

PROTOCOL SYNOPSIS

Title: A Three-Arm, Randomized, Placebo-Controlled, Double-Blind Phase 3 Study to Evaluate the Safety and Efficacy of Once-Daily and Twice-Daily Dosing of a Novel Hydrocortisone Acetate 90 milligrams (mg) Suppository Formulation Administered with the Sephure[®] Suppository Applicator in Subjects with Ulcerative Colitis of the Rectum.

Sponsor: Cristcot HCA LLC

Protocol No.: CHS1221

Study Name: cessa

Development Phase: 3

Study Drug Name: Hydrocortisone Acetate 90 mg Suppository

Study Locations: This study will be conducted at study sites inside and outside of the United States.

Objectives

Primary Objective

To evaluate the efficacy of two dosage regimens of the study drug (hydrocortisone acetate 90 mg suppository) administered with the Sephure suppository applicator compared to placebo in the treatment of ulcerative colitis (UC) of the rectum using the Modified Mayo Score.

Secondary Objectives

The following secondary objectives will be evaluated:

- Rectal bleeding sub-score of 0 (Modified Mayo Disease Activity Index (MMDAI)).
- Reduction of stool frequency.

Dose-Response Objective

- In addition, the dose-response effect for the primary efficacy endpoint (remission) will be assessed across the three treatment arms.

Exploratory Objectives

The following exploratory objectives will be evaluated:

- Quality of Life assessed using The Inflammatory Bowel Disease Questionnaire (IBDQ).
- Physician's Global Assessment.
- Recent recall and daily diary entries for the collection of the Mayo sub-scores stool frequency and rectal bleeding.

Pharmacokinetic (PK) Objective

To evaluate exposure of hydrocortisone acetate and its hydrolysis end product hydrocortisone following single and multiple doses of hydrocortisone acetate 90 mg suppository and to evaluate

the relationship, if any, between multiple dose exposures and hypothalamic pituitary adrenal (HPA) axis suppression. Plasma hydrocortisone acetate and hydrocortisone levels will be analyzed by population-based (NONMEM) and intensive-sampling (Noncompartmental Analysis, WinNonlin) methodologies. All subjects will participate in either the sparse or intensive PK.

Safety Objective

To evaluate the safety of hydrocortisone acetate 90 mg suppository compared with placebo.

Design

This is a randomized, multi-center, double-blind, three arm placebo-controlled study in male and non-pregnant, non-lactating female subjects aged 18 years and older. The study design is summarized in Figure 1 below.

The full study includes up to 21 days for study inclusion screening which will include an initial screening visit, a flexible sigmoidoscopy visit, and a pre-treatment medication wash-out period (if necessary). The screening period may be extended an additional 7 days to accommodate holidays, subject scheduling, delays in data acquisition (e.g., laboratory, central reading, etc.) and/or disruptions due supply chain and transportation issues. Subjects who meet the inclusion criteria will proceed with 28 days for treatment, 10 days for tapering including one day for end of treatment assessment and one day for tapering assessment, and then 14 days for targeted safety follow-up.

Table PS-1: Clinical Trial Schedule

Visit Name	Visit Number	Day
Screening ¹	1	-21 to -6 (+7)
Flexible Sigmoidoscopy ²	2	-20 to -5 (+7)
Baseline/PK Sampling ³	3	1
Telephone Interview 1	4	8 (±3)
Follow Up/Sparse PK Sampling ³	5	15 (±3)
Telephone Interview 2	6	22 (±3)
End of Treatment/Early Termination/Sigmoidoscopy/PK Sampling ³	7	29 (+3)
End of Tapering	8	39 (+3)
Targeted Safety Follow Up (for abnormal ACTH)	9	53 (+3)

¹ The screening period of 21 days may be extended an additional 7 days to accommodate holidays, subject scheduling, delays in data acquisition (e.g., laboratory, central reading, etc.) and/or disruptions due to other factors.

² At the medical discretion of the Investigator, a colonoscopy can be performed in place of a flexible sigmoidoscopy for determining eligibility at Visit 2.

³ Subjects in the Intensive PK Sampling group will follow the Intensive PK Sampling Schedule, not the Sparse PK Sampling schedule.

Table PS-2: Intensive PK (IPK) Sampling Schedule

Visit Name	Visit Number	Day
Initial/Intensive PK Sampling	IPK 1 ¹	1
Intensive PK Morning Sample (24-hour sample)	IPK 2	2
Steady State/Intensive PK Sampling	IPK 3 ²	28 (-3)
Intensive PK Morning Sample (24-hour sample)	IPK 4 ³	29 (-3)

¹ Visit IPK 1 (Day 1) is on the same day as Clinical Trial Schedule Visit 3. Subjects in the Intensive PK Sampling group will have a longer Visit 3 (Day 1) with additional PK sampling.

² Intensive PK sampling at Visit IPK 3 is intended to evaluate PK at steady state over an approximately 12-hour period. Visit IPK 3 may be scheduled any day no earlier than 3 days before Day 28 and no later than Day 28 (Day 25 through Day 28). Subjects in the Intensive PK Sampling group are expected to complete all Visits outlined in the Clinical Trial Schedule and are expected to complete 28 days of treatment.

