2. SYNOPSIS

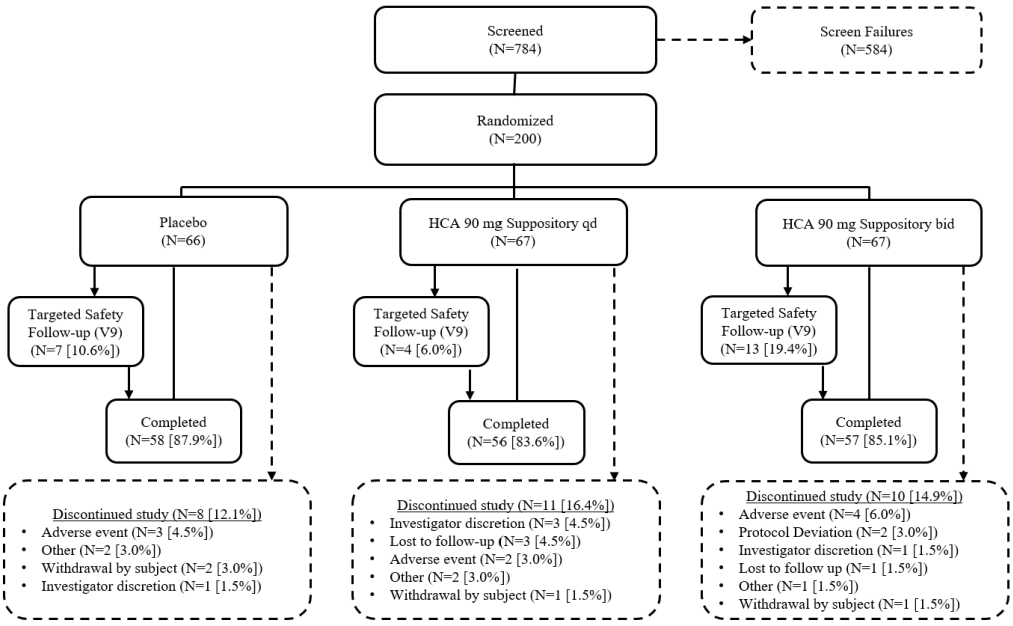
Name of Sponsor:	Cristcot HCA LLC
Name of Finished Product:	Hydrocortisone Acetate 90 mg Suppository
Name of Active Ingredient:	Hydrocortisone acetate
Title of Study:	A Three-Arm, Randomized, Placebo-Controlled, Double-Blind Phase 3 Study to Evaluate the Safety and Efficacy of Once-Daily and Twice-Daily Dosing of a Novel Hydrocortisone Acetate 90 mg Suppository Formulation Administered with the Sephure® Suppository Applicator in Subjects with Ulcerative Colitis of the Rectum
Coordinating Investigator:	Matthew Bohm, DO
Number of Study Centers and Countries:	United States (46), Bulgaria (6), Georgia (5), Romania (8), Russia (7), Moldova (3), Ukraine (8), Germany (4), Poland (15), Italy (5), Spain (5), Denmark (3), France (6), Philippines (10), Vietnam (10), Hong Kong (4), India (14), Saudi Arabia (6), South Africa (5), Serbia (6), Turkey (5), Jordan (7), Lebanon (4)
Study Period:	Date of First Consent: 24 September 2020 Date of Last Patient Last Visit: 19 September 2024
Phase of Development:	3
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** • Rectal bleeding subscore of 0. • Reduction of stool frequency. **Dose-Response Objective** • The dose-response effect trend for the primary efficacy endpoint (remission) will be assessed across the three treatment arms. **Exploratory Objectives** • 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 subscores stool frequency and rectal bleeding.
Methodology:	The study was designed as a three-arm, randomized, multicenter, placebo-controlled, double-blind study to evaluate the safety and efficacy of once-daily and twice-daily dosing of a novel hydrocortisone acetate 90 mg suppository formulation (HCA 90 mg) administered with the Sephure suppository applicator in subjects with ulcerative colitis of the rectum. This study planned to randomize 199 male and non-pregnant, non-lactating female subjects recruited in the United States and internationally. Eligible subjects were randomized 1:1:1 to one of three treatment arms. Subjects were stratified by region (Asia-Pacific-South Africa-Middle East, Europe, and United States), (2) gender, and (3) "user" or "nonuser" (depending on use of permitted concomitant medications intended to treat ulcerative colitis).

