CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-555/S-008

19-555/S-016

STATISTICAL REVIEW(S)

STATISTICAL CONSULTATION

NDA #:	19,555/SE–5; 17,691/SE–5; 17,536/SE–5; 17,781/SE–5
Applicant:	Schering Plough Corporation
Name of Drug:	Diprolene AF Cream; Diprosone Ointment; Diprosone Cream; Diprosone Lotion
Indication:	Atopic dermatitis
Route of Administration:	Topically twice daily for 2 or 3 weeks
Documents Reviewed:	Pediatric Study Report (dated 10/5/00 and 6/1/01) SAS data submission (dated 5/31/01)
Medical Officer:	Denise Cook, M.D., HFD-540
Statistical Reviewer:	Shiowjen Lee, Ph.D., HFD-725

I. Introduction and Background:

Background

Sponsor's current submission is a supplement to NDA 19-555, 17-691, 17-536 and 17-781. The pediatric study report for four studies (Studies P01260, P01261, P01262 and P01263) is included. The primary objective of the submission is to respond to a Pediatric Written Request dated 7/16/1999 and amended on 4/19/2000 for betamethasone dipropionate products in the treatment of atopic dermatitis.

The Pediatric Written Request asked for a minimum of 50 evaluable subjects treated for 2 or 3 weeks with one of the four topical formulations (i.e. a minimum total of 200 subjects for the four studies) to evaluate the safety of betamethasone dipropionate products in pediatrics. Though the Sponsor's Study P01263 enrolled only 25 subjects, this statistical consultation will provide analysis for each study.

Study Parameters

The primary objective of the four studies was safety. The primary safety variables in the protocols included

- the serum cortisol levels in response to Cortrosyn stimulation (HPA axis function),
- clinical signs of cutaneous atrophy

The HPA axis function was evaluated by assessing levels of serum cortisol prior to and 30 minutes after Cortrosyn challenge at baseline (Day 1) and at endpoint (Day 22). Several secondary safety variables were also included in the protocol. They were

- clinical laboratory parameters
- topical and systemic adverse events
- global evaluation of change in disease status

Statistical Methods

Since the study was in response to the Pediatric Written Request and was not powered to detect any difference in efficacy assessment, only summary/descriptive statistics were proposed in the studies.

Reviewer's Comments:

1. The medical reviewer asked for a statistical consultation on the following questions for each study:
   (a) Number of evaluable subjects for HPA axis suppression and the proportion of subjects who had HPA axis suppression at endpoint
   (b) Relationship between the amount of drug product used, percent of body surface area (%BSA) involved, weight and the presence of HPA axis suppression
   (c) Number of subjects suppressed by gender and age

   Since the above questions are concerning the HPA axis suppression, this statistical consultation will focus only on the evaluation of HPA axis suppression. Results of other safety parameters are not reported.

2. After consultation with the medical reviewer, the following criteria are used for subjects' evaluability of HPA axis suppression according to the definition for Cortrosyn label:
   (1) subjects with pre-stimulation cortisol level greater than 5 ug/dL at baseline;
   (2) subjects with post-Cortrosyn cortisol level greater than 18 ug/dL at baseline,
   (3) the difference of baseline post- and pre- cortisoal levels is at least 7 ug/dL; and
   (4) the presence of endpoint data.

   The HPA axis suppression is assumed to be present if any one of the above (1), (2) and (3) is not satisfied at the endpoint.

II. Study Results

II.1. Study P01260

Study Design:

Study P01260 was a Phase IV, multicenter, open-label safety study in pediatric subjects with atopic dermatitis conducted in the US. Total of 67 subjects was enrolled. The enrolled subjects aged from 3 months to 12 years old (inclusive) and were treated with Diprolene AF cream twice daily for 2 or 3 weeks, with a 2- to 4-week post-treatment follow-up.

Evaluable Subjects:

Based on the criteria for subjects' evaluability of HPA axis suppression stated in the statistical comments, 58 subjects were evaluable. However, after consultation with the medical reviewer, subjects 0001/000012 and 0002/000019 were included as evaluable subjects. Subject 0001/000012 had endpoint data showing HPA not suppressed though he had missing post-stimulation data at baseline. Subject 0002/000019 had 2-week post-baseline cortisol level data though not at Day 22. This yielded a total of 60 evaluable subjects in this study.

Table A.1 of the Appendix gives the listing of patients who were evaluable for the presence of HPA suppression. The results can be summarized by the following:

- Among 60 evaluable subjects, 28 are females (46.7%) and 32 males (53.3%).
- For the distribution of age groups, 4, 16, 28, and 12 subjects were in 3 mo/1yr, 2yr/5yr, 6yr/8yr, and 9yr/12yr groups, respectively.

Presence of HPA Suppression:
The following table gives a summary of the baseline/demographic results in Table A.1 of the Appendix.

