1. TITLE PAGE

STUDY TITLE: An Open Label Evaluation of the Adrenal Suppression Potential and Pharmacokinetic Properties of Twice Daily Halobetasol Propionate Foam, 0.05% in Subjects 12 to Less Than 18 Years of Age with Plaque Psoriasis Receiving Two Weeks of Treatment

TEST ARTICLE:	Halobetasol Propionate Foam, 0.05%
INDICATION:	Plaque Psoriasis
SPONSOR:	Mayne Pharma LLC
PROTOCOL NUMBER:	122-0551-209
IND NUMBER:	107,302
NCT NUMBER:	NCT03992261
EudraCT Number:	2018-003845-40
FILENAME:	122-0551-209_csr_20Feb2020_v1.0.docx
DEVELOPMENT PHASE:	4
FIRST SUBJECT ENROLLED:	June 14, 2019
LAST SUBJECT COMPLETED:	December 30, 2019
SPONSOR'S RESPONSIBLE MEDICAL OFFICER:	Daniel J. Piacquadio, M.D. Therapeutics, Inc. 9025 Balboa Avenue, Suite 100 San Diego, CA 92123 (858) 571-1800, ext. 107 (office) (619) 889-7058 (cell) (858) 571-1234 (facsimile) danp@therapeuticsinc.com
SPONSOR CONTACT:	Phoevos Hughes Associate Director, Clinical Operations Mayne Pharma LLC 1240 Sugg Parkway Greenville, NC 27834

This study was performed in compliance with Good Clinical Practices for Clinical Research Studies as outlined in 21 CFR parts 50, 54, 56, 312, and 314.

REPORT DATE: February 20, 2020

2. SYNOPSIS

Name of Sponsor/Company: Mayne Pharma LLC **Name of Finished Product:** Halobetasol Propionate Foam, 0.05% **Name of Active Ingredient:** Halobetasol Propionate	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)

Title of Study: An Open Label Evaluation of the Adrenal Suppression Potential and Pharmacokinetic Properties of Twice Daily Halobetasol Propionate Foam, 0.05% in Subjects 12 to Less Than 18 Years of Age with Plaque Psoriasis Receiving Two Weeks of Treatment

Investigators: Eleven investigators received IRB/IEC approval to screen/enroll subjects; 8 of these screened subjects of which 7 (1 in the US, 2 in Poland, 3 in Ukraine, and 1 in the Republic of Georgia) enrolled at least 1 subject. See the complete list of investigators in Appendix 16.1.4.

Study Center(s): Eleven sites received IRB/IEC approval and were activated; 8 of these sites screened subjects of which 7 sites (1 site in the US, 2 sites in Poland, 3 sites in Ukraine, and 1 site in the Republic of Georgia) enrolled at least 1 subject. See the complete list of study centers in Appendix 16.1.4.

Publication (Reference): None.

Study Period (Years): < 1 year • June 14, 2019 (date of first subject enrolled) • December 30, 2019 (date of last subject completed)	**Phase of Development:** 4

Objectives: The objective of this study was to determine the adrenal suppression potential and the pharmacokinetic (PK) properties of halobetasol propionate (HBP) foam, 0.05% applied twice daily in subjects who were 12 to less than 18 years of age with stable plaque psoriasis.

Methodology: Multicenter, open label

Number of Subjects: 25 planned, 24 enrolled, 24 analyzed [N=24 (Safety), N=23 (Evaluable)]

Diagnosis and Main Criteria for Inclusion: Male and female subjects 12 to less than 18 years of age with stable plaque psoriasis.

Test Article:

- HBP Foam, 0.05% [Lot: 32014, Expiration date: 05/2021; Lot: 32018, Expiration date: 05/2021].

Duration of Treatment: Up to 2 weeks.

Reference Therapy: None.

Study Endpoints:

Efficacy Endpoints:

The primary objective of this study was to assess safety, not efficacy. However, Investigator's Global Assessment (IGA) and percent body surface area (BSA) treated and affected with disease were assessed to document any changes that were observed with regard to IGA and percent BSA.

Safety Endpoints:

Hypothalamic-pituitary-adrenal Axis Responses to Cosyntropin

Hypothalamic-pituitary-adrenal (HPA) axis responses to stimulation by cosyntropin were dichotomized to "normal" and "abnormal". An abnormal HPA axis response was defined as a 30-minute post-stimulation serum cortisol level that was ≤18 µg/dL at the end of study (EOS).

