Clostridium histolyticum collagenase injection treatment for urethral disease: a prospective, single-center, open-label study

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Abbreviations and Acronyms:

DVIU – Direct vision internal urethrotomy

CHC – Clostridium histolyticum collagenase

AUA – American Urological Association

RUG – Retrograde urethrogram

VCUG – Voiding cystourethrogram

PVR – Post-void residual

ET – Early termination

DSMB – Data safety monitoring board

AE – Adverse events

1.0 Synopsis

Title	Clostridium histolyticum collagenase injection treatment for urethral disease: a prospective pilot, single-center, open-label study
Protocol Number	CHC
Phase	II
Study Design	Pilot, open label drug study
Study Center(s)	Single-center (University of South Florida, Tampa, FL)
Objectives	<u>Primary Objectives</u> The primary objective is to assess the safety of clostridium histolyticum collagenase (XIAFLEX®) in treating urethral strictures. Safety variable: o The primary safety variable will be complication rates following XIAFLEX® treatment Complications – specifically focus on pain, fever, genital lesions, or postoperative adverse events related to XIAFLEX® treatment <u>Secondary Objectives</u> The secondary objectives are to assess the efficacy of XIAFLEX® treatment in improving obstructive voiding dysfunction, safety of XIAFLEX® administration into urethral strictures via a transurethral approach and the quality of life following XIAFLEX® treatment. Secondary efficacy variables: o The percentage of subjects needing further intervention for treatment of urethral stricture during the 2 years follow-up Further intervention – defined as any medical or surgical intervention for treatment of urethral stricture. o Urethral stricture recurrence during the 2 years follow-up o Elapsed time to urethral stricture recurrence during the 2 years follow-up o Elapsed time to additional intervention for urethral stricture treatment during the 2 years follow-up o Improvement of obstructive voiding dysfunction – defined as change in uroflow and post-void residual measurements at baseline and 6-week post treatment and follow-up visits o Quality of Life – change in AUA scores at baseline and 6-week post treatment and follow-up visits Secondary safety variable: o Spongiofibrosis - incidence of formation of spongiofibrosis or change in length and extent of spongiofibrosis between

	the baseline and follow-up visits on ultrasound and cystoscopic evaluation o Normal urethra proximal to injected tissue – incidence of change in normal urethra structure proximal to injected tissue between baseline and follow-up visits
Number of Subjects	5 Patients
Inclusion Criteria	1) Males 2) Age ≥ 18 years 3) Failed prior proven conservative measures, including DVIU or balloon dilation of the stricture will be included in this study 4) Able and willing to undergo regular intervention as well as evaluation as described below will be included in the study 5) With a single bulbar stricture ≤2cm in size that can be identified on retrograde urethrogram or voiding cystourethrogram and visible with urethral ultrasonography will be included in the study. 6) Must agree not to participate in a clinical study involving another investigational drug or device throughout the duration of this study 7) Must be competent to understand the information given in IRB approved ICF and must sign the form prior to the initiation of any study procedure
Exclusion Criteria	1) Has not yet undergone proven non-invasive measures, including DVIU or balloon dilation. 2) Multiple strictures or a single stricture larger than 2cm in size, measured with retrograde urethrogram, voiding cystourethrogram, or urethral ultrasonography. 3) Corporal spongiosum tissues < 5 mm in depth at proposed injection site 4) Grade 5 spongiofibrosis 5) Age <18 6) Females 7) Prior urethroplasty 8) Urethral fistula 9) History of penile cancer, prostate cancer, or urinary tract malignancy (bladder, urethral, ureteral, or kidney). 10) History of radiation (external or brachytherapy) to the pelvic organs, penis or groin. 11) History of autoimmune or inflammatory bowel disease 12) Contraindication to suprapubic tube placement 13) Pre-procedure PVR >250mL 14) Allergy or sensitivity to CHC 15) Bleeding disorder or anticoagulant use other than aspirin up to 150mg/day

	16) Untreated or recurrent urinary tract infection 17) Inability to perform intermittent self-catheterization 18) Participation in another clinical study or treatment with an investigational drug or device 19) Serious or active medical or psychiatric condition which, in the opinion of the Investigator, may interfere with treatment, assessment, or compliance with the protocol
Study Product, Dose, Route, Regimen	Patients will first be identified and evaluated with fluoroscopic and ultrasound imaging. Based on the inclusion and exclusion criteria they will be counseled about eligibility for the study along with discussion of standard management options and possible risks of the investigation including full informed consent. On day of treatment, patients will undergo instillation of local anesthesia (20 mL of 2% urethral lidocaine jelly), the patient will undergo cystoscopy, transurethral injection (via a 70 cm 4.8 Fr flexible cystoscopic needle with a 23 gauge needle tip manufactured by Laborie®, Ontario, Canada) of 0.08ml of XIAFLEX® (0.58 mg of XIAFLEX® mixed with 0.39 mL of sterile diluent) in a single location within the stricture, chased by an additional 0.25 mL of reconstituted XIAFLEX® to allow for clearance of the original 0.08 mL of reconstituted XIAFLEX® from the transurethral syringe into the urethral stricture. This is based on 0.25 mL residual fluid that remains within the lumen of the injeTAK syringe. Thus, by adding the additional 0.25 mL of XIAFLEX® as a chase, we are expecting the original total of 0.08 mL of XIAFLEX® to be injected into the area of scarring. The depth and location of the needle will be determined pre-procedurally with urethral ultrasonography with the needle in a semi-parallel manner into the plaque as to avoid perforation into nearby structures. Injections will be performed at a single site identified on ultrasound as appropriate, and avoiding the 6 o'clock and 12 o'clock sites where potential perforation can lead to additional complications. The site of injection will be recorded accordingly for safety monitoring following treatment. The remaining 0.25 mL that remains in the injection syringe will be discarded per institutional policy for biohazard disposal.
Statistical Methodology	Data analysis will be conducted using de-identified data in SPSS or SAS statistical software. Study Population Analysis The distributions of the following characteristics will be tabulated and presented with descriptive statistics (i.e. mean, standard deviation, median, minimum, maximum, and patient count for continuous variables, and counts with percentages for categorical variables): - Demographics - Medical and surgical history - Final study exit classification (completed, discontinued, withdrew)