	The study consisted of a 21-day screening phase, during which subjects were to undergo sigmoidoscopy to confirm study eligibility and provide baseline imaging results as well as wash out any prohibited prior medications, a 28-day dosing period (with end of treatment assessments performed on Day 29), a 10-day drug taper period (with end of tapering assessments performed on the final day), and a 14-day follow up safety period. During the 28-day dosing phase, all subjects were to administer one suppository in the morning and one suppository in the evening as follows: HCA 90 mg Suppository bid group (active in morning and evening), HCA 90 mg Suppository qd group (active in morning, placebo in evening), placebo group (placebo in morning and evening). After the 28-day dosing period, study treatment was tapered during the 10-day tapering period. Efficacy assessments were conducted every 14 days during the dosing period and included the total Mayo score (inclusive of the rectal bleeding subscore, stool frequency subscore, and Physician's Global Assessment subscore), endoscopic subscore (via sigmoidoscopy, performed during Screening and at End of Treatment only), and quality of life assessment via the Inflammatory Bowel Disease Questionnaire (IBDQ). Safety assessments during the dosing period included collection of adverse events, physical examination, vital signs, laboratory testing, urine pregnancy testing, and ACTH stimulation test (performed during Screening and at End of Treatment). Any subject with an abnormal response to the ACTH stimulation test (as determined by the Supervising Endocrinologist) at the End of Tapering visit (Day 39) was required to return for the Targeted Safety Follow-up (Day 53) to repeat the ACTH stimulation test. If abnormal response to the ACTH stimulation test persisted, the subject was referred to an outside endocrinologist for further management; such subjects were not followed for further safety evaluation by the Sponsor.
Number of Subjects (planned and analyzed):	Initially, approximately 432 subjects were planned (estimating 324 subjects completing); this was adjusted to a target of 199 subjects (estimating 63 per treatment arm). 945 subjects were screened; 200 subjects were randomized
Diagnosis and Main Criteria for Inclusion and Exclusion:	**Inclusion criteria**: For inclusion into the trial, subjects were required to fulfill all of the following main criteria at screening: 1. Males or non-pregnant, non-lactating females aged 18 years and older. 2. Able to provide a signed informed consent. 3. Confirmed diagnosis of UC with an endoscopic score of 2-3 no further than 15 cm (5.9 inches) from the anal verge as assessed by the endoscopy performed at the Flexible Sigmoidoscopy visit (Days -20 to -5 [Visit 2]). For clarity, subjects with an endoscopic score of 2-3 up to 15 cm from the anal verge and deceleration of disease severity (endoscopic score 0-1) beyond 15 cm from the anal verge were inclusionary. 4. Modified Mayo subscore for stool frequency of 1-3 at Screening visit (Days -21 to -6 [Visit 1]) and Baseline visit (Day 1 [Visit 3]). 5. Modified Mayo subscore for rectal bleeding of 0-2 at Screening visit (Days -21 to -6 [Visit 1]) and Baseline visit (Day 1 [Visit 3]). 6. Modified Mayo endoscopic subscore of 2-3 at Flexible Sigmoidoscopy visit (Days -20 to -5 [Visit 2]) as determined by Central Reading. 7. Modified Mayo Total Score (without physician global assessment) of 4-8. 8. Females of childbearing potential must have been either sexually inactive (abstinent) for 21 days prior to the first dose and willing to have been sexually inactive throughout the study or must have been using one of the following acceptable methods of birth control: a) Surgically sterile (bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) for a minimum period of 1 month prior to screening; b) Intrauterine device in place for at least 1 month prior to screening; c) Barrier methods (condom, diaphragm) with spermicide for at least 21 days prior to screening and willing to continue throughout the study; or d) Hormonal contraceptives for at least 6 weeks prior to screening.

