**CASE COMPREHENSIVE CANCER CENTER**

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| STUDY NUMBER: | CASE 1Z12 |
| STUDY TITLE: | A prospective, multi-center, double-blind, randomized, placebo-controlled study to evaluate the efficacy of abobotulinumtoxinA (BTX-A) in improving forehead wounds after Mohs micrographic surgery and reconstruction for skin cancer |
| PRINCIPAL INVESTIGATORS: | Kevin Cooper, MD<br>Department of Dermatology<br>University Hospitals Cleveland Medical Center<br>Case Western Reserve University<br>11100 Euclid Avenue<br>Cleveland, OH 44106<br>(216) 844-8200 |
| CO- INVESTIGATORS: | Joel Cohen, MD<br>AboutSkin Dermatology and DermSurgery<br>Englewood, CO<br><br>David Ozog, MD<br>Department of Dermatology<br>Henry Ford Health Systems<br>Detroit, MI<br><br>Roy Moy, MD<br>Department of Dermatology, UCLA<br>Moy-Fincher-Chipps Facial Plastics & Dermatology<br>Los Angeles, CA |
| SPONSOR: | Investigator Initiated |
| SUPPORT: | Medicis Pharmaceutical Corporation |
| CLINICAL FACILITY: | University Hospitals Cleveland Medical Center<br>UH- Bolwell Clinic<br>UH- Westlake |
| APPROVALS: | Protocol Review and Monitoring Committee: Approved July 3, 2012<br>Case Cancer IRB: Pending |

**SCHEMA**

| Procedure | Visit 1: Screening & Dysport Administration | Visit 2: Op Visit | Visit 3: 1-2 wk f/u | Visit 4: 6 wk f/u | Visit 5: 6 month f/u |
|---|---|---|---|---|---|
| Informed Consent | **X** | | | | |
| Pre-op Evaluation | **X** | | | | |
| Injection of Dysport or Placebo | **X** | | | | |
| Adverse Events | **X** | **X** | **X** | **X** | **X** |
| Medical/Medication History | **X** | **X** | **X** | **X** | **X** |
| Photography | **X** | **X** | **X** | **X** | **X** |
| Skin Evaluation | | **X** | **X** | **X** | **X** |
| Urine Pregnancy Test | **X** | | | | **X** |
| **Assessments** | | | | | |
| Physician VAS | | | | **X** | **X** |
| Patient POSAS | | **X** | **X** | **X** | **X** |
| Physician POSAS | | **X** | **X** | **X** | **X** |
| Patient survey | | | | | **X** |

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## 1.0 INTRODUCTION

### 1.1 Scarring after Mohs Surgery

A common and significant risk and side effect of surgery is scarring. A major obstacle in wound healing is the tension caused by the surrounding muscles. Although surgeons can close a wound to minimize this tension, the repeated contraction of the surrounding muscles in every day movement put recurrent stress on the wound, prolonging the healing process. This can also lead to the formation of hypertrophic scars. Botulinum toxin is a protein produced by the bacterium Clostridium botulinum, and it is well known as a neurotoxin. It blocks neuromuscular transmission, thereby preventing the affected muscle group from contracting. It was postulated that the injection of a botulinum toxin into the surrounding area of a scar would decrease contraction and thereby improve wound healing and scarring. Since then, there have been several studies describing the benefit of using botulinum toxin A (BTX-A) in improving aesthetic outcomes in facial wounds. The use of BTX-A is becoming an increasing part of common practice to minimize scarring. To date, no such studies exist using abobotulinumtoxinA (aboBTX-A, Dysport) nor are there studies looking specifically at post-Mohs reconstruction for skin cancer removal. Mohs surgery is a specific technique of dermatologic surgery used to treat skin cancer. A specific study on the use of aboBTX-A prior to repair of skin cancer defects on the forehead would be valuable and may prove to facilitate this practice into more general use among skin cancer surgeons to help in optimizing scar appearance.

### 1.2 Investigational Agents

#### 1.2.1 Dysport

Dysport (abobotulinumtoxinA) contains botulinim toxin A. It is a purified neurotoxin type A complex that is produced from fermentation of the bacterium *Clostridium botulinum* type A, Hall strain. Dysport is currently indicated for use in reducing glabellar lines and in cervical dystonia.

Dysport is supplied in single-use, sterile vials for intramuscular injection. Each vial contains 300 units of lyophilized abobotulinumtoxinA with 125mcg of human serum albumin and 2.5mg of lactose. Prior to use, it is reconstituted with 2.5 ml of sterile, bacteriostatic 0.9% sodium chloride solution. This yields a solution equivalent to 10 units per 0.08cc.

##### 1.2.1.1 Mechanism of Action

*Dysport* inhibits release of the neurotransmitter, acetylcholine, from peripheral cholinergic nerve endings. Toxin activity occurs in the following sequence: Toxin heavy chain mediated binding to specific surface receptors on nerve endings, internalization of the toxin by receptor mediated endocytosis, pH-induced translocation of the toxin light chain to the cell cytosol and cleavage of SNAP25 leading to intracellular blockage of neurotransmitter exocytosis into the neuromuscular junction. This accounts for the therapeutic utility of the toxin in diseases characterized by excessive efferent activity in motor nerves. Recovery of transmission occurs gradually within 3 months as the neuromuscular junction recovers from SNAP25 cleavage and as new nerve endings are formed.

##### 1.2.1.2 Summaries of and clinical significance of non-clinical and clinical studies

Please see below and the Dysport package insert for more information.

##### 1.2.1.3 Non-clinical and Clinical Pharmacokinetics

Please see below and the Dysport package insert for more information.

#### 1.2.1.4 Major route of Elimination

Please see below and the Dysport package insert for more information.

#### 1.2.1.5 Safety Profile

Dysport is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle

**Contraindications:** Dysport is contraindicated in individuals with any allergy to any component of the preparation, including milk allergy. It is also contraindicated if there is a current infection at the proposed injection site.