Plasma Levels of Halobetasol Propionate

Trough HBP concentrations in plasma on Day 8 and Day 15 were calculated and summarized.

Other Safety Endpoints

Other safety endpoints included adverse events (AEs), local skin reactions (LSRs) associated with topical application of corticosteroids (telangiectasia, skin atrophy, burning/stinging, and folliculitis), clinical laboratory tests, urine pregnancy tests (UPTs), and extent of exposure.

Statistical Methods:
All statistical analyses and summaries were prepared using SAS® unless otherwise stated.

Frequency counts and percentages were reported for categorical data and sample size, mean, standard deviation (SD), median, minimum and maximum values were reported for the continuous variables.

In general, all summary tables were supported by a relevant subject data listing which was sorted by study site, subject identification, and visit, as applicable.

Analysis Populations:
All subjects were classified into the Safety, Evaluable, and PK populations according to the following definitions.

All subjects enrolled in the study who were dispensed and applied test article at least once were included in the analysis of safety and were considered the Safety population. Subjects applied the initial dose of test article in the clinic on Day 1.

The Evaluable population included those subjects in the Safety population who had both Screening and EOS serum cortisol data (pre- and post-cosyntropin stimulation) and met the following criteria:

- Met all inclusion/exclusion criteria, including normal response to cosyntropin stimulation defined as a Screening cosyntropin stimulation test (CST) with a 30-minute post-stimulation cortisol level of >18 μg/dL.
- Screening and EOS CST were conducted between 7AM – 9AM.
- EOS CST was conducted within ±1 hour of the Screening CST.
- Applied at least 80% and no more than 120% of the expected number of applications and applied the final dose no more than 14 hours prior to the start of the CST.
- Had not taken or applied any medications that may have interfered with HPA axis function.
- Did not have any other significant protocol deviations.

Subjects included in the PK analysis (PK population) included those subjects who did not have any significant protocol deviations and must have had at least an 80% – 120% dose compliance based on number of applications.

Dosing Compliance:
Descriptive statistics were used to summarize test article compliance for the Evaluable and PK populations. Measures of test article compliance included the duration of treatment (number of days dosed = last dose date - first dose date + 1), the total number of applications (determined from the actual number of applications reported by the subject), and the percent of expected doses applied. The expected number of doses for subjects who were clear at Day 8 and discontinued from the study was 14. Subjects who continued to Day 15 or early term had the compliance rate based on an expected 28 doses. If a subject had the EOS visit occur late outside the visit window (i.e., after Day 9 if subject was clear at Visit 3, or after Day 17 if the subject was not clear at Visit 3) and continued dosing until the day before the EOS visit, the number of expected doses was increased according to the Study Day of the EOS visit. A subject was considered compliant with the dosing regimen if the subject applied at least 80% but no more than 120% of the expected number of applications.

Efficacy Analyses:
The primary objective of this study was to assess safety, not efficacy. However, IGA and percent BSA treated and affected with disease were assessed to document any changes that were observed with regard to IGA and percent BSA. Frequency distributions of the observed and change from Baseline IGA severity scores were presented for each visit for the Evaluable population. Descriptive statistics were provided for observed and changes from Baseline with respect to both the percent BSA affected and treated for the Evaluable and PK populations.

Safety Analyses:

Extent of Exposure

The total amount of test article used (grams of test article applied) by each subject was calculated by subtracting the weights of the returned canisters from the weights of the canisters when initially dispensed to the subject. Descriptive statistics (mean, median, SD, minimum and maximum) was determined for the total amount of test article used by each subject in the Safety, Evaluable, and PK populations.

An approximation of the amount of test article applied per cm^2 was determined based on the average amount of test article used per application and an estimate of the percent BSA treated with the test article at Visit 2/Baseline. The BSA treated with test article (in square centimeters) was determined from the Mosteller calculation[1]. The Mosteller formula for total BSA takes the square root of the height (cm) multiplied by the weight (kg) divided by 3600. This result is multiplied by 10,000 to convert to BSA in cm^2.