	Primary Safety Endpoint The primary safety variable will be complication rates following treatment (XIAFLEX®). Complications – specifically focus on pain, fever, genital lesions, or postoperative adverse events related to treatment (XIAFLEX®) Secondary Efficacy Endpoints The secondary endpoints will be evaluated with the following tests: - The percentage of subjects needing further intervention for treatment of urethral stricture during the 2 years follow-up. Further intervention – defined as any medical or surgical intervention for treatment of urethral stricture. - Incidence of urethral stricture recurrence within 2 years following initial treatment will be calculated and presented with descriptive statistics - Elapsed time to urethral stricture recurrence and elapsed time to additional intervention for urethral stricture treatment within 2 years following initial treatment will be calculated and presented with descriptive statistics - Efficacy of XIAFLEX® treatment in improving obstructive voiding dysfunction will be analyzed using paired t-test for the difference in uroflow and post-void residual measurements before and after study treatment (collected at baseline, 6-week post treatment and follow-up visits) - Quality of life will be analyzed using paired t-test for the difference in AUA scores before and after study initial treatment (collected at baseline, 6-week post treatment and follow-up visits) Secondary Safety Endpoints The results of the following safety endpoints will be calculated and presented with descriptive statistics for all patients receiving study treatment. - Incidence of formation of spongiofibrosis or change in length and extent of spongiofibrosis - Incidence of change in normal urethra structure proximal to injected tissue - Incidence and severity of treatment-emergent AEs/SAEs during the study - Proportion of patients completing study treatment - Proportion of patients discontinuing due to treatment related complications

2.0 Background

2.1 Urethral Stricture Disease

Urethral stricture disease can be difficult and expensive problem for urologists to manage. The total cost of urethral stricture diseases in 2000 was approximately $200 million. A diagnosis of urethral stricture increased health care expenditures by more than $6,000 per individual yearly[1]. Conservative management involves frequent straight catheterization or management with an indwelling foley catheter; options that can decrease the patient's quality of life and increase the patient's risk of urinary tract infections[2].

2.1.1 Treatment of Urethral Stricture

Minimally invasive treatment options include direct vision internal urethrotomy (DVIU) and urethral dilation; these have been shown to be effective primarily on single, small bulbar strictures (<2cm), with repeated treatment being almost entirely ineffective[3]. Other minimally invasive treatments including urethral stents, transurethral injection with Rapamycin, botulinum toxin, or glucocorticoids have shown limited efficacy or have fallen out of favor because of increased morbidity[4, 5]. The gold standard for treatment of anterior urethral strictures involves excision of the stricture with primary anastomosis of the urethra or urethroplasty. Both surgical options, however, require extensive anesthesia and are often poor options for elderly patients, patients with significant comorbidities, or patient who simply do not wish to undergo such extensive surgery.

2.2 Clostridium Histolyticum Collagenase

Clostridium histolyticum collagenase (CHC) is an injectable pharmacologic agent that works by hydrolyzing collagen under physiologic environments, with in vitro studies showing CHC to be specifically selective for collagen type I and III, the predominant types found in Peyronie's plaque's and Dupuytren's contractures. Additionally, CHC spares collagen type IV, which is present within connective tissue of surrounding arteries, large veins, and nerves, limiting surrounding nerve or vessel damage[6]. CHC, marketed as XIAFLEX®, has been FDA approved for treatment of Dupuytren's disease, as well as Peyronie's disease. Large double blind studies have shown a statistically significant improvement in penile deformity following CHC injections[7]. Additionally, studies have shown significant improvement in curvature in patients who performed penile modeling with CHC.

2.2.1 Animal Studies: Toxicity Data

Based on a previously conducted study on local toxicity of Auxilium's collagenase (AA4500) injected into various locations within the dogs penis, including the urethra, primary side effects were dose related and included discoloration of the penis/prepuce, persistence of swollen penis, and bruising.[8] At a dose of 6.1 µg/kg, which corresponds to 1.1 fold on the mg/kg basis of the human dose, 4 out of 6 dogs were able to receive all three doses (total 3 dosing cycles). The primary toxicity findings at all dose levels were hemorrhage, edema, necrosis, inflammation, and neovascular proliferation with increasing severity based on dosing.

Histopathology indicated resolution was in progress at the end of the 28-day treatment-free period. There was no significant systemic toxicity following intrapenile injections. Necrosis did not affect non-collagenous strictures within or adjacent to the injected tissue, nor was there any evidence of residual effects on these structures in recovery animals in all phases of the study. In particular, arteries, veins, nerves, and large veins were unaffected, with necrosis only seen in smaller veins comprised mostly of collagen and minimal smooth muscle.

Antibodies to AA4500 were detected in all repeat-dose dogs following their last dose on Day 61. The consequence of antibody formation is unknown. However, the author did note that the presence of antibodies did not result in any apparent adverse systemic effects. Nor did the production of antibodies appear to alter the toxicokinetics or pharmacodynamics effects of aA4500.

In another animal study, injecting clostridial collagenase (both 150 units and 300 units injected) into rats tail tendon showed local collagen lysis of injection at the site of injection only at 1 and 24 hours.[9] At both doses, no adverse collagenase extravasation was seen at either time at the injection site or 0.5 cm proximal or distal to the injection site.

2.3 Rationale for Urethral Stricture Treatment with XIAFLEX®

Urethral strictures, like Dupuytren's contractures and Peyronie's disease, are associated with a total increase in type I and type III collagen smooth muscle[10]. A recent study investigated injecting urethral strictures with high dose CHC in rats showed reduction in urethral fibrosis as well as a reduction in collagen type I and III expression in the rodents' urethral strictures[11]. We wish to investigate if CHC would have a similar impact on urethral strictures in men when administered in a similar fashion to the Peyronie's disease algorithm.

