2. SYNOPSIS

Protocol Number	DSXS-1303
Title	An Open Label, Safety Study to Assess the Potential for Adrenal Suppression and Pharmacokinetics Following Maximal Use Treatment with TOPICORT® (desoximetasone) Topical Spray, 0.25% in Pediatric Patients with Plaque Psoriasis
Objectives	The objective of this study is to evaluate the potential of TOPICORT® (desoximetasone) Topical Spray, 0.25% to suppress HPA axis function. The secondary objectives are to evaluate the efficacy parameters, pharmacokinetics and adverse event (AE) profile.
Sponsor	TARO Pharmaceuticals USA, Inc.
Test Product	TOPICORT® (desoximetasone) Topical Spray, 0.25%
Study Design	An open label, post marketing safety study to assess the potential of a TOPICORT® (desoximetasone) Topical Spray, 0.25% to suppress HPA axis function following twice daily dosing for 28 days. Up to one hundred (100) patients 2-17 years of age with a confirmed diagnosis of moderate to severe plaque psoriasis with involvement of ≥ 10% of their body surface area (excluding face and scalp). The participants will be serially enrolled into 3 cohorts. **Cohort 1:** 12 years to 17 years and 11 months of age (up to 20-40 subjects) **Cohort 2:** 6 years to 11 years and 11 months of age (up to 20-30 subjects) **Cohort 3:** 2 years to 5 years and 11 months of age (up to 10-30 subjects) Approximately 12 patients from each cohort will be included in a subgroup for PK profile determination. To minimize blood collection in young subjects in Cohorts 2 and 3 more sparse samplings may be done with lower age groups based on the PK profiles observed in Cohort 1. Prior to Cohort 2, all PK data from Cohort 1 will be analyzed and the protocol will be amended and submitted for IRB approval. The same procedure will be followed to analyze Cohort 2 data prior to Cohort 3. If during the study more than 35% of dosed subjects from each cohort are considered to be exhibiting signs (confirmed by the results of a cortisol response test) and/or symptoms (nausea, headache, fatigue, myalgia or loose stool) of HPA axis suppression, the enrollment for this cohort will be stopped and the enrollment for a younger cohort(s) will not be initiated. A patient will be considered to have potential HPA axis suppression if they meet at least one of the criteria: • their 30 minute post injection cortisol level is not at least 7 mcg/100 ml greater than the basal level (< basal + 7) • the post stimulation level is ≤ 18 mcg/100 ml Two planned interim analyses will be conducted to evaluate safety following the end of the treatment periods for cohorts 1 and 2.
Study Population	Up to one hundred (100) patients 2-17 years of age with a confirmed diagnosis of plaque psoriasis with involvement of ≥ 10% of their body surface area (excluding

	face and scalp) will be enrolled. The participants will be serially enrolled into 3 cohorts. **Cohort 1:** 12 years to 17 years and 11 months of age (up to 20-40 subjects) **Cohort 2:** 6 years to 11 years and 11 months of age (up to 20-30 subjects) **Cohort 3:** 2 years to 5 years and 11 months of age (up to 10-30 subjects) Enrollment for each cohort will be open for 6 months or less if the cohort is filled. Approximately 12 patients from Cohort 1 will be included in a subgroup for PK profile determination. To minimize blood collection in young subjects in Cohorts 2 and 3 more sparse samplings may be done with lower age groups based on the PK profiles observed in Cohort 1. Prior to Cohort 2, all PK data from Cohort 1 will be analyzed and the protocol will be amended and submitted for IRB approval. The same procedure will be followed to analyze Cohort 2 data prior to Cohort 3. If during the study more than 35% of dosed subjects from each cohort are considered to be exhibiting signs (confirmed by the results of a cortisol response test) and/or symptoms (nausea, headache, fatigue, myalgia or loose stool) of HPA axis suppression, the enrollment for this cohort will be stopped and the enrollment for a younger cohort(s) will not be initiated. A patient will be considered to have potential HPA axis suppression if they meet at least one of the criteria: • their 30 minute post injection cortisol level is not at least 7 mcg/100 ml greater than the basal level (< basal + 7) • the post stimulation level is ≤ 18 mcg/100 ml
Study Conduct	All patients will attend the clinic for 3 scheduled visits: **Visit 1**: Baseline (Day 1) **Visit 2**: Day 15 ± 2 (Interim visit) **Visit 3**: Day 29 ± 2 (End of treatment or Early Termination) Approximately 12 patients from Cohort 1 will be included in a subgroup for PK profile determination. The following visits will be scheduled for this subset of patients: Cohort 1: **Visit 1**: Baseline (Day 1) **Visit 2**: Day 8 ± 2 (interim visit) **Visit 3**: Day 15 ± 2 (interim visit) **Visit 4**: Day 22 ± 2 (interim visit) **Visit 5**: Day 29 ± 2 (End of treatment or Early Termination) **Visit 6:** Day 30 + 1 (Post Treatment Visit – Cortisol Response Test) Morning pre-dose blood samples will be collected at Visits 1-5 with PK sampling at 15 min, 30 min, 40 min, 50 min, 60 min, 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 12 hr post-dose at Visit 5. Cohort 2: Visit and blood sampling schedules will be included in the protocol amendment after completion of Cohort 1. Cohort 3: Visit and blood sampling schedules will be included in the protocol amendment after completion of Cohort 2. There will be 3 planned safety follow-up visits (Day 56, Day 84 and Day 112 after discontinuing treatment) for patients who exhibited signs of adrenal suppression