³ Intensive PK sampling at Visit IPK 4 is intended to evaluate PK at steady state at the approximately 24-hour timepoint following the sampling started at Visit IPK 3. Visit IPK 4 is the day following IPK 3 for completion of the 24-hour sample. For clarity, if IPK 3 occurs on a day earlier than Day 28, the subject will continue the study treatment (BID suppository dosing) through Day 28. The subject will visit the site for IPK 4 the day following IPK 3 for 24-hour intensive PK sampling, and PK samples will be collected prior to administering the morning dose. For the fewest number of visits to the site, a subject in the Intensive PK Sampling group may schedule Visit IPK 3 on Day 28 and Visit IPK 4 on Day 29, therefore combining Visit IPK 4 with Visit 7 (End of Treatment/Early Termination/Sigmoidoscopy).

Subjects will be provided with a paper diary at the first Screening Visit (Visit 1) to record stool frequency and rectal bleeding from the first Screening Visit (Visit 1) until screen failure or End of Treatment Visit (Visit 7). Subjects will be provided with an electronic dose reminder application at the Baseline Visit (Visit 3) to encourage drug dosage regimen and paper diary compliance. The subject will respond to the electronic dose reminder application daily from Screening Visit (Visit 3) until the End of Treatment Visit (Visit 7).

The dropout rate assumptions may be periodically assessed in a blinded manner to recalculate the final randomized subject target.

Eligible subjects will be randomly assigned in a 1:1:1 ratio across the three arms of the study to receive dosage regimens of study drug or placebo stratified by region, gender and subjects on stable doses of study permitted concomitant medication to treat UC (user or non-user). Subjects using study permitted concomitant medications for the treatment of UC are "users".

