Human Pharmacokinetics of Subcutaneous Collagenase Clostridium Histolyticum and Preclinical Safety of Inadvertent Intravenous Administration

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INTRODUCTION

- Cellulite is a localized, normal female characteristic of subcutaneous tissues that results in an alteration of skin topography (eg, dimpling) and affects almost all postpubertal women to some degree[1]
  - Although the pathophysiology of cellulite has not been fully elucidated, the combination of subcutaneous adipose protrusion and vertical orientation and thickening of collagen-rich septae appears to play a role in the altered skin topography[2,3]
- Collagenase clostridium histolyticum (CCH) for injection is composed of 2 purified collagenases (AUX-I and AUX-II [Clostridial class I and II collagenases]) that hydrolyze collagen under physiologic conditions, resulting in disruption of collagen structures[4]
  - CCH is currently indicated in the United States for the treatment of collagen-associated disorders (ie, adults with Dupuytren's contracture with a palpable cord or Peyronie's disease in adult men with a palpable plaque and penile curvature deformity of ≥30° at start of therapy)[4]
- A novel presentation of CCH is being investigated as a treatment to correct cellulite-related contour alterations in women via enzymatic disruption of the septae, which creates a skin-smoothing effect
  - In one phase 2 (N=375) and two phase 3 (N=423 and N=422), randomized, double-blind, placebo-controlled studies that enrolled women with moderate to severe cellulite on the buttocks or posterolateral thighs (phase 2) or the buttocks (phase 3), subcutaneous CCH significantly improved appearance of cellulite versus placebo based on both clinician and patient ratings and was generally well tolerated[5,6]
- Although CCH acts locally when injected subcutaneously 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 potential systemic impact if CCH were inadvertently administered intravenously

AIMS

- To assess preclinical toxicity to further understand the potential safety impact of CCH if administered inappropriately (eg, inadvertent intravenous dosing)
- To evaluate human pharmacokinetics (PK) and safety of a single subcutaneous dose of CCH in humans

METHODS

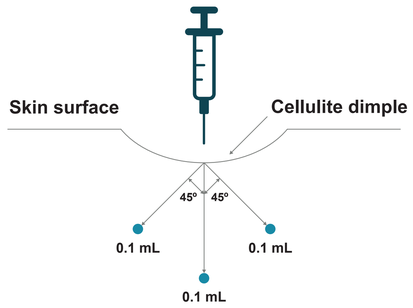
Preclinical

- Sprague-Dawley rats (10-15 per sex, per dose) received 0, 0.029, 0.13, or 0.29 mg/dose of intravenous CCH every other day for 16 days (total of 8 doses, each dose separated by ~48 hours)
  - Plasma samples were collected, and concentrations of AUX-I and AUX-II were measured
  - Animals underwent gross histopathologic evaluation at Day 16 (end of treatment) or at Day 30 (after 14-day recovery)
- Toxicity and toxicokinetic profiles were assessed as well as reversibility of any changes during the 14-day recovery period
- The human equivalent dose (HED) of the proposed therapeutic dose/treatment area in rats (on a mg/kg basis) is 0.012 mg/kg

Human Pharmacokinetics and Safety

- Two PK studies were conducted in adult women with cellulite on the thigh or buttock
  - In Study 1, a single overall CCH dose of 0.84 mg was administered as 12 subcutaneous injections in 1 area (thigh/buttock) containing cellulite (**Figure**)
  - In Study 2, a single overall CCH dose of 1.68 mg was administered as 0.84 mg (12 subcutaneous injections; **Figure**) in each of 2 areas containing cellulite (thigh/buttock)
- Blood samples were collected at baseline, at 5, 10, 20, and 30 minutes post-dose, and at 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours post-dose
- Anti-AUX-I and anti-AUX-II antibodies and neutralizing antibodies to AUX-I and AUX-II in plasma were measured at baseline and 504 hours post-dose using enzyme-linked immunosorbent assay (ELISA)
- The safety population included all women enrolled in the study who received ≥1 injection of CCH
- The PK population included all women enrolled in the study who received the full CCH dose and had sufficient data for evaluation of PK parameters

Figure. Three-Directional Delivery Technique*



*Each injection was administered 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° to the left and ~45° to the right of the perpendicular axis.