	during the study or at Visit 6 (Cohort 1).
Inclusion Criteria	1. Male or female 2-17 years of age (inclusive) at Screening: **Cohort 1:** male or female 12 years to 17 years and 11 months of age **Cohort 2:** male or female 6 years to 11 years and 11 months of age **Cohort 3:** male or female 2 years to 5 years and 11 months of age 2. Signed IRB approved informed consent given by parent(s) or legally acceptable guardian(s) following their receipt of verbal and written information about the study. 3. Patients ages 7 years and older must have provided IRB approved written assent; this written assent must be accompanied by an IRB approved written informed consent from the Subject's legally acceptable representative (i.e., parent or guardian). 4. Female patients of childbearing potential (post-menarchal), in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study from the day of the first dose administration to 30 days after the last administration of study drug. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (stabilized for at least 3 months) NuvaRing® (vaginal contraceptive); Implanon™ (contraceptive implant) double barrier methods (e.g. condom and spermicide), IUD, or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. A sterile sexual partner is NOT considered an adequate form of birth control. 5. A definite clinical diagnosis of stable plaque psoriasis with involvement of ≥10% BSA (excluding face and scalp) . If subject has both guttate and plaque psoriasis, majority of lesions must be plaque type and plaque type psoriasis must cover a minimum of 5% BSA. 6. Physicians Global Assessment (PGA) score of 3 (moderate) or 4 (severe) at baseline for the overall disease severity.

Route of Administration	Topical
Criteria for Evaluation	**Primary Outcome Measures:** Hypothalamic Pituitary Adrenal (HPA) Axis Response to Cosyntropin demonstrating the absence or presence of adrenal suppression at the end of the treatment **Secondary Outcome Measures:** • Changes on the Physician Global Assessment (PGA) score at the end of treatment. • Changes on the Clinical Signs and Symptoms (erythema, scaling, plaque elevation) at the end of treatment. • Pharmacokinetic parameters for desoximetasone at the end of treatment.
Statistical Analysis	**Primary analysis:** • Proportion of patients in the study with HPA axis suppression following treatment with the study medication. **Secondary analyses:** • Proportion of patients in each cohort with HPA axis suppression following treatment with the study medication. • The frequency, severity, and relationship to study drug for AEs will be used to evaluate the safety profile of the study drug. • A descriptive analysis on changes in PGA and Clinical Signs and Symptoms. Two planned interim analysis will be conducted following the end of the treatment periods for cohorts 1 and 2.

6. STATISTICAL ANALYSIS METHODS

If not otherwise specified, statistical significance is defined as $p < 0.05$ and is two-tailed. Data will be summarized with respect to demographic and baseline characteristics, efficacy variables and safety variables.

For categorical variables, the number and percent of each category within a parameter will be calculated for non-missing data. For continuous variables, statistics will include number of observations, mean, standard deviation, median, minimum and maximum values.

All statistical analyses will be conducted using SAS®, Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and ADaM (Analysis Dataset Model).

6.1 Baseline Characteristics

6.1.1 Demographics

Demographic information collected at baseline includes the following:

- Age (years)
- Gender (Male/Female)
- Ethnicity (Hispanic/non Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)
- Weight
- Height

Summary tables by cohort and by PK subgroup within a cohort will be presented. Continuous variables will be summarized using descriptive statistics (n, median, minimum, maximum, mean, standard deviation). Categorical variables will be summarized using frequencies and percentages.

