest of the three measurements. If any of the measurements are greater than 10 degrees of each other, the sequence should be repeated. The unaffected arm should be measured first, followed by the affected arm.



Picture 1

Picture 2

Passive Shoulder External Rotation With the Elbow up to 90° Abduction

1. To evaluate external rotation, the subject should be lying in a supine position with the knees bent. The subject's arm will be abducted as far as possible up to 90 degrees with the elbow bent at 90 degrees. The forearm and the hand will be facing the ceiling. A towel should be placed under the humerus to maintain the necessary positioning. The weight of the trunk will provide the necessary stabilization of the scapula.
2. The axis or center of the goniometer is placed over the olecranon process of the ulna. The stationary arm of the goniometer will remain perpendicular to the floor during external rotation of the shoulder. The moveable arm of the goniometer will remain parallel to the longitudinal axis of the ulna. The moveable goniometer arm will remain pointed at the ulnar styloid process (**Picture 1**).
3. Place one hand under the elbow and the other hand will be just proximal to the wrist. While supporting the elbow begin to move the dorsal aspect of the hand to the floor. Continue to move the hand and the goniometer so that the subject's hand begins to point to the floor as the upper arm twists in the shoulder joint. Move the arm in this direction as far as the subject can tolerate or until the anterior shoulder begins to lift and come off the table. This will indicate the end of external rotation (**Picture 2**).
4. The measurement should be repeated a total of three times. If the measurements are within 10 degrees of each other, please record the highest of the three measurements. If any of the measurements are greater than 10 degrees of each other, the sequence should be repeated. The unaffected arm should be measured first, followed by the affected arm.

Picture 1

Picture 2

Passive Shoulder Internal Rotation With the Elbow up to 90° Abduction

1. To evaluate internal rotation, the subject should be lying in a supine position with the knees bent. The subject's arm will be abducted as far as possible up to 90 degrees with the elbow bent at 90 degrees. The forearm and the hand will be facing the ceiling. A towel should be placed under the humerus to maintain the necessary positioning. The weight of the trunk will provide the necessary stabilization of the scapula.
2. The axis or center of the goniometer is placed over the olecranon process of the ulna. The stationary arm of the goniometer will remain perpendicular to the floor during internal rotation of the shoulder. The moveable arm of the goniometer will remain parallel to the longitudinal axis of the ulna. The moveable goniometer arm will remain pointed at the ulnar styloid process (**Picture 1**).
3. Place one hand under the elbow and the other hand will be just proximal to the wrist. While supporting the elbow begin to move the ventral aspect of the hand to the floor. Continue to move the hand and the goniometer so that the arm begins to point to the floor as the upper arm twists in the shoulder joint. Move the arm in this direction as far as the subject can tolerate or until the posterior shoulder begins to lift and come off the table. This will indicate the end of internal rotation (**Picture 2**).
4. The measurement should be repeated a total of three times. If the measurements are within 10 degrees of each other, please record the highest of the three measurements. If any of the measurements are greater than 10 degrees of each other, the sequence should be repeated. The unaffected arm should be measured first, followed by the affected arm.