**Pregnancy**: Dysport is Pregnancy category C. *Dysport* produced embryo-fetal toxicity when given to pregnant rats at doses similar to or greater than the maximum recommended human dose (MRHD) of 1000 Units on a body weight (Units/kg) basis. In an embryo-fetal development study in which pregnant rats received intramuscular injections daily (2.2, 6.6, or 22 Units/kg on gestation days 6 through 17) or intermittently (44 Units/kg on gestation days 6 and 12 only) during organogenesis, increased early embryonic death was observed with both dosing schedules. The no-effect dose for embryo-fetal developmental toxicity was 2.2 Units/kg (one-tenth the MRHD on a body weight basis). Maternal toxicity was seen at 22 and 44 Units/kg. In a pre-and post-natal development study in which female rats received 6 weekly intramuscular injections (4.4, 11.1, 22.2, or 44 Units/kg) beginning on day 6 of gestation and continuing through parturition to weaning, an increase in stillbirths was observed at the highest dose, which was maternally toxic. The no-effect dose for pre- and post-natal developmental toxicity was 22.2 Units/kg (approximately equal to the MRHD on a body weight basis).

There are no adequate studies in pregnant women, and therefore, no one pregnant or that could possibly become pregnant will be in enrolled in the study unless they use adequate contraception. It is unknown whether Dysport is excreted in human milk.

Dysport has not been shown to be associated with male-mediated fetal toxicity. The reproductive NOEL following intramuscular injection of 0, 4, 8, and 16 U/kg was 4 U/kg in male rats and 8 U/kg in female rats. Higher doses were associated with dose-dependent reductions in fertility in male rats (where limb weakness resulted in the inability to mate), and an altered estrous cycle in female rats. There were no adverse effects on the viability of the embryos. In clinical practice, male contraception is not required with Dysport administration.

#### 1.2.1.6 Rationale for the Proposed starting doses and dose escalation scheme

Please see below.

#### 1.2.1.7 Metabolism of Investigational study agent in humans and its potential for drug interactions.

Not applicable.

### 1.3 Pre-Clinical Data

Not applicable.

### 1.4 Clinical Data

Three double-blind, randomized, placebo-controlled, clinical studies have evaluated the efficacy of *Dysport* for use in the temporary improvement of the appearance of moderate to severe glabellar lines. These three studies enrolled healthy adults (ages 19–75) with glabellar lines of at least moderate severity at maximum frown. Subjects were excluded if they had marked ptosis, deep dermal scarring, or a substantial inability to lessen glabellar lines, even by physically spreading them apart. The subjects in these studies received either *Dysport* or placebo. The total dose was 50 units delivered in equally divided aliquots to specified injection sites. Additional endpoints for each of the studies were post-treatment glabellar line severity of none or mild with at least a 1-grade improvement from baseline for separate investigator and subject assessments at Day 30.

Investigators and subjects assessed efficacy at maximum frown by using a 4-point scale (none, mild, moderate, severe). Overall treatment success was defined as post-treatment glabellar line severity of none or mild with at least 2 grade improvements from Baseline for the combined investigator and subject assessments (composite assessment) on Day 30 (see Table 6). Additional endpoints for each of the studies were post-treatment glabellar line severity of none or mild with at least a 1 grade improvement from Baseline for the separate investigator and subject assessments on Day 30.

After completion of the randomized studies, subjects were offered participation in a two-year, open-label re-treatment study to assess the safety of multiple treatments.

**Table 6. Treatment Success at Day 30 (None or Mild with at least 2 Grade Improvement from Baseline at Maximum Frown for the combined Investigator and Subject Assessments (Composite))**

| | 2 Grade Improvement | |
|---|---|---|
| **Study** | ***Dysport*** **n/N (%)** | **Placebo n/N (%)** |
| GL-1 | 58/105 (55%) | 0/53 (0%) |
| GL-2 | 37/71 (52%) | 0/71 (0%) |
| GL-3 | 120/200 (60%) | 0/100 (0%) |

Treatment with *Dysport* reduced the severity of glabellar lines for up to four months.

Please see attached package insert for more information.

### 1.5 Clinical Pharmacokinetics of Dysport

Using currently available analytical technology, it is not possible to detect *Dysport* in the peripheral blood following intramuscular injection at the recommended doses.

### 1.6 Placebo: Sterile Bacteriostatic 0.9% sodium chloride solution

Sterile, bacteriostatic 0.9% sodium chloride solution will be used as the placebo agent since abobotulinumtoxinA is reconstituted with the same solution. An equivalent unit to volume ratio will be used (10 units per 0.08cc). i.e. if the patient would be receiving 30 units, 0.25cc of bacteriostatic 0.9% sodium chloride would be drawn. See Standard Reconstitution table below.

**Standard Reconstitution Table**

Mix 1 vial of Dysport (300 units) with 2.5cc's of Bacteriostatic 0.9% Sodium Chloride
Concentration = 10 units per 0.08cc.

| Dysport | Volume |
|---|---|
| 6 units | 0.05cc |
| 12 units | 0.1cc |
| 15 units | 0.125cc |
| 24 units | 0.2cc |
| 30 units | 0.25cc |
| 36 units | 0.3cc |
| 54 units | 0.4cc |
| 60 units | 0.5cc |

### 1.7 Rationale

The use of botulinum toxin A (BTX-A) induced chemoimmobilization of facial wounds to minimize scarring is becoming an increasing part of common practice. Several case reports and small clinical trials describe the benefit of using BTX-A in improving aesthetic outcomes in facial wounds. [1-5]

The major factor impeding successful wound healing and therefore improved cosmesis is wound tension caused by surrounding muscles. Although surgeons can approximate wound edges to minimize this tension, repeated contractions of the surrounding muscle cause recurrent microtrauma. This prolongs the inflammatory response and increases localized metabolic activity, which can lead to hypertrophic scars.

A recent prospective clinical study evaluated the use of botulinum toxin A (Botox, Allergan, Irvine, CA) in improving facial wound healing found a statistically significant improvement in scar outcome compared with placebo.[2] No serious adverse events were reported.

To date, no such studies exist using abobotulinumtoxinA (aboBTX-A, Dysport) nor are there studies looking specifically at post-Mohs reconstruction for skin cancer removal.