Baseline comparability of the treatments will be presented using Cochran-Mantel-Haenszel (CMH) test for the categorical variables, and Analysis of Variance for the continuous variables.

All data will be listed by cohort, PK subgroup within a cohort, and patient.

6.2 Statistical Analyses

Patients are required to apply a total of 56 doses for the study. Patients will dose twice daily for 28 days. Patients in the PK Sampling Group will dose in the office at End of Treatment Visit. All patients who are enrolled and used at least 75%-125% of scheduled doses (i.e., between 42 - 70 doses) of the study drug and have data from a post-treatment cortisol response test will be included in the analysis.

6.2.1 Primary Analysis

<u>Potential HPA axis suppression</u>

The following criteria indicate a normal cortisol response (all criteria must be met):

1. Their basal (pre-Cortrosyn™ injection) cortisol concentration is > 5 mcg/100 mL
2. Their 30 minute post injection cortisol level is at least 7 mcg/100 mL greater than the basal level (≥ basal value + 7)
3. The post stimulation level is > 18 mcg/100 mL

Patients found to have abnormal adrenal function after the baseline Cortisol Response Test will not be enrolled in the study.

The test at the End of Study visit should not be performed if the patient dosed within 8 hours.

HPA axis suppression will be defined as a 30 minute post-Cortrosyn™ injection level cortisol level of ≤ 18 mcg/100 mL.

Any patient with abnormal test results, as defined above, will be considered to be exhibiting signs of HPA axis suppression. As the study treatment period will be over, any patients with abnormal results will be advised not to initiate any new steroid therapy, topical or otherwise, and to return to the site in 28 days at which time they will be assessed for HPA axis suppression.

Any patient presenting with symptoms of HPA axis suppression, such as nausea, headache, myalgia, fatigue or loose stool, will be referred to an endocrinologist. As an additional safety precaution, wristbands identifying the patient as someone suffering from adrenal suppression secondary to steroid withdrawal will be provided to alert medical personnel should any emergencies arise before adrenal function returns to normal.

If the results of the cortisol response test still show signs of HPA axis suppression 28 days after discontinuing therapy they will be asked to return in 28 days (56 days after discontinuing steroid therapy) for another follow-up test. If the patient is still showing signs of HPA axis suppression 56 days after discontinuing steroid therapy and presents with related symptoms they will be referred to an endocrinologist.

If HPA axis suppression persists for 56 days after discontinuing steroid therapy, but the patient has no symptoms they will be asked to return in 28 days (84 days after discontinuing steroid therapy) for another follow-up test. If HPA axis suppression persists for 84 days after discontinuing steroid therapy patients will be referred to an endocrinologist regardless of symptoms.

Descriptive Summary

The primary analysis will be proportion of evaluable patients across all age cohorts with HPA axis suppression, as observed from results of a cortisol response (ACTH stimulation) test at Day 30 (Post Treatment). Evaluable subjects are those that have both a baseline and end-of-study Cortisol Response Test results and have not been identified as having enrolled in the study previously. Patients found to have abnormal adrenal function after the baseline Cortisol Response Test will not be included in the evaluable patients for analysis.

6.2.2 Secondary Analyses

- Proportion of evaluable patients in each cohort with HPA axis suppression after the end of treatment.
- Pharmacokinetic parameters for desoximetasone at the end of treatment.
- Change from baseline/descriptive statistical analyses for the Physician Global Assessment (PGA) score at the end of treatment.

- Change from baseline/descriptive statistical analyses for clinical signs and symptoms (erythema, scaling, plaque elevation) of psoriasis at the end of treatment.

6.2.2.1 HPA Axis Suppression Analysis by Cohort

Similar to the primary analysis above, descriptive summary (frequency and proportion) of evaluable patients in each cohort with HPA axis suppression after the end of treatment will be presented.

6.2.2.2 Pharmacokinetic Analysis – PK Sampling Group Only

Concentrations of desoximetasone in plasma will be measured by the central laboratory using a fully validated analytical method. Pharmacokinetic and statistical analyses will be performed by Novum Pharmaceutical Research Services. The Statistical Analysis System (SAS®, Version 9.4 or higher) will be used for all pharmacokinetic and statistical calculations.