HPA Axis Suppression

Subjects discontinued from the study at Visit 2 due to abnormal screening laboratory test results or other ineligibility criteria (screen failures) were excluded from the HPA axis suppression summaries.

The proportion of subjects manifesting laboratory based evidence of adrenal suppression at EOS were presented along with 95% confidence intervals (CIs) for the Evaluable and Safety populations. The observed serum cortisol levels (pre-and post-cosyntropin stimulation) and the changes in serum cortisol levels after stimulation at Screening, EOS, and, if any, at follow-up visits were also summarized. In addition, descriptive statistics for the daily dose of test article were tabulated separately for suppressed and non-suppressed subjects.

Pharmacokinetic Analyses

Morning trough concentrations of HBP in plasma at Screening, Day 8, and Day 15 were summarized for the PK population using geometric mean, coefficient of variation in addition to n, mean, median, SD, minimum, and maximum.

Adverse Events

All AEs reported during the study were listed, documenting onset, whether therapy was required, any change in test article dosing, severity, possible relationship to test article, and outcome. Verbatim terms on the electronic case report forms (eCRFs) were linked to preferred terms and system organ class using the Medical Dictionary for Regulatory Activities version 22.0.

Local Skin Reactions

The frequency distributions of the severities of LSRs associated with topical application of corticosteroids including telangiectasia, skin atrophy, burning/stinging, and folliculitis were summarized for the Safety population at Baseline and all follow-up visits.

Clinical Laboratory Tests

Clinical laboratory tests were evaluated for any clinically significant changes during the study period. All laboratory data (chemistry, hematology, and urinalysis) were listed and reported in the units received by the laboratory. Shift tables by analyte and by out of range flag were presented to facilitate the evaluation of change from Visit 1/Screening to Visit 4/Day 15/EOS for the Safety population.

Urine Pregnancy Tests

A listing of UPT results was also provided for the Safety population.

[1] Mosteller RD. Simplified calculation of body-surface area. New Eng. J. Med. 1987; 317, 1098.

Concomitant Medications and Concurrent Therapies/Procedures
A subject listing of the concomitant medications was provided. Concomitant medications were coded using the World Health Organization (WHO) Drug Dictionary version Global database version March 2019 and summarized by ATC Level 3 for the Safety population. A separate listing of concurrent procedures and therapies was also provided. No coding of therapies or procedures was performed.

Summary of Results:

Subject Disposition, Demographics:

In total, 34 subjects were screened for this study; 24 subjects were enrolled into the study and 10 subjects were screen failures. Reasons for screen failures included meeting exclusion criterion #17 (9 subjects had a screening CST with a post 30-minute stimulation cortisol level of ≤ 18 µg/dL), and 1 subject met exclusion criterion #1 (spontaneously improving or rapidly deteriorating plaque psoriasis) and failed to meet inclusion criterion #3 (had a clinical diagnosis of stable plaque psoriasis involving a minimum of 10% BSA excluding the face, scalp, groin, axillae and other intertriginous areas). All enrolled subjects completed the study.

There were 11 females (45.8%) and 13 males (54.2%) enrolled into the study. All enrolled subjects were White (24/24, 100.0%) and the majority were not of Hispanic or Latino origin (18/24, 75.0%) with the remaining being of Hispanic or Latino origin (6/24, 25.0%). The average age of enrolled subjects was 14.7 years with a range of 12.1 years to 17.7 years.

All enrolled subjects were included in the Safety population. One subject (Subject 21-002) was excluded from the Evaluable and PK populations due to use of a prohibited medication (i.e., Squamax Emulsion which contained urea and salicylic acid).[2]

Efficacy Results:

The main objective of this study was to assess safety, not efficacy. However, by Day 15, all but 1 subject (95.5%) had improvements in IGA by at least a 1-point shift. Subject 32-008 did not show any change from Baseline in IGA nor percent BSA affected and/or treated. There were 72.7% (16/22) of subjects with at least a 2-point change (improvement) from Baseline in IGA at Day 15 (2-point: 11/22, 50%; 3-point: 5/22, 22.7%). Overall, the mean percent BSA affected with disease decreased from 15.1% at Baseline to 9.1% by Day 15 and the mean percent BSA treated with test article decreased from 14.5% at Baseline to 12.6% by Day 8.