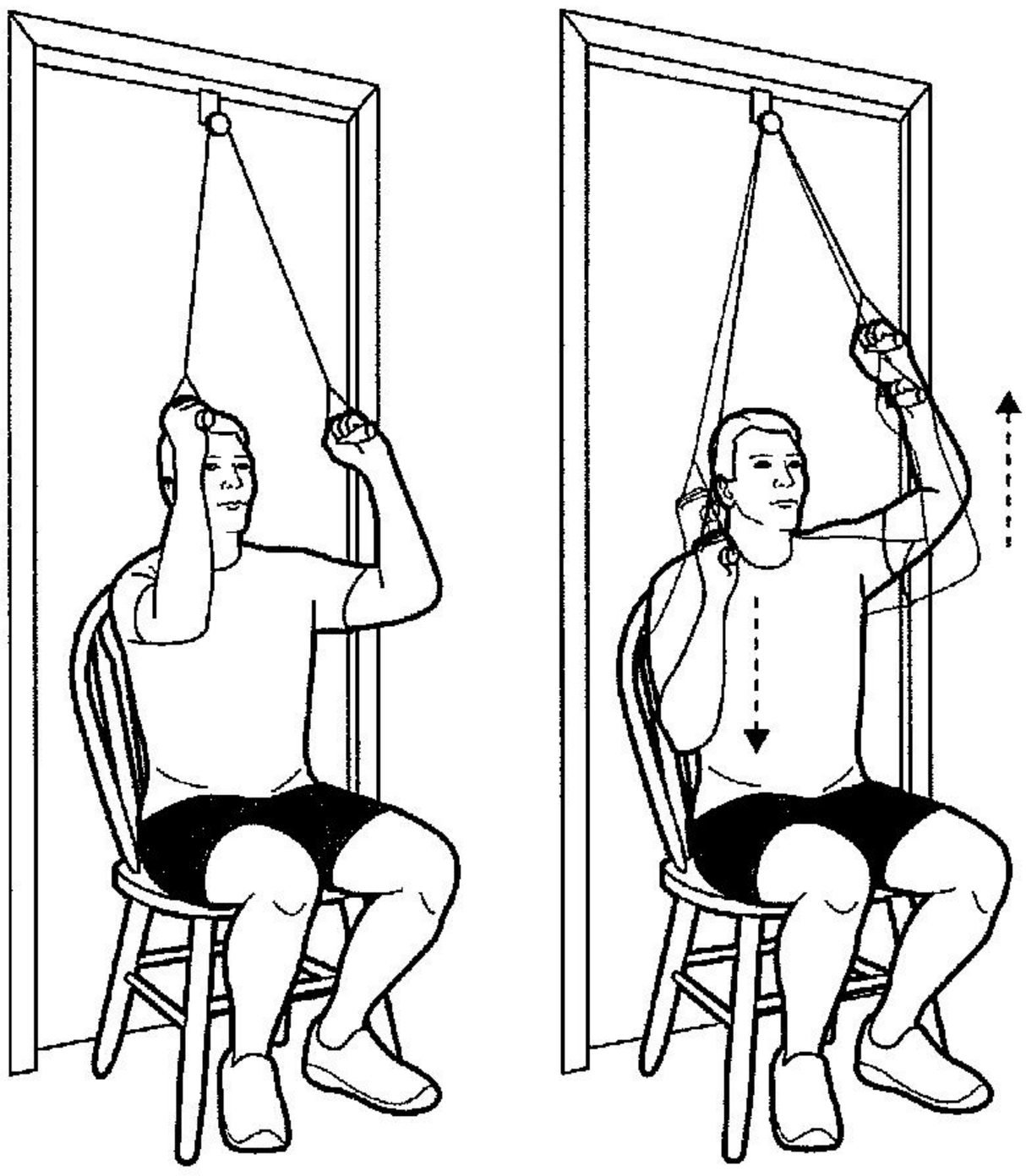
Picture 1

Picture 2

APPENDIX C HOME SHOULDER EXERCISES

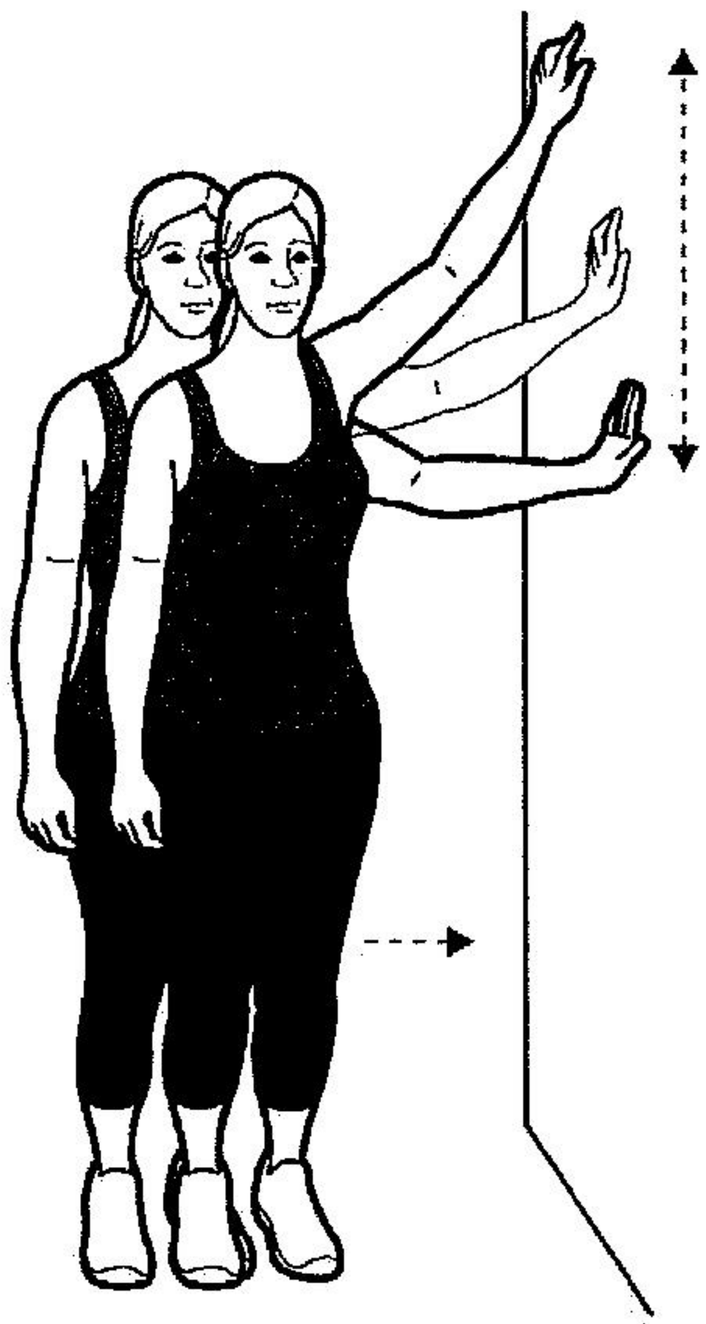
Flexion: Shoulder Flexion with Pulleys

Begin sitting. Hold the pulley handles in each hand and use the unaffected arm to move the affected arm forward and upwards. Move the arm upward in a comfortable range. Feel a gentle stretch and stop before there is pain. Hold 30 seconds and repeat 5 times.