	9. Postmenopausal females with amenorrhea for at least 12 months prior to screening. 10. Subjects must have been willing to abstain from receiving anal sex, anal bleaching, anal waxing, etc. 11. Availability of all the screening assessment results, such as: serum pregnancy test (for females of childbearing potential), medical history, concomitant medication, AEs, vital signs, physical examination, electrocardiogram (ECG), documented endoscopy assessment, complete blood count, clinical chemistry and serology, urinalysis and stool test results. 12. Subjects were allowed to be re-screened for the study after consultation and approval from the Global Medical Monitor but could be enrolled (randomized) only once. **Exclusion criteria**: Subjects were to be excluded from the study if any of the following criteria applied: 1. Endoscopic subscore of 0 or 1 within 15 cm from the anal verge assessed by the Investigator during the endoscopy at Flexible Sigmoidoscopy visit (Days -20 to -5 [Visit 2]) (no video sent to Central Reading). 2. Endoscopic subscore of 2 or 3 beyond 15 cm from the anal verge assessed by the Investigator during the endoscopy at Flexible Sigmoidoscopy visit (Days -20 to -5 [Visit 2]) (no video sent to Central Reading). 3. Endoscopic subscore of 0 or 1 as assessed by the Central Reading using the video obtained during the endoscopic procedure at Flexible Sigmoidoscopy visit (Days -20 to -5 [Visit 2]). 4. History or current diagnosis of bacterial or other infectious colitis, radiation-enteritis and radiation-proctitis, Crohn's disease, collagenous colitis and indeterminate colitis. 5. 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. 6. Concomitant active gastrointestinal disease affecting the colon or rectum (except irritable bowel syndrome) or distortion of intestinal anatomy. 7. Bleeding hemorrhoids at the time of screening. 8. Acute diverticulitis at the time of screening. 9. Acute pancreatitis at the time of screening. 10. Uncontrolled, previously diagnosed type 1 or 2 diabetes mellitus. 11. Uncontrolled abnormal thyroid function. 12. Mean value for triplicate sitting systolic blood pressure >160 mm Hg and/or diastolic blood pressure >100 mm Hg after at least a 5- minute seated rest at the Screening visit (Days -21 to -6 [Visit 1]). The Investigator or the treating physician was allowed to adjust background blood pressure medication(s) to lower blood pressure values in order for the subject to be re-assessed for randomization eligibility. 13. Clinically significant ECG abnormality at screening that requires further diagnostic evaluation or intervention (e.g., new, clinically significant arrhythmia or a conduction disturbance). 14. Serum hemoglobin levels <7.5 g/dL (<4.65 mmol/L). 15. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST], alkaline phosphatase [ALP], and alanine aminotransferase [ALT] ≥ 2× the upper limit of normal). 16. History of sclerosing cholangitis, cirrhosis, or hepatic impairment. 17. Renal disease manifested by serum creatinine >2.0 mg/dL (176.8 µmol/L). 18. Positive test result at screening for cytomegalovirus, tuberculosis (confirmed as active with x-ray), human immunodeficiency virus, hepatitis B or C infection. 19. History of ocular herpes simplex or ocular varicella zoster infection. 20. History of unresolved malignant disease, with the exception of basal cell carcinoma and/or squamous cell carcinoma in situ of the skin. 21. Diagnosis of Addison's disease, congenital adrenal hyperplasia, or other form of adrenal insufficiency. 22. Subjects with abnormal response to the ACTH stimulation test performed at the Screening visit (Days -21 to -6 [Visit 1]).

	23. Active systemic infection. 24. Toxic megacolon, fistula, perforation, or abscess. 25. Uncontrolled psychiatric disorders or seizure disorders. 26. History of non-responsive UC to steroid treatment. 27. History of medical condition requiring use of inhaled steroids during the study (for treatment of asthma, COPD, etc.). 28. History of drug or alcohol abuse within the last 6 months. Alcohol abuse was defined as more than 14 drinks per week for men and more than 7 drinks per week for women. 29. Other current diagnosis of severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral diseases. 30. History of evidence of any medical condition that would, in the opinion of the Investigator, make the subject unsuitable for the study. 31. Positive stool test result at screening for enteric pathogens, *Clostridium difficile*, or presence of ova and parasites. 32. Vaccination with a live-attenuated vaccine within 28 days prior to randomization or that would occur during the study (other types of vaccines including those for COVID-19 are allowed). 33. Allergies to hydrocortisone acetate or to any other ingredients of the investigational product. 34. Taking a permitted medication outside of the permitted criteria. 35. Taking a prohibited medication. 36. Pregnant, confirmed with a positive serum test for pregnancy at screening, or lactating females and females of childbearing potential who did not meet the inclusion criteria. 37. Participation in another research study for an investigational drug within 30 days of the Screening visit (Days -21 to -6 [Visit 1]) and during the study.
Test Product, Dose, Mode of Administration	**Test products**: Hydrocortisone Acetate 90 mg rectal suppository **Dose and mode of administration**: one suppository once daily (qd) (with matching placebo given in evening) or twice daily (bid) administered with the Sephure Suppository Applicator
Duration of Treatment:	Treatment phase: 28 days Tapering phase: 10 days
Control Product, Dose, Mode of Administration, Batch Numbers:	**Control product**: Vehicle suppository (placebo) **Dose and mode of administration**: one suppository twice daily (bid) administered with the Sephure Suppository Applicator
Endpoints:	**Efficacy**: *Primary Efficacy Variable* • proportion of subjects with clinical remission at the End of Treatment visit (Day 29). Clinical remission is defined as the Modified Mayo Score of 0 to 2, with stool frequency subscore of 0 or 1 (minimum 1 point decrease from a Baseline score of 1 or 2), rectal bleeding subscore of 0, and endoscopic subscore of 0 or 1 *Secondary Efficacy Variables* The following secondary endpoints were evaluated hierarchically with Baseline (Day 1) compared to End of Treatment (Day 29) and then Follow-up (Day 15): • proportion of subjects with a rectal bleeding subscore of 0. • proportion of subjects with a reduction of stool frequency. Treatment response was defined as a score of 0 or 1, with at least a 1-point decrease from Baseline (Day 1) The secondary endpoints were evaluated as measured by the Modified Mayo Score according to the following: • Change in stool frequency from Baseline (Day 1) to End of Treatment (Day 29).