Figure PS-1: Study Design

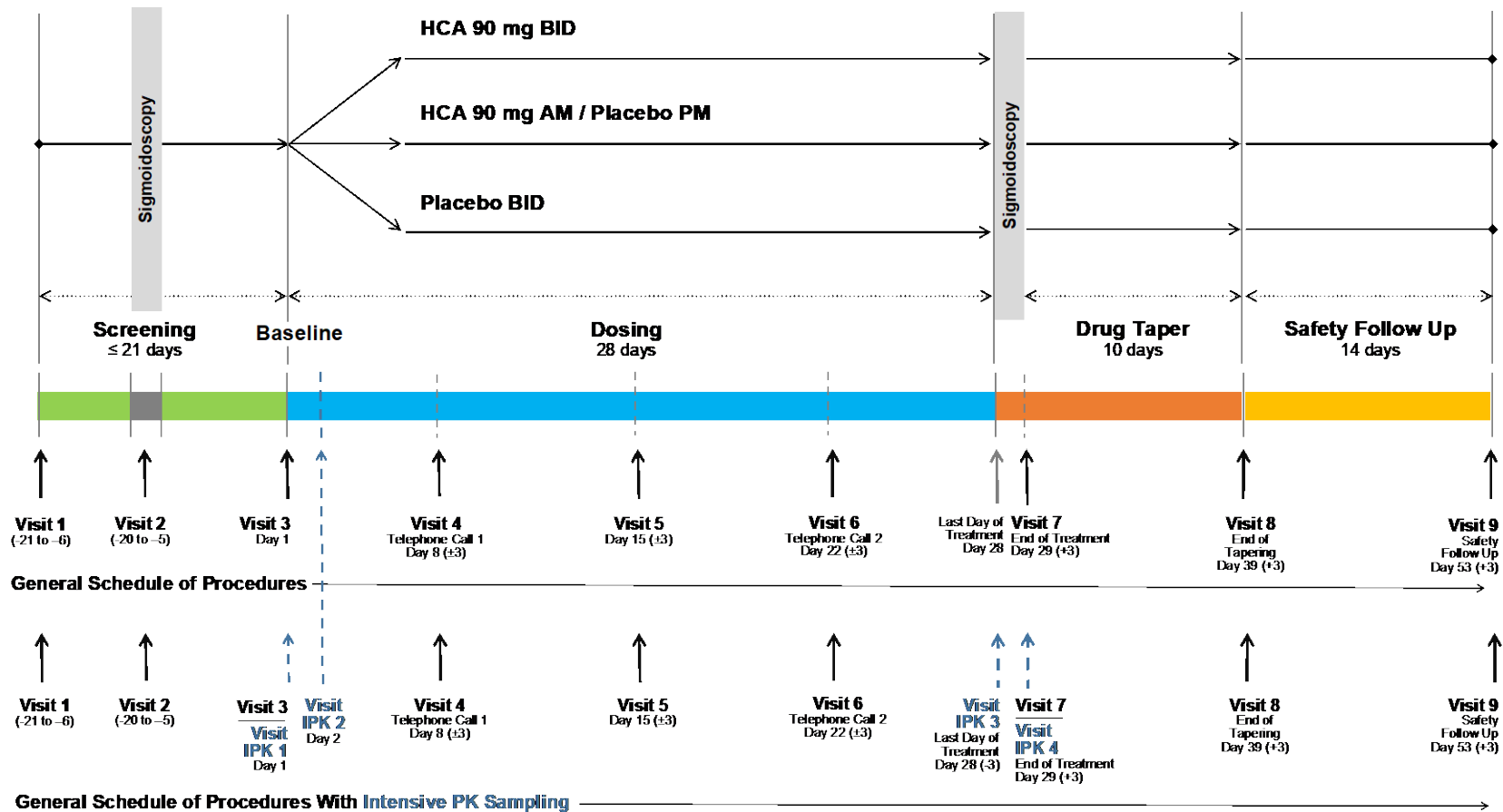


Table PS-3: General Schedule of Procedures

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 ⁸
Visit Name	Screening	Flexible Sigmoidoscopy	Baseline	Telephone Interview 1	Follow Up	Telephone Interview 2	End of Treatment/ Early Termination ¹⁶ / Sigmoidoscopy	End of Tapering	Targeted Safety Follow Up (abnormal ACTH only)
Days	-21 to -6 (+7)	-20 to -5 (+7)	1	8 (±3)	15 (±3)	22 (±3)	29 (+3)	39 (+3)	53 (+3)
Informed consent	X								
Inclusion/exclusion criteria	X		X						
Medical/disease history and previous medication history	X								
Evaluate stable dose of UC treatment medications ¹	X	X	X						
Determine User or Non-User Stratification ¹			X						
Concomitant medications	X	X	X	X	X	X	X	X	X
Distribute Daily Diary	X								
Enter Daily Diary Input			X		X		X		
Partial Mayo Score ²	X	X			X				
Full physical examination ³	X						X		X
ECG	X								
Brief physical examination ⁴			X		X			X	
IBDQ assessment			X		X		X		
Demography	X								
Serum pregnancy test	X								
Urine pregnancy test ⁵			X		X		X	X	X
Blood sample for laboratory variables ⁶	X		X		X		X	X	
Serology	X								

A horizontal timeline with two segments. The first segment is labeled "Day 1-28" and the second segment is labeled "Day 29-36".

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 ⁸
Visit Name	Screening	Flexible Sigmoidoscopy	Baseline	Telephone Interview 1	Follow Up	Telephone Interview 2	End of Treatment/ Early Termination ¹⁶ / Sigmoidoscopy	End of Tapering	Targeted Safety Follow Up (abnormal ACTH only)
Days	-21 to -6 (+7)	-20 to -5 (+7)	1	8 (±3)	15 (±3)	22 (±3)	29 (+3)	39 (+3)	53 (+3)
Return of study drug kit								X	
AEs/SAEs	X	X	X	X	X	X	X	X	X

Abbreviations

ACTH: Adrenocorticotrophic Hormone; AE: Adverse Event β -hCG: beta human chorionic gonadotropin; ECG: Electrocardiogram; IBDQ: The Inflammatory Bowel Disease Questionnaire; HEENT: Head, Eye, Ear, Nose, and Throat; PK: Pharmacokinetic(s); SAE: Serious Adverse Event

Footnotes

1. Evaluate subject use of concomitant medications intended to treat UC. Subject using a stable dose of study permitted concomitant medications for the treatment of UC (listed in Table 9) are “users”. Subjects who do not use medication in Table 9 and meet the other inclusion criteria are “non-users”.
2. Partial Mayo Score will include only stool frequency and rectal bleeding sub-scores based on subject recall for the past 3 days (see Section 6.2). Additionally, the physician’s global assessment will be recorded as an exploratory endpoint.
3. See [Section 6.5.4](#) for Full physical examination list of tests.
4. See [Section 6.5.4](#) for Brief physical examination list of tests.
5. If the subject has a positive urine pregnancy test result, a serum β -hCG test will be performed to confirm the pregnancy.
6. Complete blood profile including hematology, clinical chemistry, and liver enzymes; see [Section 6.5.2](#).
7. Stool culture for enteric pathogens panel, *Clostridium difficile*, *Clostridium difficile* toxin test, ova and parasite exam. Subjects who are unable to provide a stool sample on Visit 1 will be provided with a stool collection kit to take home and then return it to the clinic.
8. Synthetic Adrenocorticotrophic Hormone (ACTH) provided by study. Only subjects with abnormal ACTH at End of Tapering Visit (Visit 8) need to attend Targeted Safety Follow Up Visit (Visit 9). If the subjects have abnormal ACTH stimulation test results at Visit 9, they will be referred to an endocrinologist for further management. Refer to ACTH Stimulation Test Manual for additional information.
9. The flexible sigmoidoscopy at Screening (Visit 2) should be performed within 10 days of the consent date when possible and will be performed to; exclude subjects with a colonic mucosal inflammation endoscopic score of 2 or 3 extending beyond 15 centimeters (cm) from the anal verge, and to establish the baseline endoscopic sub-score of the Mayo Score. At the medical discretion of the Investigator, a colonoscopy can be performed in place of sigmoidoscopy for determining eligibility at Visit 2. Flexible sigmoidoscopy will be performed at End of Treatment/Early Termination Visit (Visit 7) to determine the end of treatment endoscopic sub-score for the Mayo Score. Saline enema will be used for bowel preparation prior to the sigmoidoscopy and polyethylene glycol (or study approved alternative preparations) will be used for bowel preparation prior to a colonoscopy.
10. The Investigator will assess the preliminary score for endoscopic finding and exclude subjects with an endoscopic score of 0-1 within 15 cm from the anal verge. Subjects with an endoscopic score of 2-3 extending beyond 15 cm from the anal verge will be excluded. Subjects with a preliminary endoscopic score of 2-3 no further than 15 cm from the anal verge (and may have disease score of 0-1 beyond 15 cm from the anal verge) will have their endoscopy video submitted to Central Reading for the endoscopic sub-score assessment.

