

**STUDY REPORT:**

**ORAL SUPPLEMENTATION OF NICKEL AND BROMIDE  
IN PSORIASIS VULGARIS  
USING NICKEL DIBROMIDE AND SODIUM BROMIDE**  
*Groups A and B*

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**Tulsa, Oklahoma**  
*December 23, 1994*

## STUDY ABSTRACT

An open study consisting of a sixteen-week active treatment phase and an eight-week follow-up phase with 53 adult psoriasis vulgaris subjects treated with daily oral administration of nickel dibromide and sodium bromide was performed. An aqueous solution with a constant nickel level (15 µg/kg/day) and two different dosage levels of bromide (300 µg/kg/day and 1200 µg/kg/day) in two study groups yielded efficacy data showing favorable improvements in the Psoriasis Area and Severity Index\* scores and other parameters evaluated for both study groups. Eighty-eight percent of subjects exhibited a moderate or marked improvement in their PASI scores (≥25%) after sixteen weeks of treatment. Analysis of the PASI indicates a high degree of statistical significance in improvement of psoriasis at every evaluation during the treatment period ( $p < 0.0001$ ). A relatively low frequency of minor adverse reactions was reported during the study period; none of these necessitated withdrawal from the study. This study supports the hypothesis that daily oral administration of nickel and bromide improves the psoriatic skin, nail and scalp condition and is very well tolerated.

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\* PASI (Psoriasis Area and Severity Index) as originally defined by T. Fredriksson and U. Pettersson in *Dermatologica* 157:238-244 (1978).

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IN PSORIASIS VULGARIS  
USING NICKEL DIBROMIDE AND SODIUM BROMIDE**

**1. OBJECTIVES :**

This study was designed to investigate the effect of daily oral administration of the ultra-trace minerals nickel and bromide in psoriasis patients over an extended time period. Two dose formulations in aqueous solution were employed, with Group A receiving a dosage of 15 µg/kg/day of nickel and 1200 µg/kg/day of bromide, and Group B receiving a dosage of 15 µg/kg/day of nickel and 300 µg/kg/day of bromide, in order to evaluate any efficacy difference with increased bromide administration. Safety and efficacy monitoring were conducted throughout a 16 week Supplement Period and an 8 week Post-Supplement Period.

**2. BACKGROUND AND RATIONALE:**

The use of nickel salts (NiBr<sub>2</sub> and NiSO<sub>4</sub>) and bromides (NiBr<sub>2</sub>, KBr and NaBr) as human therapeutic agents have been disclosed in the medical literature since the 1850's. The nickel salts were administered in doses ranging up to 7.5 mg of Ni(II) per kilogram of body weight per day for as long as 75 days, with no serious adverse effects reported. The therapeutic use of nickel salts declined in the early 20th century while the use of bromide salts declined in the mid-20th century.

Researchers in recent history other than this sponsor/investigator have administered nickel salts (primarily nickel sulfate) in long term studies (up to 152 days) at levels up to 40 µg Ni/kg body weight/day, and in short term or single dose studies at levels up to 80 µg Ni/kg/day, with no reported adverse or toxic effects. The US Environmental Protection Agency has established hazard guidelines based on animal studies for nickel from ingestion of nickel compounds over 100 µg Ni/kg/day for short term (10 day) exposure and over 50 µg Ni/kg/day for long term (7 year) exposure.

For bromide compounds, the Acceptable Daily Intake of bromides for long term (lifetime) exposure has been set at 1000 µg Br/kg/day by the World Health Organization based on various studies. The no effect level observed in human studies using sodium bromide is 4,000 µg Br/kg/day.

This Sponsor/Investigator has administered nickel salts (NiBr<sub>2</sub> and NiSO<sub>4</sub>·6H<sub>2</sub>O) and bromide compounds (NaBr and NiBr<sub>2</sub>) in both controlled and open studies, including this study, involving a total of over 200 patients with favorable results. The mineral therapy was well tolerated, with a low incidence of minor adverse reactions reported.

Early studies of this therapy were done with NiBr<sub>2</sub>. It is felt that both the nickel and the bromide are active in the therapy. To further evaluate this hypothesis this study was designed to have two groups, with the only difference being

bromide dosage level. In addition, since earlier studies involved a shorter therapy period, this study is intended to evaluate the safety and efficacy of the therapy over an extended time period (16 weeks).

### **3. METHODS**

#### **3.1 Introduction:**

The study was performed from June, 1993, to July, 1994, at the offices and clinic of Dr. Steven A. Smith. Study subjects were recruited from the practice of Dr. Smith and all qualified subjects were enrolled. Each was assigned in sequential order to the Group B dose level, then to the Group A level, with no regard to individual characteristics. Written informed consent was obtained, and 53 subjects entered the study, with 45 completing the 16-week Supplement Period and 37 completing the 24-week Post-Supplement Period. Eleven subjects entered Group A and 42 entered Group B.

#### **3.2 Study design and duration:**

The study design was open label with no blinding of investigator or subject.

### **4. PATIENT SELECTION**

#### **4.1 Inclusion criteria:**

- a) Typical plaque psoriasis involving at least 1% body surface area.
- b) All psoriasis medications/treatments discontinued at least two weeks prior to initiation of study and excluded throughout the study.
- c) At least 12 years of age.
- d) Females must be of no child-bearing capacity or must prevent pregnancy during the entire study with an effective birth control method (including both Supplement and Post-Supplement Periods).
- e) Adequate renal function.
- f) No excessive use of alcohol.
- g) Able to fulfill the requirements listed in the Informed Consent.

#### **4.2 Initial and subsequent exclusion criteria:**

Subjects that did not fulfill the initial inclusion criteria were excluded.

### **5. CONDUCT OF STUDY**

#### **5.1 Screening and Subject Enrollment:**

Subjects were taken off their existing psoriasis therapies. Risks and possible benefits were explained to all subjects in depth, and both the subject and the study investigator signed the Informed Consent in the presence of a witness. Medical histories were documented for each subject using standardized office practice history records.