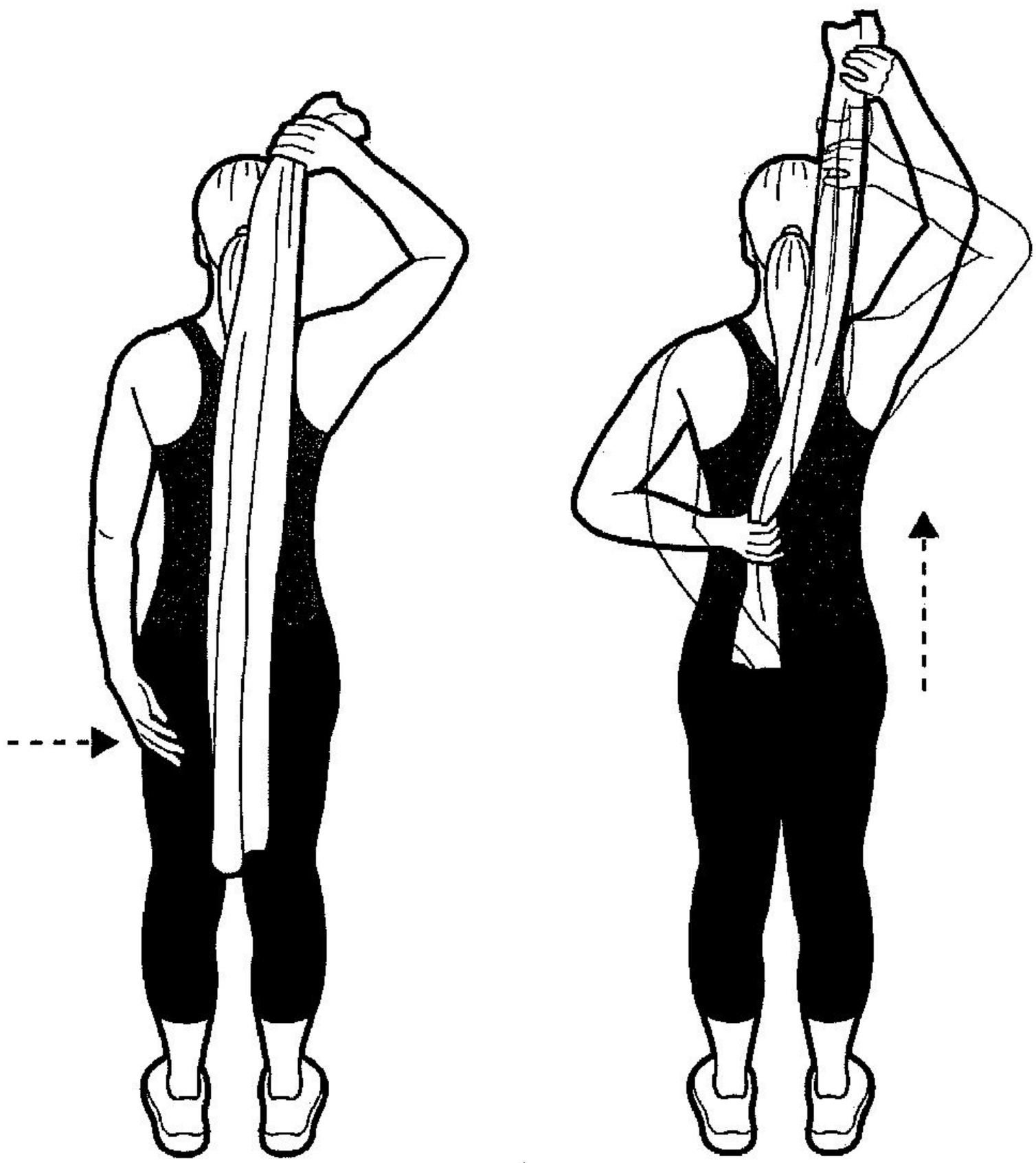
Abduction: Sideways Wall Climb for Abduction

Stand with your affected side facing the wall. Walk your fingers up the wall, climbing as high as you can. Move your body towards the wall and go as high as you can in a comfortable range. Hold your hand at the highest pain free point for 30 seconds. Walk down the wall and repeat 5 times.



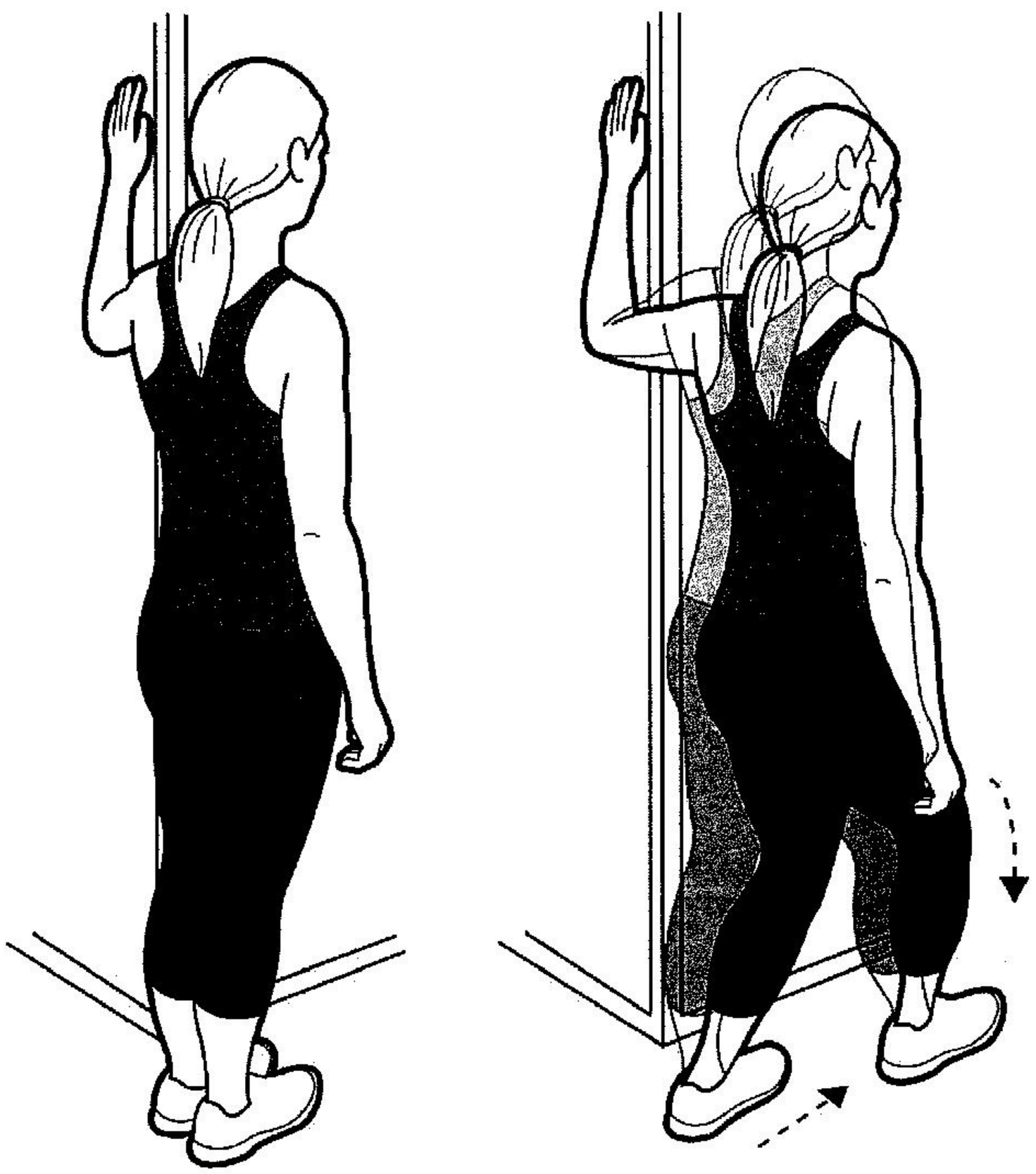
Internal Rotation: Towel Stretch for Internal Rotation