3.0 Study Objectives

We hypothesize that XIAFLEX® (Endo Pharmaceuticals, Dublin, Ireland) injection is an effective treatment for urethral strictures.

<u>Primary Objectives</u>
The primary objective is to assess the safety of clostridium histolyticum collagenase (XIAFLEX®) in treating urethral strictures.

Safety variable:

- The primary safety variable will be complication rates following treatment (XIAFLEX®)
  Complications – specifically focus on pain, fever, genital lesions, or postoperative adverse events related to treatment (XIAFLEX®)

<u>Secondary Objectives</u>
The secondary objectives are to assess the efficacy of XIAFLEX® treatment in improving obstructive voiding dysfunction, safety of XIAFLEX® administration into urethral strictures via a transurethral approach and the quality of life following XIAFLEX® treatment.

Secondary efficacy variables:

- The primary efficacy variable will be the percentage of subjects needing further intervention for treatment of urethral stricture during the 2 years follow-up

Further intervention – defined as any medical or surgical intervention for treatment of urethral stricture.
- Urethral stricture recurrence during the 2 years follow-up
- Elapsed time to urethral stricture recurrence during the 2 years follow-up
- Elapsed time to additional intervention for urethral stricture treatment during the 2 years follow-up
- Improvement of obstructive voiding dysfunction – defined as change in uroflow and post-void residual measurements at baseline and 6-week post treatment and follow-up visits
- Quality of Life – change in AUA scores at baseline and 6-week post treatment and follow-up visits

Secondary safety variables:
- Spongiofibrosis - incidence of formation of spongiofibrosis or change in length and extent of spongiofibrosis between the baseline and follow-up visits
- Normal urethra proximal to injected tissue – incidence of change in normal urethra structure proximal to injected tissue between baseline and follow-up visits

4.0 Study Population

Male patients receiving treatment at USF for obstructive voiding symptoms or catheter dependent because of urethral stricture disease.

4.1 Inclusion Criteria

Patients must meet <u>all</u> of the following inclusion criteria to be eligible for participation in this study.

1) Males
2) Age ≥ 18 years
3) Failed prior proven conservative measures, including DVIU or balloon dilation of the stricture will be included in this study
4) Able and willing to undergo regular intervention as well as evaluation as described below will be included in the study
5) With a single bulbar stricture <u>≤</u>2cm in size that can be identified on retrograde urethrogram or voiding cystourethrogram and visible with urethral ultrasonography will be included in the study will be included in the study.
6) Must agree not to participate in a clinical study involving another investigational drug or device throughout the duration of this study
7) Must be competent to understand the information given in IRB approved ICF and must sign the form prior to the initiation of any study procedure

4.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria are not eligible for participation in this study.

1) Has not yet undergone proven non-invasive measures, including DVIU or balloon dilation.

2) Multiple strictures or a single stricture larger than 2cm in size, measured with retrograde urethrogram, voiding cystourethrogram, or urethral ultrasonography.
3) Corporal spongiosum tissues < 5 mm in depth at proposed injection site
4) Grade 5 spongiofibrosis
5) Age <18
6) Females
7) Prior urethroplasty
8) Urethral fistula
9) History of penile cancer, prostate cancer, or urinary tract malignancy (bladder, urethral, ureteral, or kidney).
10) History of radiation (external or brachytherapy) to the pelvic organs, penis or groin.
11) History of autoimmune or inflammatory bowel disease
12) Contraindication to suprapubic tube placement
13) Pre-procedure PVR >250mL
14) Allergy or sensitivity to CHC
15) Bleeding disorder or anticoagulant use other than aspirin up to 150mg/day
16) Untreated or recurrent urinary tract infection
17) Inability to perform intermittent self-catheterization
18) Participation in another clinical study or treatment with an investigational drug or device
19) Serious or active medical or psychiatric condition which, in the opinion of the Investigator, may interfere with treatment, assessment, or compliance with the protocol

5.0 Study Drug and Device

5.1 Study Agent

XIAFLEX® is a combination of bacterial collagenases indicated for the treatments of adult patients with Dupuytren's contracture with a palpable cord and adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy. XIAFLEX® 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. The dosing used for this study is based on recommendations for Peyronie's disease treatment with XIAFLEX®.

5.2 Dose Rationale

A recently published comprehensive review of recent clinical trials and in vivo studies examining CHC in the treatment of Peyronie's disease reported that the clinical trials have demonstrated the efficacy and tolerability of CHC in treating Peyronie's disease and an in vivo study showed that CHC also could be applied to urethral stricture disease without serious adverse complications.[12] A recent urethral injection of rat model (300-350g) used 0.05 - 0.1mg CCH per subject. This showed no urethral or voiding complication and no urinary retention or urethral fistulas[11]. This dosing would equal 0.14-0.33mg/kg. A dose of 0.119mg (0.08ml of 0.58mg XIAFLEX in 0.39ml) in a 70kg patient would be 0.0017mg/kg.

5.3 Risks/Benefits

Urethral stricture disease can be difficult and expensive problem for urologists to manage. As observed with this patient population, conservative management involves frequent straight catheterization or management with an indwelling foley catheter that can decrease the patient's quality of life and increase the patient's risk of urinary tract infections. Other minimally invasive treatments have shown limited efficacy or have increased morbidity. Surgical options that are effective, however, involves higher risks, require extensive anesthesia and are often poor options for elderly patients, patients with significant comorbidities, or patient who simply do not wish to undergo such extensive surgery. Therefore, treatments with injections may provide sufficient potential benefit and an acceptable potential for risk for this study population.

5.4 Dosage and Administration

On day of treatment, prior to study drug administration, photographic evidence captured with urethral ultrasound will be used to confirm eligibility criterion: < Grade 5 spongiofibrosis. If the patient's urethral ultrasound for Baseline/Screening was performed more than 30 days prior to the treatment day (Day 0), it will be performed again on the treatment day (Day 0) prior to study drug administration to re-confirm the patient's study eligibility and to allow for proper procedural planning for study treatment.