11. The Mayo Score will be evaluated based on: Investigator assessment of stool frequency and rectal bleeding sub-scores based on subject recall for the past 3 days (see Section 6.2); and Central Reading result of endoscopy at the beginning of the study and the sigmoidoscopy at the end of the study. Additionally, the physician's global assessment will be recorded as an exploratory endpoint.
12. Sparse PK samples will be collected at the site during Visits 3, 5 and 7. Blood samples will be collected on: Visit 3 within 30 min pre-dose, and 2h and 4h post-dose; Visit 5 at 8h post-dose; and Visit 7 at 12h after Day 28 evening dose.
13. Study drug kit with instructions for dosing will be provided to the subjects by the designated site personnel on Day 1 (Visit 3). Subjects will self-administer the morning dose and record the event in the electronic dose reminder application at the study site. The time of morning dose will be recorded in the EDC.
14. Study drug will be self-administered by the subject from Day 1 to Day 38; see [Section 5](#) and [Table 19](#).
15. Subjects will be instructed to bring the paper diary, study drug kit, including all unused study drug for drug accountability. At this time, additional drug may be added to the study drug kit (contingent upon prior approval and directions of Cristcot) if some has been lost or damaged.
16. All observations and procedures scheduled for the End of Treatment Visit (Visit 7) should also be performed at the Early Termination Visit.
17. A negative tuberculosis (TB) testing result allows a subject to proceed with screening. An indeterminant or positive TB testing result should be evaluated with an x-ray to rule out active tuberculosis. A negative x-ray for TB allows a subject to proceed with screening.

Table PS-4: General Schedule of Procedures WITH the Intensive PK Sampling

Visit	Visit 1	Visit 2	Visit 3 Visit IPK 1	Visit IPK 2	Visit 4	Visit 5	Visit 6	Visit IPK 3	Visit IPK 4	Visit 7	Visit 8	Visit 9 ⁸
Visit Name	Screening	Flexible Sigmoidoscopy	Baseline Intensive PK Sampling	Intensive PK 24h Sampling	Telephone Interview 1	Follow Up	Telephone Interview 2	Intensive PK Sampling	Intensive PK 24h Sampling	End of Treatment/ Early Termination ¹⁶ / Sigmoidoscopy	End of Tapering	Targeted Safety Follow Up (abnormal ACTH only)
Days	-21 to -6 (+7)	-20 to -5 (+7)	1	2	8 (±3)	15 (±3)	22 (±3)	28 (-3)	29 (-3)	29 (+3)	39 (+3)	53 (+3)
Informed consent	X											
Inclusion/exclusion criteria	X		X									
Medical/disease history and previous medication history	X											
Evaluate stable dose medications for UC ¹	X	X	X									
Determine User vs Non-User Stratification ¹			X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Distribute Daily Diary	X											
Enter Daily Diary Input			X			X				X		
Partial Mayo Score ²	X	X				X						
Vital signs				X					X			
Full physical examination ³	X									X		X

Visit	Visit 1	Visit 2	Visit 3 Visit IPK 1	Visit IPK 2	Visit 4	Visit 5	Visit 6	Visit IPK 3	Visit IPK 4	Visit 7	Visit 8	Visit 9 ⁸
Visit Name	Screening	Flexible Sigmoidoscopy	Baseline Intensive PK Sampling	Intensive PK 24h Sampling	Telephone Interview 1	Follow Up	Telephone Interview 2	Intensive PK Sampling	Intensive PK 24h Sampling	End of Treatment/ Early Termination ¹⁶ / Sigmoidoscopy	End of Tapering	Targeted Safety Follow Up (abnormal ACTH only)
Days	-21 to -6 (+7)	-20 to -5 (+7)	1	2	8 (±3)	15 (±3)	22 (±3)	28 (-3)	29 (-3)	29 (+3)	39 (+3)	53 (+3)
ECG	X											
Brief physical examination ⁴			X			X					X	
IBDQ assessment			X			X				X		
Demography	X											
Serum pregnancy test	X											
Urine pregnancy test ⁵			X			X				X	X	X
Blood sample for laboratory variables ⁶	X		X			X				X	X	
Serology	X											
Tuberculosis test ¹⁷	X											
Urinalysis	X									X	X	
Stool test ⁷	X											
Pre ACTH-stimulation blood sample	X									X	X	X
Administer a Synthetic Adrenocorticotrophic ⁸	X									X	X	X
Post ACTH- stimulation blood samples	X									X	X	X

[illegible]

Visit	Visit 1	Visit 2	Visit 3 Visit IPK 1	Visit IPK 2	Visit 4	Visit 5	Visit 6	Visit IPK 3	Visit IPK 4	Visit 7	Visit 8	Visit 9 ⁸
Visit Name	Screening	Flexible Sigmoidoscopy	Baseline Intensive PK Sampling	Intensive PK 24h Sampling	Telephone Interview 1	Follow Up	Telephone Interview 2	Intensive PK Sampling	Intensive PK 24h Sampling	End of Treatment/ Early Termination ¹⁶ / Sigmoidoscopy	End of Tapering	Targeted Safety Follow Up (abnormal ACTH only)
Days	-21 to -6 (+7)	-20 to -5 (+7)	1	2	8 (±3)	15 (±3)	22 (±3)	28 (-3)	29 (-3)	29 (+3)	39 (+3)	53 (+3)
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations

ACTH: Adrenocorticotrophic Hormone; AE: Adverse Event; β -hCG: beta human chorionic gonadotropin; ECG: Electrocardiogram; IBDQ: The Inflammatory Bowel Disease Questionnaire; HEENT: Head, Eye, Ear, Nose, and Throat; PK: Pharmacokinetic(s); SAE: Serious Adverse Event

Footnotes

1. Evaluate subject use of concomitant medications intended to treat UC. Subject using a stable dose of study permitted concomitant medications for the treatment of UC (listed in Table 9) are “users”. Subjects who do not use medication in Table 9 and meet the other inclusion criteria are “non-users”.
2. Partial Mayo Score will include only stool frequency and rectal bleeding sub-scores based on subject recall for the past 3 days (see Section 6.2). Additionally, the physician’s global assessment will be recorded as an exploratory endpoint.
3. See [Section 6.5.4](#) for Full physical examination list of tests.
4. See [Section 6.5.4](#) for Brief physical examination list of tests.
5. If the subject has a positive urine pregnancy test result, a serum β -hCG test will be performed to confirm the pregnancy.
6. Complete blood profile including hematology, clinical chemistry, and liver enzymes; see [Section 6.5.2](#).
7. Stool culture for enteric pathogens panel, *Clostridium difficile*, *Clostridium difficile* toxin test, ova and parasite exam. Subjects who are unable to provide a stool sample on Visit 1 will be provided with a stool collection kit to take home and then return it to the clinic.
8. Synthetic Adrenocorticotrophic Hormone (ACTH) provided by study. Only subjects with abnormal ACTH at End of Tapering Visit (Visit 8) need to attend Targeted Safety Follow Up Visit (Visit 9). If the subjects have abnormal ACTH stimulation test results at Visit 9, they will be referred to an endocrinologist for further management. Refer to ACTH Stimulation Test Manual for additional information.
9. The flexible sigmoidoscopy at Screening (Visit 2) should be performed within 10 days of the consent date when possible and will be performed to; exclude subjects with a colonic mucosal inflammation endoscopic score of 2 or 3 extending beyond 15 centimeters (cm) from the anal verge, and to establish the baseline endoscopic sub-score of the Mayo Score. At the medical discretion of the Investigator, a colonoscopy can be performed in place of sigmoidoscopy for determining eligibility at Visit 2. Flexible sigmoidoscopy will be performed at End of Treatment/Early Termination Visit (Visit 7) to determine the end of treatment endoscopic sub-score for the Mayo Score. Saline enema will be used for bowel preparation prior to the sigmoidoscopy and polyethylene glycol (or study approved alternative preparations) will be used for bowel preparation prior to a colonoscopy.
10. The Investigator will assess the preliminary score for endoscopic finding and exclude subjects with an endoscopic score of 0-1 within 15 cm from the anal verge. Subjects with an endoscopic score of 2-3 extending beyond 15 cm from the anal verge will be excluded. Subjects with a preliminary endoscopic

score of 2-3 no further than 15 cm from the anal verge (and may have disease score of 0-1 beyond 15 cm from the anal verge) will have their endoscopy video submitted to Central Reading for the endoscopic sub-score assessment.

11. The Mayo Score will be evaluated based on: Investigator assessment of stool frequency and rectal bleeding sub-scores; and Central Reading result of endoscopy at the beginning of the study and the sigmoidoscopy at the end of the study. Additionally, the physician's global assessment will be recorded as an exploratory endpoint.
12. Intensive PK samples will be collected in the PK sub-population with a sampling of approximately 16 subjects per arm. Blood samples in the intensive sampling PK population (Arms A, B, C) will be collected on: Visit IPK 1 and IPK Visit 3 at up to 30 min pre-dose, and post-dose at 2h, 4h, 8h, and 12h (prior to the evening dose); IPK Visit 2 at 12h after Day 1 evening dose and before morning dose; and IPK Visit 4 at 12h after IPK Visit 3 evening dose. Blood samples for the 24h sample will be collected the mornings of IPK Visit 2 and IPK Visit 4 (prior to the morning dose); see [Section 6.4.2](#). If the IPK Visit 3 intensive PK sampling scheduled for Day 28 occurs earlier (Protocol allows up to 3 days earlier), the 24h sample (IPK Visit 4) will be collected on the morning following the scheduled IPK Visit 3, prior to the administration of the morning dose.
13. Study drug kit with instructions for dosing will be provided to the subjects by the designated site personnel on Day 1 (Visit 3). Subjects will self-administer the morning dose and record the event in the electronic dose reminder application at the study site. The time of morning dose will be recorded in the EDC.
14. Study drug will be self-administered by the subject from Day 1 to Day 38; see [Section 5](#) and [Table 19](#).
15. Subjects will be instructed to bring the paper diary, study drug kit, including all unused study drug for drug accountability. At this time, additional drug may be added to the study drug kit (contingent upon prior approval and directions of Cristcot) if some has been lost or damaged.
16. All observations and procedures scheduled for the End of Treatment Visit (Visit 7) should also be performed at the Early Termination Visit.
17. A negative tuberculosis (TB) testing result allows a subject to proceed with screening. An indeterminant or positive TB testing result should be evaluated with an x-ray to rule out active tuberculosis. A negative x-ray for TB allows a subject to proceed with screening.

