

Pilot Meta-Analysis for HPA Axis Suppression Studies through ADaM Datasets from derived Legacy Data



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Introduction

- Topical corticosteroids are a mainstay of dermatologic therapy because of their anti-inflammatory and anti-pruritic effects and have been classified according to their effect on dermal erythema into different potency levels based on vasoconstriction activity.
- It has been postulated that such potency levels may relate to drug safety and efficacy, but formal proof is wanting.
- We intend to examine potency levels of topical corticosteroids in relation to systemic safety using hypothalamic-pituitary-adrenal (HPA) axis suppression with Cortrosyn® stimulation, which represents a relatively clean system with few confounders.
- HPA axis suppression in the labeling of Cortrosyn® can be established by any one of three criteria (basal, post-stimulation, and rise in plasma cortisol levels); however, many studies base suppression on the post-stimulation level alone.
- In the pilot study described below, the data from HPA axis suppression studies conducted by different pharmaceutical companies over a substantial time period have been standardized into CDISC-compliant datasets.

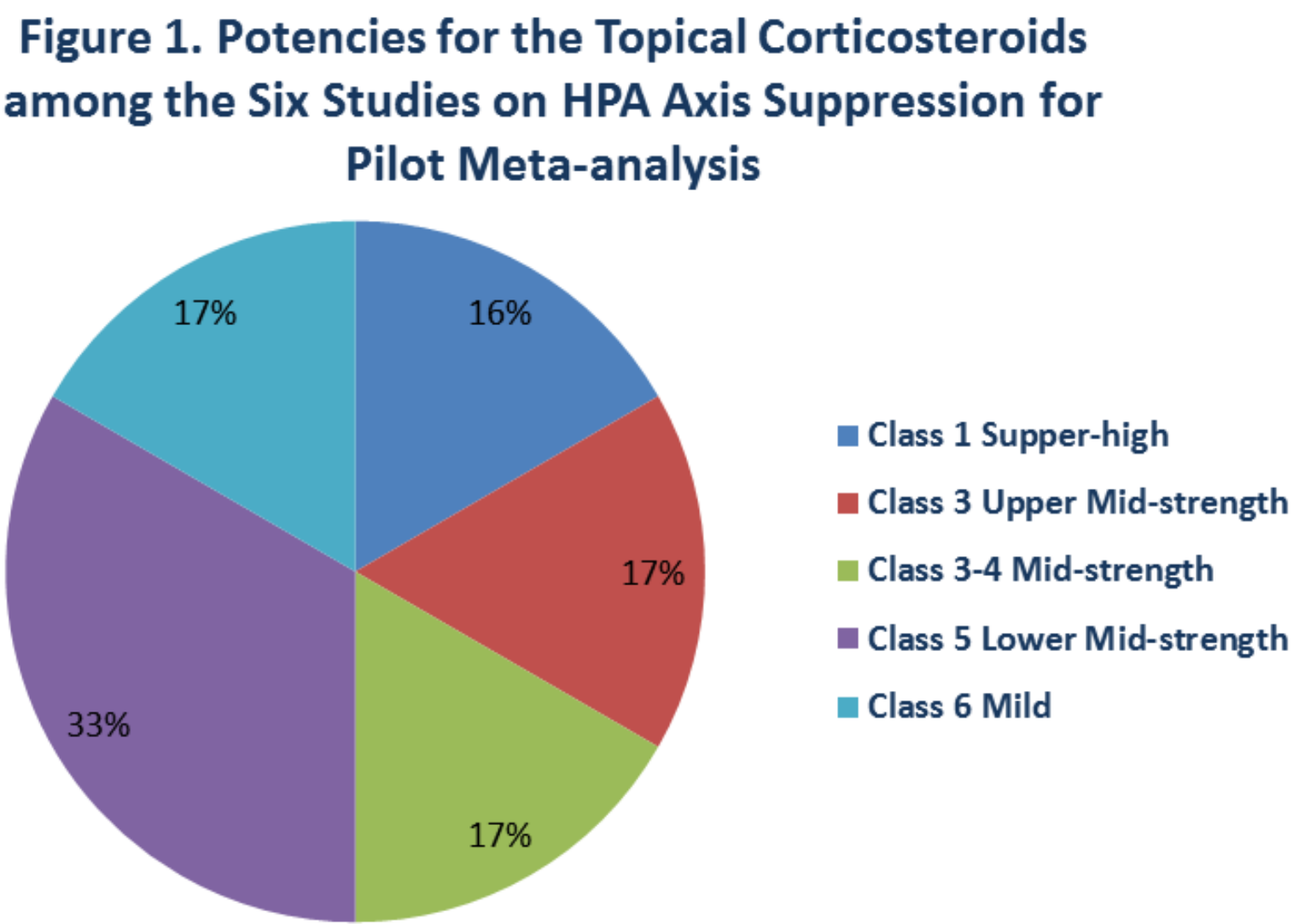
Materials

- Legacy data from 11 New Drug Application (NDA) submissions containing a total of 60 trials have been converted into over 740 SDTM datasets, including efficacy/safety studies, HPA axis suppression studies, and dermal safety studies. Potency information on the products is shown in Table 1.

Table1. NDA Submissions for Topical Corticosteroid Products with Legacy Data Standardized into CDISC-compliant Datasets

NDA	Steroid 1	Steroid 2	Steroid 3	Steroid 4	Steroid 5	Steroid 6	Steroid 7	Steroid 8	Steroid 9	Steroid 10	Steroid 11
Potency Class	Class 1 Super-high	Class 1 Super-high	Class 5 Lower mid-strength	Class 5 Lower mid-strength	Class 3 Upper mid-strength	Class 1 Super-high	Class 1 Super-high	Class 6 Mild	Class 1 Super-high	Class 1 Super-high	Class 3-4 Mid-strength

- The pilot meta-analysis on HPA axis suppression studies used Analysis Data Model (ADaM) from 6 NDA studies. The potencies for the topical corticosteroid products in the studies for pilot meta-analysis are provided in Figure 1, which shows 3 psoriasis studies with topical corticosteroids of potency from super-potent to mid-strength (Class 1 to 4), and 3 atopic dermatitis studies with topical corticosteroids of potency from lower mid-strength to mild (Class 5 to 6).



Methods

