

Human Pharmacokinetics and Safety of Subcutaneous Collagenase Clostridium Histolyticum in Women

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ABSTRACT

Background: Clostridium collagenase histolyticum (CCH) is being evaluated in women as a cellulite treatment.

Objective: To report preclinical safety and human pharmacokinetics (PK) and safety data for CCH.

Methods: Across 3 PK studies, 41 women received 12 subcutaneous injections per thigh/buttock in 1 session (up to 3.36 mg/dose). Blood samples were taken at baseline; at 5, 10, 20, and 30 minutes postdose; and at 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours postdose. In a preclinical study, rats received 0, 0.029, 0.13, or 0.29 mg/dose of CCH intravenously (IV) every other day (QOD) for 16 days (total, 8 doses) and were evaluated for histopathologic changes.

Results: In human PK studies, no quantifiable plasma concentrations of AUX-I or AUX-II were observed postdose (n= 39 evaluable). Adverse events were injection site-related (bruising [97.6%], pain [87.8%], and edema/swelling [46.3%]). Antidrug antibodies were seen in most women at 504 hours postdose. In rats, plasma concentrations of AUX-I and AUX-II (CCH components) were measurable for 30 minutes and 1-2 hours, respectively, after IV administration. At $\geq 43\times$ proposed human therapeutic dose on a mg/kg basis, rats experienced elevated liver enzyme levels, increased liver weights, and histologic changes that were mostly reversed during a 14-day recovery period.

Conclusions: In human studies, no quantifiable circulating CCH levels were observed after a single subcutaneous dose of CCH up to 3.36 mg. Preclinical data indicated that repeat IV dosing (QOD; 8 doses) at $\geq 43\times$ proposed human dose on a mg/kg basis for CCH was generally well tolerated.

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INTRODUCTION

Cellulite is a localized alteration of skin topography (eg, dimpling) and affects 80% to 98% of postpubertal women of all ages and ethnicities.^{1,2} Although the pathophysiology of cellulite has not been fully elucidated, data suggest the number, type, and orientation of the collagen-rich (fibrous) septae play a primary structural role.^{1,3} Other factors may include subcutaneous (SC) edema and fibrogenesis; SC adipose protrusion; and decreased dermal thickness with age.^{1,3} Several procedures and technologies that target the dermis and adipose tissue, in addition to fibrous septae, have shown improvements in skin texture and the dermal-SC interface; however, these improvements could be secondary to the effects of releasing the fibrous septae.⁴⁻⁷

Collagenase clostridium histolyticum (CCH) for injection is composed of 2 purified bacterial collagenases (AUX-I and AUX-II [clostridial class I and II collagenases]) that hydrolyze Types I and III collagen under physiologic conditions, resulting in disruption of collagen structures.⁸ CCH (0.58 mg; Xiaflex[®], Endo Pharmaceuticals Inc., Malvern, PA) is currently indicated in the

United States for the treatment of collagen-associated disorders (ie, adults with Dupuytren contracture [DC] with palpable cord or Peyronie's disease [PD] in adult men with a palpable plaque and penile curvature deformity of ≥ 30 degrees at the start of therapy).⁸ Safety and immunogenicity data reported in patients with DC or PD demonstrated that CCH treatment is safe and generally well tolerated.⁹⁻¹² Clinical trial and postmarketing surveillance data indicate that the most common adverse events (AEs) associated with CCH administration for the treatment of DC and PD were localized to the injection site, mostly mild to moderate in intensity, and transient.⁹⁻¹¹ In 5-year posttreatment follow-up studies of patients with DC (n=644) or PD (n=280), no long-term safety issues with CCH therapy were identified.^{9,12} At 5 years posttreatment, $>90\%$ of patients treated with CCH for DC and PD were seropositive for anti-AUX-I and anti-AUX-II antibodies.^{9,12} Patients with DC or PD treated with CCH produced serum neutralizing antibodies; however, the presence of neutralizing antibodies in patients with PD or DC had no apparent effect on the clinical response or the frequency of adverse reactions.^{8,9}