		Gender		Age Group			
	Total	**Female**	**Male**	**3mo.-1 yr**	**2 yr – 5 yr**	**6 yr – 8 yr**	**9 yr – 12 yr**
Without HPA	41	18	23	2	10	19	10
With HPA	19 (31.7%)	10 (35.7%)	9 (28.1%)	2 (50%)	6 (37.5%)	9 (32.1%)	2 (16.7%)
Total	60	28	32	4	16	28	12

- 19 out of 60 subjects (31.7%) were classified as having HPA axis suppression, which included 10 females and 9 males. Among the suppressed subjects, 2, 6, 9 and 2 subjects were in age groups of 3 mo/1yr, 2yr/5yr, 6yr/8yr, and 9yr/12yr groups, respectively.
- The 95% confidence interval of the proportion of subjects having HPA axis suppression is (19.9%, 43.4%).

Relationship between HPA and Amount of Drug Used, % Body Surface Area Involved, Weight:
To investigate the effect of the amount of drug used in the presence of HPA axis suppression, a logistic regression analysis was performed. The analysis indicates that the effect is not significant (p-value = 0.9084).

Results from the logistic regression analysis showed a significant result (p-value = 0.0099) for the relationship between subject's percent body surface area involved with disease (%BSA) and the presence of HPA axis suppression. The estimate of the coefficient of the variable "*%BSA*" is 0.043 with standard error of 0.0167; which suggests that an increase in %BSA resulted in an increase in the odds, and therefore the probability, of the presence of HPA suppression. Specifically, the corresponding odds ratio is 1.044 which implies that, for an increase of 1% of body surface area involved, there is an increase in the odds of the presence of HPA suppression by 4.4% (i.e. 1.044–1 = 0.044).

For the relationship between the presence of HPA and subject's weight, logistic regression analysis does not show significant association (p-value $\geq$ 0.2478).

Table A.2 of the Appendix classifies subjects (i.e. with and without the presence of HPA suppression) with respect to age, the amount of drug used, the length of treatment duration, percent of body surface area involved, and weight.

- The mean age of subjects who had HPA axis suppression was 6.2 years with a minimum of 1.3 years and a maximum of 11.2 years. This is compared to the mean of 7.2 years with a minimum of 1.2 years and a maximum of 12.986 years for subjects without suppression. The observed difference in age between the two groups is small and not statistically significant.
- Subjects having HPA suppression used numerically larger mean amount of drug (i.e. 58.78 grams vs. 57.90 grams) with a minimum of 21.5 grams and a maximum of 108.5 grams. However, the different is not statistically significant.
- The observed difference between subjects with and without HPA suppression is small with respect to the length (in days) of treatment duration (i.e. mean of 20.6 vs. 21.5 days, respectively).

- For percent of body surface area involved, subjects having HPA axis suppression had higher percent body surface area involved than those without HPA suppression (67.37% vs. 53.85%). Such difference is statistically significant using both parametric and nonparametric methods (p-value $\leq$ 0.0102).
- For the comparison in weight between two groups, HPA suppression subjects had relatively lower mean weight than those without HPA for Visit 1 and Visit 4 (i.e. 52.54 lbs vs. 60.22 lbs at Visit 1; and 52.94 lbs vs. 60.49 lbs at Visit 4). However, the difference is not statistically significant.

II.2. Study P01261

Study Design:

Study P01261 was a Phase IV, multicenter, open-label safety study. Total of 80 pediatric subjects was enrolled. The enrolled patients were treated with Diprosone Ointment, 0.05%, twice daily for 2 or 3 weeks, with a 2- to 4-week post-treatment follow-up.

Evaluable Subjects:

Subjects 0008/000006 and 0008/000016 (out of 80) withdrew from the study. For the remaining 78 subjects, the mean amount of drug used was 48.14 grams with minimum and maximum of 3.3 grams and 294.4 grams, respectively. It should be noted that Subject 0001/000001 used 294.4 grams of drug which is considered to be extreme compared to others. The mean amount of drug used was 44.9 grams excluding the extreme value of 294.4 grams. The mean treatment duration was 21.71 days with a minimum of 9 days and a maximum of 31 days.

Among the 78 subjects, only 52 subjects (66.7%) were evaluable based on the criteria for subjects' evaluability of HPA axis suppression stated in the statistical comments. However, after consultation with the medical reviewer, Subject 0003/000002 was included since her HPA axis value was not suppressed at the endpoint even though she had missing baseline data. This yielded a total of 53 evaluable subjects (67.9%) in this study.

Table A.3 of the Appendix gives the listing of evaluable patients as well as the classification of HPA suppression at the endpoint. Results are summarized below:

		Gender		Age Group			
	Total	Female	Male	3mo.-1 yr	2 yr – 5 yr	6 yr – 8 yr	9 yr – 12 yr
Without HPA	38	21	17	7	15	11	5
With HPA	15 (28.3%)	2 (8.7%)	13 (43.3%)	4 (36.4%)	6 (28.6%)	4 (26.7%)	1 (16.7%)
Total	53	23	30	11	21	15	6

- Fifteen out of 53 subjects (28.3%) were classified as HPA axis suppression positive, which included 2 females and 13 males. Of the suppressed subjects, 4, 6, 4 and 1 subjects were in age groups of 3 mo/1yr, 2yr/5yr, 6yr/8yr, and 9yr/12yr groups, respectively.
- The 95% confidence interval for the proportion of subjects having HPA axis suppression is (16.2%, 40.4%).