A specific study on the use of aboBTX-A prior to repair of skin cancer defects on the forehead would be valuable and may prove to facilitate this practice into more general use among skin cancer surgeons to help in optimizing scar appearance.
In this study, each patient will be able to receive up to 120 units of Dysport/placebo at the initial visit to treat the entire forehead area (the frontalis, procerus, and corrugator muscles) to insure cosmetic symmetry. Toxin will be placed a minimum of 1.5cm above the orbital rim at the mid papillary line to minimize the risk of lid ptosis. The actual amount to be injected will be at the discretion of the Mohs surgeon based on his or her opinion of what amount is needed for sufficient wound paralysis and cosmetic symmetry. At the completion of the study, all subjects will be offered additional Dysport at no cost to the glabella as an on-label indication for improvement of glabella frown lines.

## 2.0 OBJECTIVES

To quantify the improvement in scar appearance, we propose the use of two well-established methods of measurement: The Visual Analogue Scale (VAS) and the Patient and Observer Scar Assessment Scale (POSAS)[6,7] The VAS will be used as the primary end point. It consists of a 10 point scale to assess global scar assessment. Scar photographic images are assessed by independent physicians, and previous studies have shown very high intrarater consistency. The POSAS consists of two numeric scales. One scale is completed by the patients, the other by the clinician. This scale is different than previous scales because it takes the patient's input into consideration. It has good internal consistency and interobserver reliability.[8,9]

**2.1 Primary Objective:**

To evaluate the efficacy of using aboBTX-A to improve wound healing prior to Mohs micrographic surgery and reconstruction for skin cancer as measured by the Visual Analogue Scale (VAS) at 6 weeks post surgery.

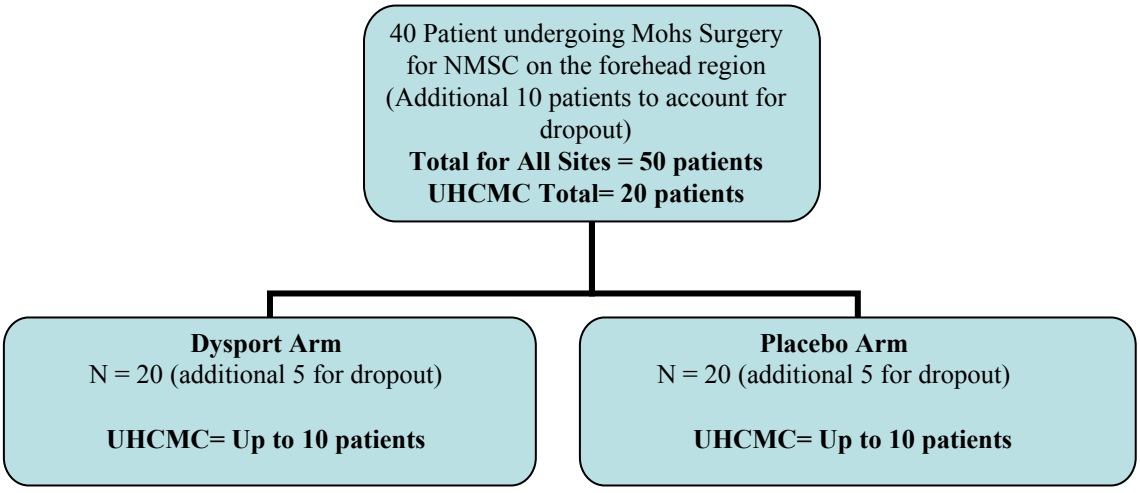
**2.2 Secondary Objective:**

- To evaluate efficacy of using aboBTX-A to improve wound healing prior to Mohs micrographic surgery and reconstruction for skin cancer as measured by the Patient and Observer Assessment Scale (POSAS) at week 1, 6, and 24.
- To evaluate the efficacy of using aboBTX-A to improve wound healing prior to Mohs micrographic surgery and reconstruction for skin cancer as measured by the Visual Analogue Scale (VAS) at week 1 and 24 post surgery.
- To evaluate patient satisfaction
- To evaluate safety (adverse events)

## 3.0 STUDY DESIGN

**3.1** Study Design including dose escalation/cohorts/subject numbers

This is a 6 month, prospective, multicenter, double-blinded, randomized, placebo-controlled study. A total of 40 male or female healthy volunteers, 20 in each arm, will be enrolled. Up to 10 more patients can be enrolled to account for patient drop-out. Subjects will all undergo Mohs micrographic surgical removal of a skin cancer lesion on the forehead followed by reconstruction. Subjects will be randomized to receive either aboBTX-A injection or placebo injection in the frontalis, procerus, and corrugator muscles prior to reconstruction. Photographs, POSAS, and clinical assessments will be taken immediately after initial wound closure, at 1 week follow-up, at 6 weeks follow-up, and at 6 months follow-up. Adverse events will also be reviewed at each study visit. After the completion of the study, the photographs will be assessed (blinded as to the patient identifiers) using a 10 cm visual analog scale (VAS). The first few photographs will be evaluated by the surgeons together to calibrate the VAS and ensure inter-reliability.



| Procedure | Visit 1: Screening & Dysport Administration | Visit 2: Op Visit | Visit 3: 1 wk f/u | Visit 4: 6 wk f/u | Visit 5: 6 month f/u |
|---|---|---|---|---|---|
| Informed Consent | **X** | | | | |
| Pre-op Evaluation | **X** | | | | |
| Injection of Dysport or Placebo | **X** | | | | |
| Adverse Events | **X** | **X** | **X** | **X** | **X** |
| Medical/Medication History | **X** | **X** | **X** | **X** | **X** |
| Photography | **X** | **X** | **X** | **X** | **X** |
| Skin Evaluation | | **X** | **X** | **X** | **X** |
| Urine Pregnancy Test | **X** | | | | **X** |
| **Assessments** | | | | | |
| Physician VAS | | | | **X** | **X** |
| Patient POSAS | | **X** | **X** | **X** | **X** |
| Physician POSAS | | **X** | **X** | **X** | **X** |
| Patient survey | | | | | **X** |

### 3.2 Number of subjects

Subjects for this study will be recruited from up to five clinical sites. A total of forty healthy evaluable subjects will participate in this study. Up to fifty subjects will be enrolled to account for projected dropout. It is anticipated that at least 10 subjects will be enrolled in the first year at UHCMC. An evaluable subject is one who has passed the inclusion and exclusion criteria; given informed consent; received and followed the treatment schedule, and has been adequately followed to establish valid endpoints of efficacy and tolerance.