#### **5.2 Schedule of Activities and Evaluations:**

##### **a) Pre-Supplement Period:**

Various baseline examinations and laboratory tests were conducted prior to initiating study medication. These consisted



of routine history and physical examination, routine hematology and serum chemistry, serum nickel and bromide, and routine urinalysis. Serum pregnancy tests were obtained from women of child-bearing potential. In addition, various psoriatic symptoms were rated and the PASI score (Psoriasis Area and Severity Index) was determined (see Section 8.2). A routine patch test to document cutaneous nickel allergy status was also conducted prior to initiating study medication. Photographs were taken of selected subjects.

b) Supplement Period

Study subjects were assigned to Dose Group B (15  $\mu\text{g}$  Ni/kg/day and 300  $\mu\text{g}$  Br/kg/day) in consecutive order as they entered the study, and when Group B assignment was filled, the remaining subjects were assigned to Dose Group A (15  $\mu\text{g}$  Ni/kg/day and 1200  $\mu\text{g}$  Br/kg/day). They received supplies of the study medication at office visits every four weeks, and records of interval history and physical were maintained. Compliance was assessed by comparing theoretical consumption to actual consumption, determined from the remaining study medication in returned storage containers. Laboratory tests were performed at Weeks 8 and 16 of the active treatment period. PASI scores and other measures of psoriatic involvement were evaluated at each visit, as well as any adverse reactions encountered during the dosing period. Photographs were taken of selected subjects. Study medication was discontinued at the end of 16 weeks.

c) Post-Supplement Period

This 8-week period was designed to monitor any prolonged effects of the study medication that may have lasted beyond the active treatment period. Subjects received the same interval history and physical and PASI evaluations as during the Supplement Period, with laboratory tests performed at Week 24, the last week of the follow-up phase and of the study. Photographs were taken of selected subjects.

5.3 Drug Administration:

The study medication consisted of  $\text{NiBr}_2$  and  $\text{NaBr}$  in aqueous solution. The Ni dosage was held constant at 15  $\mu\text{g}/\text{kg}/\text{day}$  in both dose groups, the Br dosage in Dose Group A was 1200  $\mu\text{g}/\text{kg}/\text{day}$ , and the Br dosage in Dose Group B was 300  $\mu\text{g}/\text{kg}/\text{day}$ . The vehicle for the compounds was distilled water, with no other preservatives, flavorings, or colorings present in the solutions. ACS Reagent Grade Nickel Dibromide and photographic grade highly purified Sodium Bromide suitable for human use was used to prepare the study medication (See Section 7).

Daily oral dosing was self-administered. The medication was taken on an empty and fasted stomach, and fasting for at least one hour after dosing was required to ensure maximum absorption. Compliance was measured by comparing actual residual study solution volume returned with the theoretical residual based on the determined daily dosage and the number of doses theoretically taken.

**5.4 Concomitant Therapy:**

Subjects with known compliance discrepancies or that used therapies known to have an interaction with psoriasis (such as various topical corticosteroids or tar treatments) during the treatment period were excluded from statistical evaluations of PASI scores and related psoriasis symptoms (5 subjects in Group A and 16 subjects in Group B). Subjects with material compliance discrepancies were excluded from the evaluation of laboratory results (1 subject in Group A and 11 subjects in Group B).

**5.5 Treatment Visits:**

The medication was self-administered by the subjects. An evaluation of the disease state was scheduled every 4 weeks, and laboratory test specimens were collected every 8 weeks.

**5.6 Evaluation of Safety:**

The safety of each subject enrolled in the study was monitored by the results of the physical examinations and laboratory tests conducted at the treatment visits.

**5.7 Dosing Modification in Event of Toxicity:**

No dosing modifications were necessary since no indications of toxicity were manifested.

**5.8 Data Collection:**

All physical examination clinical notes, laboratory reports, clinical photographs, and administrative records were collated in individual subject file folders. These records are archived in the office of the study clinical investigator.

**6. PATIENT WITHDRAWAL**

Of the 53 originally enrolled subjects, 45 (84.9%) completed the 16 weeks of the Supplement Period. The 8 dropouts are detailed in the following table:

Table 6.1. Patient Withdrawal Before End of Supplement Period

<b>Subject</b>	<b>Last Visit (Week)</b>	<b>Reason</b>
B-41	4	Electively terminated participation due to lack of clinical improvement.
B-3	8	Terminated participation due to relocation.
B-7	8	Lost to follow-up.
B-9	8	Electively terminated participation in the study.
B-13	8	Failure to schedule follow-up appointment due to traveling.
B-35	8	Lost to follow-up.
B-1	12	Electively terminated participation due to father's death.
B-44	12	Lost to follow-up.



Of the 45 subjects that completed the entire 16-week Supplement Period, 37 (69.8% of all subjects that entered the study) completed the entire eight-week follow-up period through Week 24 of the study. The 8 post-treatment dropouts are presented in the following table:

Table 6.2. Patient Withdrawal During Post-Supplement Period

Subject	Last Visit (Week)	Reason
A-11	16	Lost to follow-up.
B-11	16	Electively terminated participation due to financial difficulties.
B-19	16	Failure to schedule follow-up appointment due to traveling.
B-29	16	Electively terminated participation due to lack of improvement.
B-40	16	Lost to follow-up.
A-8	20	Lost to follow-up.
B-20	20	Lost to follow-up.
B-43	20	Lost to follow-up.

## 7. DRUG SUPPLY

### 7.1 Purity:

Reagent grade Nickel Dibromide and photograde Sodium Bromide was obtained from Morre-Tec Industries, Carteret, New Jersey, in powder form. Certificates of Analysis were obtained showing greater than 99% purity. Appropriate amounts of these powders were weighed on an analytical balance and carefully mixed with appropriate amounts of distilled water by a licensed local pharmacist to the concentrations specified by the Investigator for Groups A and B respectively. A sample of each batch prepared was assayed by the University of Virginia Laboratories (Charlottesville, VA) to verify that the specified nickel and bromide concentrations were present.

### 7.2 Packaging:

The study medication was packaged in brown pharmacy bottles with dropper tops and stored at the Investigator's clinic at room temperature.

### 7.3 Coding:

The drug solutions were labeled with the Investigator's name and address, the study subjects' names, instructions to use only as directed by physician, the contents and the study group designation (A or B), batch (B, B-1, B-2, etc.) and the date of preparation.

## 8. CRITERIA FOR SAFETY AND EFFICACY

### 8.1 Criteria For Safety:

The criteria for safety assessment were as follows:

- a) No major change in laboratory test results.
- b) Physical examination every 4 weeks.



### 8.2 Criteria for Efficacy:

The clinical investigator assessed the condition of each subject's psoriasis. **Objective measures** included a standardized PASI (Psoriasis Area and Severity Index) rating as well as measures of the severity of nail, scalp and genital psoriasis. The global PASI rating, which ranges from 0 to 72 in steps of 0.1, consists of a simple formula which measures the severity of erythema, infiltration, and desquamation of each body region and takes into account the relative contribution of the major body surface area regions in figuring the total score. Thus, a given PASI value may reflect either quite severe psoriasis symptoms in a localized region of the body or milder psoriasis covering more extensive regions. **Subjective evaluations** of various symptoms, such as itching, skin pain, and a global self-assessed overall change in disease severity from start of treatment were also documented at each visit.