- For suppression by gender, a significantly higher proportion of males than females were suppressed (i.e. 43.3% vs. 8.7% with a p-value of 0.006). However, no statistically significant difference among age groups was indicated in terms of proportion of subjects having suppression (i.e. 36.4%, 28.6%, 26.7%, and 16.7% with p-value of 0.408).

Relationship between HPA and Amount of Drug Used, % Body Surface Area Involved, Weight:
To investigate the effect of the amount of drug used, subject's percent body surface area involved with the disease, and subject's weight in the presence of HPA axis suppression, logistic regression analyses were performed. Results did not show statistically significant effect.

Table A.4 of the Appendix classifies subjects (i.e. with and without the presence of HPA suppression) with respect to age, the amount of drug used, the length of treatment duration, percent of body surface area involved, and weight.

- The mean age of subjects who had HPA axis suppression was 4.6 years with a minimum of 0.58 years and a maximum of 11.2 years. This is compared to mean of 5.4 years with a minimum of 1.2 years and a maximum of 12.6 years for subjects without suppression. The observed difference in age between the two groups is not statistically significant.
- Subjects having HPA suppression used numerically larger mean amount of drug (i.e. 73.4 grams vs. 44.7 grams) with a minimum of 3.7 grams and a maximum of 294.4 grams. However, the difference is not statistically significant.
- The observed difference between subjects with and without HPA suppression is small with respect to the length (in days) of treatment duration (i.e. mean of 20.7 vs. 22.1 days, respectively).
- For percent of body surface area involved, subjects having HPA axis suppression had numerically higher percent body surface area involved than those without HPA suppression (67.6% vs. 55.11%).
- For the comparison in weight between two groups, HPA suppression subjects had relatively higher mean weight than those without HPA for Visit 1 and Visit 4 (i.e. 55.08 lbs vs. 48.81 lbs at Visit 1; and 57.53 lbs vs. 49.29 lbs at Visit 4). However, the difference is not significant.

II.3. Study P01262

Study Design:
The design of Study P01262 was similar to that of P01260 and P01261. Sixty-three subjects were enrolled and were treated with Diprosone Cream twice daily for 2 or 3 weeks. The post-treatment follow-up period was 2- to 4-week.

Evaluable Subjects:
Among the 63 enrolled subjects, forty-three (68.3%) of them were evaluable based on the criteria for Cortrosyn label. Following the consultation with the medical reviewer, Subjects 0005/000003 and 0007/000002 need to be excluded due to the use of a prohibited medication and a higher dose of Cortrosyn at baseline, respectively. However, Subjects 0002/000002 and 0006/000001 were included since their HPA axis values were not suppressed at endpoint even though they had missing baseline data. This yielded a total of 43 evaluable subjects in the study.

The listing of evaluable patients as well as the classification of HPA suppression at endpoint is presented in Table A.5 of the Appendix. The summary is shown below:

		Gender		Age Group			
	Total	Female	Male	3mo.-1 yr	2 yr – 5 yr	6 yr – 8 yr	9 yr – 12 yr
Without HPA	33	14	19	3	14	10	6
With HPA	10 (23.3%)	1 (6.7%)	9 (32.1%)	0	6 (30%)	3 (23.1%)	1 (14.3%)
Total	43	15	28	3	20	13	7

- Ten out of the 43 evaluable subjects (23.3%) were classified as HPA axis suppression positive, which included 1 female and 9 males (6.7% vs. 32.1%). Of the suppressed subjects, 0, 6, 3 and 1 subjects were in age groups of 3 mo/1yr, 2yr/5yr, 6yr/8yr, and 9yr/12yr groups, respectively.
- The 95% confidence interval for the proportion of subjects having HPA axis suppression is (10.6%, 35.9%).
- For HPA suppression by gender, a numerically higher proportion of males than females were suppressed (i.e. 32.1% vs. 6.7%) with a marginal statistical significance (p-value = 0.063). However, no statistically significant difference among age groups was indicated in terms of proportion of subjects having suppression (i.e. 0%, 30%, 23.1%, and 14.3% with a p-value of 0.806).

Relationship between HPA and Amount of Drug Used, % Body Surface Area Involved, Weight:
The effect of the amount of drug used, subject's percent body surface area involved with the disease, and subject's weight in the presence of HPA axis suppression was studied. Table A.6 of the Appendix classifies subjects (i.e. with and without the presence of HPA suppression) with respect to age, the amount of drug used, the length of treatment duration, percent of body surface area involved, and weight.