	• Change in rectal bleeding from Baseline (Day 1) to End of Treatment (Day 29). • Change in stool frequency from Baseline (Day 1) to Follow-up (Day 15). • Change in rectal bleeding from Baseline (Day 1) to Follow-up (Day 15). Exploratory endpoints are described in Section 8.2.3 of the full CSR. **Dose-response:** Comparing the primary efficacy endpoint results of subjects administered the investigational product once daily (qd) versus twice daily (bid) versus placebo. **Safety**: • Adverse events • Blood (hematology and clinical chemistry) and urinalysis laboratory results • Physical examination • Vital signs • Adrenocorticotropic hormone (ACTH) stimulation test
Statistical Methods:	**Sample Size Calculation**: The sample size calculation was based on an active response rate of 35%, a placebo response rate of 10%, an estimated screen failure rate of 80%, and a dropout rate of <5%. The sample size requires 189 subjects (63 per treatment arm) to demonstrate a 25% absolute improvement using an overall one-sided Fisher Exact test with $\alpha = 0.0125$ and 85% power when comparing each active dose separately with placebo. **Study Populations**: The **Full Analysis Set (FAS)** consisted of all randomized subjects, analyzed according to the treatment arm in which they were randomized. This population was used for disposition, demographics and baseline characteristics, and efficacy listings. The **Intent-to-Treat (ITT) Set** consisted of all subjects who were randomized using the Interactive Response Technology (IRT) system. This population was used for efficacy analyses. The **Safety Set** consisted of all randomized subjects who received at least one dose of study treatment, analyzed according to the treatment received. This population was used for medical history, disease history, concomitant medications, and safety variables. Other populations for which outputs are provided are described in Section 9.7.1.3 of the full CSR. **Statistical Analyses**: Tables are presented by treatment arm (and overall, when applicable) and visit date. Listings are sorted by treatment arm, subject number, visit date, and collection time, if applicable. Continuous data is summarized by treatment group using descriptive statistics (i.e., number of observations (n), mean, median, standard deviation, interquartile range, minimum, and maximum). Categorical data is summarized by treatment group using frequency tables. For efficacy analyses, missing data at the End of Treatment (Day 29) was imputed as treatment failures (worst case), regardless of reason. Missing data at Follow-up (Day 15) was not imputed. Missing data for the Inflammatory Bowel Disease Questionnaire (IBDQ) and Mayo Score Physician's Global Assessment were not imputed. There was no imputation of missing data for safety variables. The overall study-wise one-sided type I error rate for efficacy was 0.025, and due to multiplicity introduced by the two active treatment groups, a test of each dose group versus placebo was conducted at a one-sided type I error level of 0.0125, based on a Bonferroni correction to allow separate testing for each active treatment group versus placebo control. The primary efficacy endpoint was specified as the between-treatment group (HCA Suppository 90 mg bid versus placebo and HCA Suppository 90 mg qd versus placebo) difference in the proportion of subjects with clinical remission at the End of Treatment visit (Day 29). Clinical remission was defined as a Modified Mayo Total Score of 0 to 2, with stool frequency subscore of 0 or 1 (minimum 1 point decrease from baseline), rectal bleeding subscore of 0, and endoscopic subscore of 0 or 1. The primary efficacy variable, clinical remission, was analyzed using a logistic regression with treatment, sex, concomitant ulcerative colitis medication use, and