On day of treatment, patients will undergo instillation of local anesthesia (20 mL of 2% urethral lidocaine jelly), the patient will undergo cystoscopy, transurethral injection (via a 70 cm 4.8 Fr flexible cystoscopic needle with a 23 gauge needle tip manufactured by Laborie®, Ontario, Canada) of 0.08ml of XIAFLEX® (0.58 mg of XIAFLEX® mixed with 0.39 mL of sterile diluent) in a single location within the stricture, chased by an additional 0.25 mL of reconstituted XIAFLEX® to allow for clearance of the original 0.08 mL of reconstituted XIAFLEX® from the transurethral syringe into the urethral stricture. This is based on 0.25 mL residual fluid that remains within the lumen of the injeTAK syringe. Thus, by adding the additional 0.25 mL of XIAFLEX® as a chase, we are expecting the original total of 0.08 mL of XIAFLEX® to be injected into the area of scarring. The depth and location of the needle will be determined pre-procedurally with urethral ultrasonography with the needle in a semi-parallel manner into the plaque as to avoid perforation into nearby structures. Injections will be performed at a single site identified on ultrasound as appropriate, and avoiding the 6 o'clock and 12 o'clock sites where potential perforation can lead to additional complications. The site of injection will be recorded accordingly for safety monitoring following treatment. The remaining 0.25 mL that remains in the injection syringe will be discarded per institutional policy for biohazard disposal.

Reconstitution of the Lyophilized Powder for Peyronie's Disease (taken from XIAFLEX® package insert)

1. Before use, remove the vial containing the lyophilized powder of XIAFLEX® and the vial containing the diluent for reconstitution from the refrigerator and allow the two vials to stand at room temperature for at least 15 minutes and no longer than 60 minutes. Visually inspect the vial containing XIAFLEX®. The cake of lyophilized powder should be intact and white in color.
2. After removal of the flip-off cap from each vial, using aseptic technique swab the rubber stopper and surrounding surface of the vial containing XIAFLEX® and the vial containing the diluent for reconstitution with sterile alcohol (no other antiseptics should be used).

3. Use on the supplied diluent for reconstitution. The diluent contains calcium which is required for the activity of XIAFLEX®.
4. Using a 1 mL syringe with 0.01 mL graduations with a 27-gauge ½-inch needle, withdraw a volume of 0.39 mL of the diluent supplied.
5. Inject the diluent slowly into the sides of the vial containing the lyophilized powder of XIAFLEX®. Do not invert the vial or shake the solution. Slowly swirl the solution to ensure that all of the lyophilized powder has gone into solution.
6. The reconstituted XIAFLEX® solution can be kept at room temperature (20º to 25ºC/68º to 77ºF) for up to one hour or refrigerated at 2º to 8ºC (36º to 46ºF) for up to 4 hours prior to administration. If the reconstituted XIAFLEX® solution is refrigerated, allow this solution to return to room temperature for approximately 15 minutes before use.
7. Discard the syringe and needle used for reconstitution and the diluent vial.

5.5 Formulation

XIAFLEX® will be supplied in single-use glass vials containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder for reconstitution. Sterile diluent for reconstitution will be provided in a package in a single-use glass vial containing 3 mL of 0.3 mg/mL calcium chloride dehydrate in 0.9% sodium chloride.

5.6 Packaging and Labeling

Study drugs packaging and labeling will be provided as marketed. No modifications to the packaging and labeling will be made. A single-use package will consist of one carton containing a single-use vial for XIAFLEX® and a single-use vial of sterile diluent.

5.7 Storage and Handling

Prior to reconstitution, the vials of XIAFLEX® and diluent should be stored in a refrigerator at 2ºC to 8ºC (36º to 46ºF). The reconstituted XIAFLEX® solution can be kept at room temperature (20º to 25ºC/68º to 77ºF) for up to one hour or refrigerated at 2º to 8ºC (36º to 46ºF) for up to 4 hours prior to administration. The Clinical Research Center's personnel at USF Health South Tampa Center for Advanced Healthcare will be monitoring study drug storage integrity (i.e. refrigerator temperature monitoring). Records and notifications of temperature excursions will be provided to the Principal Investigator and study coordinator accordingly. The Principal Investigator and study coordinator will ensure the integrity and monitoring of the drug prior to use. The time of each step in the process (i.e. removal from refrigerator, reconstitution, re-refrigeration and/or administration) will be recorded accordingly. Study drug will not be used of the integrity of study drug is compromised.

5.8 Drug Accountability

The Principal Investigator and study coordinator will maintain records of product's delivery and receipt from Endo Pharmaceuticals, Inc. to the drug storage site (USF Health South Tampa Center for Advanced Healthcare, Clinical Research Center at 2 Tampa General Circle, Room 4064, Tampa, FL 33606 – only accessible to Clinical Research Center's personnel), the inventory at the site, the use by each patient, and disposal of unused products. These records will include dates, quantities, log/batch/serial numbers, expiration or use-by dates, and unique code numbers assigned to the study drugs and study patients.

At each treatment visit, the drugs will be obtained by the study coordinator and will be transported to USF Health South Tampa Center for Advance Healthcare (storage and clinic are in same area), where the treatment will occur.

5.9 Concomitant and Prohibited Medications

XIAFLEX® should be used with caution in patients receiving concomitant anticoagulants (except for low-dose aspirin). For this study, patients with bleeding disorder or anticoagulant use (up to 150 mg/day) other than aspirin are excluded.

5.10 Injection Device

The injection device will be the 70 cm 4.8 Fr flexible injeTAK® cystoscopic needle with a 23 Gauge needle tip manufactured by Laborie®, Ontario, Canada. The 4.8 Fr allows for use with smaller working channels. The black indicator tip provides visual proximity to tissue for accurate placement, safe penetration and gauged puncture depth. The angle and 3-bevel tip is engineered to minimize puncture force. The cannula design also provides easy injection and flexibility while maintaining structural integrity. The needle tip can be adjusted to 0, 2, 3, 4, and 5 mm to accommodate thickness. For this study, the depth of the needle will be set based on pre-operative urethral ultrasound to determine needle location and depth. The needle will be injected in a semi-parallel manner into the plaque as to avoid perforation into nearby structures.

