# Clinical Pharmacology Review

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| **NDA Number** | 208813/S-002 |
| **Link to EDR** | *\\CDSESUB1\evsprod\NDA208183\208183.enx (eCTD 0054)* |
| **Submission Date** | 10/31/2019 (SDN 83) |
| **Submission Type** | Efficacy/Labeling supplement |
| **Brand Name** | Ultravate ® |
| **Generic Name** | Halobetasol propionate lotion, 0.05% |
| **Related Indication** | For the topical treatment of plaque psoriasis in patients aged ≥12 to ≤17 years |
| **Applicant** | Sun Pharmaceutical Industries, Inc. |
| **Primary Reviewer** | Da Zhang, Ph.D. |
| **Secondary Reviewer** | Chinmay Shukla, Ph.D. |
| **OCP Division** | Division of Inflammation and Immune Pharmacology |
| **OND Division** | CDER/ODEIII/DDDP |

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## 1. EXECUTIVE SUMMARY

Halobetasol propionate (HBP) is a super-potent topical corticosteroid. The FDA approved Ultravate® HBP Lotion, 0.05% for the treatment of plaque psoriasis in adults on November 6, 2015. The approval was based on seven clinical studies, three Phase 1 studies, two Phase 2 studies, and two pivotal Phase 3 studies.

In the current supplemental NDA, pursuant to a postmarketing requirement (PMR) as a result of the original approval, the Applicant conducted a clinical study (177-0551-201) to evaluate the pharmacokinetic (PK) properties and hypothalamic pituitary adrenal (HPA) axis suppression potential of Ultravate® Lotion under maximal use conditions in adolescent subjects (12 to less than 17 years old) with plaque psoriasis (assigned PMR No. 2973-1).

Another goal of this submission is to expand the approved patient population in adults to include adolescent patients; thus, revising the indication statement in the product label to patients 12 years of age or older.

### 1.1 Recommendation

The Office of Clinical Pharmacology, Division of Clinical Pharmacology III has reviewed the final study report of the PMR (2958-1) and have found it acceptable and concluded that the Applicant has fulfilled this PMR.

## 2. SUMMARY OF MAXIMAL USE PK AND HPA AXIS SUPPRESSION POTENTIAL STUDY 177-0551-201

***Title:*** An Open Label Evaluation of the Adrenal Suppression Potential and Pharmacokinetic Properties of Twice Daily Halobetasol Propionate Lotion, 0.05% in Subjects 12 to 16 Years 11 Months of Age with Plaque Psoriasis Receiving Two Weeks of Treatment

