Study Number: IP157-003

Title of Study: Phase I, Double-Blind Study to Evaluate the Allergic Potential of NEBIDO® and Formulation Components in Patients Who Have Exhibited Anaphylactic-Like Reactions Following Intramuscular Injection of NEBIDO®

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Publications (reference): None

Studied Period (years):	**Phase of Development**: 1
Date first patient enrolled: 13-Sep-2010	
Date last patient completed: 15-Sep-2010	

Objectives: The overall objective of the study was to evaluate, using skin prick testing and intramuscular (IM) injection, the possible nature and etiology of anaphylactic-like reactions to NEBIDO and its formulation components (castor oil and benzyl benzoate) in patients who were reported to have experienced spontaneous anaphylactic-like adverse events (AEs) following injection of NEBIDO.

Methodology: A diagnostic workup was to be performed in this Phase 1 double-blind, single-center study in 4 patients identified from postmarketing safety surveillance with reported anaphylactic-like reactions to NEBIDO following IM injection. The NEBIDO preparation as well as each ingredient in the preparation was to be tested for its allergic potential in these patients.

The study included:

1. A telephone interview for screening purposes by the investigator at time of recruitment to assess detailed patient history, to ascertain special needs during the stay of the patients (eg, special meals). The telephone interview included:
   - Medical history, including current medications;
   - Medicinal, food and environmental allergies; and
   - Past and present pulmonary history
2. A telephone call directly prior to travel to make sure patients had no acute infectious disease (eg, common cold with bronchitis); and
3. Two (2) study days (day 1 and day 2) for evaluation.
   - Day 1 included both a baseline phase and an evaluation phase. The baseline phase included physical examination, vital signs, laboratory tests, and electrocardiogram (ECG) assessment. The day 1 evaluation phase included 2 skin prick testing procedures and the first sequence (of 2) IM injection testing procedures.
   - Day 2 included a continuation of the evaluation phase, with a second IM testing procedure.

Following the completion of day 2 procedures, patients were to remain overnight in the clinic for further observation and then be released on day 3, approximately 16 to 24 hours following the last day 2 injection. Vital signs, IM injection test article challenge assessments, and a physical examination were to be collected just prior to discharge on day 3.

Baseline Phase:

Patients were to arrive on the morning of day 1. Following informed consent (in the patient's native language) baseline assessments and evaluations were to be collected that included the following:

- Update of medical history, including current medications; medicinal, food and environmental allergies; and past and present pulmonary history
- Complete physical examination to rule out clinically significant pre-existing findings, eg, mastocytosis which is characterized by skin lesions that are dark-brown and fixed, itching, abdominal cramping, abdominal discomfort, low blood pressure, bone and muscle pain, nausea, low body temperature, skin and eye coloration (specifically assessed because the skin and whites of eyes may turn red in the presence of an allergic reaction)
- Vital signs (eg, blood pressure, pulse, respiratory rate, temperature, weight, height, and body mass index [BMI])
- ECG
- Spirometry
- Complete blood and platelet count
- Blood clotting time
- Blood tests to rule out contraindications for testing (eg, erythrocyte sedimentation rate [ESR], serum chemistry)
- Blood test for baseline tryptase
- Blood sample for baseline total IgE
- Blood sample for baseline IgE antibodies specific to latex IgE (with avoidance of latex products prior to sample collection)
- Collection of a 30-mL blood sample for serum, to be stored for possible future testing for antigen-specific antibodies.

Note: The time for receiving results of the blood test noted above was around 4 hours.

Evaluation Phase:

Following the day 1 baseline phase assessments, patients were to continue into the day 1 evaluation phase. The day 1 evaluation phase included a skin prick testing regimen in which patients were to undergo concurrent skin prick testing (ie, test articles from 1 set were applied and skin was pricked during the same time period). Following the completion of the 2 sets of skin prick tests on day 1, if the findings from these skin prick tests were negative, NEBIDO or normal saline (administered in a blinded fashion) was to be administered by IM injection.

Allergen test article sets were to be tested in 2 concurrent skin prick testing periods, separated by a 60-minute observational period. If the skin prick tests were negative for set 1 throughout the 1-hour observation period, the testing proceeded to set 2. Additional time between skin prick tests may have been warranted if a suspected or positive reaction was encountered. If a positive reaction was observed, testing of that test article antigen causing the reaction was to cease and further testing of remaining test articles could continue at the discretion of the Principal Investigator. In addition, the Investigator and patient had the option to stop at any time during the escalation approach from set 1 to set 2 or prior to the IM injections on day 1 or day 2. They could also opt for part of the test article testing (eg, a patient could elect to participate only in the skin prick testing; however, a patient could not have the IM injection without at least 1 skin prick test application).