## **9. STATISTICAL METHODOLOGY**

All calculations were performed on STATISTICA™, a software program designed to execute a variety of statistical manipulations.

### 9.1 Efficacy:

The mean difference in improvement in PASI score at Week 16 and Week 24 was compared to Week 0 data, and the t-test for dependent samples was used to account for differences in baseline, end of treatment, and end of follow-up values and evaluate statistical significance of efficacy. The mean difference in improvement in PASI values for the head only was also evaluated, using the same methodology.

Ordinal data was analyzed using the Wilcoxon Matched Pairs Test. Differences among subgroups such as age, gender, initial severity and previous effective therapy were evaluated using the t-test for independent samples.

Subjects who started concomitant psoriasis therapy and subjects with significant compliance problems were excluded from relevant analyses.

### 9.2 Laboratory Values:

Mean laboratory values at Week 0 were compared to values recorded at subsequent visits, and any trends were analyzed for statistically significant differences using the t-test for dependent samples.

9.3 Vital Signs: No statistical methodology was required or used.

9.4 Adverse Effects: No statistical methodology was required or used.

## **10. RESULTS**

### 10.1 Investigators and Sites:

The sole Investigator and site for this clinical study was as follows:

Steven A Smith, M.D.

3010 South Harvard, Suite 234

Tulsa, Oklahoma 74114-6114  
 The monitor for this clinical study was as follows:  
 Timothy R. Young, M.D.  
 4720 South Harvard, Suite 102  
 Tulsa, Oklahoma 74135

#### 10.2 Disease Classification:

The major disease classification treated in this study was non-infected glabrous skin plaque psoriasis vulgaris. Inverse psoriasis, nail psoriasis, pustular psoriasis and psoriatic arthritis were also treated.

#### 10.3 Protocol Deviations:

The deviations from the protocol are detailed in the following table:

Table 10.3 Protocol Deviations

<b>Subject</b>	<b>Deviation</b>	<b>Comments</b>
A-8	Off 14 days (Wk 7-8)	Poor compliance
A-10	Off 5 days (Wk 1)	Adverse rxn; resumed treatment
B-16	Off 8 days (Wk 16)	Poor compliance
B-19	Off 1 mo. (Wks 12-15)	Trip to Israel
B-21	Alcohol (Wks 12-16)	Excessive consumption
B-34	Drug abuse (Wks 12-16)	Cocaine, speed
B-40	Off 8 days (Wks 13-16)	Intermittently; poor compliance

#### 10.4 Subject Characteristics:

32 males and 21 females ranging from 16 to 77 years old (the mean age was 44.5 years) entered the study program. The mean PASI score at the Week 0 evaluation visit was 11.9, with a range of 0.1 to 32.4. All subjects received a nickel patch test, and two subjects tested positive with readings of 2 or greater. No statistically significant differences in population characteristics were found between dosing groups A and B.

#### 10.5 Duration of Treatment:

All subjects who completed the study completed 16 weeks of active drug administration and 8 weeks of continued follow-up visits.

#### 10.6 Concomitant Medication: See 5.4.

#### 10.7 Efficacy

Sixty-eight percent of the study subjects exhibited more than a 50% improvement in mean PASI score at Week 16. Defining 0 to 24% reduction in PASI rating as mild improvement, 25 to 74% as moderate improvement and 75 to 100% reduction as marked improvement, 52% of subjects exhibited moderate improvement and 36% exhibited marked improvement of their psoriatic skin condition. Two subjects (6%) showed no change in mean PASI score from Week 0 to Week 16, and 2 subjects exhibited a worsening of their condition over the 16 weeks of treatment. A graphical representation of selected efficacy data is presented in Exhibit A.



Analysis of the mean change in PASI scores for both groups combined from Week 0 to Week 16 (N = 31) showed a statistically significant decrease ( $p < 0.0002$ ). This N excludes 13 subjects using concomitant psoriasis therapy, 8 subjects that discontinued treatment before Week 16, and 1 subject with nail disease only. If the subjects who discontinued the study early are included, and their last documented values are considered as Week 16 values, the mean improvement and the statistical significance are not materially affected. At the end of the Post-Supplement Period at Week 24, while the mean difference in PASI from Week 0 was less than at Week 16, it was still significant ( $p < 0.02$ ), demonstrating some remittive effect of the study medication. The mean percent improvement in PASI at 16 weeks of treatment was 56.6% (95% Confidence Interval: 44.8 to 68.4). The mean percent improvement in PASI for the head alone at Week 16 was 66.5% (95% Confidence Interval: 59.7 to 73.3), with  $p < 0.00002$  for all weeks through Week 24 (N=35). Subjects using concomitant scalp therapy were excluded from relevant analyses.

A global self-assessed efficacy rating by study subjects from 1 to 7 (1=Severely Worse and 7=Markedly Improved) showed a significant increase in improvement between subjective assessments at Week 4 and at Week 16 ( $p < 0.04$ ). The rating for intensity of itching continuously decreased during the Supplement Period, with a statistically significant reduction in itching from baseline to Week 16 ( $p < 0.04$ ). Itching tended to increase after discontinuing the treatment medication (see Figure 7). Improvements from inception of treatment to Week 16 of other patient-assessed subjective measures were also statistically significant: scalp disease ( $p < 0.004$ ), nail disease ( $p < 0.03$ ), and genital disease ( $p < 0.05$ ). A maximum decline in symptom severity during the treatment period occurred at Week 16 followed by a relative increase during the Post-Supplement Period.

No statistically significant differences in response were found between dosing groups A and B for any variables. That may in part be due to the low number of Group A study subjects (11), resulting in limited diversity within the sample and thus weaker sensitivity in detecting any potentially significant effect of high or low bromide content in the study medication. No significant differences among groups classified by gender, age, level of serum nickel, initial severity of psoriasis or resistance to other therapies were found with respect to response rate of psoriasis as determined by PASI scores.