Treatment

Hydrocortisone acetate 90 mg or placebo will be administered as a rectal suppository with a Sephure suppository applicator. Two arms of the study will receive different dosage regimens of hydrocortisone acetate, and the third arm will receive placebo. All subjects will administer the study drug twice a day; once in the morning and once in the evening for 28 days starting from Day 1. All subjects will self-administer the first dose and record the event in their electronic dose reminder application on the morning of Day 1 on-site. Subjects will administer two doses per day approximately 12 hours apart, timed as evenly as possible.

The three arms of the study are twice-daily dosing of a suppository as summarized below:

Table PS-5: Treatment Arms

Treatment Arm	Morning	Evening
A	Active	Active
B	Active	Placebo
C	Placebo	Placebo

Active: dosing of 90 mg hydrocortisone acetate suppository administered with a Sephure suppository applicator

Placebo: dosing of placebo suppository administered with a Sephure suppository applicator

The study drug dose will be tapered after 28 days of treatment as described below and the study blind control will be maintained with the use of placebo and active doses. Specifically, the taper will begin with one evening dose every day for days 29 through 33. Taper Day 34 will be a skip day with no dose, taper Days 35, 36 and 37 will have one evening dose of alternating placebo or active depending on the arm of the study. The final taper (Day 38) will be a skip day with no dose.

Number of Subjects – Sample Size Calculations

Based on additional literature review and a meta-analysis by [\[Jairath 2017\]](#), the original placebo and active arm remission rates were too high. According to [\[Jairath 2017\]](#), the placebo remission rate for corticosteroids administered rectally over a study-comparable duration were reported between 7% to 13%. Independent of looking at accruing data and based on the literature, Criscot is revising the remission rate for the placebo treatment group to 10%. We similarly hypothesize 35% remission rates for both active hydrocortisone acetate 90 mg once daily and 90 mg twice daily suppository treatment groups, which maintains the originally estimated difference (25%) between remission rates for placebo compared to active arms. Using these revised assumptions, the study will require 189 completed subjects (63 subjects per treatment group) to detect this 25% absolute improvement using an overall one-sided Fisher Exact test with $\alpha=0.0125$ and 85% power separately for comparing each active dose with placebo. The number of subjects randomized in a ratio of 1:1:1 to receive either hydrocortisone acetate 90 mg once daily, hydrocortisone acetate 90 mg twice daily, or to placebo twice daily will increased in a blinded manner to account for dropouts (e.g., if 5% of the randomized subjects drop out prior to study drug administration, then the total number of subjects randomized may be increased by 5%). To accommodate an anticipated 80% screen failure rate, approximately 945 subjects may be screened. Eligible subjects will receive

dosage regimens of study drug or placebo stratified by region (Asia-Pacific-South Africa-Middle East, Europe, and United States), gender and subject on stable doses of study permitted concomitant medication to treat UC (user or non-user). This study anticipates the following:

Table PS-6: Number Study Subjects Anticipated

Criteria	Number of Subjects
Screened	945
Allowing for 5% dropouts	199
Randomized	189
Each Arm	63

PK Sub-Study: Approximately 48 subjects from selected sites will participate in the intensive PK portion of the study in order to obtain a sample size of approximately 16 subjects per treatment arm.

Population

The study population will consist of male and non-pregnant, non-lactating females aged 18 years and older with a confirmed diagnosis of active UC of the rectum. In addition, the proposed study population will present with a total Modified Mayo Score (without physician global assessment) of 4-8 and Modified Mayo sub-scores of 1-3 for stool frequency, 0-2 for rectal bleeding, and 2-3 for endoscopic findings at screening. Subjects may have a previous diagnosis of more extensive UC (e.g., pancolitis), but may only have active disease in the rectum (UC of the rectum) at the time of the screening endoscopy.

Key inclusion criteria include the following:

- Male or non-pregnant, non-lactating females aged 18 years and older.
- Subjects with a confirmed diagnosis of UC with an endoscopic score 2-3 extending no further than 15 centimeters (cm) from the anal verge as assessed by endoscopic procedure performed at Visit 2. Note: Subjects may have a history of more extensive UC (e.g., pancolitis), but have an endoscopic score of 2-3 only in the rectum at the time of the screening endoscopy (endoscopic score 0-1 beyond 15 cm from the anal verge is not exclusionary).
- Modified Mayo sub-score for stool frequency of 1-3.
- Modified Mayo sub-score for rectal bleeding of 0-2.
- Modified Mayo endoscopic sub-score of 2-3.
- Total Modified Mayo Score (without physician global assessment) of 4-8.

Key exclusion criteria include the following:

- History or current diagnosis of bacterial or other infectious colitis, radiation-enteritis and radiation-proctitis, Crohn's disease, collagenous colitis and indeterminate colitis.
- Prior gastrointestinal surgery except appendectomy, cholecystectomy, hiatal hernia repair, Nissen Fundoplication wrap around lower esophagus, Heller myotomy of lower esophageal sphincter, gastric sleeve, limited small bowel resection, partial gastrectomy/Billroth I or II, and hernia.