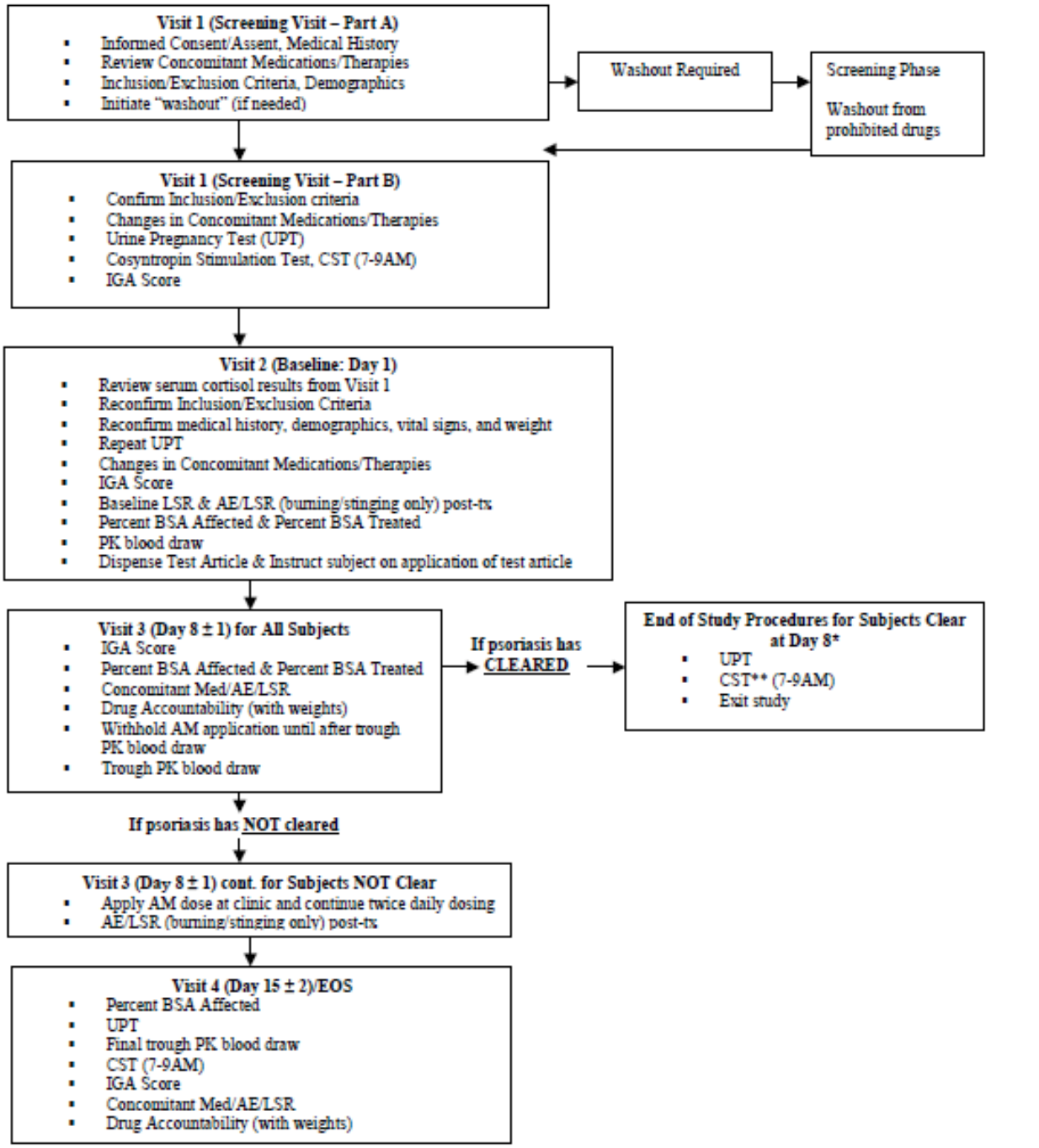
### 2.1 Study Objective

To determine the adrenal suppression potential and the pharmacokinetic (PK) properties of a lotion formulation of halobetasol propionate, 0.05% (Ultravate Lotion) applied twice daily in subjects aged 12 to 16 years 11 months with stable plaque psoriasis.

### 2.2 Study Design

This was an open label, multicenter study of a formulation of HBP Lotion, 0.05% (Ultravate Lotion) in male and female subjects 12 to 16 years 11 months of age with stable plaque psoriasis and was conducted as an FDA postmarketing commitment upon approval of HBP Lotion in adults (NDA 208183), as demonstrated in **Figure 1**.

**Figure 1. Trial Design**




* These procedures may be done on Day 9 if cannot be completed on Day 8.
** If CST demonstrates adrenal suppression, subject will be scheduled for post-treatment follow-up visits at 4-week intervals (approximately every 28 days) for CST until adrenal function returns to the pre-treatment value.

*(Source: Section 9. Study Procedure in Clinical study protocol 177-0551-201)*

Dosing Regimen

The subject and his/her parent/guardian were instructed to apply the test article every 12 hours for

2 weeks. The subject was instructed to apply test article in a thin uniform layer to the Treatment Area.

***Reviewer's comments:***

*The maximum dosage approved for adults is applying a thin layer to the affected areas twice daily, with the maximum weekly dosage of no more than 50 g.*

## 2.3 Pharmacokinetic and Pharmacodynamic Sampling

Eligible subjects had blood drawn at Visit 1/Screening for baseline HBP drug concentration in plasma. On Day 8, all subjects, regardless of lesion clearance, had blood drawn for assessment of HBP trough drug concentration in plasma. At the Day 15 visit, subjects who had continued to treat lesions had a final HBP PK blood sample collected approximately 12 hours after their Day 14 evening application and just prior to the initiation of the CST.