Hold a towel behind your back with the affected arm at the bottom of the towel. Use the unaffected arm to pull the affected arm up as far as you can. Go to the point of a gentle stretch. Stop before there is any pain. Hold 30 seconds and repeat 5 times.



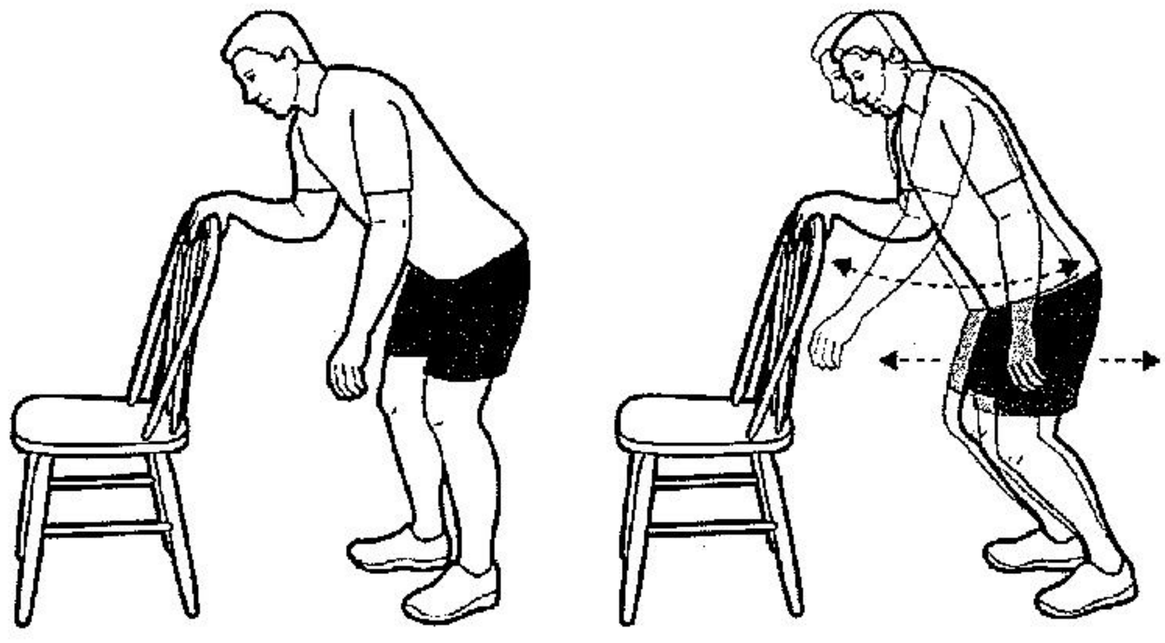
External Rotation: Doorway External Rotation Stretch

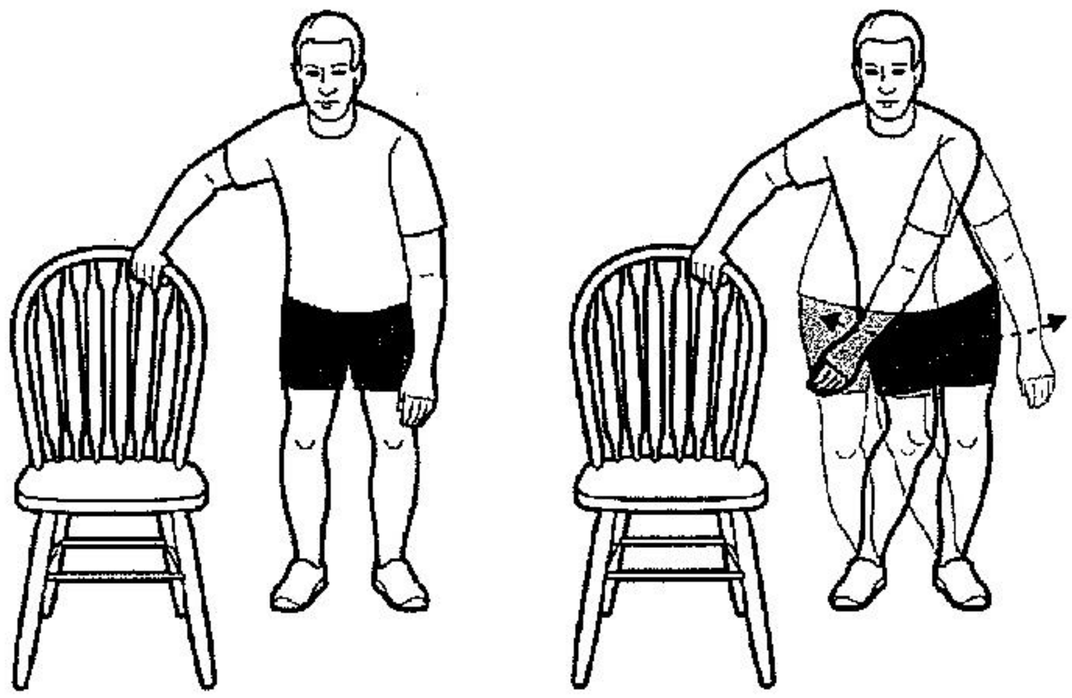
Stand at end of wall or in a doorway facing the opening in the door. Bend the elbow and raise the arm to just below shoulder height. Place the inside of the forearm on the wall. Move the leg furthest from the wall and hips forward while not moving the shoulder and elbow. Bend the knees slightly. Go to the point of a gentle stretch. Stop before there is any pain. Hold 30 seconds and repeat 5 times.