A different formulation, collagenase clostridium histolyticum-aes (Qwo™, Endo Aesthetics LLC, Malvern, PA), using a higher dose and volume and lower concentration, was approved by the US Food and Drug Administration in July 2020 for the treatment of moderate to severe cellulite in the buttocks of adult women. When injected, it causes enzymatic disruption of the fibrous septae. In one phase 2 (ClinicalTrials.gov identifier: NCT02724644) and two phase 3 (ClinicalTrials.gov identifiers: NCT03428750 [Randomized Evaluation of Cellulite Reduction by Collagenase Clostridium Histolyticum (RELEASE-1)]; NCT03446781 [RELEASE-2]), randomized, double-blind, placebo-controlled studies of women (n=1218; total for 3 studies) with moderate to severe cellulite on the buttocks and/or posterolateral thighs, SC CCH significantly improved the appearance of cellulite compared with placebo based on both clinicians' and patients' ratings and was generally well tolerated.^{13,14} Although CCH acts locally when injected SC to target the collagenase structural matrix (eg, septae), additional data would be valuable to help understand the systemic exposure profile of CCH administration for cellulite and to provide insight regarding the potential systemic impact if CCH were inadvertently administered intravenously (IV). The objective of the manuscript is to discuss the pharmacokinetics (PK) and safety of a single SC dose of CCH in women with cellulite and to summarize preclinical animal toxicity data to further understand the safety profile of a potential inadvertent IV systemic CCH exposure.

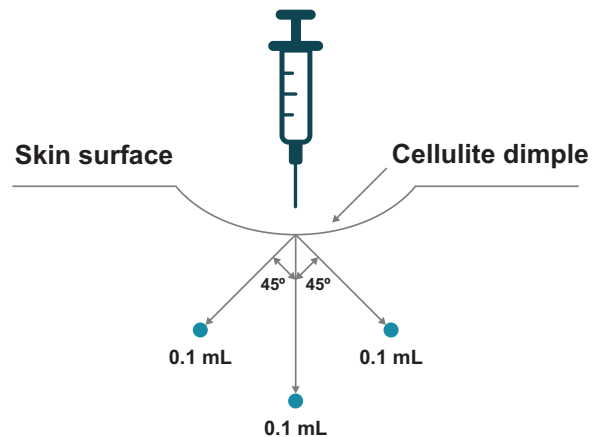
METHODS

Human Pharmacokinetics and Safety

Three PK studies were conducted in healthy adult women with cellulite on the thighs or buttocks. All 3 studies used the same CCH injection technique (Figure). In study 1 (EN3835-102), a single overall CCH dose of 0.84 mg was administered as 12 SC injections in 1 area (thigh/buttock) with cellulite. In study 2 (EN3835-104), a single overall CCH dose of 1.68 mg was administered as 0.84 mg (12 SC injections) in each of 2 areas (thigh/buttock) with cellulite. In study 3 (EN3835-103; ClinicalTrials.gov identifier: NCT03675685), a single overall CCH dose of 3.36 mg was administered as 0.84 mg (12 SC injections) in each of 4 areas (right and left thigh; right and left buttock) with cellulite. A CCH dose of 3.36 mg is twice the proposed maximum human total dose to treat cellulite in women. If a cellulite dimple required >1 SC injection, the injection sites were to be spaced approximately 2 cm apart.

Blood samples to measure plasma AUX-I and AUX-II concentrations were collected at baseline (predose) and 5, 10, 20, and 30 minutes postdose, and at 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours (day 22) postdose in all 3 studies. Pharmacokinetic variables were estimated using a noncompartmental approach (Phoenix® WinNonlin® 6.4, Certara L.P., Princeton, NJ). Serum anti-AUX-I, anti-AUX-II antibodies, and neutralizing

FIGURE 1. Three-Directional Delivery Technique.*



*A total of 12 subcutaneous injections were administered per quadrant (defined as left buttock, right buttock, left posterolateral thigh, or right posterolateral thigh) as three 0.1-mL aliquots (0.3 mL for injection). The first aliquot was administered with the needle perpendicular to the skin surface. For the second and third aliquots, the needle was withdrawn slightly and oriented ~45 degrees superior and ~45 degrees inferior to the perpendicular axis.

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antibodies to AUX-I and AUX-II were measured at baseline and 504 hours postdose. AUX-I and AUX-II concentrations and antibody levels were determined using validated enzyme-linked immunosorbent assay methods. Safety was assessed through 504 hours (day 22) post-dose for the 3 studies.

The safety population included all women enrolled in the studies who received ≥ 1 injection of CCH. The PK population was defined as all women enrolled who received the full CCH dose and had sufficient 24-hour data to determine key PK parameters (eg, observed maximum concentration, elapsed time to maximum concentration, and area under the curve).