- Concomitant active lower gastrointestinal disease (except irritable bowel syndrome) or distortion of intestinal anatomy.
- Bleeding hemorrhoids at the time of screening.
- Acute diverticulitis at the time of screening.
- Acute pancreatitis at the time of screening.
- Unmanaged celiac disease at the time of screening.
- Positive stool test for enteric pathogens, *Clostridium difficile*, or presence of ova and parasites.
- Taking a prohibited medication. Some medications to treat UC and/or irritable bowel syndrome (IBS) are prohibited during participation in the study. Prohibited medications include non-study corticosteroids, laxatives and antidiarrheal medications, and any medication delivered rectally (e.g., rectal 5-aminosalicylic acid [5-ASA medication]); however, oral 5-ASA agents at stable doses up to 4.8 g/day and daily fiber supplements are allowed. Subjects taking 5-ASA, and/or immunomodulatory agents will be stratified appropriately. Other medications (e.g., antibiotics, anti-seizure and anticoagulant medicines) are also prohibited unless approved by the Global Medical Monitor ([Section 5.8.2](#)).
- Live-attenuated vaccines (other types of vaccines including those for COVID-19 are allowed).

Criteria for Evaluation of Efficacy

Primary Endpoint:

Primary endpoint is the proportion of subjects with clinical remission at the End of Treatment Visit (Visit 7). As shown in the table below, clinical remission is defined as the Modified Mayo Total Score of 0 to 2, with, stool frequency sub-score of 0 or 1 (minimum 1 point decrease from a Baseline score of 1 or 2), rectal bleeding sub-score of 0 and endoscopic sub-score of 0 or 1.

Table PS-7: Modified Mayo Scoring System

	MODIFIED MAYO SCORING SYSTEM		
Category	Score Range	Inclusion Criteria Score Range	Remission Score Range³
Stool Frequency ⁴	0-3	1-3 ¹	0-1 ⁵
Rectal Bleeding ⁴	0-3	0-2 ¹	0
Endoscopic Findings	0-3	2-3 ²	0-1
Total Score	0-9	4 ⁶ -8	0-2

¹ Inclusion criteria (baseline) score assessed at Baseline Visit 3 (Day 1)

² Inclusion criteria score based on endoscopy performed at Visit 2

³ Remission scores based on assessments at End of Treatment Visit 7

⁴ Stool frequency and rectal bleeding scores will be collected from subject recent recall of the prior 3 days at Baseline Visit 3 (Day 1), Follow Up Visit 5 (Day 15) and End of Treatment Visit 7 (Day 29)

⁵ Sub-score must be at least a 1-point decrease from a Baseline (Visit 3/Day 1) score of 1 or 2 to achieve clinical remission

⁶ Total score at screening must be equal to or greater than 4 for study eligibility.

Criteria for Evaluation of Secondary Endpoints

The following secondary endpoints will be evaluated, based on the change at End of Treatment (Day 29/Visit 7) from Baseline (Day 1/Visit 3):

- Absence of rectal bleeding (MMDAI sub-score of 0).
Treatment response will be defined as a reported score of 0.
- Reduction of stool frequency.
Treatment response will be defined as a reported score of 0 or 1, with at least a reduction of 1 point from a Baseline score of 1 or 2.

In addition, for each endpoint, if the change at End of Treatment is significant, the change from Baseline at Follow up (Day 15/Visit 5) will also be evaluated to determine if onset of response was present by Follow up (Day 15/Visit 5).

Criteria for Evaluation of Exploratory Variable

- Quality of Life will be assessed using The Inflammatory Bowel Disease Questionnaire (IBDQ).
- Physician's Global Assessment will be collected as a part of the Mayo Score but will be assessed and reported as an exploratory endpoint.
- Ability of subjects to recall their symptoms and the variability of symptoms day to day using recent recall versus averaging of daily diary entry for data collection of stool frequency and rectal bleeding.

Criteria and Sampling Schedule for Evaluation of PK

Plasma hydrocortisone acetate and hydrocortisone concentrations will be analysed after single and multiple doses of the study drug. Intensive PK sampling will be performed on a subgroup of the study population. The sparse and intensive PK sampling schedules are presented in the tables below.

Table PS-8: Sparse PK Sampling

Sparse PK	
Day 1 (Visit 3)	
1	pre-dose (up to 30 minutes pre-dose)
2	2 hours (+/-10 minutes) post-dose
3	4 hours (+/-10 minutes) post-dose
Day 15 (±3) (Visit 5)	
1	8 hours (+/-10 minutes) post-dose (morning dose at home)
Day 29 (+3) (Visit 7)	
1	morning 12 hours (+/-10 minutes) after Day 28 evening dose

Table PS-9: Intensive PK Sampling

Intensive PK	
Day 1 (IPK Visit 1)	
1	pre-dose (up to 30 minutes pre-dose)
2	2 hours (+/-10 minutes) post-dose
3	4 hours (+/-10 minutes) post-dose
4	8 hours (+/-10 minutes) post-dose
5	12 hours (+/-10 minutes) post-dose (before evening dose)
Day 2 (IPK Visit 2)	
1	morning pre-dose, 12 hours (+/-10 minutes) after Day 1 evening dose
Day 28 (-3) (IPK Visit 3)	
1	pre-dose (up to 30 minutes pre-dose)
2	2 hours (+/-10 minutes) post-dose
3	4 hours (+/-10 minutes) post-dose
4	8 hours (+/-10 minutes) post-dose
5	12 hours (+/-10 minutes) post-dose (before evening dose)
Day 29 (-3) (IPK Visit 4)	
1	morning 12 hours (+/-10 minutes) after Day 28 evening dose

Criteria for Evaluation of Dose-Response

- Dose-response effect for the primary efficacy endpoint (remission).

Dose-response will be defined as an increasing trend across the ordered treatment arms.