All Planes: Pendulum

Begin by leaning forwards with your unaffected arm supported on a table or chair. Keep your back straight, bend the knees slightly and relax your shoulder. Gently move your hips forward and backward in a rocking motion allowing momentum to gently swing your arm. Swinging the hips side to side will allow the arm to swing right to left. The motion needs to be pain free. Repeat 30 times up and back followed by 30 side to side.





CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6, 8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Disclosed

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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BB
Bb Bellberry Limited supporting research and ethics
bB
bb

129 Glen Osmond Rd
Eastwood SA 5063
Phone: 08 8361 3222
Fax: 08 8361 3322

02-Oct-14

Dr. Jane Fitzpatrick
Sports Medicine Professionals Pty Ltd
21 Erin Street
Richmond VIC 3121

Dear Dr. Fitzpatrick

Re: Application No: 2013-10-535-AE-A-1
Study Title: AUX-CC-871 - A randomized, double-blind, placebo-controlled study of the safety and efficacy of AA4500 for the treatment of adhesive capsulitis of the shoulder
Type of Application: Amendment/Investigator Brochure Form

Name of the Documents Submitted and Approved:
Attachments

Includes:
The Committee notes the change of study site address from Suite 5, Level 7, 32 Erin Street, Richmond VIC 3121 to 21 Erin St, Richmond VIC 3121. Updated CTN, HREC Indemnity and Standard Indemnity have been received at Bellberry.

Date of Approval: 01-Oct-14

Thank you for submitting the above mentioned application.

The Bellberry Human Research Ethics committee (HREC) has scientifically and ethically reviewed this study.

This Bellberry HREC is constituted and operates in accordance with the National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research (2007, incorporating all updates as at March 2014) (National Statement).

I wish to advise that the Bellberry Human Research Ethics Committee has ethically approved these documents/changes.

Details of Ethics Committee:

It is the process of the Bellberry Human Research Ethics Committee not to disclose personal details of its reviewing members. This Project was considered by a Committee that fulfilled the requirements of the National Statement (2007) section 5.1.29-30. Please note that the Principal Investigator and Co-Investigators are not members of the Bellberry Human Research Ethics Committees and were not involved in the review of this study.

Please do not hesitate to contact me if further clarification is required.

Yours sincerely

Michael James

Michael James
Chair, Committee C
BELLBERRY HUMAN RESEARCH ETHICS COMMITTEE

Clinical Study for the Treatment of Adhesive Capsulitis of the Shoulder (AC)

Study is a Phase 2b, double-blind, placebo-controlled study of the safety and efficacy of AA4500 for the treatment of adhesive capsulitis of the shoulder. To be eligible for treatment, a subject must have unilateral idiopathic adhesive capsulitis of the shoulder with restricted range of motion in the affected shoulder for at least 3 months but not more than 12 months. Subjects will be screened for study eligibility within 28 days before injection of study drug.

Approximately 300 adult women and men are to be enrolled in this study. Following screening and determination of study eligibility, subjects will be randomized 3:1 to receive 0.58 mg of AA4500 or placebo. Subjects will receive up to 3 injections of study drug. Each injection will be separated by a minimum of 21 days. Subjects will also be instructed in home shoulder exercises after the first injection.

First Submitted Date ICMJE	December 2, 2013
First Posted Date ICMJE	December 10, 2013
Results First Submitted Date	April 18, 2017
Results First Posted Date	May 25, 2017
Last Update Posted Date	October 5, 2017
Study Start Date ICMJE	November 2013
Actual Primary Completion Date	December 2014 (Final data collection date for primary outcome measure)
Current Primary Outcome Measures ICMJE **(submitted: April 18, 2017)**	Change From Baseline to Day 95 in Active Forward Flexion [Time Frame: Baseline, day 95] Active range of motion (AROM) measurement using a goniometer to assess forward flexion in the affected shoulder

Original Primary Outcome Measures ICMJE (submitted: December 5, 2013)	The change (degrees) from baseline to the Day 95 follow-up in active forward flexion in the affected shoulder. [Time Fr
Change History	Complete list of historical versions of study NCT02006719 on ClinicalTrials.gov Archive Site
Current Secondary Outcome Measures ICMJE (submitted: April 18, 2017)	• Change From Baseline to Day 95 in Adapted American Shoulder and Elbow Surgeons (ASES) Function Subscale Function subscale score ranging from 0-50, with 0 being most dysfunctional, derived from participant assessment of ab 0=unable to do to, 1=very difficult to do, 2=somewhat difficult, and 3=not difficult, and calculated as (cumulative total s Standardized Shoulder Assessment Form, Patient Self-Evaluation (United States adapted version). • Change From Baseline to Day 95 in Pain With Movement Using 11-point Numeric Rating Scale (NRS) [Time Fra Participant assessment of pain in response to "How bad is the pain upon movement of your affected shoulder at its wor pain at all and 10=pain as bad as it can be. • Change From Baseline to Day 95 in Active Abduction [Time Frame: Baseline, day 95] AROM measurement using a goniometer to assess abduction in the affected shoulder • Change From Baseline to Day 95 in Passive Forward Flexion [Time Frame: Baseline, day 95] Passive range of motion (PROM) measurement using a goniometer to assess forward flexion in the affected shoulder • Change From Baseline to Day 95 in Passive Abduction [Time Frame: Baseline, day 95] PROM measurement using a goniometer to assess abduction in the affected shoulder • Change From Baseline to Day 95 in Active Internal Rotation [Time Frame: Baseline, day 95]