6.0 Methods

6.1 Subject Identification

Potential subjects will be identified through physician referrals (internal/external physicians will only share availability of trial, same information as that already shared with the public on clinicaltrials.gov, to their patients and provide USF urology clinic or research member's contact information for further evaluation – all study recruitment will still occur at the USF urology clinic) and USF urology clinic at the USF Health South Tampa Center for Advanced Healthcare.

6.2 Limited Waiver of Consent

Potential subjects will be identified through physician referrals (internal/external physicians will only share availability of trial, same information as that already shared with the public on clinicaltrials.gov, to their patients and provide USF urology clinic or research member's contact information for further evaluation – all study recruitment will still occur at the USF urology clinic) and USF urology clinic at the USF Health South Tampa Center for Advanced Healthcare – the PI's and sub-investigator's clinic. If the patient has urethral stricture, the PI/sub-investigator will consider the patient for recruitment for the study. The PI/sub-investigator will discuss the study with the patient first, then the research coordinator will be introduced to the patient to complete the informed consent process. During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility prior to study consent – the investigators have a treatment relationship with the potential subjects and the study coordinators do not. They will use the information provided by

the patient and/or medical record (USF EPIC electronic medical record system) to confirm that the patient is eligible and to approach the patient regarding study enrollment. Record review for screening purposes will be completed prior to receiving signed consent. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be used as part of a screening process. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of 1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; 2) conversing with patients regarding possible enrollment; 3) handling of PHI contained within those records and provided by the potential subjects.

6.3 Consent Process

Patients who meet the inclusion and exclusion criteria will be considered for the study and will be asked to sign an informed consent form.
In order to provide ample opportunity for the patient to consider participation, a copy of the consent form will be provided to all patients that verbally express interest to participate in the study. All study discussions will take place in a private exam room.

Patients will be recruited from physician referrals (internal/external physicians will only share availability of trial, same information as that already shared with the public on clinicaltrials.gov, to their patients and provide USF urology clinic or research member's contact information for further evaluation – all study recruitment will still occur at the USF urology clinic) and within our urology practice by the PI and sub-investigators. Recruitment may occur in the clinic at USF. After identifying a patient who meets minimum eligibility criteria and before collecting any study data, the study will be explained in detail to the participant including: (1) that the study represents a research effort, (2) that participation is voluntary, and there is no penalty for withdrawal, (3) any anticipated costs to the patient for participation, (4) potential risks and benefits for participation, (5) the procedures to ensure privacy of their medical information, and (6) contact information for addressing additional concerns. Patients will be informed of the purpose of the study. Only with the full and complete understanding of the study, and signed informed consent, will the evaluation of the potential participant continue. The subject will be given sufficient time to read the consent and ask any questions. Once the informed consent is signed, the subject will be given a copy of the document.

6.4 Duration of Study Participation

Study participation will require up to 2 years involvement.

6.5 Study Visits

This is a prospective, single-center, open-label study. Patients eligible for the study will undergo informed consent. Once consented, patients will be enrolled and treated with an approved open-label treatment – XIAFLEX® injection.

6.5.1 Baseline/Screening

The following procedures will be performed at the Baseline/Screening visit:

- Screen inclusion/exclusion criteria
- Obtain informed consent
- Record demographics and medical and surgical history
- Evaluate and record concomitant medications
- Administer American Urological Association (AUA) questionnaire
- Perform physical exam (as occur per standard of care)
- Perform retrograde urethrogram (RUG), voiding cystourethrogram (VCUG), post-void residual (PVR), uroflow, and cystoscopy to evaluate and document the anatomy and length and extent of spongiofibrosis at baseline related to the urethral stricture (as occur per standard of care).
- Perform clinic urethral ultrasound to grade urethral stricture based on previously described grading system. (Figure 1)

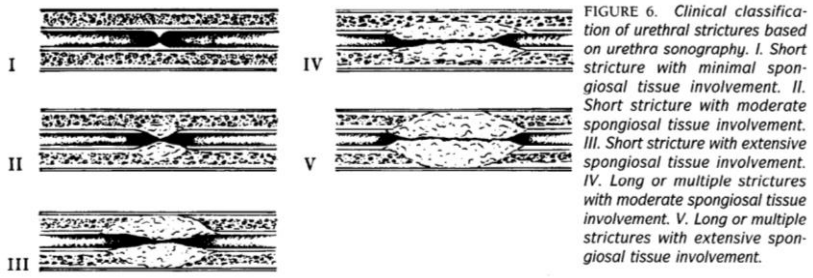

FIGURE 6. *Clinical classification of urethral strictures based on urethra sonography. I. Short stricture with minimal spongiosal tissue involvement. II. Short stricture with moderate spongiosal tissue involvement. III. Short stricture with extensive spongiosal tissue involvement. IV. Long or multiple strictures with moderate spongiosal tissue involvement. V. Long or multiple strictures with extensive spongiosal tissue involvement.*

Figure 1. Urethral stricture grading scale based on urethral ultrasound

6.5.2 Treatment (Day 0)

The following procedures will be performed on day of XIAFLEX® injection treatment:

- Evaluate and record concomitant medications
- Perform study treatment
- Assess for adverse events. Patients will be kept in clinic with vitals at 60min following injection to ensure no allergic reaction. Patients will be kept on campus until they have voided twice with a PVR <250ml or no more than 20% greater than their pre-procedural PVR.