### 3.3 Replacement of subjects

If a subject withdraws from the study prior to the 6 month follow-up, a replacement subject will be enrolled and will be assigned to the same drug or placebo group.

### 3.4 Expected Duration of Subject Participation

#### 3.4.1 Duration of Therapy

Study subjects will be given a one time treatment with Dysport at their first visit. This one time injection of Dysport is expected to cause an effect for approximately 3 months.

#### 3.4.2 Duration of Follow-up

Patients will be followed for toxicity and effect for 6 months after treatment the one time treatment with Dysport. If there are adverse events the clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

## 4.0 PATIENT SELECTION

### 4.1 Inclusion Criteria:

Patients must meet all of the following inclusion criteria to be eligible for enrollment:

1. Adults 18 years or older.
2. Ability to understand the risks, benefits, and alternative to participation and give informed consent
3. Have biopsy proven skin cancer on the medial forehead that is amenable to Mohs surgery. Medial forehead is defined as the area superiorly from the hairline, inferiorly at the eyebrow, and laterally to the tip of the lateral brow (see diagram).
4. Undergoing elective reconstruction of biopsy proven skin cancer that is amenable to Mohs surgery with defect size measuring 1.0 cm or greater
5. If female, not currently pregnant, no potential for pregnancy, or if of child-bearing age, must agree to use adequate contraception (e.g., hormonal or barrier method of birth control; abstinence) for 30 days after the last dose of study drug. A negative urine pregnancy test is required at study entry for female subjects of childbearing potential: a woman is considered to be of child bearing potential unless she has had a tubal ligation, total hysterectomy, bilateral oopherectomy, or is postmenopausal (without a menstrual period for at least one year)
6. Agrees to not use disallowed concomitant medications (retinoids)

### 4.2 Exclusion Criteria

The presence of any of the following will exclude a patient from study enrollment.

1. Pregnant women, women who are breastfeeding, or women of child bearing age who are unwilling to use adequate contraception (described above) during the study period
2. Current or past history of a neuromuscular disease (such as myasthenia gravis, amyotrophic lateral sclerosis, Eaton-Lambert syndrome)
3. Currently taking aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents)
4. History of radiation therapy or chemotherapy
5. History of keloid or other hypertrophic scar formation
6. Current or past history of scleroderma
7. Has used botulinum toxin in the forehead area within one year.
8. Has significant resting eyebrow ptosis
9. Has used any topical retinoids to the forehead area within the past 4 weeks
10. Undergo any scar revision procedure for the duration of the study including intralesional kenalog, laser treatment, and/or scar revision surgeries
11. Any hypersensitivity to any component of abobotulinumtoxinA (i.e. cow milk protein) or any previous hypersensitivity to any botulinum toxin A or related product.
12. Non-English speaking: These patients are excluded since translation of the informed consent into other languages is time-consuming and expensive as it requires a bona fide translator for the particular language of interest and this type of person may be difficult to locate.
13. House staff and students, medical students on a clerkship, and employees related to study personnel or who work for any study personnel, and members of the study team are not eligible to participate in this study as a subject.
14. The investigator feels that for any reason the subject is not eligible to participate in the study

### 4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

## 5.0 REGISTRATION

### 5.1 Registration

All subjects who have been consented will be registered in the OnCore Database. For those subjects who are consented, but not enrolled, the reason for exclusion will be recorded. All subjects from Collaborating Centers will also be registered through UHCMC and will be provided a study number by calling the telephone number of the Study Coordinator.

### 5.2 Randomization

Block randomization will be used to ensure equal or near equal numbers of subjects per study arm. Subjects from Collaborating Centers will be randomized upon receiving a study number from UHCMC.

## 6.0 TREATMENT PLAN

### 6.1 Dysport

Each patient will be able to receive up to 120 units of Dysport/placebo at the initial visit to treat the entire forehead area (the frontalis, procerus, and corrugator muscles) to insure cosmetic symmetry. Injections will be placed a minimum of 1.5cm above the orbital rim at the mid papillary line to minimize the risk of lid ptosis. The actual amount to be injected will be at the discretion of the Mohs surgeon based on his or her opinion of what amount is needed for sufficient wound paralysis and cosmetic symmetry.

Appropriate dose modifications for Dysport are described in Section 7.0.

Reported adverse events and potential risks of Dysport are described in Section 8.0

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's Mohs incision site.

### 6.2 Definition of Dose-Limiting Toxicity

Not applicable to this study as a single dose of disport/placebo will be administered. There will be no dose escalations. Reported adverse events and potential risks of Dysport are described in Section 8.0.

### 6.3 General Concomitant Medications and Supportive Care Guidelines

Aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents) may potentiate the effects of Botox. Patients currently receiving these agents are excluded from the study.

Using currently available analytical technology, it is not possible to detect *Dysport* in the peripheral blood following intramuscular injection at the recommended doses. Dysport is not known to interfere with cytochrome P450.

Patients should receive full supportive care, including transfusions of blood and blood products, cytokines, antibiotics, antiemetics, etc when appropriate.

### 6.4 Duration of Therapy

Study subjects will be given a one time treatment with Dysport at their first visit. This one time injection of Dysport is expected to cause an effect for approximately 3 months.

### 6.5 Duration of Follow Up

Patients will be followed for toxicity and effect for 6 months after treatment the one time treatment with Dysport. If there are adverse events the clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

## 7.0 DOSE DELAYS/DOSE MODIFICATIONS

Not applicable. No dose delays or modifications are anticipated.

## 8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

### 8.1 Adverse Events and Potential Risk List

The following is a list of AEs (Section 8.1) and the reporting requirements associated with observed AEs (Sections 8.3 and 8.4).