For Cohort 1, steady-state pre-dose (trough) plasma desoximetasone concentrations ($C_{pre(Dx)}$) x = 1, 8, 15, 22, 29) will be measured from morning pre-dose blood draws at Visits 2-6 (Days 1, 8, 15, 22 and 29). At Visit 6 (Day 29), in addition to the pre-dose draw, patients will have blood collections following a dose applied in the clinic. The blood collection schedule will be as follows: 0 (pre-dose), 15 min, 30 min, 40 min, 50 min, 60 min, 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 12 hr ($C_{post(D29),12hr}$) following the morning dose. Linear and semi-logarithmic graphs of each patient's plasma concentration-time profile for desoximetasone will be constructed using the actual times of sample collections.

For Cohort 2, steady-state pre-dose (trough) plasma desoximetasone concentrations ($C_{pre(Dx}$), x = 1, 8, 15, 22, 29) will be measured from morning pre-dose blood draws at Visits 2-6 (Days 1, 8, 15, 22 and 29). At Visit 6 (Day 29), in addition to the pre-dose draw, patients will have blood collections following a dose applied in the clinic. The blood collection schedule will be as follows: 0 (pre-dose) 1 hr and 3 hr following the morning dose. Linear and semi-logarithmic graphs of each patient's plasma concentration-time profile for desoximetasone will be constructed using the actual times of sample collections.

If sufficient data are available and pending review of the individual pre-dose profiles, the approach to steady-state concentrations may be evaluated from the measurable morning pre-dose concentrations ($C_{pre(Dx)}$) on Days 8, 15, 22 and 29, using Helmert contrasts comparing Day 22 and Day 29, Day 15 and the average of Days 22 and 29, and Day 8 and the average of Days 15, 22 and 29. The individual pre-dose profiles will be first reviewed visually to determine if the steady-state analysis is warranted and can be reliably assessed.

Graphical presentations of mean results will use the scheduled times of sample collections. A complete listing of the scheduled and actual times of sample collections for each patient and the concentration reported for each collected sample will be provided.

No concentration estimates will be provided for missing sample values. Any sample with a missing value will be treated as if the sample had not been scheduled for collection.

For the derivation of PK parameters for Cohort 1 on Day 29, plasma concentrations recorded as below the lower limit of quantitation (LLOQ) of 25 pg/mL (i.e., BLQ) will be handled per Sections 5.2.1.1, 5.2.1.2 and 5.2.3.1 of Novum's SOP 6102C (*Handling Below Lower Limit of Quantitation Data in Pharmacokinetic Studies*) and assigned a value of zero (i.e., 0) if they occur at the beginning or end of the 12-hour concentration-time profile and assigned a missing value if they occur in the middle of the PK profile for each patient. All BLQ values for $C_{pre(Dx)}$ in Cohorts 1 and 2 will be assigned a value of zero.

Data from patients with missing concentration values (missed blood draws, lost samples, samples unable to be quantified) may be used if pharmacokinetic parameters can be estimated using remaining data points, otherwise data from these patients will be excluded from the final descriptive statistics.

For Cohorts 1 and 2 on Day 29, the peak exposure at steady-state ($C_{max\text{-}ss}$) will be the observed maximum plasma concentration and the steady-state time to peak exposure ($T_{max\text{-}ss}$) will be the collection time at which $C_{max\text{-}ss}$ is first observed.

Steady-state area under the plasma concentration-time curve over the 12-hour dosing interval from time of dosing (t = 0 hr) to the time of last sample at 12 hours post-dose (AUC_{ss}) will be calculated by the linear trapezoidal method for Cohort 1 on Day 29. An AUC profile must have at least three consecutive measurable concentrations (i.e., > LLOQ), including $C_{max\text{-}ss}$, to be considered evaluable. No AUC_{ss} and $C_{max\text{-}ss}$ values will be reported for those PK profiles with fewer than three consecutive measurable concentrations. For those PK profiles with 0-concentration values at the end of the profile, AUC_{ss} will include the triangle area portion from t_z (time of last measurable concentration) to time of the first 0-concentration value at the end of the profile. If the 12-hour concentration is missing then AUC_{ss} will be calculated up to t_z but this value will not be included in the descriptive statistics for AUC_{ss}. AUC_{ss} will not be calculated for Cohort 2.