	AROM measurement using a goniometer to assess internal rotation in the affected shoulder • Change From Baseline to Day 95 in Active External Rotation [Time Frame: Baseline, day 95] AROM measurement using a goniometer to assess external rotation in the affected shoulder • Change From Baseline to Day 95 in Passive Internal Rotation [Time Frame: Baseline, day 95] PROM measurement using a goniometer to assess internal rotation in the affected shoulder • Change From Baseline to Day 95 in Passive External Rotation [Time Frame: Baseline, day 95] PROM measurement using a goniometer to assess external rotation in the affected shoulder • Change From Baseline to Day 95 in Adapted ASES Pain Subscale [Time Frame: Baseline, day 95] Pain subscale score ranging from 0-50, with 0 being greatest pain, derived from participant overall assessment of pain i today?" using an 11-point NRS where 0=no pain at all and 10=pain as bad as it can be and calculated as (10 - NRS score) Form, Patient Self-Evaluation • Subject Satisfaction With Treatment at Day 95 [Time Frame: Day 95] Participant assessment of satisfaction with treatment rated as very satisfied, quite satisfied, neither satisfied nor dissat • Investigator Assessment of Improvement With Treatment at Day 95 [Time Frame: Day 95] Investigator assessment of degree of improvement in severity of the participant's treated shoulder compared with scre minimally improved, no change, minimally worse, much worse, or very much worse.
Original Secondary Outcome Measures ICMJE **(submitted: December 5, 2013)**	• Change from baseline to Day 95 in American Shoulder and Elbow Surgeons Standardized Shoulder Assessment • Change (degrees) from baseline to the Day 95 follow-up in abduction [Time Frame: Day 95] • Change from baseline to the Day 95 follow-up in pain with movement using a 11-point Visual Analogue Scale (V

	• Change (degrees) from baseline to the Day 95 follow-up in internal rotation [Time Frame: Day 95] • Change from baseline to the Day 95 follow-up in external rotation [Time Frame: Day 95] • Change from baseline to the Day 95 follow-up in ASES pain sub-scale [Time Frame: Day 95] • Investigator satisfaction with treatment at the Day 95 follow-up [Time Frame: Day 95] Degree of improvement in the severity of the subject's treated shoulder compared with screening assessed by question 1. Very Much Improved 2. Much Improved 3. Minimally Improved 4. No Change 5. Minimally Worse 6. Much Worse 7. Very Much Worse • Subject satisfaction with treatment at the Day 95 follow-up [Time Frame: Day 95] Determined by questionnaire and rated as follows: 1. Very Satisfied 2. Quite Satisfied 3. Neither Satisfied nor Dissatisfied 4. Quite Dissatisfied 5. Very Dissatisfied
Current Other Outcome Measures ICMJE	*Not Provided*
Original Other Outcome Measures ICMJE	*Not Provided*

Descriptive Information

Study Type	**Interventional**
Study Design	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor); Primary Purpose: Treatment
Conditions	**Adhesive Capsulitis** Frozen Shoulder
Interventions	Biological: **Collagenase** Clostridium Histolyticum Other: Placebo
Enrollment	322

Participant Flow

Go to ▼

Top of PageParticipant FlowBaseline CharacteristicsOutcome MeasuresAdverse EventsLimitations and Caveats InformationMore Information

Recruitment Details		
Pre-assignment Details		
Arm/Group Title	AA4500	Placebo

▼Arm/Group Description	Up to 3 injections of 0.58 mg/1 mL collagenase clostridium histolyticum (AA4500), minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Period Title: **Overall Study**		
Started	237	85
Completed	219	80
Not Completed	18	5
Reason Not Completed		
Withdrawal by Subject	10	2
Lost to Follow-up	5	1
Protocol Violation	2	0
Adverse Event	1	1
Other/Unknown	0	1

Baseline Characteristics

Go to ▼

Top of PageParticipant FlowBaseline CharacteristicsOutcome MeasuresAdverse EventsLimitations and Caveats InformationMore Information

Arm/Group Title	AA4500	Placebo	Total

▼Arm/Group Description		Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise	Total of all reporting groups
Overall Number of Baseline Participants		237	84	321
▼Baseline Analysis Population Description		All participants who received at least 1 administration of study drug (1 participant excluded)		
Age, Continuous Median (Full Range) Unit of measure: Years				
	Number Analyzed	237 participants	84 participants	321 participants
		53.0 (29 to 75)	51.0 (22 to 70)	52.0 (22 to 75)
Age, Customized Measure Type: Count of Participants Unit of measure: Participants	Number Analyzed	237 participants	84 participants	321 participants
<45		30	14	44

		12.7%	16.7%	13.7%
45-54		114 48.1%	44 52.4%	158 49.2%
55-64		75 31.6%	23 27.4%	98 30.5%
65-74		17 7.2%	3 3.6%	20 6.2%
≥75		1 0.4%	0 0.0%	1 0.3%
Sex: Female, Male Measure Type: Count of Participants Unit of measure: Participants				
	Number Analyzed	237 participants	84 participants	321 participants
	Female	162 68.4%	60 71.4%	222 69.2%
	Male	75	24	99