- The mean age of subjects who had HPA axis suppression was 5.5 years with a minimum of 2.52 years and a maximum of 11.0 years. This is compared to mean of 6.0 years with a minimum of 1.2 years and a maximum of 11.5 years for subjects without suppression. The observed difference in age between the two groups is not statistically significant.
- Subjects having HPA suppression used statistically larger mean amount of drug (i.e. 81.34 grams vs. 37.17 grams with p-value < 0.001) with a minimum of 33.8 grams and a maximum of 125.1 grams.
- The observed difference between subjects with and without HPA suppression is small with respect to the number of days of treatment (i.e. mean of 20.4 vs. 21.2 days, respectively).
- For percent of body surface area involved, subjects having HPA axis suppression had numerically higher percent body surface area involved than those without HPA suppression (57.3% vs. 43.5%).
- For the comparison of weight between two groups (i.e. with and without suppression), suppressed patients had numerically lower mean weight than that of un-suppressed patients (51.8 vs. 60.5 at Visit 1; 52.0 vs. 60.8 at Visit 4). However, no significant difference is indicated.

II.4. Study P01263

Study P01263 enrolled only 25 subjects aged between 6 years and 12 years. This included 19 females (76%) and 6 males (24%). The study did not satisfy the Pediatric Written Request for a

minimum of 50 evaluable subjects to evaluate the safety of Diprosone Lotion in pediatrics. However, the results are summarized by the following. No formal statistical testing is performed due to a relatively small sample size.

Evaluable Subjects:
Only 15 subjects (60%) were evaluable based on the criteria for subjects' evaluability of HPA axis suppression according to Cortrosyn label.

Table A.7 of the Appendix presents the listing of evaluable patients as well as the classification of HPA suppression at the endpoint. The summary is presented below:

		Gender		Age Group			
	Total	**Female**	**Male**	**3mo.-1 yr**	**2 yr – 5 yr**	**6 yr – 8 yr**	**9 yr – 12 yr**
Without HPA	4	3	1	--	--	3	1
With HPA	11 (73.3%)	7 (70%)	4 (80%)	--	--	7 (70%)	4 (80%)
Total	15	10	5	--	--	10	5

- Eleven out of the 15 evaluable subjects (73.3%) were classified as having HPA axis suppression, which included 7 females and 4 males. Of the suppressed subjects, 7 and 4 subjects were in age groups of 6yr/8yr, and 9yr/12yr groups, respectively. The observed difference among gender as well as age groups in terms of proportion of subjects having HPA suppression is small.

Relationship between HPA and Amount of Drug Used, % Body Surface Area Involved, Weight:
Table A.8 of the Appendix classifies subjects (i.e. with and without the presence of HPA suppression) with respect to age, the amount of drug used, the length of treatment duration, percent of body surface area involved, and weight.

- The mean age of subjects who had HPA axis suppression was 8.4 years with a minimum of 6.5 years and a maximum of 11.3 years. This is compared to mean of 8.8 years with a minimum of 6.5 years and a maximum of 11.2 years for subjects without suppression. The observed difference in age between the two groups is small.
- Subjects having HPA suppression used numerically larger mean amount of drug (i.e. 92.8 grams vs. 69.4 grams) with a minimum of 15.2 grams and a maximum of 165.7 grams.
- The observed difference between subjects with and without HPA suppression is small with respect to the number of days of treatment (i.e. mean of 19.3 vs. 19.8 days, respectively).
- For percent of body surface area involved, subjects having HPA axis suppression had higher percent body surface area involved than those without HPA suppression (45.8% vs. 41.8%).
- Subjects having suppression had numerically lower mean weight at Visits 1 and 4 than those without suppression (i.e. 64.73 vs. 81.75 at Visit 1; 64.68 vs. 80.25 at Visit 4).

III. Summary and Conclusion:
The Sponsor in this submission presented pediatric study report for Studies P01260, P01261, P01262 and P01263 to support the Pediatric Written Request for Diprolene AF Cream, Diprosone ointment, Diprosone cream and Diprosone lotion in the treatment of atopic dermatitis. During the studies, pediatric subjects were treated with one of the four topical formulations twice daily for 2 or

3 weeks followed by a 2- to 4-week post-treatment follow-up. Even though Study P01263 did not satisfy the required minimum of 50 evaluable subjects, the results on the presence of HPA axis suppression are summarized.

- For study P01260, the assessment of HPA suppression was based on 60 evaluable subjects (89.6% of enrolled subjects):
  - Nineteen out of the 60 evaluable subjects (31.7%) had the presence of HPA axis suppression at the endpoint. The 95% confidence interval for the proportion of pediatric subjects who had HPA suppression ranges from 19.9% to 43.4%.
  - Among the 19 subjects who had HPA suppression, 10 are females and 9 are males. The 19 subjects who had HPA suppression were distributed as 2, 6, 9 and 2 subjects in 3 mo/1yr, 2yr/5yr, 6yr/8yr, and 9yr/12yr age groups, respectively.
  - Results of the logistic regression analysis suggest that, for an increase of 1% of body surface area involved, there is an increase in the odds of the presence of HPA suppression by 4.4%. Such change is statistically significant (based on both parametric and nonparametric methods).
  - Analyses showed that the relationship between the presence of HPA suppression and age, amount of drug used, treatment duration, and weight are not significant.