Preclinical Safety

For the general toxicology study, Sprague-Dawley rats (10-30 per sex, per dose level) received 0, 0.029, 0.13, or 0.29 mg/dose of IV CCH every other day (QOD) for 16 days (total of 8 doses, each dose separated by ~48 hours). Histopathologic evaluation was performed at the end of the treatment or after a 14-day recovery period. Toxicity and toxicokinetic profiles were assessed, as was reversibility of any changes during the 14-day recovery period. The dose/kg in rats at the highest dose (on a mg/kg basis) was 1.16 mg/kg (which is 97-fold higher than the proposed therapeutic treatment dose for a human with the average body weight of 70 kg [ie, 0.012 mg/kg of body weight]).

A fertility reproductive toxicology study evaluated fertility and embryo-fetal development. Male and female Sprague-Dawley rats (25 per sex, per dose) received 0, 0.0145, 0.0435, or 0.13 mg/

dose of IV CCH (0.52 mg/kg [43-fold higher than proposed human therapeutic dose]) QOD starting before cohabitation (males, 28 days; females, 15 days); during cohabitation (maximum of 21 days for both); and on gestation days 0, 3, 5, and 7 (females) or continuing through 1 to 2 days before euthanasia (males). Viability and other clinical observations (eg, abortion, premature delivery) during the fertility and embryo-fetal development studies were made twice and three times daily, respectively, for the study duration and once daily during the postdose period for female rats. After euthanasia (dosing days 64–67 [males] or gestation day 13 [females]), histopathologic evaluation of reproductive organs was performed.

An embryo-fetal reproductive toxicology study evaluated embryo-fetal development; presumed pregnant female Sprague-Dawley rats (25 per dose) received 0, 0.0145, 0.0435, or 0.13 mg/dose of IV CCH (0.52 mg/kg [43-fold higher than proposed human therapeutic dose]) once daily during presumed gestation, days 7 through 17. Viability and other clinical observations (eg, abortion, premature delivery) were made twice daily for the study duration and once daily during the postdose period. Rats were euthanized on gestation day 21, and histopathologic evaluation of reproductive organs and fetuses was performed.

RESULTS

Human Pharmacokinetics and Safety

A total of 41 women were included in the safety and PK populations from the 3 studies (Table 1). There were no quantifiable plasma concentrations of AUX-I or AUX-II at any time point postdose for 39 evaluable women (2 individuals were excluded because of potential serum component interference with the enzyme-linked immunosorbent assay used). The most common treatment-emergent AEs were injection-site related (Table 2) and were mild or moderate in intensity. The majority of all treatment-related AEs resolved within 14 to 30 days. The 2 most common treatment-related AEs were injection-site bruising (93 AEs) and injection-site pain (90 AEs), and overall these AEs resolved in approximately 21 and 14 days, respectively. No serious AEs were reported and no AEs resulted in discontinuation from any study.

At day 22, more than half of 41 women had antibodies to AUX-I (68.3%) or AUX-II (56.1%). In Study 1, 1 of 6 women who tested positive for anti-AUX-I or anti-AUX-II antibodies developed neutralizing antibodies, and 0 of 14 patients had neutralizing antibodies in Study 2. In Study 3, 5 of 8 women developed neutralizing antibodies for AUX-II, one of whom also developed neutralizing antibodies to AUX-I. One woman who was seropositive for anti-AUX-II antibodies was not tested for neutralizing antibodies.

Preclinical Safety

A repeat IV dose general toxicity rat study (QOD; 8 doses over

TABLE 1.

Demographics and Baseline Characteristics in Human Pharmacokinetic Studies of Women			
Parameter	Study 1 (N=11)	Study 2 (N=18)	Study 3 (N=12)
Age, y, mean (SD)	51.9 (9.9)	44.3 (11.6)	49.3 (10.2)
Range, y	36-66	28-67	31-67
Race, n (%)			
Black	9 (81.8)	11 (61.1)	4 (33.3)
White	2 (18.2)	6 (33.3)	6 (50.0)
Other	0	1 (5.6)	2 (16.7)
BMI, kg/m ² , mean (SD)	29.3 (3.0)	30.7 (2.8)	29.9 (3.6)

BMI = body mass index; SD = standard deviation.

TABLE 2.