		31.6%	28.6%	30.8%
Ethnicity (NIH/OMB) Measure Type: Count of Participants Unit of measure: Participants				
	Number Analyzed	237 participants	84 participants	321 participants
	Hispanic or Latino	17 7.2%	4 4.8%	21 6.5%
	Not Hispanic or Latino	220 92.8%	80 95.2%	300 93.5%
	Unknown or Not Reported	0 0.0%	0 0.0%	0 0.0%
Race (NIH/OMB) Measure Type: Count of Participants Unit of measure: Participants				

	Number Analyzed	237 participants	84 participants	321 participants
	American Indian or Alaska Native	0 0.0%	1 1.2%	1 0.3%
	Asian	6 2.5%	4 4.8%	10 3.1%
	Native Hawaiian or Other Pacific Islander	2 0.8%	0 0.0%	2 0.6%
	Black or African American	22 9.3%	7 8.3%	29 9.0%
	White	205 86.5%	72 85.7%	277 86.3%
	More than one race	1 0.4%	0 0.0%	1 0.3%

	Unknown or Not Reported	1 0.4%	0 0.0%	1 0.3%

Outcome Measures

Go to ▼

Top of PageParticipant FlowBaseline CharacteristicsOutcome MeasuresAdverse EventsLimitations and Caveats InformationMore Information1.Primary Outcome

Title	Change From Baseline to Day 95 in Active Forward Flexion
▼Description	Active range of motion (AROM) measurement using a goniometer to assess forward flexion in the affected shoulder
Time Frame	Baseline, day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 25 participants missing either baseline or day 95 active forward flexion measurement also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	217	79

Mean (Standard Deviation) Unit of Measure: degrees		
	41.0 (28.89)	35.9 (23.36)

2.Secondary Outcome

Title	Change From Baseline to Day 95 in Adapted American Shoulder and Elbow Surgeons (ASES) Function Subscale
▼Description	Function subscale score ranging from 0-50, with 0 being most dysfunctional, derived from participant assessment of ability to do 10 activities with affected shoulder/arm where 0=unable to do to, 1=very difficult to do, 2=somewhat difficult, and 3=not difficult, and calculated as (cumulative total score for the 10 activity items) × (5/3); adapted from ASES Standardized Shoulder Assessment Form, Patient Self-Evaluation (United States adapted version).
Time Frame	Baseline, day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 34 participants missing either baseline or day 95 function subscale scores also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	211	76

Mean (Standard Deviation) Unit of Measure: units on a scale		
	17.0 (11.65)	14.8 (11.14)

3.Secondary Outcome

Title	Change From Baseline to Day 95 in Pain With Movement Using 11-point Numeric Rating Scale (NRS)
▼Description	Participant assessment of pain in response to "How bad is the pain upon movement of your affected shoulder at its worst in the last 24 hours?" using an 11-point NRS where 0=no pain at all and 10=pain as bad as it can be.
Time Frame	Baseline, day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 33 participants missing either baseline or day 95 pain with movement scores also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	211	77
Mean (Standard Deviation)		

Unit of Measure: units on a scale		
	-4.4 (2.83)	-3.9 (2.93)

4.Secondary Outcome

Title	Change From Baseline to Day 95 in Active Abduction
▼Description	AROM measurement using a goniometer to assess abduction in the affected shoulder
Time Frame	Baseline, day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 25 participants missing either baseline or day 95 active abduction measurement also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	217	79
Mean (Standard Deviation) Unit of Measure: degrees		

	49.0 (33.10)	43.8 (30.71)

5.Secondary Outcome

Title	Change From Baseline to Day 95 in Passive Forward Flexion
▼Description	Passive range of motion (PROM) measurement using a goniometer to assess forward flexion in the affected shoulder
Time Frame	Baseline, day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 25 participants missing either baseline or day 95 active forward flexion measurement also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	217	79
Mean (Standard Deviation) Unit of Measure: degrees		
	39.3 (29.47)	34.1 (22.37)

6.Secondary Outcome

Title	Change From Baseline to Day 95 in Passive Abduction
▼Description	PROM measurement using a goniometer to assess abduction in the affected shoulder
Time Frame	Baseline, day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 25 participants missing either baseline or day 95 passive abduction measurement also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	217	79
Mean (Standard Deviation) Unit of Measure: degrees		
	45.4 (33.69)	42.8 (32.12)

7.Secondary Outcome

Title	Change From Baseline to Day 95 in Active Internal Rotation

▼Description	AROM measurement using a goniometer to assess internal rotation in the affected shoulder
Time Frame	Baseline, day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 25 participants missing either baseline or day 95 active internal rotation measurement also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	217	79
Mean (Standard Deviation) Unit of Measure: degrees		
	23.1 (25.21)	20.9 (23.58)

8.Secondary Outcome

Title	Change From Baseline to Day 95 in Active External Rotation
▼Description	AROM measurement using a goniometer to assess external rotation in the affected shoulder

Time Frame	Baseline, day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 25 participants missing either baseline or day 95 active external rotation measurement also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	217	79
Mean (Standard Deviation) Unit of Measure: degrees		
	28.6 (21.30)	26.1 (22.67)

9.Secondary Outcome

Title	Change From Baseline to Day 95 in Passive Internal Rotation
▼Description	PROM measurement using a goniometer to assess internal rotation in the affected shoulder
Time Frame	Baseline, day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 25 participants missing either baseline or day 95 passive internal rotation measurement also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	217	79
Mean (Standard Deviation) Unit of Measure: degrees		
	24.1 (23.77)	20.3 (23.61)