Eligible subjects who fulfilled the inclusion/exclusion criteria had a screening Cosyntropin Stimulation Test (CST) to assess their HPA axis response at Visit 1/Screening. All subjects had a CST to reassess their HPA axis response at End of Study (EOS) (or earlier if the investigator verified the subject's psoriasis had cleared). In this study, an abnormal HPA axis response to a 0.25 milligram dose of cosyntropin was defined as a post-CST serum total cortisol level of ≤ 18 μg/dL.

## 2.4 Pharmacokinetic and HPA Axis Suppression Results

Pharmacokinetics:

In total, 19 subjects were screened for this study; 16 subjects were enrolled into the study and 3 subjects failed the screening due to the CST with a post 30-minute stimulation cortisol level of ≤ 18 μg/dL. The test article was applied to 16 pediatric patients 12 to less than 17 years of age with moderate to severe plaque psoriasis affecting a mean body surface area of 11.5% (range from 10% to 14%). The mean dose used was 3.6 grams applied twice daily for two weeks.

The PK population included 14 subjects with demographics illustrated in **Table 1**. There were 2 enrolled subjects ((b) (6) and (b) (6)) excluded from the PK population, because their end of study CST was completed 6 days after their last dose.

**Table 1.** Demographics (Evaluable and Pharmacokinetic Population)

| CHARACTERISTIC | HBP Lotion, 0.05% N=14 |
|---|---|
| SEX, n (%) | |
| Female | 6 (42.9) |
| Male | 8 (57.1) |
| | |
| AGE (years) | |
| N | 14 |
| Mean | 14.2 |
| Standard Deviation | 1.56 |
| Median | 14.3 |
| Min., Max. | 12.5, 16.9 |
| | |
| ETHNICITY, n (%) | |
| Hispanic or Latino | 14 (100.0) |
| Not Hispanic or Latino | 0 (0.0) |
| | |
| RACE, n (%) | |
| White | 14 (100.0) |

*(Source: Clinical Study Report Table 14.1.3.2)*

Blood for PK analysis was drawn for 3 times: at Screening (pre-application, time=0), Day 8, and Day 15 (unless IGA=0 at Day 8), approximately 12 hours after the dose on the previous day.

Morning trough concentration ($C_{12}$) of HBP in plasma was below quantification limit (BQL) (LLOQ of 0.02 ng/mL) for all subjects at all time points, with the exception of Subject (b) (6) at Day 15/EOS who was near the LOQ with a trough concentration of halobetasol propionate of 0.0282 ng/mL.

HPA Axis Response and Serum Cortisol Levels

There was 1 (1/14 or 7.1%) subject (Subject (b) (6)) in the Evaluable population who had an abnormal HPA axis response at Day 15/EOS. Post-CST cortisol levels had returned to normal for the suppressed subject at a follow-up visit approximately 6 months after Day 15/EOS, as shown in **Table 2**. In a prior study in adult patients, Ultravate lotion produced HPA axis suppression in 5 out of 20 (25%) adult patients with plaque psoriasis when used twice daily for two weeks.

**Table 2.** Subject(s) Who Had Adrenal Suppression at Day 15

| Subject # | Screening Post-CST Cortisol (µg/dL) | Day 15 Post-CST Cortisol (µg/dL) | Follow-Up Post-CST Cortisol (µg/dL) | Total Test Article Used (grams) |
|---|---|---|---|---|
| (b) (6) | 24.4 | 16.2 | 28.2 | 102.2 |

*(Source: Clinical Study Report Listing 16.2.6.1 and Listing 16.2.4.2.)*

## 2.4 Bioanalytical Methods

Plasma HBP:

The analysis of HBP in human plasma was done using an adequately validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a range of 20 – 4000 pg/mL. At least 67% of the calculated concentrations for all quality controls (QC) samples and at least 50% of QC samples at each concentration level were acceptable. The relative error (%bias) of the mean QC sample concentrations was demonstrated to be between -9.8% to 1.3%, with a CV of not more than 12.4%. The maximum low temperature storage time until extraction was 146 days. Sample storage stability was demonstrated at -20 ºC for 532 days**.** The standard curve and quality control (QC) samples, and study samples of plasma were stored at -80 ºC. Temperatures designated throughout this report and associated test method (e.g., -80 °C, -20 °C, refrigerator, room/ambient) were considered equivalent to the closest temperature conditions defined in SOP 04-C031. Since all values were BQL or very close to BQL, there were no samples to select for incurred sample reanalysis (ISR).