The allergen test articles were to be prepared by the pharmacist at the site; the pharmacist was not to be blinded to arrangement and order of each test article within each set or IM injection administered. The patient and the examiner of the allergy observations and assessments each were to remain blinded to the arrangement of the test articles administered in each of the 2 skin prick tests, as well as the IM injections (ie, normal saline or NEBIDO) administered on day 1 and day 2. In addition, an unblinded nurse or doctor was to administer each IM injection by slowly depressing the plunger carefully and at a constant

rate across injections using proper IM technique including gluteus medius muscle location and aspiration prior to injection. An additional inpatient study day may have been required to complete testing that was not performed on study day 1 or day 2 and/or in the event that additional observation period was required for suspected or observed allergic or other adverse reaction to testing.

***Details of Skin Prick Assessments**:*

The following assessments were to be performed to collect specific observations regarding the skin prick testing.

- Prior to the first (set 1) skin prick test, a baseline set of vital signs was to be measured. These vital signs were to be measured 15 minutes prior to the allergy testing. In addition, in order to establish a baseline (pre-treatment) assessment of the set 1 skin test area, a skin prick assessment (SPA) was to be performed immediately prior to the skin prick testing procedure.
- Set 1 test articles were then to be given, concurrently at hour 0.
  - Fifteen (15) minutes following the set 1 skin prick test, vital signs, and SPA were to be performed.
  - Sixty (60) minutes following the set 1 skin prick test, vital signs and 2 SPAs were to be performed; one SPA at set 1 site post-administration and the other SPA at set 2 site (pre-administration). Note that this assessment was to be performed just prior to the administration of the set 2 test articles. It was important that the second skin prick testing procedure occur 60 minutes after the first skin prick test and be administered to a different skin site location than set 1.
- Set 2 test articles were to be given, concurrently.
  - Fifteen (15) minutes following the set 2 skin prick test, vital signs and SPA were to be obtained.
  - Sixty (60) minutes following the set 2 skin prick test, vital signs and SPA were to be performed.

The health professional performing the skin prick test was to conduct the testing for set 1 and set 2 using the following method:

- Baseline SPA was conducted
- The test site (lower arm) was cleaned with alcohol or antiseptic
- Concurrent skin prick testing set on the skin was performed
- Vital signs were collected and the skin was checked for red, raised itchy areas (ie, wheals) after 15 minutes post skin prick administration

***Details of IM Injection Test Assessments**:*

If the 2 sets of skin prick tests on day 1 resulted in negative findings, the day 1 evaluation phase continued with the first set of IM injection testing, as follows:

- On day 1, 1 hour after the set 2 skin prick testing, vital signs, spirometry test, and IM injection test article challenge assessment were performed.
- Patients were to receive the first of 2 consecutive IM injections separated by 1 hour:
  - Normal saline 0.4 mL as the first IM injection and normal saline 3.6 mL as the second injection, OR;
  - NEBIDO 0.4 mL as the first IM injection and NEBIDO 3.6 mL as the second injection.
- Fifteen (15) minutes and 60 minutes following each injection, vital signs and IM injection assessment were to be collected. In addition, a spirometry test was to be collected 15 minutes following each injection.

- On day 2, the alternate set of IM injections were to be administered in the morning, again with pre-injection vital signs, spirometry, and IM test article challenge assessment.
- Fifteen (15) minutes and 60 minutes following each injection, vital signs and IM test article challenge assessment were to be collected. In addition, a spirometry test was to be collected 15 minutes following each injection.

Following the completion of day 2 procedures, patients were to remain overnight in the clinic for further observation and then be released on day 3, approximately 16 to 24 hours following the last day 2 injection. Vital signs, IM injection test article challenge assessments, and a physical examination were to be collected just prior to discharge on day 3. If further observation was determined to be necessary by the Investigator, an additional day of observation may have been extended beyond day 3.

On either day 1 or day 2, if there was a positive reaction with objective signs of anaphylaxis, the blind was to be broken for the test article(s). Appropriate care was to be given for a positive hypersensitivity reaction until the patient's condition has stabilized per the Investigator. If a hypersensitivity reaction was noted on day 1 but was related to the normal saline, then the testing was to be repeated on the following day using the double-blind NEBIDO test article, which may have prolonged the inpatient stay by an additional day.

Number of Patients (Planned and Analyzed):

Planned: Up to 8

Enrolled: 1

Completed: 0

Discontinued: 1

Diagnosis and Main Criteria for Inclusion: Male patients aged ≥18 years who had exhibited suspicion of anaphylactic-like reactions following IM injection of NEBIDO and were willing to consent to evaluation of repeat exposure to NEBIDO and its ingredients.

Test Product, Dose and Mode of Administration, Batch Number: Test articles including NEBIDO and its ingredients (castor oil and benzyl benzoate), sodium chloride, histamine, and an antiseptic were to be administered for evaluation of allergy via skin prick testing (2 complete sets) or IM injection (2 sets, 4 total), as identified below.