The apparent first-order terminal disposition rate constant (K_{el}) will be estimated, when possible, from the negative of the slope of the regression line for the terminal ln-linear concentration-time values for Cohort 1 on Day 29. The values to be included in the regression lines will be selected by examination of each patient's semi-logarithmic concentration-time plot. The first-order terminal disposition half-life ($T_{½}$) will be estimated as $\ln(2)/K_{el}$.

Descriptive statistics for all PK parameters (n, mean, SD, % coefficient of variation (%CV), minimum, median, maximum, geometric mean, geometric %CV) and for each time point (n, mean, SD, % coefficient of variation (%CV), minimum, median, maximum) will be reported by cohort. All BLQ concentration values will be replaced with 0 for the purpose of descriptive statistics for each time point.

6.2.2.3 Physician Global Assessment (PGA) Score

At all Visits a visual inspection to confirm a diagnosis of chronic plaque psoriasis will be done. PGA scores will be assessed at each visit on a 5-point scale (Appendix B): 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe, 5=very severe.

Frequency and percentage will be presented for PGA scores by cohort and study day.

Descriptive summary (n, mean, standard deviation, minimum, median and maximum) will be presented for PGA scores by cohort and study day as well as change from baseline to end of treatment. Baseline is defined as the PGA score at Day 1 (Visit 1).

PGA scores will be listed by cohort, patient and study day.

6.2.2.4 Clinical Signs and Symptoms of Psoriasis

At all Visits a visual inspection to confirm a diagnosis of chronic plaque psoriasis will be done.

Clinical signs and symptoms (erythema, scaling, plaque elevation) will be assessed at each visit on a 5-point scale: 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe, 5=very severe.

Frequency and percentage will be presented for clinical signs and symptoms by cohort and study day.

Descriptive summaries (n, mean, standard deviation, minimum, median and maximum) will be presented for clinical signs and symptoms by cohort and study day as well as change from baseline to end of treatment. Baseline is defined as the clinical signs and symptoms at Day 1 (Visit 1).

Clinical signs and symptoms will be listed by cohort, patient and study day.

6.3 Safety Analysis

Safety analysis will be conducted on all patients who applied at least one dose of study drug.

6.3.1 Adverse Events

All the adverse events (AEs) reported throughout the study will be coded and classified according to the MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary (Version 16.0 or higher). Each adverse event is to be evaluated for date of start and end, seriousness, severity, causal relationship with the study drugs, action taken and outcome.

All AEs will be listed by cohort and patient.

A summary table of the number and percent of patients with AEs by system organ class, preferred term, and cohort will be presented. Each patient will be counted only once within each preferred term.

A frequency summary table of the number of AEs by system organ class, preferred term, severity, and cohort will be presented. Severity will be classified as "Mild", "Moderate", or "Severe".

Similarly, a frequency summary table of the number of AEs by system organ class, preferred term, and relationship to a study drug, and cohort will be presented. Relationship to a study drug will be classified as "Not Related" or "Related" where "Related includes "Possible", "Probable", or "Definite".

6.3.2 % BSA Assessment

The Subject's body weight (kg) and height (cm) will be measured while the Subject is lightly clothed (e.g., no coat or shoes) to calculate the subject's BSA. %BSA will be assessed at every visit using instructions in Appendix A. To be eligible for inclusion, the patient must have an affected BSA of ≥10%.

Descriptive summary (n, mean, standard deviation, median, minimum, maximum) will be presented for %BSA by cohort and study day.

% BSA data will be listed by cohort, patient and study day.

6.3.3 Concomitant Medications

At Visit 1 subjects and parents/legal guardians will be questioned about current and concomitant medication use over the previous 12 weeks. At all Interim and End of Study Visits subjects and parents/legal guardians will be questioned about ongoing or new concomitant medication use.

All prior and concomitant medications taken since screening until the end of the study will be listed by cohort and patient.

6.4 Multiple Comparisons

No multiple comparison adjustment will be made in this study.

6.5 Methods for Handling Missing Data

For demographic and baseline characteristics, each variable will be analyzed using all available data. Patients with missing data will be excluded only from analyses for which data are not available.

6.6 Interim Analyses

Two planned interim analyses will be conducted to evaluate safety following the end of the treatment periods for Cohorts 1 and 2. Before Cohorts 2 and 3 are initiated, all data from Cohort 1 will be analyzed and the protocol will be amended and submitted for IRB approval.