	geographical region in the model. Covariate terms remained in the model regardless of their significance. The placebo group served as the reference group; a Firth correction was applied to project unbiased clinical remission rates. In addition to the odds ratios from the logistic regressions, risk differences with two-sided 97.5% confidence intervals were reported unadjusted and adjusted for the covariates. The one-sided significance level was 0.0125 to account for the multiple testing for the comparisons of the two HCA suppository 90 mg groups (qd and bid) with placebo. For secondary efficacy endpoints, the same model as for the primary endpoint was used. Hierarchical testing of the secondary endpoints followed the order below, with each treatment arm versus the placebo tested separately at a one-sided type I error rate of 0.0125: 1. Proportion of subjects with clinical remission at End of Treatment (Day 29) 2. Proportion of subjects with rectal bleeding subscore of 0 at End of Treatment (Day 29) 3. Proportion of subjects with stool frequency score of 0 or 1, with at least a 1-point reduction from baseline, at End of Treatment (Day 29) 4. Rectal bleeding subscore of 0 at Follow-up (Day 15) 5. Proportion of subjects with stool frequency score of 0 or 1, with at least a 1-point reduction from baseline, at Follow-up (Day 15) Additional secondary efficacy endpoints and exploratory endpoints were analyzed and summarized as described in Section 9.7.1 of the full CSR.
Summary of Results and Conclusions:	**Subject Disposition**:  **Demography and Baseline Characteristics**: In the FAS, the mean and median ages were 43.1 and 41.5 years, respectively, with a range of 18 to 80 years. More subjects were female (54.5%) than male (45.5%). The majority of subjects were White (80.0%), followed by Asian (17.5%), Black or African American (2.0%), and American Indian or Alaska Native (0.5%). Nearly all subjects (93.5%) were not of Hispanic or Latino ethnicity. The majority of subjects were in Europe (55%), followed by Asia-Pacific-South Africa-Middle East (24%) and the United States (21%). Proctitis was the most common primary diagnosis in all treatment groups (61 to 72%), followed by proctosigmoiditis (15 to 16%) and left-sided colitis (9 to 17%); other primary diagnoses included extensive colitis and pancolitis). Total Modified Mayo scores at baseline ranged from 3 to 8, with most subjects (~60%) having a score of 5 or 6.

Treatment groups were similar with respect to these demographic and baseline characteristics.

Efficacy Results:

Primary Endpoint: The proportion of subjects proportion of subjects with clinical remission at the End of Treatment visit (Day 29) was significantly improved with HCA 90 mg Suppository qd and HCA 90 mg Suppository bid compared with placebo.

The odds ratio of the proportion of subjects who achieved clinical remission at End of Treatment (Day 29) was estimated by the model as 10.3 (97.5% CI: 1.5 to 69.2) for the HCA 90 mg Suppository qd group and 8.9 (97.5% CI: 1.3 to 60.8) for the HCA 90 mg Suppository bid group. Both analyses favored treatment with HCA 90 mg, with p-values of 0.0061 and 0.0105 for the once daily and twice daily treatment groups, respectively.

The proportion of subjects who achieved clinical remission at End of Treatment (Day 29) using a one-sided Fisher Exact Test was 21.2% in the HCA 90 mg Suppository qd group and 16.4% in the HCA 90 mg Suppository bid group, compared with 1.5% in the placebo group. Both analyses favored treatment with HCA 90 mg Suppository, with p-values of 0.0005 and 0.0044 for the once daily and twice daily treatment groups, respectively.

Proportion of Subjects with Clinical Remission[a]: HCA 90 mg Suppository qd versus Placebo - Intent-To-Treat Set (ITT)

Endpoint	HCA 90 mg qd (N=66)	HCA 90 mg bid (N=67)	Placebo (N=66)
Clinical Remission at End of Treatment (Day 29), n (%)			
Yes	14 (21.2)	11 (16.4)	1 (1.5)
No	52 (78.8)	56 (83.6)	65 (98.5)
p-value[b]	0.0005	0.0044	--
Odds Ratio[c]			
Estimate	10.2893	8.9331	--
97.5% CI	(1.5305, 69.1744)	(1.3126, 60.7941)	--
p-value	0.0061	0.0105	--

Source: Table 14.2.1.1.1; Table 14.2.1.2.1

Abbreviations: CI=confidence interval; HCA=hydrocortisone acetate; ITT=intent-to-treat; qd=once daily; UC=ulcerative colitis

[a] Clinical remission defined as a Modified Mayo Score of 0 to 2 at the End of Treatment visit (Day 29).

[b] From one-sided Fisher Exact Test

[c] Based on a logistic regression model with treatment, sex, concomitant UC medication use (user vs. nonuser), and geographical region as covariates.