RESULTS

Preclinical

- There were no consistent differences between male and female rats within any of the dosing groups; therefore, data from both sexes were combined for toxicokinetic analysis
- Deaths or euthanizations related to dose-limiting signs at injection site occurred in no rats at ≤43x HED and 4 of 54 rats at 96x HED (3 female; 1 male)
- In rats, intravascular injection-site macroscopic findings consisted of perivascular edema, hemorrhage, inflammation, fibrosis, and/or necrosis; the latter 2 occasionally expanded into adjacent tissue (muscle and tendon sheaths)
  - Partial to complete reversal of injection-site findings occurred during recovery
- Liver changes were observed in both male and female rats at CCH ≥0.13 mg (≥43× HED; **Table 1**)

Table 1. Liver Effects of CCH by Intravenous Dose in Rats

CCH Dose	HED	Preclinical Liver Effects
≥0.13 mg	≥43×	• Elevated AST and ALT levels and increased liver weights in male rats • Macroscopic observations* in both male and female rats corresponded to histologic changes of minimal/marked chronic inflammation and/or bile duct hyperplasia • During recovery period: all liver findings were mostly reversed, with signs of ongoing reversal
0.29 mg	96×	• Additional liver findings (minimal/marked multifocal hemorrhage/hematoma, fibrosis, and/or hepatocellular necrosis noted) correlated with gross necropsy observations • During recovery period: all liver findings were partially reversed, with signs of ongoing reversal

*Masses, raised or dark foci or areas.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CCH = collagenase clostridium histolyticum; HED = human equivalent dose (on a mg/kg basis).

- Plasma concentrations of AUX-I and AUX-II (2 components of CCH) were generally measurable for up to 30 minutes and up to 1 to 2 hours post-intravenous dose, respectively
  - There was no evidence of plasma accumulation of AUX-I or AUX-II

Human Pharmacokinetics and Safety

- 29 women were included in the safety and PK populations (**Table 2**)

Table 2. Demographics and Baseline Characteristics

Parameter	Study 1 (N=11)	Study 2 (N=18)
Mean age ± SD, y (range)	51.9 ± 9.9 (36-66)	44.3 ± 11.6 (28-67)
Race, n (%) Black White Other	 9 (81.8) 2 (18.2) 0	 11 (61.1) 6 (33.3) 1 (5.6)
BMI, kg/m^2, mean (SD)	29.3 (3.0)	30.7 (2.8)

BMI = body mass index; SD = standard deviation.

- In clinical trials, there were no quantifiable plasma concentrations of AUX-I or AUX-II at any time point post-dose for the 28 evaluable women (1 woman was excluded due to issues related to potential serum component interference during the ELISA test)
- The most common adverse events were injection-site related (**Table 3**)

Table 3. Adverse Event Profile in Clinical Studies

Women With an AE, n (%)	Study 1 (N=11)	Study 2 (N=18)	Pooled (N=29)
≥1 AE	11 (100)	18 (100)	29 (100)
Serious AE	0	0	0
AE leading to discontinuation	0	0	0
Most common AEs*			
Bruising	10 (90.9)	18 (100)	28 (96.6)
Pain	9 (81.8)	15 (83.3)	24 (82.8)
Edema	3 (27.3)	10 (55.6)	13 (44.8)
Pruritis	0	2 (11.1)	2 (6.9)
Ear pain	1 (9.1)	0	1 (3.4)
Ecchymosis	1 (9.1)	0	1 (3.4)

*Occurring in >5.0% of women in the CCH 0.84-mg group at least once.
AE = adverse event; CCH = collagenase clostridium histolyticum.

- Antidrug antibodies (to AUX-I and/or AUX-II) were reported in 20 of 29 (69.0%) women at 504 hours post-dose
  - Only 1 of the 20 women (5.0%; from Study 1) developed neutralizing antibodies

CONCLUSIONS

- Repeat-dose intravenous administration (every other day; 8 dose administrations) at 43× HED dose in rats (on a mg/kg basis) was reasonably well tolerated
- No quantifiable circulating CCH levels were observed in humans after a single subcutaneous dose of CCH up to 1.68 mg, and CCH was generally well tolerated

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DISCLOSURE

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