Treatment Group – XIAFLEX® injection

On day of treatment, patients will undergo instillation of local anesthesia (20 mL of 2% urethral lidocaine jelly), the patient will undergo cystoscopy, transurethral injection (via a 70 cm 4.8 Fr flexible cystoscopic needle with a 23 gauge needle tip manufactured by Laborie®, Ontario, Canada) of 0.08ml of XIAFLEX® (0.58 mg of XIAFLEX® mixed with 0.39 mL of sterile diluent) in a single location within the stricture, chased by an additional 0.25 mL of reconstituted XIAFLEX® to allow for clearance of the original 0.08 mL of reconstituted XIAFLEX® from the transurethral syringe into the urethral stricture. This is based on 0.25 mL residual fluid that remains within the lumen of the injeTAK syringe. Thus, by adding the additional 0.25 mL of XIAFLEX® as a chase, we are expecting the original total of 0.08 mL of XIAFLEX® to be injected into the area of scarring. The depth and location of the needle will be determined pre-procedurally with urethral ultrasonography with the needle in a semi-parallel manner into the

plaque as to avoid perforation into nearby structures. Injections will be performed at a single site. The remaining 0.25 mL that remains in the injection syringe will be discarded per institutional policy for biohazard disposal.

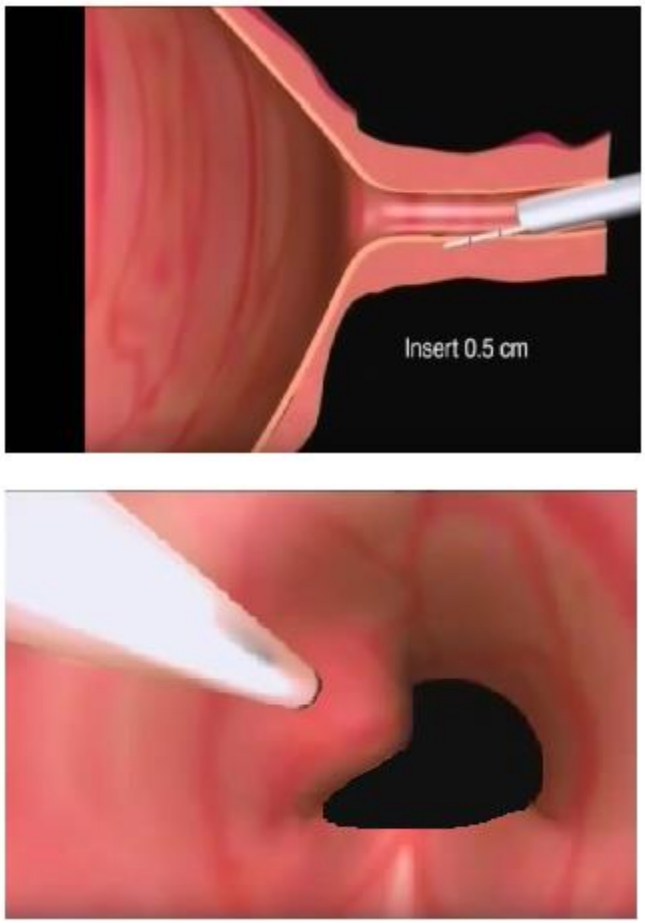

Figure 2: Illustration of transurethral injection method for CCH injection. Note: the insertion of the needle, parallel to the direction of the urethra, to decrease the likelihood of injury to structures adjacent to the urethra.

6.5.3 Post-treatment (Days 2 or 3)

The patient will be instructed to return to clinic within 2-3 days of the injection

- Perform physical exam
- Perform uroflow, post-void residual (PVR) measurements
- Administer AUA questionnaire
- Evaluate and record concomitant medications
- Assess for adverse events

6.5.4 Post-treatment (Days 14, 28, 42, 56, 70, 84 ± 3 days)

The patient will be instructed to return to clinic every 2 weeks following treatment.

The following procedures will be performed at this visit:

- Perform physical exam
- Perform uroflow, post-void residual (PVR) measurements, and evaluate and document length and extent of spongiofibrosis every 2 weeks
- Cystoscopy and urethral ultrasonography will be performed every 4 weeks
- Administer AUA questionnaire
- Evaluate and record concomitant medications and post treatment interventions, if any
- Assess for adverse events
- Test for antibodies to AUX I and AUX II at 6 weeks and neutralizing antibodies at 12 weeks.

6.5.5 Follow-up (6, 9, 12, 18 and 24 months (± 7 days))

The patient will have follow-up evaluations in clinic at 6, 9, 12, 18, and 24 (± 7 days) months following the first treatment visit.

The following procedures will be performed at these visits:

- Perform physical exam
- Perform cystoscopy, urethral ultrasound, uroflow, PVR measurements, and evaluate length and extent of spongiofibrosis.
- Administer AUA questionnaire
- Evaluate and record concomitant medications and post treatment interventions, if anyAssess for adverse events

6.5.6 Unscheduled Visits

If there is any medical or safety concern, the patient will be brought in earlier for re-evaluation in clinic.

The following procedures will be performed at these visits:

- Perform physical exam
- Perform cystoscopy, urethral ultrasound, uroflow, PVR measurements, and evaluate length and extent of spongiofibrosis, if applicable
- Evaluate and record concomitant medications and post treatment interventions, if any
- Assess for adverse events

6.5.7 Early Termination

Early Discontinuation

Reasons for discontinuation of treatment may include, but are not limited to, the following:

- Patient withdrawal of consent
- Any medical condition that the Investigator determines may jeopardize the patient's safety if he continues in the study
- Investigator determines it is in the best interest of the patient
- Patient noncompliance, such as missing scheduled visits, non-adherence with concomitant medications, etc.
- Lost to follow-up
- If patients have no clinical response to the intervention and have persistent clinical manifestations of their stricture disease they may elect to undergo definite management in

the form of urethral dilation, urethrectomy, or urethral reconstruction. They will still be followed per above protocol and included in all statistical analysis.

After study treatment is discontinued, patient will be asked to remain in the study whenever possible and complete all study visits according to the planned schedule of assessments (except for patients who have withdrawn consent and are lost to follow-up). The primary reason for premature discontinuation of study treatment should be documented appropriately. If a patient chooses to discontinue study treatment and withdraw from the study, then the patient will be asked to return to the clinic for the early termination (ET) visit and complete all assessments.

Patients who prematurely discontinue study treatment will not be replaced.

Early Withdrawal
All patients have the right to withdraw from study participation without prejudice at any time during the study. If a patient terminates participation in the study, the Investigator will make a reasonable effort to determine the cause of study withdrawal. If, for whatever reason, a patient withdraws from the study or the study is terminated while the patient is receiving study treatment, an early termination (ET) visit will be performed.