Note: Subjects with intercurrent events or missing assessments at End of Treatment are included but considered failures (No response)

Secondary Efficacy Endpoints:

The secondary efficacy endpoints were evaluated using the same logistic regression test as the primary efficacy analysis and demonstrated significant benefit in rectal bleeding score and improvement (non-significant) in stool frequency following treatment with HCA 90 mg Suppository qd over placebo both at the end of treatment (Day 29) as well as at follow-up (Day 15). Treatment with HCA 90 mg Suppository bid demonstrated a significant benefit in rectal bleeding score compared with placebo at end of treatment (Day 29). Treatment with HCA 90 mg Suppository bid was favored over placebo for reduction in rectal bleeding at follow-up (Day 15) and stool frequency score at both the end of treatment (Day 29) and follow-up (Day 15), but did not achieve statistical significance.

Proportion of Subjects with Rectal Bleeding Subscore of 0 or with Reduction in Stool Frequency: HCA 90 mg Suppository qd versus Placebo - Intent-To-Treat Set (ITT)

Endpoint	End of Treatment (Day 29)		Follow-up (Day 15)	
	HCA 90 mg qd (N=66)	Placebo (N=66)	HCA 90 mg qd (N=64)	Placebo (N=63)
Rectal Bleeding Score of 0, n (%)				
n[a]	55	51	53	49
Yes	31 (56.4)	10 (19.6)	26 (49.1)	11 (22.4)
No	24 (43.6)	41 (80.4)	27 (50.9)	38 (77.6)
p-value[b]	0.0001		0.0072	
Odds Ratio[c]				
n[a]	55	51	53	49
Estimate	5.082		3.176	
97.5% CI	(1.831, 14.106)		(1.151, 8.761)	
p-value	0.0004		0.0107	
Reduction in Stool Frequency[d], n (%)				
N	66	66	64	63
Yes	38 (57.6)	26 (39.4)	32 (50.0)	21 (33.3)
No	28 (42.4)	40 (60.6)	32 (50.0)	42 (66.7)
p-value[b]	0.0550		0.0723	
Odds Ratio[c]				
N	66	66	64	63
Estimate	2.007		1.903	
97.5% CI	(0.898, 4.486)		(0.835, 4.337)	
p-value	0.0523		0.0802	

Source: Table 14.2.4.2.1; Table 14.2.4.1.1; Table 14.2.5.2.1; Table 14.2.5.1.1
Abbreviations: CI=confidence interval; HCA=hydrocortisone acetate; ITT=intent-to-treat; qd=once daily; UC=ulcerative colitis
[a] Excludes subjects with a baseline rectal bleeding score of 0.
[b] From one-sided Fisher Exact Test
[c] Based on a logistic regression model with treatment, sex, concomitant UC medication use (user vs. nonuser), and geographical region as covariates.
[d] Defined as reduction in stool frequency to 0 or 1 and a reduction of at least 1 from Baseline.
Note: Subjects with intercurrent events or missing assessments at End of Treatment are included but considered failures (No response).
Note: Follow-up only includes subjects with assessments at Follow-up.

Proportion of Subjects with Rectal Bleeding Score of 0 or with Reduction in Stool Frequency: HCA 90 mg Suppository bid versus Placebo - Intent-To-Treat Set (ITT)

Endpoint	End of Treatment (Day 29)		Follow-up (Day 15)	
	HCA 90 mg bid (N=67)	Placebo (N=66)	HCA 90 mg bid (N=60)	Placebo (N=63)
Rectal Bleeding Score of 0, n (%)				
n[a]	62	51	55	49
Yes	34 (54.8)	10 (19.6)	21 (38.2)	11 (22.4)
No	28 (45.2)	41 (80.4)	34 (61.8)	38 (77.6)
p-value[b]	0.0002		0.0931	
Odds Ratio[c]				
n[a]	62	51	55	49
Estimate	5.836		2.524	
97.5% CI	(2.098, 16.232)		(0.894, 7.130)	
p-value	0.0001		0.0456	
Reduction in Stool Frequency[d], n (%)				

N	67	66	60	63
Yes	34 (50.7)	26 (39.4)	27 (45.0)	21 (33.3)
No	33 (49.3)	40 (60.6)	33 (55.0)	42 (66.7)
p-value[b]	0.2238		0.2006	
Odds Ratio[c]				
N	67	66	60	63
Estimate	1.631		1.679	
97.5% CI	(0.730, 3.646)		(0.720, 3.912)	
p-value	0.1728		0.1700	