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

#### 8.1.1 Dysport

##### 8.1.1.1 Adverse events most likely to occur in this study

- Bleeding
- Bruising
- Infection
- Asymmetric / Unsatisfactory results
- Injection site pain or reaction

##### 8.1.1.2 Reported common adverse events (>=2%) in placebo-controlled clinical trials of Dysport for glabellar lines

- Nasopharyngitis
- Headache
- Injection site pain or reaction
- Upper respiratory infection
- Eyelid edema
- Eyelid ptosis
- Sinusitis
- Nausea

##### 8.1.1.3 AEs identified from extensive post-marketing data

- Vertigo
- Eyelid psosis
- Diplopia
- Amyotrophy

- Photophobia
- Dysphagia
- Nausea
- Malaise
- Flu like illness
- Hypersensitivity
- Burning sensation
- Facial paresis
- Hypoesthesia
- Erythema
- Excessive granulation tissue

**8.1.1.4** The most current version of the prescribing information sheet should be consulted for more detailed information on adverse events. As with all therapeutic proteins, there is always a chance for immunogenecity and the production of anti-bodies. No formal drug interactions have been identified in studies using Dysport. Excessive overdose of the drug may be expected to produce neuromuscular weakness with a variety of symptoms. Depending on the extent of overdose, respiratory arrest requiring respiratory support may occur. In the event of an overdose, an antitoxin is available. However, it will not reverse toxin-induced effects already apparent by the time of antitoxin administration. The antitoxin is available from the Centers for Disease Control and Prevention in Atlanta, GA.

**8.1.2 Adverse Events and Potential Risks- Mohs Surgery and Reconstruction**

There are risks involved with Mohs and reconstruction surgical procedure that are independent of this study including but not limited to:

- Pain
- Infection
- Bleeding
- Swelling
- Hematoma
- Scar Formation
- Wound Dehiscence
- Failure of flap or skin graft
- Temporary or Permanent Nerve Damage
- Distortion/Alteration of surrounding anatomic features
- Tumor Recurrence

**8.1.3 Adverse Events and Potential Risks- Questionnaires**

There may be risks involved with completing the questionnaires. Some of the questions may be upsetting, or the patient may feel uncomfortable answering them (e.g. regarding how their scar looks). If they do not wish to answer a question, they will be offered the opportunity of skipping it and going on to the next question. The patient may also become bored when answering the questions and if so, will be offered the opportunity to stop and resume completing the questionnaire after a rest period.

## 8.2 Definitions

### 8.2.1 Adverse Events

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory

findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject. In general, adverse events that are at least partially the result of (a) or (b) would be considered related to the research, whereas adverse events solely related to (c) or (d) would be considered unrelated to the research.

**External adverse events** are adverse events experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the Institutional Review Board has jurisdiction.

**Internal adverse events** are adverse events experienced by subjects enrolled at the site(s) under the IRB's jurisdiction for either multicenter or single-center research projects.

**8.2.2 The significance of an adverse event** is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). Based on the National Cancer Institute Guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

**Grades 1** are mild adverse events. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)

**Grades 2** are moderate adverse events (e.g., minimal intervention; local intervention; non-invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

**Grades 3** are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

**Grades 4** are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life–threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

**Grades 5** are fatal adverse event resulting in death.

**8.2.3 Serious Adverse Events**

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will

be considered as Serious, UNLESS at least one of the following expectations is met:

- The admission results in a hospital stay of less than 12 hours OR
- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR
- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### 8.2.4 Expectedness

Adverse Events can be Expected or Unexpected.

**An expected adverse event** is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

**An unexpected adverse event** is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

### 8.2.5 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

## 8.3 Reporting Procedures for All Adverse Events

All participating investigators will assess the occurrence of AEs throughout the subject's participation in the study. Subjects will be followed for toxicity for 6 months after treatment has been discontinued. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Participants will be given a phone number to call if they suspect they may be experiencing an adverse event. In addition, we will telephone the participant at 24 hrs following the procedure. If the participant reports any such reaction, they will be asked to return for an examination and any needed treatment. This visit will be considered a research visit and no clinical charge will be entered. The event will be followed until the event resolves, the subject does not desire further follow-up, the subject withdraws from the study, or the subject is lost to follow-up.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's case report form, subject's medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event.

The investigator will provide the following for all adverse events:

- Description of the event
- Date of onset and resolution
- Grade of toxicity
- Attribution of relatedness to the investigational agent
- Action taken as a result of the event
- Outcome of event

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 available at http://ctep.cancer.gov will be utilized for AE reporting.

Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

### 8.4 Serious Adverse Event Reporting Procedures

Serious adverse events that occur beginning with the signing of the informed consent form, during treatment, or within 6 months of the last dose of treatment must be reported to the **UHCMC** Principal Investigator.

Investigative sites will report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting serious adverse events.

#### 8.4.1 Medicis Reporting

Not applicable**.**

#### 8.4.2 FDA Reporting

There is no IND for this study, therefore this is not applicable.

#### 8.4.3 Multi-Center Trials with UHCMC Investigator as Principal Investigator

For multi-site trials where a **UHCMC** investigator is serving as the Principal Investigator, each participating investigator is required to abide by the reporting requirements set by the protocol.

Participating investigators must report all serious adverse events that occur after the subject has signed the informed consent form to the **UHCMC** Principal Investigator within 24 hours of discovery or notification of the event. Initial serious adverse event information and all amendments or additions must be recorded in Oncore. Relevant medical records should be faxed as soon as they become available. The **UHCMC** Principal Investigator will review and assess the SAE and follow the

reporting requirements in Section 8.4.1 and 8.4.2 and communicate results to all investigational sites. The participating investigator must provide follow-up information on the SAE. Report Serious Adverse Events by telephone, email or facsimile to:

***Contact Name: Kevin Cooper, MD.***
***Contact Email: Kevin.Cooper@gmail.com***
***Telephone: 216-844-7834***
***Fax: 216-844-8993***

Serious adverse events occurring after conclusion of the study AND thought to be possibly related to the investigational agent will be collected and reported within 24 hours of discovery or notification of the event.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described above.

### 8.4.4 Data Safety Toxicity Committee

It is the Case Comprehensive Cancer Center's Principal Investigator's responsibility to ensure that ALL serious adverse events are reported to the Case Comprehensive Cancer Center's Data Safety Toxicity Committee. This submission is simultaneous with their submission to the Sponsor or other Regulatory body.