Patients who prematurely withdraw from the study will not be replaced.

The following procedures will performed at the ET visit if allowed by patient:
- Perform physical exam
- Perform cystoscopy, urethra ultrasound, uroflow, PVR measurements, and evaluate length and extent of spongiofibrosis
- Administer AUA questionnaire
- Evaluate and record concomitant medications, medical and surgical history
- Assess for adverse events

6.6 Sample Size Justification
Sample size selection was based on the feasibility of completing a small number of subjects in a pilot study for safety assessments. A total of 5 patients will be enrolled in this study.

6.7 Statistical Analysis Plan
Data analysis will be conducted using de-identified data in SPSS or SAS statistical software.

Study Population Analysis
The distributions of the following characteristics will be tabulated and presented with descriptive statistics (i.e. mean, standard deviation, median, minimum, maximum, and patient count for continuous variables, and counts with percentages for categorical variables):
- Demographics
- Medical and surgical history
- Final study exit classification (completed, discontinued, withdrew)

Primary Safety Endpoint

The primary safety variable will be complication rates following treatment (XIAFLEX®). Complications – specifically focus on pain, fever, genital lesions, or postoperative AEs related to treatment (XIAFLEX®)

Secondary Efficacy Endpoints

The secondary endpoints will be evaluated with the following tests:

- The percentage of subjects needing further intervention for treatment of urethral stricture during the 2 years follow-up. Further intervention – defined as any medical or surgical intervention for treatment of urethral stricture.
- Incidence of urethral stricture recurrence within 2 years following initial treatment will be calculated and presented with descriptive statistics
- Elapsed time to urethral stricture recurrence and elapsed time to additional intervention for urethral stricture treatment within 2 years following initial treatment will be calculated and presented with descriptive statistics
- Efficacy of XIAFLEX® treatment in improving obstructive voiding dysfunction will be analyzed using paired t-test for the difference in uroflow and post-void residual measurements before and after study treatment (collected at baseline, 6-week post treatment and follow-up visits)
- Quality of life will be analyzed using paired t-test for the difference in AUA scores before and after study initial treatment (collected at baseline, 6-week post treatment and follow-up visits)

Secondary Safety Endpoints

The results of the following safety endpoints will be calculated and presented with descriptive statistics for all patients receiving study treatment.

- Complication rates following treatment – specifically pain, fever, genital lesions, or postoperative complaints secondary to treatment
- Incidence of formation of spongiofibrosis or change in length and extent of spongiofibrosis
- Incidence of change in normal urethra structure proximal to injected tissue
- Incidence and severity of treatment-emergent AEs/SAEs during the study
- Proportion of patients completing study treatment
- Proportion of patients discontinuing due to treatment related complications

7.0 Benefits

This study may not directly benefit participants but may provide information that may accede a larger study that will benefit future clinical practice and patients.

8.0 Risks

The following adverse reactions have been associated with XIAFLEX® in treatment of Peyronie's disease:

- Penile hematoma (includes injection site hematoma and penile hematoma)

- Penile swelling (includes injection site swelling, penile edema, penile swelling, local swelling, scrotal swelling, and injection site edema)
- Penile pain (includes injection site pain, penile pain, and injection site discomfort)
- Penile ecchymoses (includes contusion, ecchymoses, penile hemorrhage, and injection site hemorrhage)
- Blood blister
- Penile blister
- Pruritus genital
- Painful erection
- Erectile dysfunction
- Skin discoloration
- Procedural pain
- Injection site vesicles
- Localized edema
- Dyspareunia
- Injection site pruritus
- Nodule
- Suprapubic pain
- Corporal rupture (penile fracture)
- Penile "popping" sounds or sensations

These adverse reactions were reported in XIAFLEX® clinical trials in patients with Peyronie's disease, from which most adverse reactions were reported as local events of the penis and groin and the majority of these events were of mild or moderate severity, and most (79%) resolved within 14 days of injection. The adverse reaction profile was similar after each injection, regardless of the number of injections administered [10].

Risks related to lidocaine injections include, but are not limited to:

- Hypotension
- Edema
- Redness at injection site
- Small red or purple spots on skin
- Skin irritation
- Constipation
- Nausea
- Vomiting
- Confusion
- Tremors
- Dizziness
- Headache
- Numbness and tingling
- Drowsiness
- Severe allergic reactions
- Dark urine
- Sudden feeling of warmth with muscle stiffness and pain
- Feeling hot or cold

- Anxiety

Other risks related to the injections include, but are not limited to:
- Bleeding
- Infection
- Fistula
- New stricture or scar tissue
- Inefficacy
- Incontinence
- Need for surgical intervention
- Lymphadenopathy
- Lymph Node Pain
- Inguinal Pain
- Need for suprapubic tube
- Need for extensive reconstruction in the future
- Fistula (urethrocutaneous)
- Periuretheral abscess
- Urethral diverticulum
- Acute urinary retention
- Need for urethral catheterization

Risk related to breach of confidentiality
The risks of participants in this project involve the use of PHI for the initial access to study-related data. Anytime such data is accessed and stored by handlers outside the domain of clinical routine, the risk of breached data security is increased, however all means necessary have been inputted to secure the information. Medical record numbers and patient names will be used to access the patient's medical record. Once the data collection is complete, the medical record numbers, patient names, and any other PHI will be destroyed.

Risks related to completing the surveys
The cognitive assessments ask about disease and health. Thinking about these things may make the patient uncomfortable. The patient may also feel a loss of privacy by answering the questions. The responses will be kept confidential and the patient may skip any questions he does not want to answer.

9.0 Safety Monitoring
A Data and Safety Monitoring Board (DSMB) will be established to monitor adverse reactions and the safety of the study. The DSMB will consist of experts in the relevant biomedical fields of urology and biostatistics. The members will have no direct relationship to the study (will not involve in any study related activities but may have their inputs in the study design and changes). The DSMB will review the protocol of the study and periodically monitor the progress, data, outcomes and safety during the study. An analysis will be performed after 5 patients have completed their study treatment and 6-week post treatment visits. All adverse events and reactions will be tabulated and presented to the DSMB. Further safety analysis will be performed by the biostatistician on the DSMB as necessary.