Source: Table 14.2.4.2.1; Table 14.2.4.1.1; Table 14.2.5.2.1; Table 14.2.5.1.1
Abbreviations: CI=confidence interval; HCA=hydrocortisone acetate; bid=twice daily; ITT=intent-to-treat; UC=ulcerative colitis
[a] Excludes subjects with a baseline rectal bleeding score of 0.
[b] From one-sided Fisher Exact Test
[c] Based on a logistic regression model with treatment, sex, concomitant UC medication use (user vs. nonuser), and geographical region as covariates.
[d] Defined as reduction in stool frequency to 0 or 1 and a reduction of at least 1 from Baseline.
Note: Subjects with intercurrent events or missing assessments at End of Treatment are included but considered failures (No response).
Note: Follow-up only includes subjects with assessments at Follow-up.

Subgroup analyses: Subgroup analyses were performed based on the stratification factors (sex, concomitant ulcerative colitis medication use [user vs. nonuser], and geographical region) as well as age (<50 years, ≥50 years) and race (White, Other). However, the study was not adequately powered to detect a treatment effect in these individual groups. A statistically significant benefit for treatment with HCA 90 mg Suppository qd or bid over placebo was maintained for the proportion of subjects achieving clinical remission in certain subgroups females, subjects <50 years old, White subjects, concomitant users of ulcerative colitis medications (as well as nonusers with HCA 90 mg Suppository qd only), and subjects outside the United States. In the subgroups that did not achieve statistical significance (generally those smaller in sample size), treatment with HCA 90 mg Suppository qd or bid was still generally favored over placebo.

Safety Results:

Exposure: Of the 200 subjects in the FAS, all received treatment during the study; one subject randomized to randomized to HCA 90 mg Suppository qd per the IRT scheme but received placebo dosing due to manual "randomization." (and is excluded from the ITT Set). In total, 184 subjects completed the dosing period of the study, with mean exposure ranging from 53.1 to 55.5 suppositories administered out of the expected 56.

Treatment-Emergent Adverse Events (TEAEs): Overall, TEAEs were reported in 62 subjects (31%), with more subjects experiencing TEAEs in the HCA 90 mg Suppository bid group (39%) than in the HCA 90 mg Suppository qd (26%) or placebo (28%) groups. The most common TEAEs in the HCA 90 mg Suppository bid and qd treatment groups were gastrointestinal disorders, with more subjects receiving HCA 90 mg Suppository bid (10.4%) reporting TEAEs than placebo (9.0%) and HCA 90 mg Suppository qd (7.6%). In total, 14 subjects (7%) reported at least 1 TEAE that was judged to be treatment-related, including 6 subjects (9%) in the HCA 90 mg Suppository bid group, 5 subjects (7%) in the placebo group, and 3 subjects (4%) in the HCA 90 mg Suppository qd group. No treatment-related TEAEs were reported by more than one subject in either HCA 90 mg Suppository treatment group and at a greater incidence than in the placebo group.

The majority of subjects had TEAEs that were mild or moderate in intensity. In total, 3 subjects had severe TEAEs, 1 subject (2%) in the HCA 90 mg Suppository bid group (haematochezia) and 2 subjects (3%) in the HCA 90 mg Suppository qd group (frequent bowel movements and ulcerative colitis, each reported in 1 subject), all of which resulted in discontinuation of study treatment. Subgroup analyses of TEAEs based on age (<50 years, ≥50 years), sex (female, male),