10.Secondary Outcome

Title	Change From Baseline to Day 95 in Passive External Rotation
▼Description	PROM measurement using a goniometer to assess external rotation in the affected shoulder
Time Frame	Baseline, day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 25 participants missing either baseline or day 95 passive external rotation measurement also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	217	79
Mean (Standard Deviation) Unit of Measure: degrees		
	24.8 (22.31)	24.4 (26.16)

11.Secondary Outcome

Title	Change From Baseline to Day 95 in Adapted ASES Pain Subscale
▼Description	Pain subscale score ranging from 0-50, with 0 being greatest pain, derived from participant overall assessment of pain in response to "How bad is the pain in your affected shoulder today?" using an 11-point NRS where 0=no pain at all and 10=pain as bad as it can be and calculated as (10 - NRS score) x 5; adapted from ASES Standardized Shoulder Assessment Form, Patient Self-Evaluation
Time Frame	Baseline, day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 33 participants missing either baseline or day 95 pain subscale scores also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	211	77
Mean (Standard Deviation) Unit of Measure: units on a scale		
	15.9 (13.46)	13.5 (13.45)

12.Secondary Outcome

Title	Subject Satisfaction With Treatment at Day 95
▼Description	Participant assessment of satisfaction with treatment rated as very satisfied, quite satisfied, neither satisfied nor dissatisfied, quite dissatisfied, or very dissatisfied.
Time Frame	Day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 11 participants not completing questionnaire also excluded

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	229	81
Measure Type: Number Unit of Measure: participants		
Very satisfied	142	43
Quite satisfied	38	22
Neither satisfied nor dissatisfied	32	8
Quite dissatisfied	10	2
Very dissatisfied	7	6

13.Secondary Outcome

Title	Investigator Assessment of Improvement With Treatment at Day 95
▼Description	Investigator assessment of degree of improvement in severity of the participant's treated shoulder compared with screening rated as very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.
Time Frame	Day 95

▼ Outcome Measure Data

▼Analysis Population Description

All participants who have a baseline AROM measurement of the affected shoulder and at least 1 measurement of AROM of the affected shoulder following the first administration of study drug (1 participant excluded); 10 participants also excluded for incomplete questionnaire

Arm/Group Title	AA4500	Placebo
▼Arm/Group Description:	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise
Overall Number of Participants Analyzed	229	82
Measure Type: Number Unit of Measure: participants		
Very much improved	94	27
Much improved	73	31
Minimally improved	41	16
No change	13	8
Minimally worse	6	0
Much worse	1	0
Very much worse	1	0

Adverse Events

Go to

Top of PageParticipant FlowBaseline CharacteristicsOutcome MeasuresAdverse EventsLimitations and Caveats InformationMore Information

Time Frame	130 days (up to 28 day screening period and 95±7 day study period)
Adverse Event Reporting Description	[Not Specified]

Arm/Group Title	AA4500	Placebo
Arm/Group Description	Up to 3 injections of 0.58 mg/1 mL AA4500, minimum of 21 days apart and home shoulder exercise	Up to three 1-mL injections of placebo, minimum of 21 days apart and home shoulder exercise

All-Cause Mortality

	AA4500		**Placebo**	
	Affected / at Risk (%)		Affected / at Risk (%)	
Total	--/--		--/--	

Serious Adverse Events

	AA4500		Placebo	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	4/237 (1.69%)		1/84 (1.19%)	
Cardiac disorders				
Atrial fibrilation * [1]	1/237 (0.42%)	1	0/84 (0.00%)	0
Gastrointestinal disorders				
Gastric ulcer * [1]	0/237 (0.00%)	0	1/84 (1.19%)	1
Injury, poisoning and procedural complications				
Overdose * [1]	1/237 (0.42%)	1	0/84 (0.00%)	0
Post procedural bile leak * [1]	1/237 (0.42%)	1	0/84 (0.00%)	0
Procedural pain * [1]	1/237 (0.42%)	1	0/84 (0.00%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Glioblastoma * [1]	1/237 (0.42%)	1	0/84 (0.00%)	0

*

Indicates events were collected by non-systematic assessment

1

Term from vocabulary, MedDRA (16.1)

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	5%			
	AA4500		**Placebo**	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	188/237 (79.32%)		37/84 (44.05%)	
General disorders				
Injection site bruising [*1]	52/237 (21.94%)	65	10/84 (11.90%)	13
Injection site pain [*1]	50/237 (21.10%)	77	11/84 (13.10%)	17
Localised oedema [*1]	20/237 (8.44%)	28	1/84 (1.19%)	1
Injury, poisoning and procedural complications				
Contusion [*1]	71/237 (29.96%)	106	2/84 (2.38%)	2

Musculoskeletal and connective tissue disorders				
Musculoskeletal pain * [1]	90/237 (37.97%)	138	18/84 (21.43%)	24
Pain in extremity * [1]	13/237 (5.49%)	16	4/84 (4.76%)	5
Skin and subcutaneous tissue disorders				
Ecchymosis * [1]	47/237 (19.83%)	69	3/84 (3.57%)	4
Pruritus * [1]	12/237 (5.06%)	15	0/84 (0.00%)	0

*

Indicates events were collected by non-systematic assessment

1

Term from vocabulary, MedDRA (16.1)

Limitations and Caveats

Go to

Top of PageParticipant FlowBaseline CharacteristicsOutcome MeasuresAdverse EventsLimitations and Caveats InformationMore Information[Not Specified]

More Information

Go to

Top of PageParticipant FlowBaseline CharacteristicsOutcome MeasuresAdverse EventsLimitations and Caveats InformationMore Information**Certain Agreements**

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Results Point of Contact

Name/Title:Clinical Trial Coordinator

Organization:Endo Pharmaceuticals Inc.

EMail:clinicalsite.inquiries@endo.com

Responsible Party:	Endo Pharmaceuticals
ClinicalTrials.gov Identifier:	NCT02006719 History of Changes
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