Safety Results:

There were 6 subjects that demonstrated laboratory based evidence of abnormal HPA axis response at Day 15/EOS as documented by a 30-minute post-stimulation serum cortisol level of ≤18 µg/dL. All "suppressed" subjects returned to normal HBP axis function (as assessed by CST) at their initial follow-up visit approximately 4 weeks after Day 15/EOS and none of these subjects demonstrated any clinical signs or symptoms of adrenal suppression.

Morning trough concentration (C_{12}) of halobetasol propionate in plasma were BQL (<20.0 pg/mL) at Screening. At Day 8, 14 of the 23 PK subjects had morning trough concentrations (C_{12}) of halobetasol propionate in plasma that were BQL with the average plasma HBP concentration for the 9 PK subjects with measurable levels being 154.6 pg/mL with a range of 23 pg/mL to 975 pg/mL. At Day 15/EOS, 13[3] of the 23

[2] The protocol stated that a bland emollient was allowed to be used to treat areas of psoriasis not treated with the test article. Subject 21-002 used Squamax Emulsion on the face (non-treatment area) throughout the entire study. This was a protocol deviation since Squamax Emulsion is not a bland emollient but the study site refused to report it as a protocol deviation. Based upon Medical Monitor review, Subject 21-002 may have been considered evaluable given that the prohibited medication was a minor protocol deviation since it is not a steroid and would not have affected HPA response. However, due to site discrepancy, subject was not evaluable.

[3] PK blood and HBP plasma concentration data at Day 15 is missing for Subject 21-003 (see Listing 16.2.8.2) due to lab testing deviation (i.e., blood for PK was drawn less than 12 hours from previous dose; see Listing 16.2.2).

PK subjects had morning trough concentrations (C_{12}) of halobetasol propionate in plasma that were BQL with the average plasma HBP concentration for the 9 PK subjects with measurable levels being 59.9 pg/mL with a range of 21 pg/mL to 299 pg/mL. Of the 6 subjects with laboratory based evidence of HPA axis suppression at Day 15/EOS, 3 were noted to have measurable trough concentrations at Day 15.

No material safety issues were noted for HBP Foam as determined from AE reporting and LSR evaluations. A total of 7 subjects (7/24, 29.2%) reported 8 TEAEs. Of the 8 TEAEs, 6 were deemed related (ACTH stimulation test abnormal) and 2 were deemed not related (gastritis and red blood cells urine positive) to HBP Foam. All but 1 TEAE (moderate gastritis) were mild in severity. None of the TEAEs were serious, none were within the Treatment Area, none required a change in test article dosing or discontinuation from the study, and all TEAEs recovered/resolved by EOS. Burning/stinging and folliculitis were absent for all subjects at all visits. With the exception of 1 case of severe telangiectasia at Baseline prior to test article application, all other cases of telangiectasia and skin atrophy were moderate or mild in severity during the study. Telangiectasia and skin atrophy were observed in 6 subjects; all from the same study site (Site 12). There were no subjects who had an LSR that worsened during the study.

Most individual safety laboratory tests (hematology, chemistry, and urinalysis values) were within the normal range and/or classified as not clinically significant by the investigator. Any clinical laboratory result that was noted as clinically significant (2 subjects) was consistent with the value at Screening. Mean changes from Screening to Day 15/EOS for all clinical laboratory values were generally small, within expected limits of normal variation.

Conclusion:
Results of this study support the safety of HBP Foam, 0.05% with respect to adrenal suppressive effects and systemic exposure in this population. Of the 23 evaluable subjects, 6 (26.1%) demonstrated an abnormal HPA axis response. All subjects with laboratory based evidence of HPA axis suppression returned to normal HPA axis function at their initial follow-up visit approximately 4 weeks after Day 15/EOS and none of these subjects demonstrated any clinical signs or symptoms of adrenal suppression. Morning trough concentrations (C_{12}) of halobetasol propionate in plasma were BQL (<20.0 pg/mL) at Screening. At Days 8 and 15, 14 and 13 subjects, respectively, from the PK population had morning trough concentrations (C_{12}) of halobetasol propionate in plasma that were BQL. Other safety findings (AEs, LSRs, and clinical laboratory tests) were consistent with expectations for a trial of this type and no material safety issues were identified.

Report Date: February 20, 2020