- For study P01261, the assessment of HPA suppression was based on 53 evaluable subjects (66.3% of enrolled subjects):
  - Fifteen out of the 53 evaluable subjects (28.3%) had HPA suppression at the endpoint. The 95% confidence interval for the proportion of pediatric subjects who had HPA suppression ranges from 16.2% to 40.4%.
  - Among the 15 subjects having suppression, 2 are females and 13 are males. Four, 6, 4 and 1 suppressed patients were in 3 mo/1yr, 2yr/5yr, 6yr/8yr, and 9yr/12yr age groups, respectively.
  - Analyses showed that the relationship between the presence of HPA suppression and age and amount of drug used, percent of body surface area involved, treatment duration, and weight are not significant.

- For study P01262, the assessment of HPA suppression was based on 43 evaluable subjects (68.3% of enrolled subjects):
  - Ten out of the 43 evaluable subjects (23.3%) had suppression at the endpoint. The 95% confidence interval for the proportion of pediatric subjects who had HPA suppression ranges from 10.6% to 35.9%.
  - Among the 10 subjects having HPA suppression, 1 is female and 9 are males. Zero, 6, 3 and 1 suppressed patients were in 3 mo/1yr, 2yr/5yr, 6yr/8yr, and 9yr/12yr age groups, respectively.
  - A numerically higher proportion of males than females (i.e. 32.1% vs. 6.7% with p-value = 0.063) were suppressed and the comparison is marginally significant.
  - Analyses showed that the subjects having HPA suppression used statistically <u>larger</u> mean amount of drug (i.e. 81.34 grams vs. 37.17 grams with a p-value of < 0.001).
  - Analyses showed that the relationship between the presence of HPA suppression and age, treatment duration, percent of body surface area involved and weight are not significant.

- The summary of Study P01263 in the assessment of HPA suppression was based on only 15 evaluable subjects (60% of enrolled subjects):
  - Eleven subjects (73.3%) had suppression at the endpoint. This included 7 females and 4 males; while 7 and 4 subjects were distributed in 6yr/8yr, and 9yr/12yr age groups, respectively.
  - Summaries showed that subjects having suppression had relatively higher mean amount of drug used as well as lower mean weight.

Shiowjen Lee, Ph.D.
Mathematical Statistician, Biometrics III

Concur: Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

cc:
Archival NDA 19-555/SE-5, 17-691/SE-5, 17-536/SE-5, 17,781/SE–5
HFD-540/Dr. Wilkin
HFD-540/Dr. Walker
HFD-540/Dr. Cook
HFD-540/Ms. Cintron
HFD-700/Dr. Anello
HFD-725/Dr. Huque
HFD-725/Dr. Alosh
HFD-725/Dr. Lee

This review contains 17 pages.

APPENDIX

Table A.1: Evaluable Subject Listing With/Without HPA Axis Suppression: Study P01260

	Subject ID	Age	Sex	Drug used	Duration	%BSA	Wt B	Wt E	HPA
1	0001/000001	12.986	M	42.1	21	50	134.2	135	0
2	0001/000002	11.165	M	74	18	80	91.5	91	0
3	0001/000003	6.092	M	37.7	27	60	93	92	0
4	0001/000005	7.132	M	61.7	23	40	56.2	57.2	0
5	0001/000006	7.009	M	53.6	24	40	50	48.4	0
6	0001/000009	6.593	M	69	20	80	50.6	57.6	0
7	0001/000010	1.196	F	29.4	23	50	23	22.5	0
8	0001/000011	5.993	M	77.3	23	80	45	46	0
9	0001/000012	3.124	M	64.6	22	90	31.2	29.7	0
10	0001/000013	3.469	M	44.8	23	40	30.8	31	0
11	0001/000017	1.35	M	62.9	22	60	22	24.2	0
12	0002/000001	8.397	M	96	21	75	62	62	0
13	0002/000002	8.285	F	24.1	21	50	61	61	0
14	0002/000004	9.681	M	29.5	21	45	80	80	0
15	0002/000006	9.276	F	35.8	21	45	84	84	0
16	0002/000007	11.324	F	73.4	21	45	105	105	0
17	0002/000008	6.94	M	41.1	21	65	66	66	0
18	0002/000009	8.895	F	65.5	21	50	86	86	0
19	0002/000011	7.943	M	74.5	21	65	54	54	0
20	0002/000012	7.436	F	46.8	21	35	74	74	0
21	0002/000014	6.631	F	34.7	21	40	44	44	0
22	0002/000015	7.313	M	27.7	21	70	44	44	0
23	0002/000017	7.159	M	19.8	21	60	62	62	0
24	0002/000020	7.554	M	18.3	21	60	56	56	0
25	0004/000001	8.419	M	75.2	21	35	48.5	48.5	0
26	0004/000002	10.231	M	36.8	21	47	55	55	0
27	0004/000004	4.246	F	79.7	21	51	36	36	0
28	0004/000005	5.99	F	87.4	21	54	46	45.5	0
29	0004/000006	6.379	F	70.8	20	42	55	55	0
30	0004/000007	5.487	F	87.9	22	50	56	56.5	0
31	0004/000008	3.693	F	67.1	23	40	35	35	0
32	0005/000004	7.74	F	27	21	39	57	57	0
33	0006/000001	10.842	F	88.6	21	35	111	109	0
34	0006/000002	8.411	M	122.6	21	40	91	96	0
35	0006/000004	9.032	M	109.3	23	40	64	65	0
36	0006/000005	11.688	M	63.4	22	35	81	82	0
37	0006/000006	10.385	M	103.6	21	40	75	74	0
38	0007/000004	3.737	F	29	22	90	41	40.5	0
39	0007/000006	5.599	F	69.4	22	88	42	43	0
40	0007/000007	2.368	F	17.7	20	63	25	25.5	0
41	0007/000008	7.622	F	34	21	44	45	44	0
42	0001/000004	11.211	M	42.1	21	80	91.3	92	1
43	0001/000007	6.001	F	35.7	21	95	41.8	42	1
44	0001/000008	6.36	F	106.3	21	90	49	47.5	1
45	0001/000014	1.563	F	38.3	21	75	22	.	1
46	0001/000016	4.255	M	88.9	21	80	33.2	33	1
47	0002/000003	7.811	F	48.7	21	75	64	64	1
48	0002/000018	8.654	M	21.5	21	50	60	60	1
49	0002/000019	6.557	F	22.5	17	60	75	.	1
50	0004/000003	5.689	M	66.1	22	60	48	46.5	1
51	0004/000009	1.303	M	73.2	22	70	22	23.5	1
52	0005/000001	7.474	M	106.2	21	70	60	60	1
53	0005/000002	7.644	F	39	14	55	85	85	1
54	0005/000003	6.486	M	30	21	36	39	39	1
55	0006/000003	10.653	M	96.8	21	40	86	85	1
56	0007/000001	4.849	F	108.5	22	36	62	61	1
57	0007/000009	5.509	M	48.3	20	90	40	39.5	1
58	0007/000010	7.817	F	37.4	22	70	45	48	1
59	0007/000011	3.606	F	29.8	21	92	34	34	1
60	0007/000012	4.575	F	77.5	21	56	41	40	1