- Legacy datasets from topical corticosteroid studies have been converted into CDISC SDTM (Standard Data Tabulation Model) and ADaM datasets by using SAS v9.3, according to an updated CDISC SDTM Implementation Guide (version 3.2) and ADaM Implementaion Guide (version 1.0).
- The traceability of the ADaM datasets for the HPA axis suppression studies in this pilot analysis has been validated through Pinnacle 21 software.
- To perform pilot safety meta-analysis for the HPA axis suppression studies, ADaM ADLB datasets from the selected NDA submissions were combined through SAS programming. The ADLB datasets for the three studies on atopic dermatitis were pooled across potencies, and the ADLB datasets for the three psoriasis studies were similarly pooled.
- To test HPA axis suppression with ACTH (Cortrosyn®) stimulation, normal HPA axis is defined in the labeling of Cortrosyn® as follows:
 - 1) pre-stimulation plasma cortisol (basal) level should exceed 5 micrograms/dL;
 - 2) the 30-minute post-stimulation cortisol level should show an increment of at least 7 micrograms/dL above the basal level; and
 - 3) the 30-minute post-stimulation cortisol level should exceed 18 micrograms/dL.

However, most pharmaceutical companies only used one criterion to define HPA axis suppression, viz., the 30-minute post-stimulation cortisol level not exceeding 18 micrograms/dL.

Both definitions are applied in the meta-analysis.

- In the meta-analysis ADLB datasets, for each combined potency group, two variables (CRIT1 and CRIT2) were assigned for the two evaluation methods for the detection of HPA axis suppression: CRIT1 represented suppression using 3 criteria and CRIT2 using 1 criterion. The HPA axis suppression rate was calculated for each combined potency group or for each topical corticosteroid product by using SAS v9.4.
- The SAS codes to generate the suppression rate variables, CRIT1 and CRIT2, are listed below (partially).

Methods (Continued)

```
DATA ADLB_SUP;  
  SET AD_1;  
  IF AVAL1 > 5 AND CHANGE >= 7 AND AVAL2 > 18 THEN CRIT1='N';  
  ELSE CRIT1='Y';  
  LABEL CRIT1='Adrenal Suppression at 3 Criteria';  
  IF AVAL2 > 18 THEN CRIT2='N';  
  ELSE CRIT2='Y';  
  LABEL CRIT2='Adrenal Suppression at 1 Criterion';  
  LABEL AVAL1='Pre-dose Cortisol Level';  
  LABEL AVAL2='Post-dose Cortisol Level';  
  LABEL CHANGE='Difference between Pre-dose and Post-dose Cortisol Level';  
  LABEL ATPT1='Analysis TimePoint at Pre-dose';  
  LABEL ATPTN1='Analysis TimePoint at Pre-dose(N)';  
  LABEL ATPT2='Analysis TimePoint at Post-dose';  
  LABEL ATPTN2='Analysis TimePoint at Post-dose(N)';  
RUN;
```