Serum Cortisol:

The analysis of serum cortisol concentration was done at (b) (4) using the validated commercial ADVIA CENTAUR XP assay with a range of 0.2 – 75 µg/dL. Precision and accuracy assessments done at the testing laboratory were within acceptable limits. The applicant provided data to support storage stability for 10 days at room temperature and refrigerator and for 8 months frozen at -20 and -80 ºC. All samples were analyzed within the defined stability for cortisol.

## 2.5 **Labeling recommendations**

Labeling recommendations on Section 5 and Section 12 of the label of NDA 208183 are summarized in **Table 3**. The text in red and ~~strikethrough in red~~ is proposed by the Applicant. The ~~strikethrough in blue text~~ indicates recommended deletion by the reviewer. The texts in blue are recommended addition to the labeling by the reviewer. For section 5, only edits to the data are noted here.

**Table 3**.Reviewer's Recommendations on Labeling

| **Proposed labeling by the Applicant** | **Reviewer's labeling recommendations** |
|---|---|
| 5. WARNINGS AND PRECAUTIONS<br><br>5.1 Effects on Endocrine System<br>The potential for hypothalamic-pituitary adrenal (HPA) suppression with ULTRAVATE lotion was evaluated in the following studies:<br><br>• In a study of 20 adult ~~subjects~~patients with moderate to severe plaque psoriasis involving ≥20% of their body surface area. ULTRAVATE lotion produced HPA axis suppression when used twice daily for two weeks in 5 out of 20 (25%) adult patients with plaque psoriasis. (b) (4) of HPA | 5. WARNINGS AND PRECAUTIONS<br><br>5.1 Effects on Endocrine System<br>The potential for hypothalamic-pituitary adrenal (HPA) suppression with ULTRAVATE lotion was evaluated in the following studies:<br><br>• In a study of 20 adult subjects ~~patients~~ with moderate to severe plaque psoriasis involving ≥20% of their body surface area. ULTRAVATE lotion produced HPA axis suppression when used twice daily for two weeks in 5 out of 20 (25%) adult patients with plaque psoriasis. The effects of (b) (4) HPA axis |

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| axis function [redacted] discontinuation of treatment *[see Clinical Pharmacology (12.2)]*.<br>• In another clinical study, 16 adolescent patients (12 to less than 17 years old) with moderate to severe plaque psoriasis involving 10% or more of their body surface area applied a maximum of approximately 50 grams of ULTRAVATE lotion to affected areas twice daily for two weeks. Of the 14 patients evaluated for HPA axis suppression, laboratory evidence of adrenal suppression occurred in 1 patient (7.1%); which recovered upon retest *[see Clinical Pharmacology (12.2)]*. | suppression were reversible on [redacted] discontinuation of the treatment *[see Clinical Pharmacology (12.2)]*.<br>• In another clinical study, 16 adolescent [redacted] subjects (12 to less than 17 years old) with moderate to severe plaque psoriasis involving 10% or more of their body surface area applied a maximum of approximately 50 grams of ULTRAVATE lotion to affected areas twice daily for two weeks. Of the 14 [redacted] subjects evaluated for HPA axis suppression, ~~laboratory evidence of~~ adrenal suppression occurred in 1 [redacted] subject (7.1%); which recovered upon retest *[see Clinical Pharmacology (12.2)]*. |
| 12. CLINICAL PHARMACOLOGY<br><br>12.2 Pharmacodynamics<br><br>A vasoconstrictor assay in healthy ~~subjects~~patients with ULTRAVATE lotion indicated that the formulation is in the super-high range of potency as compared to other topical corticosteroids; however, similar blanching scores do not necessarily imply therapeutic equivalence.<br><br>The potential for hypothalamic-pituitary adrenal (HPA) suppression was evaluated in [redacted] the criteria for HPA-axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter 30 minutes after stimulation with cosyntropin (adrenocorticotropic hormone, ACTH). In the first study, ULTRAVATE lotion was | 12. CLINICAL PHARMACOLOGY<br><br>12.2 Pharmacodynamics<br><br>*Vasoconstriction:*<br>*A vasoconstrictor assay in healthy* [redacted] subjects *with ULTRAVATE lotion indicated that the formulation is in the super-high range of potency as compared to other topical corticosteroids; however, similar blanching scores do not necessarily imply therapeutic equivalence.*<br><br>*Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression:*<br><br>The potential for hypothalamic-pituitary adrenal (HPA) suppression was evaluated in [redacted] the criteria for HPA-axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter 30 minutes after stimulation with cosyntropin (adrenocorticotropic hormone, ACTH). In the |