#### 10.8 Safety

a) Adverse Reactions: Relatively few adverse reactions were reported, none of which were major and only one which required cessation of dosing. There were no significant differences between groups A and B. A compilation of the potential adverse reactions detailed and reported at each visit is as follows, with N being the number of subjects reporting the event:

Table 10.8a Adverse Reactions (Patch Test results and related rashes are recorded separately)

Reaction	N	Comments
insomnia	3	All cases had previous history of insomnia
diarrhea	3	Mild; not watery
stomach ache	2	Mild
constipation	2	Mild
nausea	2	During 1-hour fasting after medication admin.
itching	2	First few days of therapy only
sore throat/fever	1	Erythromycin 250 qid x 7 days
abdominal pain	1	Mild
menstrual spotting	1	
bronchitis	1	Zithromax x 6 days
foot cramps	1	
papules on trunk	1	Non-psoriatic; typical folliculitis
left knee, ankles swollen	1	Possible bursitis

No subjects were hospitalized.

**b) Patch Test Results:** Of the 53 subjects that entered the study, all were nickel patch tested and only two women (10% of 21 women on the study) exhibited a patch test reading of 2+ or greater (based on a 0 to 3+ scale). The mean age of the patch-positive subjects was 30. Of the 32 men, none tested positive. One adverse skin reaction occurred. This was close to the initiation of treatment medication. This resolved and no subjects terminated the study for this reason. A summary of the subjects who tested positive can be seen in Table 10.8.b.

Table 10.8b Patch-test Positive Summary

ID	Patch Reading	Age	Sex	Skin Allergy History	Skin Reaction During Treatment
B-44	3	27	F	jewelry dermatitis; hand eczema	none
A-10	3	33	F	jewelry dermatitis;	moderate rash; off med x5 days; titration back to dose level with no further problems

**c) Laboratory Results:** Routine laboratory abnormalities were selected for reporting below only if they varied significantly from any pre-existing baseline values. Subjects were tested for routine hematology, fasting serum chemistries and urinalysis every eight weeks. The following table indicates the tests showing an abnormal reading compared to baseline readings (all parameters refer to blood samples unless otherwise indicated).



Table 10.8c Exceptional Laboratory Results (N = number of subjects)

Result	N	Range	Reference	Comments
Triglycerides	8	166-756 mg/dL	10-150mg/dL	
Iron	7	23-49 µg/dL	50-150 µg/dL	Iron supplements recommended
Cholesterol	4	225-276 mg/dL	150-200 mg/dL	
Glucose	3	143-300 mg/dL	65-110 mg/dL	
SGOT	2	102-149 u/L	0-40 u/L	Excessive alcohol
SGPT	2	123-287 u/L	0-45 u/L	Excessive alcohol
Gamma GT	2	131-345 u/L	0-65 u/L	
Potassium	2	2.9-5.9 meq/L	3.5-5.0 meq/L	
Uric Acid	2	9.8-10.9 mg/dL	2.5-8.0 meq/L	
Hematocrit	1	37.9%	40-52 %	
Serum RBC	1	4.13 mil/cu dm	4.6-6.2 mil/cu mm	
BUN	1	27 mg/dL	6-20 mg/dL	
Alk. phosphat.	1	152 u/L	30-142 u/L	
Urinary protein	3	1+	negative	
Urinary blood	2	small-large	negative	
Urinary WBC	1	6-8 /hpf	0-5 /hpf	
Urinary RBC	1	5-6 /hpf	0-2 /hpf	

### 10.9 Laboratory Evaluations

Standard laboratory blood and urine analysis results showed a general decrease in mean serum uric acid concentration, a slight decrease in serum cholesterol and a slight increase in serum glucose during the treatment period, and constant iron concentration that rose after treatment medication was discontinued. None of these results were statistically significant. Phosphorus showed a significant increase from Week 0 in mean serum level at Week 8 ( $p < 0.000001$ ), Week 16 ( $p < 0.0001$ ) and Week 24 ( $p < 0.002$ ). The mean serum level of phosphorus at Week 0 was 3.4 ( $\pm 0.5$ ) mg/dL and 3.8 ( $\pm 0.7$ ) mg/dL at Week 8, 3.8 ( $\pm 0.6$ ) mg/dL at Week 16 and 3.8 ( $\pm 0.6$ ) mg/dL at Week 24.

**11. DEATHS:** No deaths occurred.

### 12. CONCLUSIONS:

#### 12.1 Efficacy:

Analysis of efficacy data reveals good consistency of the data showing favorable active treatment ratings for all indices evaluated. Levels of statistical significance vary for these parameters, but are significant to highly significant at the  $p < 0.05$  to  $p < 0.00002$  levels. This information supports and appears to validate the original study hypothesis that oral administration of nickel and bromide improves the psoriatic condition.

Data showing a statistically significant difference in efficacy for different bromide levels was inconclusive; the small sample size for Dose Group A limits the accuracy with which results can be analyzed. More investigation is necessary in



order to more precisely determine the role of excess bromide in psoriasis therapy efficacy.

The high degree of overall effectiveness documented in this study, when combined with an excellent safety profile documented in this and previous studies on oral nickel bromide administration in humans, suggests that this therapy is useful in treating the psoriatic skin, scalp and nail condition.

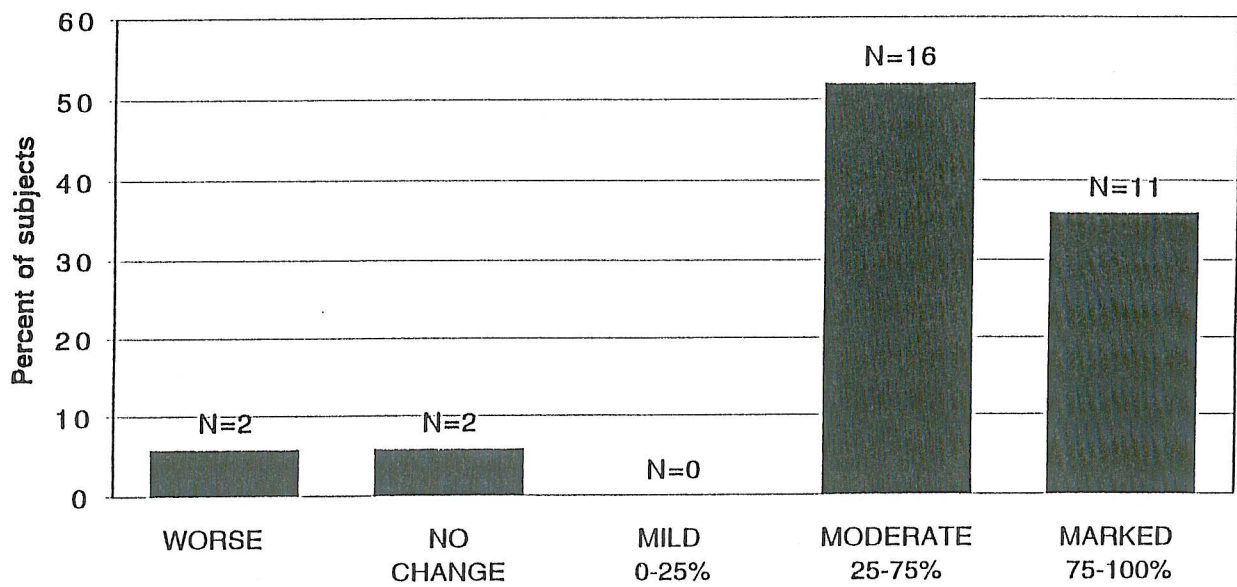
#### 12.2 Safety:

Both subjects testing positive for the nickel patch test had previous histories of jewelry dermatitis and/or hand eczema. One of them reported an initial skin rash and itching, and ceased dosing for 5 days before gradually titrating to the previous dose level. At the end of the study, the subject reported less nickel allergy than previous to entering the study. The other patch-positive subject experienced no adverse reaction. All reactions subsided within two weeks without incident.