## 9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.0

| | |
|---|---|
| **Name of Agent** | **Dysport** |
| **Chemical Name:** | abobotulinumtoxinA |
| **Other Names:** | Clostridium botulinum type toxin A toxin-haemagglutinin complex |
| **Classification:** | Prescription Medicine |
| **Molecular Formula:** | Botulinum toxin type A, the active ingredient in Dysport (abobotulinumtoxinA), is a purified neurotoxin type A complex produced by fermentation of the bacterium Clostridium botulinum type A, Hall Strain. It is purified from the culture supernatant by a series of precipitation, dialysis, and chromatography steps. The neurotoxin complex is composed of the neurotoxin, hemagglutinin proteins and non-toxin non-hemagglutinin protein. |
| **Mode of Action:** | Dysport inhibits release of the neurotransmitter, acetylcholine, from peripheral cholinergic nerve endings. Toxin activity occurs in the following sequence: Toxin heavy chain mediated binding to specific surface receptors on nerve endings, internalization of the toxin by receptor mediated endocytosis, pH-induced translocation of the toxin light chain to the cell cytosol and cleavage of SNAP25 |

| | |
|---|---|
| | leading to intracellular blockage of neurotransmitter exocytosis into the neuromuscular junction. This accounts for the therapeutic utility of the toxin in diseases characterized by excessive efferent activity in motor nerves. |
| **Metabolism:** | Using currently available analytical technology, it is not possible to detect Dysport in the peripheral blood following intramuscular injection at the recommended doses |
| **Product description**: | Dysport is supplied in a single-use, sterile vial for reconstitution intended for intramuscular injection. Each vial contains 300 Units of freeze-dried lyophilized abobotulinumtoxinA, 125 micrograms human serum albumin and 2.5 mg lactose. Box containing 1 vial—NDC 99207-500-30 |
| **Solution preparation:** | Prior to use, it is reconstituted with 2.5 ml of sterile, bacteriostatic 0.9% sodium chloride solution. This yields a solution equivalent to 10 units per 0.08cc. |
| **Storage requirements*:*** | Dysport is stored under refrigeration at 2–8°C, protected from light. |
| **Stability:** | *Not Applicable.* |
| **Route of administration*:*** | Intramuscular injection into the desired muscle. |
| **Drug Procurement:** | Dysport will be supplied for this study by Medicis and is available in 3 ml vials containing 300 units of freeze-dried abobotulinumtoxinA. **Dysport is being provided at no cost to the study subject.** Dysport will be directly supplied to each participating site for this study by Medicis. |
| **Drug Accountability:** | The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug at their site. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. |
| **Drug Destruction*:*** | At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files. |
| **Other Information:** | **Not Applicable.** |

## 10.0 CORRELATIVE/SPECIAL STUDIES

Not applicable.

## 11.0 STUDY PARAMETERS AND CALENDAR

### 11.1 Study Parameters

**11.1.1.1** Screening Evaluation and Initial Visit (1 hr)
Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed ≤ 28 days prior to administration of protocol therapy.

- Informed consent: Prior to study initiation, each subject will be screened to ensure they meet all of the inclusion and none of the exclusion criteria outlined above. Potential subjects will be interviewed and examined by the investigator or his designee to establish their eligibility for inclusion in the study. Subjects will be given a full description of the nature and purpose of the study. If a subject is willing to participate, they must provide written informed consent before proceeding with the study.
- Inclusion and Exclusion criteria
- Demographics
- Medical History
- Pre-op evaluation by Mohs surgeon, which includes focal skin exam
- Vital signs including: blood pressure, pulse, respiratory rate
- Concomitant Medications Assessment including aminoglycoside, or other agents interfering with neuromuscular transmission (e.g., curare-like agents)
- Urine pregnancy test
- Randomization
- Injection of Dysport or placebo
- Review AEs
- This visit will take place 2-4 weeks prior to planned Mohs procedure, + or – 3 days
- Baseline photographs

### 11.2 Treatment Period

Visits 2-5 can be scheduled +/- 5 days from indicated date.

**Visit 2: Op Visit (30 minutes)**

- Localized skin evaluation
- Vital signs including: blood pressure, pulse, respiratory rate
- Concomitant Medications Assessment including aminoglycoside, or other agents interfering with neuromuscular transmission (e.g., curare-like agents)
- Mohs procedure
- Reconstruction
- Photograph of wound before and after reconstruction
- POSAS
  Patient and Observer Scar Assessment Scale (POSAS): The Patient and Observer Scar Assessment Scale (POSAS) consist of two numeric scales. One scale is completed by the patients, the other by the clinician. This scale is different than previous scales because it takes the patient's input into consideration. It has good internal consistency and interobserver reliability[8-10]. Patient POSAS will be collected at visit 2, 3, 4, and 5. Physician POSAS will be collected by each surgeon at visit 2, 3, 4, and 5. In addition, at the conclusion of the study, all four participating investigators will evaluate the photos of the wound at closure, at 6 weeks, and at 6 months for PSOAS scores in vascularity, pigmentation, thickness,

and surface area. Relief and pliability will not be assessed as photographs do not allow for measurement of these values.
- Review AEs, medical history, medications

**Visit 3: 1 week follow-up (30 minutes)**
- Localized skin evaluation
- Vital signs including: blood pressure, pulse, respiratory rate
- Concomitant Medications Assessment including aminoglycoside, or other agents interfering with neuromuscular transmission (e.g., curare-like agents)
- Suture removal
- Photograph of wound
- POSAS
- Review AEs, medical history, medications

**Visit 4: 6 weeks follow-up (30 minutes)**
- Localized skin evaluation
- Vital signs including: blood pressure, pulse, respiratory rate
- Concomitant Medications Assessment including aminoglycoside, or other agents interfering with neuromuscular transmission (e.g., curare-like agents)
- Photograph of wound
- POSAS
- Review AEs, medical history, medications