	and race (White, non-White) did not alter the conclusions of safety for HCA 90 mg Suppository bid or qd. *Deaths and Serious Adverse Events:* There were no deaths or serious adverse events reported during the study. *TEAEs Leading to Discontinuation:* In total, 8 subjects (4%) discontinued study treatment due to TEAEs, including 4 subjects (6.0%) in the HCA 90 mg Suppository bid group, 2 subjects (3.0%) in the HCA 90 mg Suppository qd group, and 2 subjects (3.0%) in the placebo group. One additional subject (3 subjects [4.5%] total) treated with placebo discontinued due to worsening of a pretreatment condition. Nearly all events resulting in discontinuation were gastrointestinal disorders and no event was reported in more than one subject. *Clinical Laboratory Evaluations*: No changes over time in mean values or meaningful changes from Baseline in central tendency to abnormal high or low values for hematology (RBC indices, WBC counts, platelets), clinical chemistry (liver, renal, electrolytes, cholesterol and triglycerides, urate, or glucose), or urinalysis parameters were observed following treatment with HCA 90 mg Suppository bid or qd. As would be expected following corticosteroid treatment, more subjects treated with HCA 90 mg Suppository bid had post-ACTH stimulation test cortisol levels below 180 ng/mL than those treated with HCA 90 mg Suppository qd and the proportion of subjects in both treatment groups with such levels decreased at each assessment (end of corticosteroid treatment, tapering, and off-treatment). Out of the 171 subjects that completed the study, only 24 subjects (14.0%) were required to return for a Targeted Safety Follow-up visit (Day 53). Of those, 5 subjects, 2 treated with HCA 90 mg Suppository bid and 3 treated with placebo, were referred to an outside endocrinologist due to persistent abnormal ACTH stimulation test results. None of the 66 subjects treated with HCA 90 mg Suppository qd, were referred to an endocrinologist. *Vital Signs, Physical Examinations, and Other Safety Findings*: Vital signs and physical examinations were measured at all full and brief physical examinations performed at Screening, Day 1, Day 15, the End of Treatment (Day 29), the End of Tapering (Day 39), and at targeted safety follow-up (Day 53), if applicable. There did not appear to be any treatment-related effect on population mean values for any vital sign parameter or on physical examination results during the course of the study. One woman randomized to placebo experienced pregnancy during the course of the study. Despite repeated attempts to contact the subject after she discontinued, no information on the outcome of the pregnancy is available.
	Conclusions: Study CHS1221 is the first large, adequate and well-controlled, Phase 3 clinical study of hydrocortisone suppositories in ulcerative colitis. This study demonstrated that HCA 90 mg Suppository dosed once (qd) or twice (bid) daily produced statistically significant improvement in clinical remission rates based on total Modified Mayo Score compared to placebo at the end of the 28-day dosing period. For the primary endpoint, clinical remission was defined as achieving a total Modified Mayo Score of 0 to 2, with stool frequency subscore of 0 or 1 (minimum 1 point decrease from a Baseline score of 1 or 2), rectal bleeding subscore of 0, and endoscopic subscore of 0 or 1. HCA 90 mg Suppository qd produced a statistically significant effect compared with placebo on the proportion of subjects achieving overall clinical remission at the End of Treatment visit (Day 29). In addition, a statistically significant effect on the secondary endpoint of the proportion of subjects with a rectal bleeding subscore of 0 was noted both at the End of Treatment visit (Day 29) and at the earlier Follow-up visit (Day 15). A statistically significant effect on the proportion of subjects with a reduction of stool frequency, defined as a score of 0 or 1 with at least a 1-point decrease from Baseline, was not observed with HCA 90 mg Suppository qd, though treatment with HCA 90 mg Suppository qd was favored over placebo. HCA 90 mg Suppository bid also produced a statistically significant effect compared with placebo on the proportion of subjects achieving overall clinical remission at the End of Treatment visit (Day 29). In addition, a statistically significant effect on the secondary endpoint of the proportion of subjects with a rectal bleeding subscore of 0 was noted at the End of Treatment

	visit (Day 29) was observed, however the effect at the earlier Follow-up visit (Day 15) did not achieve statistical significance. Similar to the once daily dosing group, no significant effect on the proportion of subjects with a reduction of stool frequency was observed with HCA 90 mg Suppository bid, though treatment with HCA 90 mg Suppository bid was favored over placebo. Study CHS1221 demonstrated an excellent safety profile with minimal adverse events for both HCA 90 mg Suppository qd and bid, though a higher incidence of TEAEs was noted with twice daily dosing regimen compared with once daily or placebo. In total, 62 subjects (31%), with more subjects experiencing TEAEs in the HCA 90 mg Suppository bid group (39%) than in the HCA 90 mg Suppository qd (26%) or placebo (28%) groups. The most common TEAEs and treatment-related TEAEs with HCA 90 mg Suppository were gastrointestinal disorders. No serious adverse events were reported during the study. Out of the 171 subjects that completed the study, only 24 subjects (14%) were required to return for a Targeted Safety Follow-up visit (Day 53) due to possible secondary adrenal insufficiency. Of those, 5 subjects, 2 treated with HCA 90 mg Suppository bid and 3 treated with placebo, were referred to an outside endocrinologist due to persistent abnormal ACTH stimulation test results, while no subject treated with HCA 90 mg Suppository qd was referred to an endocrinologist. No other safety parameters (clinical laboratory parameters, urinalysis, vital signs, or physical examination) raised any safety concerns with HCA 90 mg Suppository during Study CHS1221.