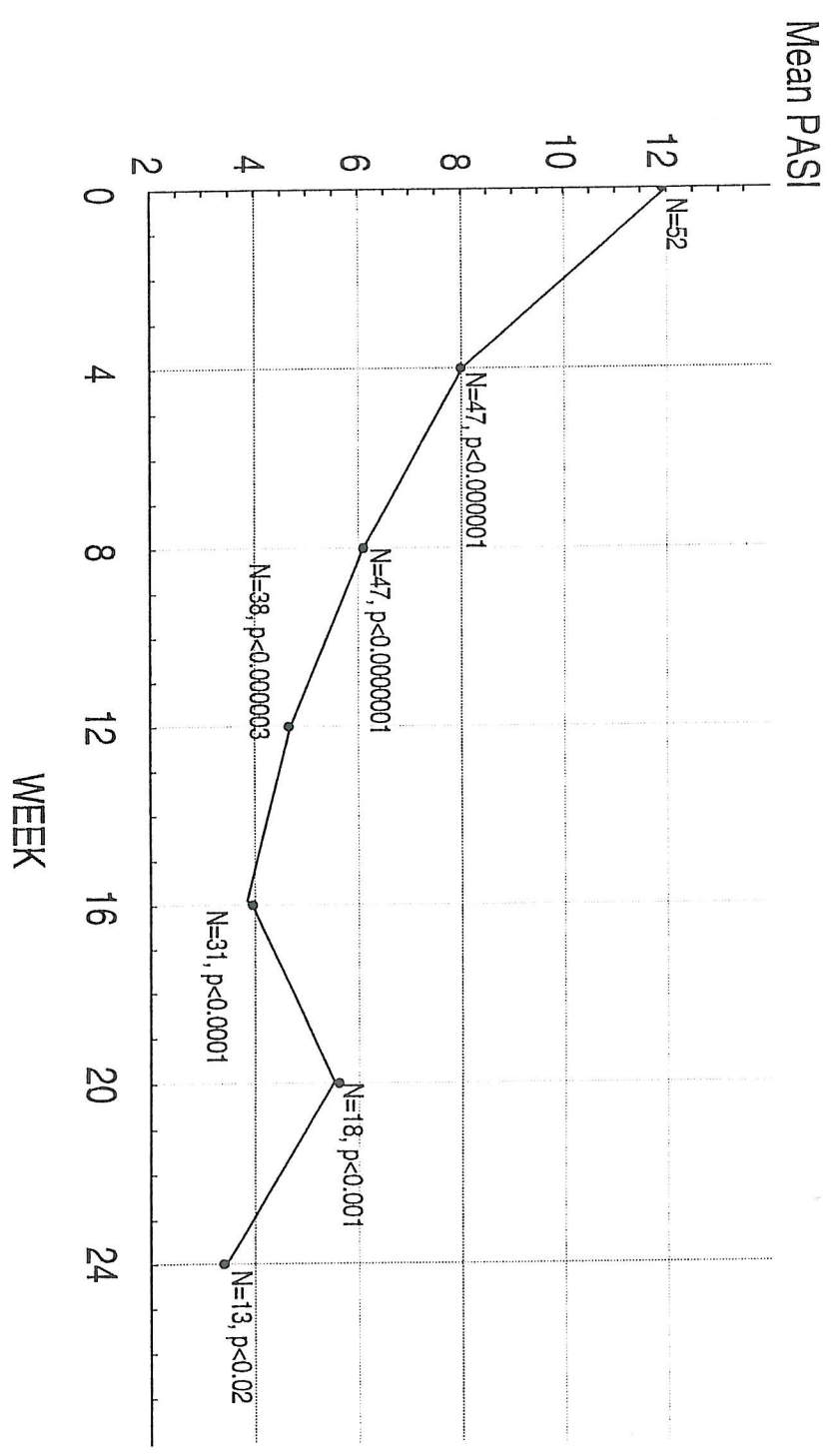
Two subjects reported minor nausea associated with the one-hour fasting period, and 5 subjects complained of various mild gastrointestinal problems (stomach ache, diarrhea, constipation). One subject experienced non-psoriatic erythematous papules on the trunk, with typical characteristics of folliculitis, which was not thought to be associated with the study medication. In addition, 3 subjects with a previous history of insomnia reported increased symptoms after beginning active treatment. All reactions were tolerable and, with one exception, resolved within 2-4 weeks of continued dosing. One subject experienced persistent insomnia until the end of dosing at 16 weeks. All subjects were able to continue with the study and none were lost due to known adverse reactions.