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| applied to 20 adult patients with moderate to severe plaque psoriasis. A mean dose of 3.5 grams ULTRAVATE lotion was applied twice daily for two weeks and produced HPA axis suppression in 5 of 20 (25%) [redacted] ]. In the second study, ULTRAVATE lotion was applied to 16 pediatric patients 12 to less than 17 years of age with moderate to severe plaque psoriasis affecting a mean body surface area of 11.5% (range from 10% to 14%). The mean dose [redacted] was 3.6 grams applied twice daily for two weeks. A subset of 14 of the 16 completed [redacted] had evaluable ACTH stimulation tests, and HPA axis suppression was observed in 1 of these 14 patients (7 [redacted]%), [redacted] | first study, ULTRAVATE lotion was applied to 20 adult ~~patients~~ subjects with moderate to severe plaque psoriasis. A mean dose of 3.5 grams ULTRAVATE lotion was applied twice daily for two weeks and produced HPA axis suppression in 5 of 20 (25%) ~~patients~~ subjects ~~). These effects were reversible as recovery of HPA axis function was generally prompt with the discontinuation of treatment~~ The effects of HPA axis suppression were reversible on retesting at least four weeks after discontinuation of the treatment ~~*[see Warnings and Precautions (5.1)]*~~. In the second study, ULTRAVATE lotion was applied to 16 pediatric patients 12 years to less than 17 years of age with moderate to severe plaque psoriasis affecting a mean body surface area of 11.5% (range from 10% to 14%). The mean dose [redacted] was 3.6 grams applied twice daily for two weeks. A subset of 14 of the 16 completed [redacted] subjects had evaluable ACTH stimulation tests, and HPA axis suppression was observed in 1 of these 14 [redacted] subjects (7 [redacted]%). [redacted] n the second study also, the effects of HPA axis suppression were reversible on retesting at least four weeks after discontinuation of the treatment. [redacted] |

## 3. QUESTION-BASED CLINICAL PHARMACOLOGY REVIEW

The current clinical pharmacology review focuses on the PK and effect of HBP on HPA axis suppression in adolescent subjects with psoriasis under maximal use conditions based on the full clinical study report of Study 177-0551-201 (PMR No. 2973-1, NDA208183/S-002).

### 3.1 How does the systemic exposure of HBP in adolescent subjects compared with adults?

A comparison of PK data between adults and adolescents following HBP lotion, 0.05% application under maximal use conditions is summarized in **Table 4** (the adult PK data is obtained from the original NDA review).

The PK results suggest systemic exposure to HBP in both adolescent and adult psoriasis patients treated under maximal use conditions were low.

**Table 4 Comparison of HBP PK Between Adults and Adolescents Following HBP lotion 0.05% Under Maximal Use Conditions**

| | Adults (n=12) [a] | | | | Adolescents (n=14) [a] | |
|---|---|---|---|---|---|---|
| Analyte | n | $C_{max}$ [b] (pg/mL) | $AUC_{last}$ [b] (h*pg/mL) | $C_{min}$ [b, c] (pg/mL) | n | $C_{12}$ [d] (pg/mL) |
| HBP | 12 | 145.9 (106.9%) | 1267.7 (89.9%) | 80.2 (79.3%) | 14 | BQL for all subjects at all time points, with the exception of Subject (b) (6) at Day 15/EOS with an HBP Ctrough of 28.2 pg/mL. |

a: Mean daily dose 6.6 grams (range 3.4 to 9.6 grams) for adults, 7.2 grams (range 2.9 to 10.4 grams) for adolescents
b: Geometric mean (CV%)
c: The minimum plasma concentration over the dosing interval
d: Approximately 12 hours after the dose on the previous day at screening (pre-application, time=0), Day 8, and Day 15 (unless IGA=0 at Day 8)
LLOQ: 20 pg/mL

