

# 28-Day Rectal Toxicology Studies of UC781 Vaginal Gel in Rats and Rabbits

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## Introduction

- As part of UCLA Microbicide Development Program (MDP), a Phase I safety trial of rectally administered UC781 Vaginal Gel was planned.
- However, there was no existing animal toxicology data on rectally administered UC781 vaginal gel to support the planned MDP clinical study.
- Therefore, animal toxicology studies in two species were conducted in order to demonstrate the local and systemic safety of the product with rectal administration.
- Rats and rabbits were selected for the rectal toxicology studies as the representative rodent and non-rodent species respectively.

## Study Design

### Test Species



- Sprague-Dawley rats
- Male and female
- 5 rats/sex/group
- New Zealand White rabbits
- Male and female
- 4 rabbits/sex/group

### Treatment Groups

Group	Treatment
1	Sham Control
2	HEC Placebo
3	Vehicle Placebo
4	0.25% UC781 Vaginal Gel
5	0.75% UC781 Vaginal Gel
6	2.5% UC781 Vaginal Gel

## In Life Treatment

- Single daily rectal administration for 28 days
  - 0.2 mL rats
  - 1.0 mL rabbits
- Cage side observations performed daily
- Body weights and food consumption (rats only) recorded weekly
- Plasma for TK analysis collected at 0, 1, 2, 4, 8, & 24 hours on Days 1 and 28

## Post Mortem Examination

- Gross necropsy performed on Day 29
- Blood samples for clinical pathology assessment collected just prior to necropsy on Day 29
- Absolute and relative weights recorded for selected organs
- Rectal, anal, and descending colon tissues collected for histological evaluation

## Statistical Analysis

- Performed by group on the following parameters:

Body weights
Food Consumption (rats only)
Organ weights
Organ/body weight ratio
Clinical chemistry values
Hematology values
Coagulation values

## Results

### Findings For Both Species

- No mortalities reported
- No test-article related findings in:
  - Clinical observations
  - Body weight
  - Food consumption
  - Clinical pathology
  - Absolute or relative organ weights
- No significant findings noted upon:
  - Macroscopic evaluation
  - Microscopic tissue evaluation

### Toxicokinetic Analyses

- Plasma levels on Day 1 for both species and Day 28 for rabbits were either not detected (ND) or below the lower limit of quantitation (LLOQ) of 25 ng/mL
- Day 28 plasma levels were between 26 – 89 ng/mL in 9 rats as follows:
  - 2 in low-dose group (0.25%)
  - 1 in mid-dose group (0.75%)
  - 6 in high-dose group (2.5%)
- Not toxicologically relevant since no adverse findings in these animals
- Day 28 plasma levels in remaining rats were either ND or below LLOQ

## Conclusions

- Overall, rectally applied UC781 vaginal gel is well tolerated in rats and rabbits for up to 28 days
- No test-article related local or systemic toxicity observed in either species
- The no-observable-adverse-effect level (NOAEL) is 2.5% for both species
- The results of these studies provided the basis for safely going into the Phase I MDP study

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