## EXHIBIT A

**FIGURE 1**  
**OVERALL IMPROVEMENT IN MEAN PASI SCORE**  
**AT WEEK 16 (N=31)**  
**Concomitant therapy excluded**



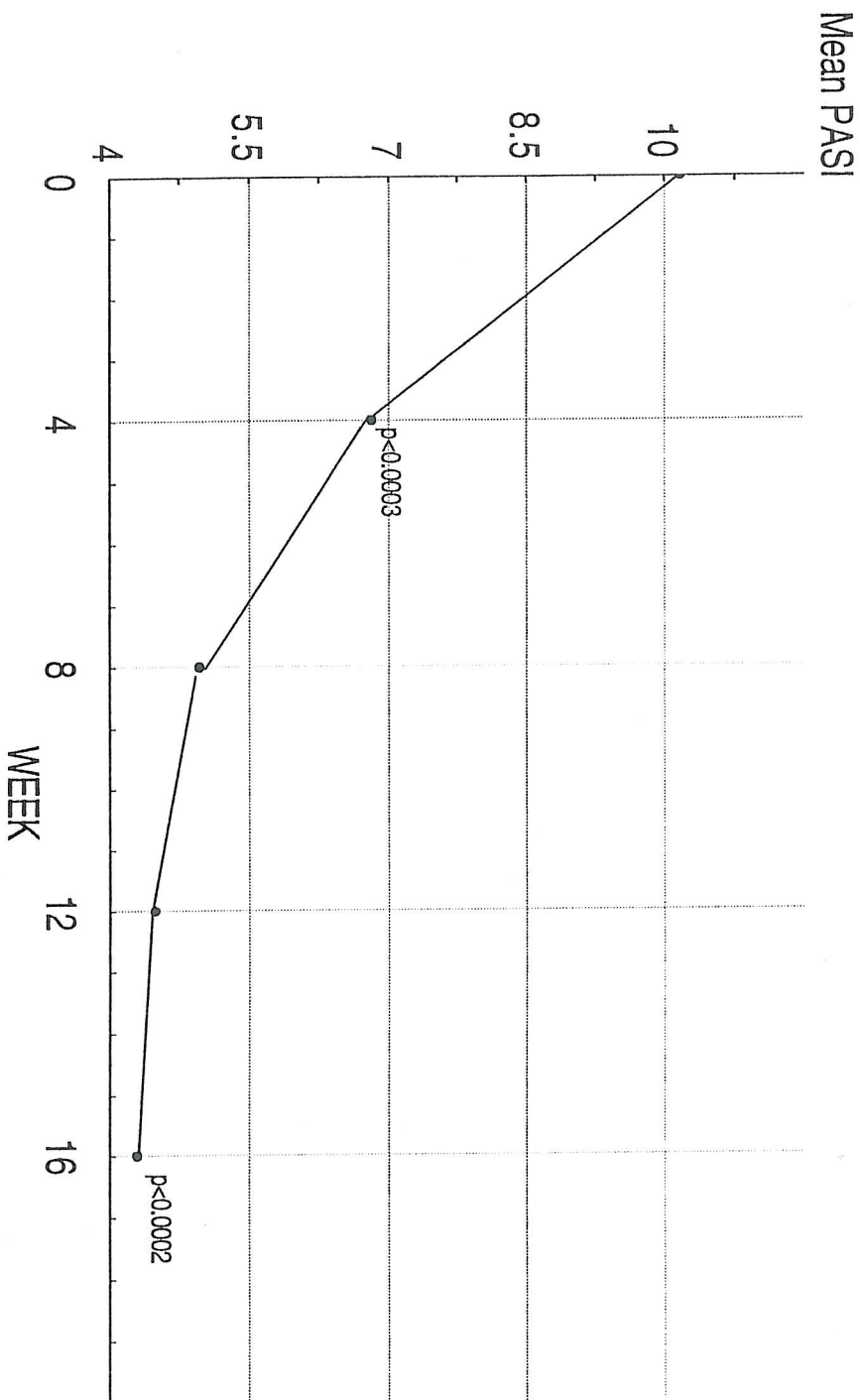
**Figure 2**  
**OVERALL MEAN PASI SCORES AT 4-WEEK INTERVALS**  
 Subjects excluded upon onset of concomitant therapy



\*Range of PASI: 0.0-72.0

Figure 3

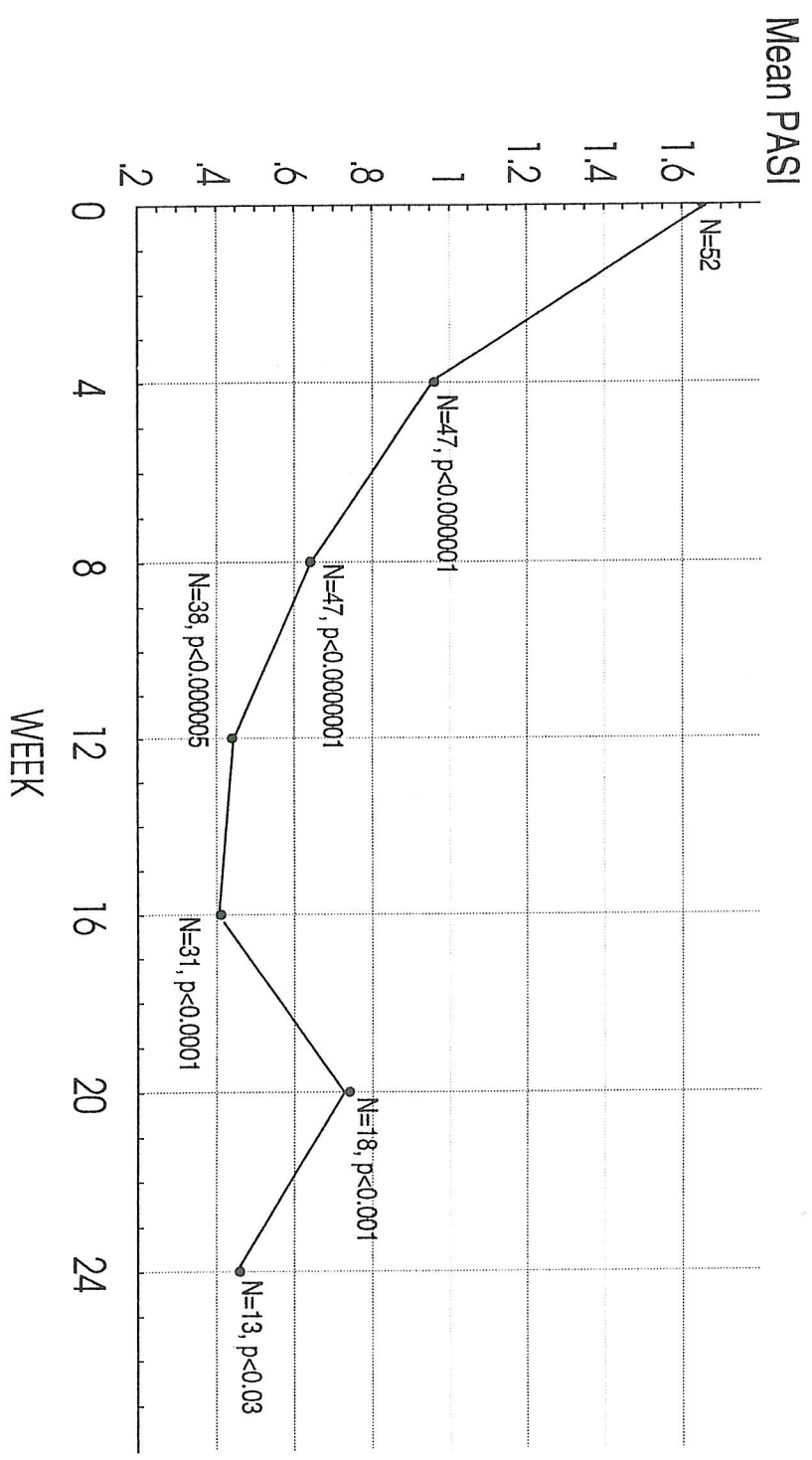
**OVERALL MEAN PASI SCORES AT 4-WEEK INTERVALS (N=39)**  
Concomitant therapies excluded; dropouts included