Note: HPA = 0 (absence of HPA); HPA = 1 (presence of HPA)
Wt_B= weight at Visit 1; Wt_E=weight at Visit 4
DURATION: duration of treatment (in days).

Table A.2: Summary of Subjects With/Without HPA with respect to Age, Amount of Drug Used, Duration of Treatment, % Body Surface Area Involved, and Weight: Study P01260

Variable: AGE Subject age at start

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	41	7.19053659	2.78704981		
With	19	6.21142105	2.59647520		

Variable: DRUGUSED Amount of drug used (in grams)

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	41	57.89756098	26.96343346		
With	19	58.77894737	30.37531123		

Variable: DURATION Days on treatment

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	41	21.51219512	1.38061492		
With	19	20.57894737	1.92399438		

Variable: %BSA Percent of body surface area involved

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	41	53.85365854	16.43253020		
With	19	67.36842105	18.64942813		

Variable: Wt_B Weight at Visit 1

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	41	60.21951220	24.98651856		
With	19	52.54210526	20.78245296		

Variable: Wt_E Weight at Visit 4

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	41	60.49024390	25.00276790		
With	17	52.94117647	19.76256116		

Table A.3: Evaluable Subject Listing With/Without HPA Axis Suppression: Study P01261

OBS	SUBJECT	AGE	SEX	DRUGUSED	DURATION	%BSA	Wt B	Wt E	HPA
1	0003/000001	5.399	M	58.7	20	50	43	42	0
2	0003/000002	3.225	F	12.5	21	50	31	31	0
3	0003/000004	7.874	M	23.8	18	45	63	63	0
4	0003/000009	1.799	F	58.3	22	75	31	31	0
5	0003/000010	1.331	F	38.7	21	60	20.5	23	0
6	0004/000002	1.536	F	63.5	21	84	25	26	0
7	0004/000003	1.875	F	35	22	90	23.3	24	0
8	0004/000004	2.642	F	68.2	21	95	40	39	0
9	0004/000005	4.575	M	43.5	21	89	33.5	33	0
10	0004/000007	5.903	M	119.2	21	44	49	49.5	0
11	0004/000010	6.951	M	95.5	21	61	51	50	0
12	0004/000011	4.022	F	75.1	22	80	36	36	0
13	0005/000001	11.02	M	48	25	35	92	91	0
14	0005/000002	12.085	F	66	25	45	114	117	0
15	0005/000004	12.624	M	32.7	22	35	121	124	0
16	0005/000005	11.321	F	7.9	20	35	121	121	0
17	0005/000007	10.768	M	19.3	21	35	72	72.5	0
18	0005/000008	6.396	M	13.4	27	35	56	56	0
19	0005/000009	7.258	F	81.5	20	40	62	63	0
20	0005/000010	7.644	F	17.4	22	40	62	63	0
21	0005/000011	7.042	M	70	26	50	64	65	0
22	0005/000012	7.655	F	33.8	21	40	62	63	0
23	0005/000013	6.99	F	20.9	26	35	46	46	0
24	0005/000015	1.227	M	17.8	22	35	21	20	0
25	0005/000016	2.39	F	21.7	23	35	28	29	0
26	0005/000017	5.974	F	18	16	35	44	47	0
27	0005/000019	7.283	F	34.7	16	35	51	50	0
28	0005/000020	2.245	M	3.3	21	40	29	29	0
29	0005/000021	4.172	M	3.3	25	35	37	38	0
30	0005/000022	7.376	F	10.1	22	60	54	53	0
31	0005/000023	2.407	M	31.3	21	85	27.5	29	0
32	0005/000024	3.915	F	115.7	26	90	33	34	0
33	0005/000025	1.76	M	14.5	25	40	30	31	0
34	0005/000026	5.815	F	9.1	24	40	40	41	0
35	0005/000027	1.487	M	47.3	28	90	26	25	0
36	0007/000003	3.803	F	120	21	90	34	34	0
37	0007/000006	2.59	F	48.6	21	76	37	38	0
38	0007/000007	6.418	M	98.5	21	60	45	46	0
39	0001/000001	11.201	M	294.4	21	96	128	132	1
40	0003/000006	1.613	M	53	24	80	27	.	1
41	0003/000008	3.316	F	37	22	85	27	27	1
42	0004/000006	1.342	M	47	22	64	24	23.5	1
43	0005/000028	2.193	M	3.7	19	35	39	38	1
44	0005/000029	2.505	M	56.7	21	50	34	32	1
45	0005/000030	5.974	F	107.6	20	99	67	70	1
46	0007/000001	8.123	M	56.5	26	60	61	61	1
47	0007/000002	1.374	M	97.2	21	99	20	20.8	1
48	0007/000004	2.368	M	61.6	21	98	30	30	1