Skin Prick Testing:

Testosterone undecanoate, 25 mg/mL in benzyl benzoate
Testosterone undecanoate, 250 mg/mL in benzyl benzoate
Benzyl benzoate
Refined castor oil (1:10 dilution)
Refined castor oil (undiluted)
NEBIDO (1:10 dilution)
NEBIDO (undiluted)
0.9% normal saline (negative control)
1 mg/mL histamine HCl (open-label positive control)
Antiseptic

Intramuscular Injection:

NEBIDO, 0.4 mL IM
NEBIDO, 3.6 mL IM
0.9% normal saline, 0.4 mL IM
0.9% normal saline, 3.6 mL IM

Duration of Treatment: Patients were expected to remain in the clinical study unit for 3 days including 2 overnight stays.

Reference Therapy, Dose and Mode of Administration, Batch Number: 0.9% normal saline was to be administered for evaluation of allergy via skin prick testing (negative control) and IM injection (0.4 and 3.6 mL IM)

Criteria for Evaluation:

Efficacy: No efficacy assessments were conducted.

Safety: Allergy testing assessments (SPA and IM injection test article challenge assessment), AEs, vital signs, spirometry, physical examinations, baseline clinical laboratory evaluations and 12-lead ECG.

SUMMARY:

SAFETY RESULTS:

There was no death or serious adverse event reported in this study.

Only 1 patient, a 44-year-old white male, was enrolled in the study. The patient's medical history showed the following known allergies: metamizole, penicillin, butylscopolamine, acetylsalicylic acid, metronidazole, and cefotiam. There were no known past or present pulmonary diagnoses. On day 1 (September 13, 2010) at baseline, the patient's physical examination was unremarkable. All laboratory parameters measured were within the normal range. The vital sign values measured at baseline were as follows: a pulse rate of 76 beats/min, a respiratory rate of 14 breaths/min, and an elevated blood pressure of 160/110 mm Hg, indicative of hypertension. A 12-lead ECG assessment was normal. The spirometry results for FEV_1, FVC, and FEV_1/FVC% were normal.

On day 1 in the evaluation phase, the patient received 2 sets of skin prick tests with NEBIDO and its components in his left forearm. Set 1 of the skin prick test included diluted refined castor oil, diluted NEBIDO (1:10), testosterone undecanoate (25 mg/mL in benzyl benzoate), and undiluted benzyl benzoate. Set 2 of the skin prick test included undiluted NEBIDO, testosterone undecanoate (250 mg/mL in benzyl benzoate), undiluted benzyl benzoate, and undiluted refined castor oil. Following the skin prick tests, the patient received 2 IM injections of saline at 0.4 mL and 3.6 mL in his right buttock.

The patient did not show any reaction following both skin prick tests (pre- and post-assessment). No reaction (normal) was defined as no raised red areas (ie, wheals, hives, or flares) observed at the test site or raised red area less than 3 mm or less than 50% of the histamine wheal. The vital signs during SPAs at various time points were normal. The IM injection test article challenge assessments for pre-IM injection and post-IM injections of saline at 0.4 mL and 3.6 mL for various time points were normal. The vital signs during pre- and post-IM injections of saline at 0.4 mL and 3.6 mL were normal. The spirometry results were normal at all time points with no change from baseline.

On day 2 (September 14, 2010) in the evaluation phase, the patient received an IM injection of NEBIDO at 0.4 mL in his left buttock. The IM injection test article challenge assessments for pre-IM injection and at 15 and 60 minutes post-IM injection (0.4 mL) of NEBIDO were performed. At 15 minutes post-IM injection (0.4 mL) of NEBIDO, the patient experienced 2 AEs of mild flushing and moderate hypertension (an elevated blood pressure of 205/130 mm Hg with a pulse of 76 beats/min). No other symptoms were reported. The AEs were treated with prednisolone, Diuretidin, and loratadine for a day and no other concomitant medications were reported. Both AEs resolved on the same day of occurrence with the blood pressure returning to a baseline elevated level as documented at screening. Both AEs were considered non-serious, pseudo-allergic reactions, and probably related to study drug as judged by the Investigator. The IM test article challenge assessments at 60 minutes post-IM injection (0.4 mL) of NEBIDO showed no allergy signs and symptoms present for any system. The vital signs consistently showed elevated blood pressure (15 minutes post-IM injection: 175/110 mm Hg; 60 minutes post-IM

injection: 180/110 mm Hg). Spirometry results for pre-IM injection showed normal results with no change from baseline.

On day 2, the 3.6-mL injection of NEBIDO was not administered as the study treatment was withdrawn due to the occurrence of 2 AEs. Hence, no day 2 IM injection test article challenge assessments or spirometry evaluations were performed for the 3.6-mL dose. The study treatment was withdrawn on September 14, 2010.

On day 3 for end of study, the patient's physical examination was unremarkable with a pulse rate of 72 beats/min, a respiratory rate of 14 breaths/min, and an elevated blood pressure of 150/95 mm Hg. The IM injection test article challenge assessments on day 3 showed no allergy signs and symptoms present for any system.