\*Range of PASI: 0.0-72.0

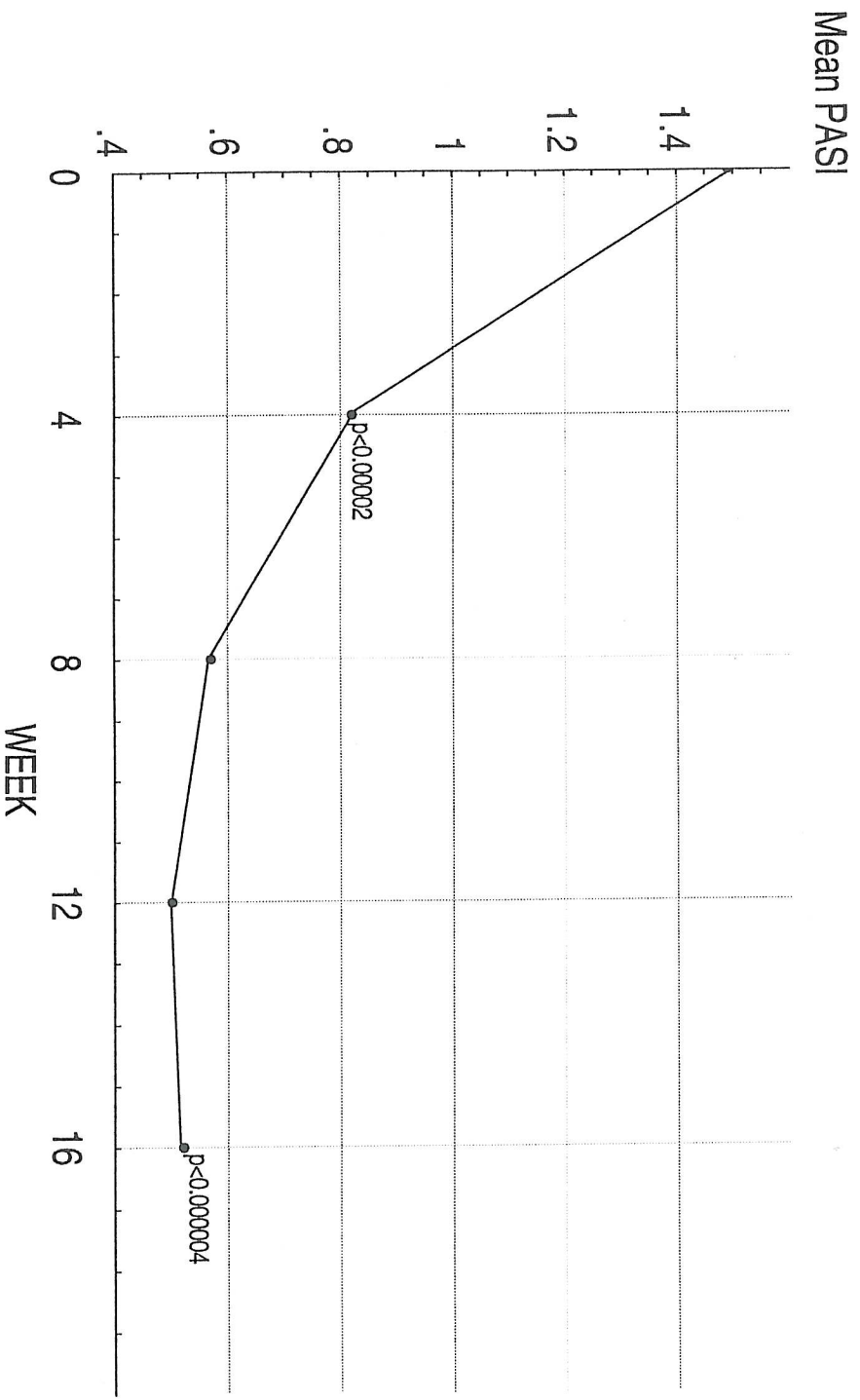


**Figure 4**  
**MEAN PASI SCORES OF HEAD ONLY AT 4-WEEK INTERVALS**  
 Subjects excluded upon onset of concomitant therapy



\*Range of PASI: 0.0-7.2

**Figure 5**  
**MEAN PASI SCORES OF HEAD ONLY AT 4-WEEK INTERVALS (N=39)**  
Concomitant therapies excluded; dropouts included