49	0007/000005	0.578	M	74.2	23	54	17.2	17.6	1
50	0007/000008	7.11	M	133	20	57	105	105	1
51	0008/000001	8.145	M	9.2	21	36	106	109	1
52	0008/000004	8.047	M	11	9	41	100	97.5	1
53	0008/000015	4.767	M	59	21	60	41	42	1

Note: HPA = 0 (absence of HPA); HPA = 1 (presence of HPA)
Wt_B = weight at Visit 1; Wt_E = weight at Visit 4
DURATION: duration of treatment (in days).

Table A.4: Summary of Subjects With/Without HPA with respect to Age, Amount of Drug Used, Duration of Treatment, % Body Surface Area Involved, and Weight: Study P01261

Variable: AGE Subject age at start

HPA	N	Mean	Std Error	Minimum	Maximum
Without	38	5.44202632	3.24548211		
With	15	4.57706667	3.29040800		

Variable: DRUGUSED Amount of drug used (in grams)

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	38	44.65263158	33.54560218		
With	15	73.40666667	70.88851878		

Variable: DURATION Days on treatment

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	38	22.05263158	2.67063479		
With	15	20.73333333	3.67358654		

Variable: %BSA percent of body surface area involved

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	38	55.10526316	21.51026087		
With	15	67.60000000	23.39658095		

Variable: Wt_B Weight at Visit 1

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	38	48.81052632	26.03525458		
With	15	55.08000000	37.16348438		

Variable: Wt_E Weight at Visit 4

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	38	49.28947368	26.31632716		
With	14	57.52857143	38.51012711		

Table A.5: Evaluable Subject Listing With/Without HPA Axis Suppression: Study P01262

OBS	SUBJECT	AGE	SEX	DRUGUSED	DURATION	%BSA	Wt B	Wt E	HPA
1	0001/000001	3.611	M	45.1	23	55	37	36	0
2	0001/000002	3.559	M	48.4	21	65	36.5	36	0
3	0001/000003	5.572	F	53.8	23	60	42	42.5	0
4	0002/000001	7.154	M	66.5	20	75	60	.	0
5	0002/000002	7.756	M	33.2	15	65	74	72	0
6	0005/000001	10.883	M	63	22	36	138	136	0
7	0005/000002	10.125	M	71.6	20	40	70	71	0
8	0005/000004	8.854	F	39.1	18	40	125	122	0
9	0005/000007	3.247	M	47.7	22	40	35	32	0
10	0005/000008	7.74	F	22.3	23	40	95	100	0
11	0005/000011	5.985	M	39.8	22	45	48	49	0
12	0005/000012	5.202	F	1	22	35	55	58	0
13	0005/000014	5.533	M	6.6	17	35	44	44	0
14	0005/000016	6.48	M	16.7	15	50	55	55	0
15	0005/000017	5.728	M	7.5	10	45	59	60	0
16	0006/000001	9.615	M	16	21	40	139	140	0
17	0006/000005	9.659	M	29.8	21	45	84.2	84.2	0
18	0006/000006	8.129	M	14.3	21	35	68.2	69	0
19	0006/000007	11.466	M	13.5	21	45	118.2	118.5	0
20	0006/000008	8.156	F	10.9	21	35	62	62	0
21	0006/000011	11.146	M	13.9	21	40	87	88	0
22	0006/000012	6.357	F	18.5	25	40	58.3	59	0
23	0006/000013	7.951	F	18.5	21	40	51.5	51.5	0
24	0006/000014	2.867	F	34.7	21	40	35	36	0
25	0006/000015	4.312	F	35.3	22	45	60	61	0
26	0006/000017	1.684	M	44.9	24	40	28	28	0
27	0006/000018	1.155	F	57.3	22	45	23	24	0
28	0006/000020	2.746	M	35.1	23	35	33	34	0
29	0006/000021	7.203	F	88.1	21	35	46.5	47	0
30	0006/000023	1.164	M	42.3	37	35	25	25	0
31	0006/000024	2.114	F	72.1	21	35	31.5	31.5	0
32	0006/000026	2.363	F	25.5	22	35	26.5	27	0
33	0006/000029	4.115	F	93.5	21	45	45	45	0
34	0005/000005	7.217	M	73.3	21	45	52	52	1
35	0005/000006	6.825	M	33.8	21	40	40	40	1
36	0005/000010	4.131	M	72.7	22	40	38	36	1
37	0005/000013	5.235	M	68.5	21	75	52	55	1
38	0006/000002	11.001	M	115.1	21	40	134.5	135	1
39	0006/000027	5.684	M	35.9	18	35	50.5	51	1
40	0007/000001	2.79	F	63.4	17	38	34	34	1
41	0007/000004	7.17	M	104.4	21	90	61	61	1
42	0007/000006	2.516	M	125.1	21	85	27	27	1
43	0007/000007	2.516	M	121.2	21	85	29	29	1