**Visit 5: 6 months follow-up/End of study visit (45 minutes)**
- Localized skin evaluation
- Vital signs including: blood pressure, pulse, respiratory rate
- Concomitant Medications Assessment including aminoglycoside, or other agents interfering with neuromuscular transmission (e.g., curare-like agents)
- Photograph of wound
- POSAS, VAS
  Visual Analog Scale (VAS): This is a 10 point scale to assess global scar assessment. At the conclusion of the study, photographs will be assessed in an independent and blinded fashion. After reviewing the photos of the wound at closure, at 6 weeks, and at 6 months, the participating raters will be asked to rate the cosmetic outcome at 6 weeks and 6 months on a 10-cm visual analog scale . The rater will be asked to assess the first patient together to establish a reference score for their respective further scores. Prior studies have shown very high intrarater consistency from VAS[7].
- Review AEs, medical history, medications
- Option: additional Dysport to glabella/forehead to reduce lines. Females of childbearing potential will undergo a urine pregnancy test.
- Patient Satisfaction Survey: This survey will ask the patient's opinion of using Dysport and if they would recommend the procedure to other patients.

### 11.3 Calendar

| Procedure | Visit 1: Screening & Dysport Administration | Visit 2: Op Visit | Visit 3: 1 wk f/u | Visit 4: 6 wk f/u | Visit 5: 6 month f/u |
|---|---|---|---|---|---|
| Informed Consent | X | | | | |
| Pre-op Evaluation | X | | | | |
| Injection of Dysport or Placebo | X | | | | |
| Adverse Events | X | X | X | X | X |
| Medical/Medication History | X | X | X | X | X |
| Photography | X | X | X | X | X |
| Skin Evaluation | | X | X | X | X |
| Urine pregnancy test | X | | | | X |
| **Assessments** | | | | | |
| Physician VAS | | | | X | X |
| Patient POSAS | | X | X | X | X |
| Physician POSAS | | X | X | X | X |
| Patient survey | | | | | X |

## 12.0 MEASUREMENT OF EFFECT

**12.1** VAS: Visual Analog Scale. This is a 10 point scale to assess global scar assessment. At the conclusion of the study, photographs will be assessed in an independent and blinded fashion. After reviewing the photos of the wound at closure, at 6 weeks, and at 6 months, the participating raters will be asked to rate the cosmetic outcome at 6 weeks and 6 months on a 10-cm visual analog scale . The rater will be asked to assess the first patient together to establish a reference score for their respective further scores. Prior studies have shown very high intrarater consistency from VAS[7]. See statistical section for more information.

**12.2** POSAS: Patient and Observer Scar Assessment Scale. The Patient and Observer Scar Assessment Scale (POSAS) consist of two numeric scales. One scale is completed by the patients, the other by the clinician. This scale is different than previous scales because it takes the patient's input into consideration. It has good internal consistency and interobserver reliability[8-10]. Patient POSAS will be collected at visit 2, 3, 4, and 5. Physician POSAS will be collected by each surgeon at visit 2, 3, 4, and 5. In addition, at the conclusion of the study, all four participating investigators will evaluate the photos of the wound at closure, at 6 weeks, and at 6 months for PSOAS scores in vascularity, pigmentation, thickness, and surface area. Relief and pliability will not be assessed as photographs do not allow for measurement of these values.

## 13.0 DATA REPORTING/REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

### 13.1 Data Reporting

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with Title 21 CFR Part 11. Access to data through OnCore is restricted by user accounts and assigned roles. Once logged into the OnCore system with a user ID and

password, OnCore defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore Administrator at oncore-registration@case.edu.

OnCore is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore database. A calendar of events and required forms are available in OnCore.

## 13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

### 13.2.1 Written Informed Consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects will also be notified that they are free to discontinue from the study at any time. The subject will be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form will be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form will be given to the subject.

Withdrawal of consent: Subjects may choose to discontinue their participation in the study at any time by notifying the PI. They will be asked to send a written letter to the PI listed on the informed consent. No further research data will be obtained nor clinical data entered into the research database. Data gathered until the time of withdrawal will be maintained.

Illiterate subjects: In the event that illiterate individuals who understand English present themselves as potential study participants and meet all inclusion/exclusion criteria, the consent form will be read to that individual in the presence of a witness and all questions answered. The study participant will sign the consent document by "making their mark" in the signature space. Both the person obtaining the consent (either the PI or his/her official delegate) and the witness will co-sign and date the consent form, noting that the informed consent process has taken place.

Non-English speaking patients, house staff and students, medical students on a clerkship, and employees related to study personnel or who work for any study personnel, and members of the study team are not eligible to participate in this study as a subject.

### 13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), each subject will sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

All data will be recorded in patient specific study binders. These binders will be kept in a locked room only accessible to research personnel. This data will then be transferred to an electronic database stored on the UHCMC secure drive that will be password protected and only accessible to research personnel. The research team, authorized UH personnel, the study sponsor (if applicable), and regulatory entities such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP), may have access to the study records to protect the subject's safety

and welfare. Any information derived from this research project that personally identifies the subject will not be voluntarily released or disclosed by these entities without a separate consent, except as specifically required by law. Research records provided to authorized, non-UH entities will not contain identifiable information about the subject. Publications and/or presentations that result from this study will not include identifiable information.

Digital photographs of the wound will be taken at each visit. The digital files will be stored on the UHCMC secure drive that only research personnel will have access to.

**13.2.3** Accessing Electronic Medical Records for University Hospitals Health System
Not applicable

**13.2.4** Retention of Records
The Principal Investigator at UHCMC supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

**13.2.5** Audits and Inspections
Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the study site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

**13.2.6** Data Safety and Monitoring Plan
This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations.

**13.2.7** Multicenter Guidelines

**Responsibility of the Coordinating Center**

- The Coordinating Center is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Coordinating Center. There will be only one version of the protocol, and each participating institution will use that document. The Coordinating Center is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Coordinating Center is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements are the responsibility of the Protocol Chair.
- The Coordinating Center is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Coordinating Center will be responsible for the review of and timely submission of data for study analysis.
- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP). The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the Coordinating Center.

- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review.
- The Coordinating Center will maintain documentation of AE reports.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the funding or regulatory agency chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order Dysport directly from Medicis. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to Medicis.