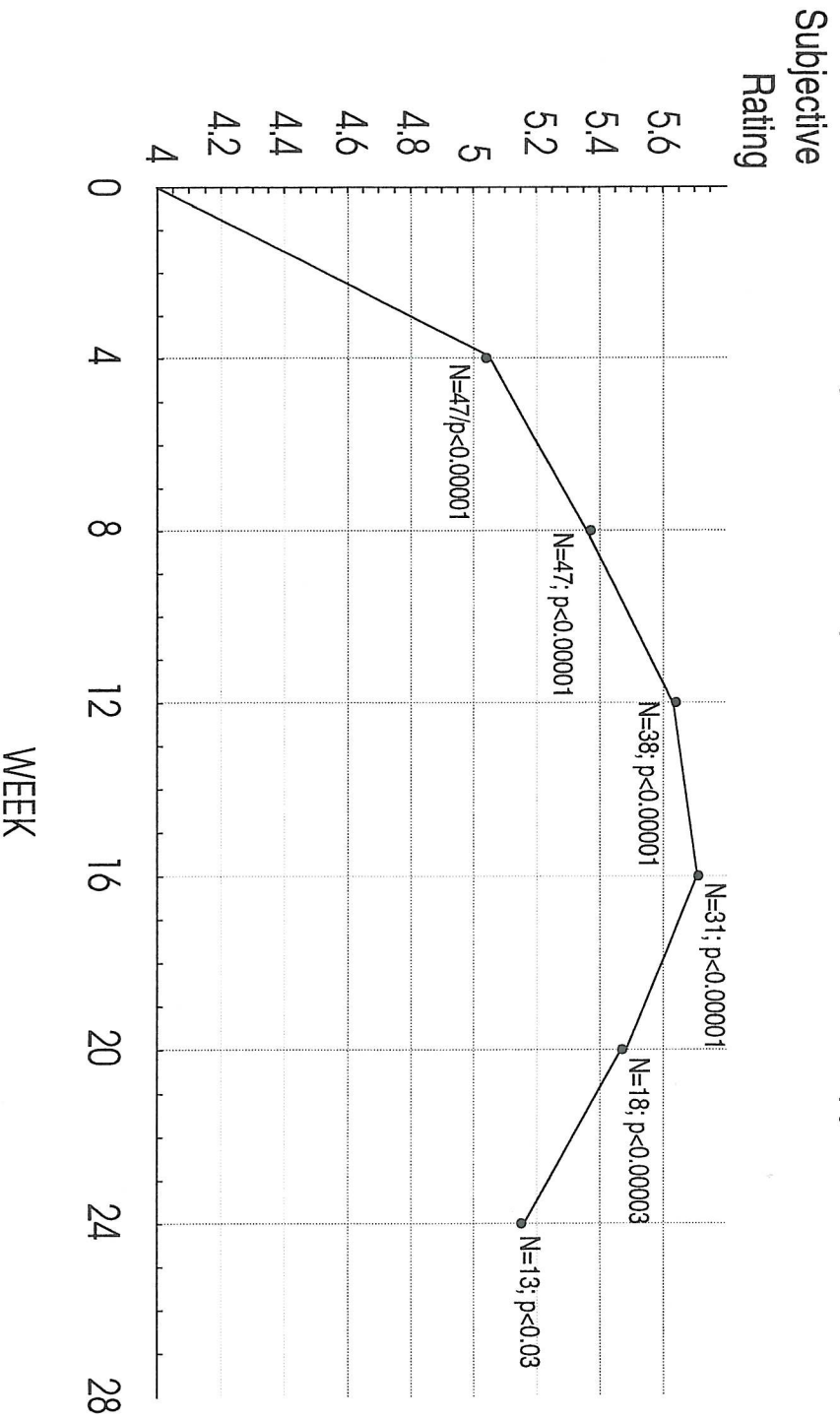


\*Range of PASI: 0.0-7.2

Figure 6

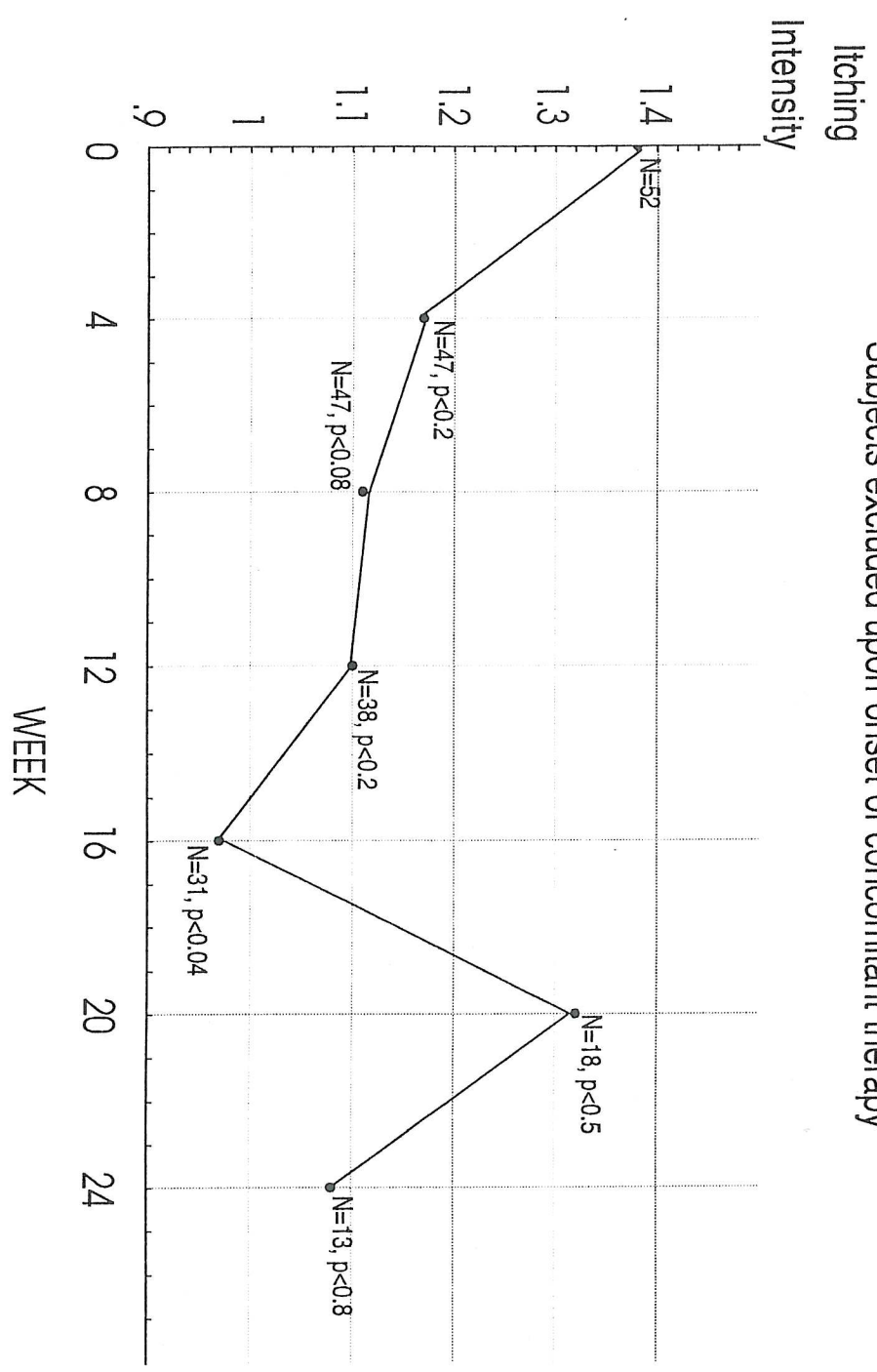
### SUBJECTIVE SELF-ASSESSMENT OF THERAPY EFFICACY

Subjects excluded upon onset of concomitant therapy



\*1=Severely worse, 4=No change, 7=Markedly improved

**Figure 7**  
**SUBJECTIVE RATING OF INTENSITY OF ITCHING**  
 Subjects excluded upon onset of concomitant therapy



\*itching Intensity Range: 0=None, 4=Very severe