Adverse Event Profile in Human Pharmacokinetic Studies of Women				
Women with an AE, n (%)	Study 1 (N=11)	Study 2 (N=18)	Study 3 (N=12)	Pooled (N=41)
Any AE	11 (100.0)	18 (100.0)	12 (100.0)	41 (100.0)
≥1 mild AE	11 (100.0)	7 (38.9)	9 (75.0)	27 (65.9)
≥1 moderate AE	0	11 (61.1)	3 (25.0)	14 (34.1)
≥1 severe AE	0	0	0	0
≥1 serious AE	0	0	0	0
AE leading to discontinuation	0	0	0	0
Most common AEs*				
Injection-site bruising	10 (90.9)	18 (100.0)	12 (100.0)	40 (97.6)
Injection-site pain	9 (81.8)	15 (83.3)	12 (100.0)	36 (87.8)
Injection-site edema/swelling	3 (27.3)	10 (55.6)	6 (50.0)	19 (46.3)
Headache	0	1 (5.6)	2 (16.7)	3 (7.3)
Injection-site pruritus	0	2 (11.1)	1 (8.3)	3 (7.3)
Ear pain	1 (9.1)	0	0	1 (2.4)
Injection-site ecchymosis	1 (9.1)	0	0	1 (2.4)

*Occurrence of >9.0% of women in the CCH 0.84-mg group in at least 1 of the studies.

AE = adverse event; CCH = collagenase clostridium histolyticum.

16 days) was undertaken with high concentrations of CCH being injected systemically to address concerns about potential inadvertent IV dosing in humans. Due to dose-limiting signs at the injection site, euthanasia was performed on 4 rats (male, 1; female, 3) at 97× the proposed therapeutic human dose (1.16 mg/kg); at the same dose, 2 male and 4 female rats died between days 9 and 11 with no adverse clinical signs apparent before their deaths. At doses ≥43× the proposed therapeutic human dose on a mg/kg basis (0.52 mg/kg CCH), rats experienced elevated liver enzyme levels (aspartate aminotransferase and alanine aminotransferase), increased liver weights, and histologic changes (chronic inflammation and/or bile duct hyperplasia). Liver findings were mostly reversed during the 14-day recovery period, although liver findings of chronic active inflammation,

hemorrhage/hematoma, fibrosis, bile duct hyperplasia, and/or hepatocellular necrosis were not completely resolved (data not shown). Plasma concentrations of AUX-I were generally measurable for up to 30 minutes post-IV dose of CCH and AUX-II, up to 1 and 2 hours post-dose. There was no accumulation of plasma AUX-I or AUX-II observed during repeat dosing.

A repeat IV dosing study of CCH evaluated fertility and reproductive toxicology in rats. Euthanasia was performed on day 1 in 1 male rat due to vocalization, forelimb swelling, and immobility of right forelimb (dose, 14x the proposed therapeutic human dose [0.17 mg/kg]); there were also 2 male rat deaths on day 15 related to restraint-associated trauma during injection procedure. None of the events were considered related to CCH treatment by the study director. In both sexes, fertility was 96.0% for placebo and ranged from 88.0% to 92.0% for the 3 CCH doses (0.0145, 0.0435, and 0.13 mg/kg [43x the proposed therapeutic human dose]).

In a repeat IV dosing study of CCH to evaluate embryo-fetal development in rats, euthanasia was performed on presumed gestation day 8 in 1 female rat (0.52 mg/kg dose, 43x the proposed therapeutic human dose) because of dose-limiting clinical signs at the injection site. Overall, CCH at 43x the proposed therapeutic human dose (0.52 mg/kg) had no effect on early embryonic development and did not harm the fetus (unpublished data).⁸

DISCUSSION

CCH has been shown to be safe and generally well tolerated for the treatment of PD and DC. The current studies were conducted to assess the PK and safety of a different presentation of CCH, which is being investigated as a treatment for cellulite in women. No quantifiable circulating CCH levels were observed in healthy women after a single SC dose up to 3.36 mg (0.84 mg CCH administered per treatment area [thigh or buttock] containing cellulite). The most common AEs reported with CCH administration were injection-site bruising, pain, and edema; events were mild or moderate in intensity and transient. Data are consistent with a phase 2, randomized, double-blind, placebo-controlled study in 375 women with moderate to severe cellulite on the buttocks and/or posterolateral thighs, in which the most common AEs reported in the CCH treatment group were injection-site bruising (75.1%) or injection-site pain (59.3%), 92.3% of which were mild or moderate in intensity.¹³ Similarly, most women treated with CCH reported injection-site bruising or injection-site pain (RELEASE-1, 76.7% and 36.2%; RELEASE-2, 92.1% and 59.3%, respectively) as the most common AEs, AEs that were mild and/or moderate (RELEASE-1, 73.5%; RELEASE-2, 86.3%) and transient (≤ 2 weeks) in two phase 3, randomized, double-blind, placebo-controlled studies in 843 women.¹⁴ Furthermore, <5% of women discontinued due to AEs in the phase 2 and phase 3 studies.^{13,14} Therefore, the AE

profile observed across the phase 1, 2, and 3 studies has been consistent.