## 14.0 STATISTICAL CONSIDERATIONS

To quantify the improvement in scar appearance, we propose the use of two well-established methods of measurement: The Visual Analogue Scale (VAS) and the Patient and Observer Scar Assessment Scale (POSAS)[6,7] The VAS will be used as the primary end point. It consists of a 10 point scale to assess global scar assessment. Scar photographic images are assessed by independent physicians, and previous studies have shown very high intrarater consistency. The POSAS consists of two numeric scales. One scale is completed by the patients, the other by the clinician. This scale is different than previous scales because it takes the patient's input into consideration. It has good internal consistency and interobserver reliability.[8,9]

**14.1** **Visual Analog Scale**: This is a 10 point scale to assess global scar assessment. VAS has been used in previous studies to assess cosmetic outcome of scars. In this study, we plan to evaluate the efficacy of using aboBTX-A to improve wound healing prior to Mohs micrographic surgery and reconstruction for skin cancer as measured by the Visual Analogue Scale (VAS) at 6 weeks post surgery as the primary endpoint.

**14.1.1** Meaningful clinically important difference: Using the data from 2 previously published clinical trials, Quinn et al[7] reported that the minimal clinically important difference on the VAS cosmesis scale is 1.5 on a 10 point VAS[11]

**14.1.2** Sample size calculation: Prior authors have reported a pooled SD of 1.4 and 2.2 among VAS scores for surgical scars, yielding an effect size (mean difference/SD) of 0.7 to 1.1. A sample size of 20 patients per treatment group would provide an 80% chance (statistical power) of detecting an effect size of 1.0, using a two-sided t-test, with a type I error level of 5%. Assuming a 5-10% dropout rate with follow-up visit and given the efficiency of the 2-sample *t* test relative to the Wilcoxon rank sum test is 95%, a total of 25 patients will be enrolled per group.

**14.1.3** Data Analysis: The VAS ratings at 6 weeks and at 6 months for each patient will be based on the average of all four physician scores. The average of the VAS scores will then be compared between the 2 treatment groups using the Wilcoxon rank sum test. All calculated *P* values are 2-sided, and $P<0.5$ is considered statistically significant.

**14.1.4** Patient Accrual is anticipated that at least 10 subjects will be enrolled in the first year at UHCMC.

**14.2 Patient and Observer Scar Assessment Scale:** This scale will allow us to assess the patient and observer's opinion of his/her scar as a secondary endpoints. In comparison to the VAS, this scale takes the patient's input into consideration. In addition, multiple parameters are evaluated including vascularity, pigmentation, thickness, and surface area. Parameters. Prior studies have shown good internal consistency and interobserver reliability[8-10]. The average PSAS and OSAS scores for each parameter will be compared between the 2 treatment groups using the Wilcoxon rank sum test. All calculated *P* values are 2-sided, and $P<0.5$ is considered statistically significant.

## 15.0 REFERENCES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## Appendices

### Appendix 1 : Visual Analog Scale

|-----|------|------|-------|--------|-------|-------|--------|--------|-------|

1cm 10cm

(Not drawn to scale)

(1 bring lowest acceptable cosmetic result, 10 being best cosmetic result)

### Appendix 2: Patient and Observer Scar Assessment Scale

Table IV. The Patient and Observer Scar Assessment Scale.*

| | | Observer Scar Assessment Scale (OSAS) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Normal skin | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst scar imaginable |
| Vascularity | | o | o | o | o | o | o | o | o | o | o | |
| Pale | | | | | | | | | | | | |
| Pink | | | | | | | | | | | | |
| Red | | | | | | | | | | | | |
| Purple | | | | | | | | | | | | |
| Mix | | | | | | | | | | | | |
| Pigmentation | | o | o | o | o | o | o | o | o | o | o | |
| Hypo | | | | | | | | | | | | |
| Hyper | | | | | | | | | | | | |
| Mix | | | | | | | | | | | | |
| Thickness | | o | o | o | o | o | o | o | o | o | o | |
| Thicker | | | | | | | | | | | | |
| Thinner | | | | | | | | | | | | |
| Relief | | o | o | o | o | o | o | o | o | o | o | |
| More relief | | | | | | | | | | | | |
| Less relief | | | | | | | | | | | | |
| Mix | | | | | | | | | | | | |
| Pliability | | o | o | o | o | o | o | o | o | o | o | |
| Supple | | | | | | | | | | | | |
| Stiff | | | | | | | | | | | | |
| Mix | | | | | | | | | | | | |
| Surface area | | o | o | o | o | o | o | o | o | o | o | |
| Expansion | | | | | | | | | | | | |
| Contraction | | | | | | | | | | | | |
| Mix | | | | | | | | | | | | |
| Overall opinion | | o | o | o | o | o | o | o | o | o | o | |
| | Patient Scar Assessment Scale (PSAS) | | | | | | | | | | | |
| | No, not at all | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Yes, very much |
| Has the scar been painful the past few weeks? | | o | o | o | o | o | o | o | o | o | o | |
| Has the scar been itching the past few weeks? | | o | o | o | o | o | o | o | o | o | o | |
| | No, as normal skin | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Yes, very different |
| Is the scar colour different from the colour of your normal skin at present? | | o | o | o | o | o | o | o | o | o | o | |
| Is the stiffness of the scar different from your normal skin at present? | | o | o | o | o | o | o | o | o | o | o | |
| Is the thickness of the scar different from your normal skin at present? | | o | o | o | o | o | o | o | o | o | o | |
| Is the scar more irregular than your normal skin at present? | | o | o | o | o | o | o | o | o | o | o | |
| | As normal skin | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Very different |
| What is your overall opinion of the scar compared to normal skin? | | o | o | o | o | o | o | o | o | o | o | |

**Appendix 3: Patient Satisfaction Questionnaire**

1. Please rate how satisfied you are with the result of scar (wound?):

    1: Excellent 2: Very good 3: Good 4: Fair 5: Poor

2. Would you recommend using Dysport (botulinum toxin A) to help reduce scarring?
    1: Yes 2: No

**Appendix 4: Dysport Prescribing Information**