*(Source: Reviewer's summary based on the original clin Pharm NDA 208183 review and Study report for 177-0551-201)*

***Reviewer's comments:***

*The HBP levels in the plasma were below the quantification limit (20 pg/mL) for all patients at all time points, with the exception of one patient at Day 15/EOS (trough concentration of HBP of 28.2 pg/mL).*

### 3.2 What are the study population and drug usage information in Study 177-051-201?

A total of 14 subjects received HBP lotion 0.05% application were included in the PK population with demographics illustrated in **Table 1**. There were 2 enrolled subjects (b) (6) and (b) (6)) excluded from the PK population, because their end of study CST was completed 6 days after their last dose.

Subjects were instructed to apply a thin uniform application of the test article to the designated treatment area every 12 hours for up to 2 weeks. The daily average test article used was 7.2 grams with a range of 2.9 grams to 10.4 grams as shown in **Table 5**.

**Table 5. Extent of Exposure (PK Population)**

| Parameter | HBP Lotion (N=14) | Suppressed (N=1) |
|---|---|---|
| Total amount of drug used (g) | | |
| N | 14 | 1 |
| Mean | 101.5 | 102.2 |
| S.D. | 31.4 | |
| Median | 98.0 | 102.2 |
| Min., Max. | 39.9, 145.8 | 102.2, 102.2 |
| Daily average test article used (g) | | |
| N | 14 | 1 |
| Mean | 7.2 | 7.3 |
| S.D. | 2.32 | |
| Median | 7.1 | 7.3 |
| Min., Max. | 2.9, 10.4 | 7.3, 7.3 |

*(Source: Study report for 177-0551-201, page 82)*

***Reviewer's comments:***

*The dose used in the maximal study (MUsT) is within the upper range as shown in **Table 5**. The test article was applied to 16 pediatric patients 12 to less than 17 years of age with moderate to severe plaque psoriasis affecting a mean body surface area of 11.5% (range from 10% to 14%). The mean dose used was 3.6 grams applied twice daily for two weeks (mean daily dose was 7.2 grams) (approximately 50 grams per week). Trough plasma concentrations of HBP were measured on Day 8 and Day 15. These study design features are considered suitable for a MUsT.*

### 3.3 What are the hypothalamic-pituitary-adrenal (HPA) axis suppression results of HBP in adolescent subjects with psoriasis in Study 177-051-201?

There was 1 (1/14, 7.1%; 95% CI: 0.2, 33.9) subject (Subject (b) (6)) in the evaluable population who had an abnormal HPA axis response at Day 15/EOS. Post-CST cortisol levels had returned to normal for the suppressed subject at a follow-up visit approximately 6 months after Day 15/EOS, as shown in **Table 2**. In a prior study in adult patients, Ultravate lotion produced HPA axis suppression in 5 out of 20 (25%) adult patients with plaque psoriasis when used twice daily for two weeks.

***Reviewer's comments:***

*A subset of 14 of the 16 completed patients had evaluable CST stimulation tests, and HPA axis suppression was observed in 1 of these 14 patients (7.1%), which recovered to normal upon retest after stopping the treatment.*

*Per the agreed iPSP, the original enrollment target for this PMR, PK and HPA suppression assessment study under MUsT in adolescents, was to be 20 'evaluable' subjects (i.e., defined as subjects with pre- and post-cosyntropin stimulation test results and completed the study without any significant protocol violations).*

*At the time, a total of 14 subjects were considered 'evaluable', of which one subject (16 years and 10 months old) showed laboratory evidence of adrenal suppression. The target enrollment was to achieve at least 20 completers. The Applicant experienced challenges in recruiting additional study subjects and clinical investigators of the study requested for premature termination of this study. In response to the Applicant's request, FDA issued a letter stating its agreement that the Applicant may terminate the study as enrollment of pediatric subjects with psoriasis is indeed a challenge (FDA's 'Prior Approval Supplement Request' Letter in DARRTS dated July 31, 2019). Clinical Pharmacology opines that the available data in 14 adolescent subjects would be adequate to support labeling of this product in adolescent subjects 12 years of age and older.*

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/s/

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08/10/2020 04:00:07 PM

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