Criteria for Evaluation of Safety

The safety variables are incidence of adverse events (AEs)/serious adverse events (SAEs), blood and urinalysis laboratory assessments, physical examination, and vital signs.

Statistical Methods

Study Design

This is a randomized, multi-center, double-blind, three arm placebo-controlled study. Subjects will be stratified by region (Asia-Pacific-South Africa-Middle East, Europe, and United States), gender and subject on stable doses of study permitted concomitant medication to treat UC (user or non-user).

Dose-response

The dose-response effect for clinical remission (using the clinical remission endpoint at Day 29/End of Treatment) will be assessed across the three treatment arms. There is 90% power to detect a trend under the alternative hypothesis. The one-sided p-value will achieve one-sided $p < 0.0125$ under the alternative hypothesis.

Type I Error Control

A one-sided 1.25% Type error will be used to allow separate comparisons for each dose group versus placebo control. In addition, a hierarchical testing plan will be used with the following testing order per dose group:

1. Clinical remission (Day 29/End of Treatment): Clinical remission is defined as the proportion of subjects with a Modified Mayo Total Score of 0 to 2 (stool frequency sub-score of 0 or 1 with a minimum 1-point decrease from a Baseline score of 1 or 2, rectal bleeding sub-score of 0 and endoscopic sub-score of 0 or 1). A 2.5 odds ratio will reach one-sided $p=0.0125$.
2. Absence of rectal bleeding (MMDAI sub-score of 0 from Day 1/Baseline to Day 29/End of Treatment;): Treatment response will be defined as a reported score of 0 (subjects with a Day1/Baseline bleeding score of 0 will not be included in the analysis). Excluding those with no rectal bleeding at baseline (estimated to be 25%), a 2.67 odds ratio will reach one-sided $p=0.0125$.
3. Reduction of stool frequency (from Day 1/Baseline to Day 29/End of Treatment): Treatment response will be defined as a reported score of 0 or 1, with at least a reduction of 1 point from Baseline. A 2.5 odds ratio will reach one-sided $p=0.0125$.
4. Absence of rectal bleeding (MMDAI sub-score of 0 from Day 1 baseline to Day 15/Follow Up): Treatment response will be defined as a reported score of 0 (subjects with a baseline bleeding score of 0 will not be included in the analysis). Excluding those with no rectal bleeding at baseline (estimated to be 25%), a 2.67 odds ratio will reach one-sided $p=0.0125$.
5. Reduction of stool frequency (from Day 1/Baseline to Day 15/Follow Up): Treatment response will be defined as a reported score of 0 or 1, with at least a reduction of 1 point from Baseline. A 2.5 odds ratio will reach one-sided $p=0.0125$.

Study Populations

The following populations will be considered in the statistical analysis of the study:

Full Analysis Set (FAS): All randomized subjects following the principle of intent-to-treat. Subjects will be included in the analysis according to the treatment to which they were randomized.

Per Protocol Set (PPS): All randomized subjects who are compliant with the study protocol, i.e., who do not experience any major protocol deviations.

Safety Set: All randomized subjects who received at least one dose of study treatment. Subjects will be included in the analysis according to the treatment received.

Sparse PK Analysis Set: All subjects who are not included in the intensive PK study sub-group and with sufficient data points such that the PK parameters are calculable.

Intensive PK Analysis Set: All subjects who are designated for intensive PK study and with sufficient data points such that the PK parameters are calculable.

Analysis Approach

The primary variable (clinical remission) will be analysed using a logistic regression model to include baseline covariates for region, gender and use of concomitant medication to treat UC (user or non-user) in addition to treatment dose; the placebo will be the referrant group.

The proportion of subjects withdrawn due to lack of efficacy will similarly be compared using the above-cited logistic regression model as used for the primary endpoint.

The dose-response effect will be assessed with an exact Kruskal-Wallis test using two-sided $p=0.05$; the three treatment arms will be ordered in the 2x3 contingency table to be analyzed.

The secondary endpoints will be classified as responders/non-responders and will be similarly analysed subject to the hierarchical testing as used for the primary endpoint.

The Modified Mayo Score and Modified Mayo sub-scores (stool frequency, rectal bleeding, and endoscopic findings) will be summarized descriptively by treatment group and separately compared to placebo using a singly ordered contingency table test (Kruskal-Wallis test).

The four dimensions of the IBDQ (bowel, systemic, social, and emotional) will be summarized using descriptive statistics (N, mean, median, quartiles, and minimum and maximum) per treatment group.

Physician global assessment sub-score of Mayo Score will be summarized by treatment group using descriptive statistics and separately compared to placebo using a singly ordered contingency table test (Kruskal-Wallis test).

Plasma hydrocortisone acetate and hydrocortisone concentrations obtained from the intensive sampling PK group will be analysed by noncompartmental methods using WinNonlin (Version 6.3 or higher). In addition, the plasma hydrocortisone acetate and hydrocortisone concentrations from the sparse sampling subjects will be summarized using descriptive statistics where possible and analysed by population-based PK methods using NONMEM (Version 7.2 or higher).

Safety variables, including AEs, concomitant medications, blood and urinalysis laboratory assessments, vital signs, and physical examinations, will be summarized using descriptive statistics and separately compared to placebo using a Fisher Exact test for comparisons vs placebo. Shift tables will show a McNemar paired comparison test within each treatment group for categorized (Low, Normal, High) crosstabulations relative to baseline.