9.1 Adverse Events

Adverse events (AE) will be monitored and collected by the study team from the point of signed consent to the end of patient's participation in the study. For each AE, a detailed explanation will be obtained from the patient and patient's medical record. All AEs are to be recorded on the case report forms located in the patient's study binder and master database maintained by the principal investigator.

Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded. Subjects will be instructed to report any adverse event they experience to the investigator/study staff. Investigators will assess for adverse events at each visit and record accordingly. Any medical condition that is present when a subject is screened or present at baseline that does not worsen or deteriorate will not be reported as an adverse event. However, medical conditions present at baseline that change in severity at any time during the study will be reported as an adverse event. The investigator will exercise his medical and scientific judgment in deciding whether an abnormal assessment is clinically significant. The investigator will rate the severity of and clarify each adverse event based on the definitions below.

Assess of Severity of Adverse Event:

- Mild – transient in nature and generally does not interfere with normal activities
- Moderate – sufficiently discomforting to interfere with normal activities
- Severe – incapacitating, causing inability to perform normal activities

Assessment of Adverse Event and Study Drug Relatedness:

No related – definitely not related to study drug and is judged clearly due to causes other than study drug

Unlikely related – follows a temporal sequence from study drug administration, such that a relationship is not likely and could be reasonably explained by the subject's current medical condition or other standard of care treatment the subject is receiving

Possibly related – follows a temporal sequence from study drug administration, but may be due to another cause and could also be reasonable explained by the subject's current medical condition or other standard of care treatment the subject is receiving

Definitely related – clearly related to study drug administration

9.2 Serious Adverse Events

An adverse event is considered serious if it results in any of the following:

- Death
- Life-threatening adverse event – subject is at immediate risk of death due to adverse event occurrence
- Requires inpatient hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Significant medical event that may require medical/surgical intervention to prevent one of the outcomes above

9.3 Unanticipated Adverse Events

The following are examples of adverse events considered to be unanticipated adverse events that must be reported to the USF Institutional Review Board (IRB) promptly, or within five (5) calendar days:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome;
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy);
- Multiple occurrences of an AE that, based on aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects;
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a frequency or severity that is inconsistent with prior observations.
- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison).
- Any other AE or safety finding that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.
- Any breaches in confidentiality that would place the participant or others at risk;
- Any change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
- Any change to the protocol that was taken without prior IRB approval to eliminate apparent immediate hazard to a research participant;
- Incarceration of a participant when enrolled on a study not approved under Subpart C provisions; or
- Breach of privacy or confidentiality including the loss of data on a computer or any electronic device which holds private or confidential information.

A comprehensive list of all adverse and serious adverse events will be submitted with each continuing review application to the USF IRB.

9.4 Study Stopping Criteria

Study termination may be recommended for any perceived safety concern based on clinical judgment, including by not limited to a higher than anticipated rate of ≥ 1% for any component resulting in an unanticipated SAEs. Subjects will also be withdrawn from the study if benefits are outweighed by the risks.

The study will be stopped altogether if there is one case of study treatment adversely affecting other post treatment intervention and/or urethroplasty in patients with recurrence of urethral stricture as determined by the principal investigator and DSMB to be related to study treatment.

10.0 Data Handling and Monitoring

Data will be monitored by the PI and coordinator on a regular basis. The collection of personal patient information will be limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.
Only study personnel will collect data. All hard copy documents will be kept in a locked room in the research coordinator's office for the duration of the study. Data entry will be completed in the REDCap secured database. REDCap data will be exported into Excel or other file format for data analysis. Only de-identified data will be used for data analysis. Collected data will be sent to a biostatistician consultant for statistical analysis.

Data will be kept secure for at least 5 years after the final study report has been submitted to the IRB. Data will ultimately be destroyed by shredding physical documents and discarding them in the HIPAA labeled bins at USF. Electronic documents will be completely removed from any databases used.

11.0 Conflicts of Interest

There are no financial conflicts of interest.

12.0 References

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13.0 Schedule of Assessments

Visit	Screening / Baseline	Treatment (Day 0)	2-Day	Q2wk[3] (0-84 days)	Q4wk (0-84 days)	6-Mo	9-Mo	12-Mo	18-Mo
Visit Window	-	+14 days from Control Visit	±1 day	±3 day	±1 days	±7 days	±7 days	±7 days	±7 days
Informed Consent	X								
Demographics and Medical History	X								
Inclusion/ exclusion criteria	X								
Concomitant Meds	X	X	X	X		X	X	X	X
AUA questionnaire	X		X	X		X	X	X	X
Retrograde urethrogram	X[1]								
Voiding cystourethrogram	X[1]								
Physical exam	X[1]		X	X		X	X	X	X
Post-void residual	X[1]		X	X		X[1]	X[1]	X	X
Uroflowmetry	X[1]		X	X		X[1]	X[1]	X	X
Cystoscopy	X[1]				X	X[1]	X[1]	X	X
Urethral ultrasound including evaluation of length and extent of spongiofibrosis	X				X	X	X	X	X
AE assessment		X	X	X		X	X	X	X
Study treatment		XIAFLEX® injection							

Visit	24-Mo	Unscheduled	Early Termination
Visit Window	±7 days	-	-
Concomitant Meds	X	X	X
AUA questionnaire	X	X	X
Retrograde urethrogram			
Voiding cystourethrogram			
Physical exam	X	X	
Post-void residual	X[1]	X[2]	X
Uroflowmetry	X[1]	X[2]	X
Cystoscopy	X[1]	X[2]	X
Urethral ultrasound including evaluation of length and extent of spongiofibrosis	X	X[2]	X
AE assessment	X	X	X

1. Collected as occurred as standard of care
2. Perform if applicable
3. Test for antibodies to AUX I and AUX II at 6 weeks and neutralizing antibodies at 12 weeks