The human PK results in the current manuscript demonstrate a lack of systemic exposure following administration of 1 SC dose of CCH (up to 3.36 mg) and are similar to the results following a single (0.58 mg) injection or 2 concurrent injections (1.16 mg) of CCH into DC cords in patients.⁸ The intensity, duration, and characteristics of injection-site AEs reported following CCH administration in the current human PK studies were similar to data reported when patients with DC or PD were injected with CCH.⁹⁻¹¹

In a pooled safety analysis of 1082 patients with DC treated with CCH, most treatment-related AEs were injection-site related (peripheral edema [77.4%], bruising [54.5%], injection-site pain [40.6%]), were mostly mild to moderate in intensity, and most resolved within 7 to 10 days.¹⁰ In a 5-year CCH posttreatment follow-up study, a subgroup of 66 patients with DC had received repeat treatment with CCH.⁹ Patients (n=28) reported AEs, mostly mild to moderate in intensity, with the most common AEs being peripheral edema (12%) and bruising (11%). A pooled safety analysis of 1044 patients with PD indicated that the most frequently reported treatment-related AEs after CCH treatment were bruising (82.7%), hematoma (50.2%), pain (33.5%), and swelling (28.9%) of the penis; most AEs were mild or moderate in intensity and resolved without intervention.¹¹

In other studies, <1% of patients with PD (9/1044) or DC (3/1082) reported serious AEs (PD: penile hematoma [n=5], corporal rupture [n=4]; DC: tendon rupture [n=3]) following treatment with CCH.^{10,11} A pooled analysis of patients with PD treated with CCH reported that 1.6% of patients (17/1044) from 6 clinical studies discontinued because of AEs¹¹; however, no patients discontinued because of AEs during 5-year follow-up after injection.¹² In 13 trials of CCH for the treatment of DC, 1.3% of patients discontinued because of AEs.

Immunogenicity profiling has shown that administration of CCH in patients with PD or DC^{9,12} or administration of CCH in women with cellulite typically results in seropositivity for anti-AUX-I and/or anti-AUX-II antibodies. In the current study, the majority of the women were seropositive for anti-AUX-I and anti-AUX-II antibodies after CCH treatment, but only 6 women developed neutralizing antibodies. In the phase 2 and two phase 3 studies, all women treated with CCH and tested for immunogenicity were seropositive for anti-AUX-I and anti-AUX-II antibodies on day 71.^{13,14} Pooling data from 270 seropositive women in the 3 studies shows that 155 (57.4%) were positive for neutralizing antibodies (anti-AUX-I, 54.4%; anti-AUX-II, 60.4%). Even so, the presence of neutralizing antibodies did not impact safety and efficacy outcomes.^{13,14} In addition, no serious hypersensitivity reactions were observed in women treated with CCH in the

phase 2 and phase 3 studies.^{13,14} Other CCH studies have reported that patients with PD and DC have reduced levels of anti-AUX I and anti-AUX-II antibodies at 5 years posttreatment,^{9,12} and the presence of neutralizing antibodies does not affect clinical response or the frequency of AEs.^{8,9}

In preclinical rat studies, repeat-dose IV administration at $\geq 43\times$ the proposed therapeutic human dose (on a mg/kg basis) was reasonably well tolerated. The repeated systemic administration (QOD; 8 IV injections) in this animal study supports the presumption that inadvertent IV administration of CCH as a treatment for cellulite on the thighs or buttocks in women would likely not have a substantial negative impact on patient safety and tolerability. Additionally, the dosing technique for CCH administration involves 12 separate SC injections in a treatment area, thus effectively eliminating the risk of inadvertently administering the full CCH dose of 0.84 mg intravenously in any one particular treatment area.

The data described in the current manuscript support the clinical safety and benign immunogenicity profile of CCH, when administered into the thigh or buttock in women with cellulite. Limitations of the studies are the small sample size of the human PK studies in which to gain additional safety information, evaluation of only single-dose (1 session) SC administration, and use of animal data alone to evaluate inadvertent IV dosing. In conclusion, no quantifiable circulating CCH levels were observed in humans after a single SC dose of CCH up to 3.36 mg, and CCH was generally well tolerated, supporting a lack of systemic exposure after injection of CCH. These data add to the overall favorable safety and tolerability profile of CCH injection.

DISCLOSURES

ACB reports being a consultant and clinical advisor for Endo Pharmaceuticals Inc.

SV and MPM are employees of Endo Pharmaceuticals Inc.

TP is a former employee of Endo Pharmaceuticals Inc.

MKG reports serving in the speakers' bureau for Endo Pharmaceuticals Inc., and serving as a consultant for BioSpecifics Technologies Corporation.

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