Note: HPA = 0 (absence of HPA); HPA = 1 (presence of HPA)
Wt_B = weight at Visit 1; Wt_E = weight at Visit 4
DURATION: duration of treatment (in days).

Table A.6: Summary of Subjects With/Without HPA with respect to Age, Amount of Drug Used, Duration of Treatment, % Body Surface Area Involved, and Weight: Study P01262

Variable: AGE Subject age at start

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	33	6.04942424	3.03601146		
With	10	5.50850000	2.68501493		

Variable: DRUGUSED Amount of drug used (in grams)

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	33	37.16666667	23.86280666		
With	10	81.34000000	33.54284822		

Variable: DURATION Days on treatment

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	33	21.18181818	4.04238903		
With	10	20.40000000	1.57762128		

Variable: %BSA percent of body surface area involved

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	33	43.51515152	10.01287051		
With	10	57.30000000	23.18069120		

Variable: WT_V1 Weight at Visit 1

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	33	60.46666667	31.97023681		
With	10	51.80000000	31.10394759		

Variable: WT_V4 Weight at Visit 4

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	32	60.75625000	32.40785386		
With	10	52.00000000	31.37231618		

Table A.7: Evaluable Subject Listing With/Without HPA Axis Suppression: Study P01263

OBS	SUBJECT	AGE	SEX	DRUGUSED	DURATION	%BSA	Wt_B	Wt_E	HPA
1	0001/000006	6.5	F	78.2	16	39	58	58	0
2	0004/000002	8.435	M	138.2	21	54	68	57	0
3	0004/000004	11.17	F	37.7	21	36	135	137	0
4	0004/000005	8.966	F	23.6	21	38	66	69	0
5	0001/000001	9.41	F	125.5	21	36	118	118	1
6	0001/000002	11.326	F	165.7	21	36	80	80	1
7	0001/000005	7.655	F	75.9	19	39	60	60	1
8	0001/000007	7.663	F	83.7	18	36	40	40	1
9	0001/000009	6.678	M	131.9	22	50	40	40	1
10	0001/000011	6.538	F	89.5	22	40	40	40	1
11	0004/000001	8.515	F	124.1	21	72	79	79.5	1
12	0004/000008	9.429	M	111.8	21	57	53	52	1
13	0004/000011	10.119	F	69.5	21	47	90	92	1
14	0004/000013	7.953	M	15.2	21	38	60	58	1
15	0004/000014	6.85	M	28	5	53	52	52	1

Note: HPA = 0 (absence of HPA); HPA = 1 (presence of HPA)
Wt_B = weight at Visit 1; Wt_E = weight at Visit 4
DURATION: duration of treatment (in days).

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Table A.8: Summary of Subjects With/Without HPA with respect to Age, Amount of Drug Used, Duration of Treatment, % Body Surface Area Involved, and Weight: Study P01263

Variable: AGE Subject age at start

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	4	8.76775000	1.92037503		
With	11	8.37600000	1.54061994		

Variable: DRUGUSED Amount of drug used (in grams)

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	4	69.42500000	51.35954147		
With	11	92.80000000	45.16215230		

Variable: DURATION Days on treatment

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	4	19.75000000	2.50000000		
With	11	19.27272727	4.88038747		

Variable: %SBA percent of body surface area involved

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	4	41.75000000	8.26135582		
With	11	45.81818182	11.45266940		

Variable: WT_V1 Weight at Visit 1

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	4	81.75000000	35.76194439		
With	11	64.72727273	24.68234555		

Variable: WT_V4 Weight at Visit 4

HPA	N	Mean	Std Dev	Minimum	Maximum
Without	4	80.25000000	38.22193960		
With	11	64.68181818	25.01826605		