- The HPA axis suppression rates with 95% and 90% confidence intervals (CIs) in the combined ADLB datasets were calculated using Fisher's Exact test and compared between diseases and drug products under the different suppression criteria through SAS v9.4. Confidence intervals (CIs) for binomial proportions were readily generated via PROC FREQ function. The codes to generate the 95% (i.e. $\alpha=0.05$) and 90% (i.e. $\alpha=0.10$) CIs for the suppression rates at 3 criteria (CRIT1) are listed below, and those for generation of rates at one criterion (CRIT2) are similar.

```
proc freq data=FPL_ET3 ORDER=formatted;  
  EXACT BINOMIAL;  
  tables CRIT1/ BINOMIAL (exact) alpha=0.05;**CI=95%**;  
  format CRIT1 $CRIT.;  
run;  
proc freq data=FPL_ET3 ORDER=formatted;  
  EXACT BINOMIAL;  
  tables CRIT1/ BINOMIAL (exact) alpha=0.10;**CI=90%**;  
  format CRIT1 $CRIT.;  
run;
```

Results

- Table 2 shows the results of combining studies for HPA axis suppression rates with topical corticosteroids of higher potency (Class 1 to 4) as well as corresponding rates with topical corticosteroids of lower potency (Class 5 to 6).

Table2. Suppression Rates by Meta-Analysis of HPA Axis Suppression Studies for Topical Corticosteroids

Topical Corticosteroid Potency Class	Proportion with Suppression using 3 Criteria*			Proportion with Suppression using 1 criterion**		
	Suppression Rate (%)	95% CI	90% CI	Suppression Rate (%)	95% CI	90% CI
[Class1~4]	36.0	27.1-45.7	28.4-44.2	13.5	8.1-20.7	8.8-19.6
[Class5~6]	10.8	5.9-17.8	6.5-16.7	0.8	0.0-4.4	0.0-3.7

*The 3 criteria are: 1) Pre-stimulation plasma cortisol level did not exceed 5 micrograms/dL; 2) the 30-minute level did not show an increment of at least 7 micrograms/dL above the basal level; 3) The 30-minute post-stimulation level did not exceed 18 micrograms/dL.

**The criterion is: the 30 minute post- stimulation cortisol level did not exceed 18 micrograms/dL.

- The confidence interval for the proportion of subjects showing suppression by topical corticosteroid products in the higher potency group does not overlap with that by topical corticosteroids in the lower potency group (either 95% or 90% confidence interval).

Discussion

- HPA axis suppression studies for topical corticosteroid products are usually based on sample sizes of about 50 subjects at the outset of the study. With meta-analysis, similar trials can be combined to give an overall estimate of average treatment effect to make up for the findings from inadequate sample size, and hence increasing the power.
- With legacy data converted into CDISC-standard format, we are able to conduct meta-analysis of HPA axis suppression rates using studies designed for maximal product use.
- The interpretation of clinical effectiveness of topical corticosteroids is complicated by multiple factors, e.g., the condition being treated, disease severity, body surface area involvement, concomitant medications, etc., while HPA axis studies afford a cleaner system for drug effect. The formulation poses substantial effects via its vasomotor potency which influences absorption and local toxicity.
- The populations in these studies might be a confounding factor, as atopic dermatitis studies involved the use of lower potency products, while the higher potency products would generally be used for psoriasis due to the fact that this condition is less responsive to treatment. A meta-analysis with standardized data from more HPA axis suppression studies would help to confirm the relationship between potency and systemic safety.

Conclusions

- This pilot study illustrates the power of using standardized datasets across studies for the comparison of corticosteroid activity.
- It also illustrates that the analysis for dermatological clinical trials is easily performed with SAS programming.
- Our results formally demonstrate a consistency of relationship between dermal vasomotor "potency" and systemic effect (HPA axis suppression).

❖ This project was funded by the US Food and Drug Administration through Oak Ridge Associated Universities and Oak Ridge Institute for Science and Education. The findings and conclusions in this project have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any agency determination or policy.
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