

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-743

MEDICAL REVIEW(S)

**Medical Officer's Review of NDA 20-743
Amendments**

Submission dates: 6/13/97 & 7/1/97

Received dates: 6/16/97 & 7/8/97

Review completed: 7/16/97 and revised: 8/6/97

AUG 29 1997

Drug name: metronidazole 1% topical cream

Generic name: metronidazole

Proposed trade name: NORITATE®

Applicant: Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

Pharmacologic category: Antiprotozoal/antibacterial

Proposed Indication: Topical treatment of rosacea including inflammatory papules, pustules and erythema

Purpose of Submission: Response to Agency's request (6/13/97) and Labeling revision (7/1/97)

Background: The Applicant was requested to provide information for review of the clinical section in May, 1997. In June, 1997, the Agency FAXed to the Applicant a copy of the label with suggested changes. These two submissions address these communications.

Responses to the Agency's Request

1. A complete and legible copy of pp 13-195 and 13-196.

These two pages are cut off and poorly copied in the original submission. They show the local adverse events in Study 63/0001, a study for pharmacokinetics and irritancy potential of topical metronidazole. This resubmission has not given any clearer version and the copy is still cut off with information missing. The Sponsor states that this study was not done by them and this is the best available.

Although data from this study are only supportive because it was not done using the current formulation, the Applicant needs to continue to attempt to obtain legible copies and has stated that it will do that.

2. Some studies were done with an "old Canadian formulation". The Applicant was asked to clarify which studies were done with what formulation.

The question is for the formulations used in the clinical studies. In this response, it is clarified that foreign studies could be with the "current formulation" or the "old Canadian formulation". In support of this, the test article identity for the Canadian trials that form the basis for marketing in that country is presented. This can be compared with the current formulation for the U.S. studies as follows:

<u>Ingredient</u>	<u>Percent</u>	
	<u>"Current U.S."</u>	<u>"Current Canadian"</u>
✓ Metronidazole, USP, micronized		
✓ Stearic acid, NF		
✓ Glyceryl monostearate, NF (Myverol 18-07)		
✓ Glycerin, USP		
✓ Methylparaben, NF		
✓ Propylparaben, NF		
✓ Triethanolamine, NF		
✓ Purified water, USP		

The "old Canadian formulation" was used in two clinical pharmacology studies in the early 1980s. For 63/0001, the composition is not available. For 63/0003, the contents are given as follows:

<u>Ingredient</u>	<u>Per Cent</u>
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However, the Applicant also gives a qualitative composition for the "old Canadian" formulation as provided before at the pre-NDA meeting. This contains

Percentages of the contents are not available.

Studies performed with the different formulations are shown as follows:

<u>Current U.S.</u>	<u>Current Canadian</u>	<u>Old Canadian</u>	<u>No information</u>
DL6027-9510 (pivotal)	CMT 1286 (phase 3)	63/0003 (PK)	63/0001 (PK & dermal safety)
DL6027-9516 (pivotal)	CMT 1487 (phase 3)		
DL6027-9511 (dermal safety)			
DL6027-9517 (dermal safety)			
DL6027-9518 (dermal safety)			
DL6027-9520 (PK)			

Comment The current Canadian formulation may be identical to the current U.S. formulation used in the U.S. pivotal studies. It appears likely that the concentration of purified water in the current Canadian formulation is an error. The Applicant needs to clarify that. [In a submission dated 7/28/97, the Applicant admitted to have made

this error and the purified water in that formulation should have been [redacted].] The different versions of the "old Canadian" formulation were used in some phase 1 studies which are supportive. More definitive data have been obtained with the current formulation in the U.S. studies.

3. In the two pivotal studies, the efficacy populations excluded patients who were noncompliant. The Study Reports state that these were mostly due to antibiotics intake. However, most of the patients listed as "noncompliant" did not show up on the concomitant medication list with an antibiotic. Full details on the antibiotics intake in the noncompliant patients in the pivotal studies were requested.

The Applicant indicated that in the original submission, the concomitant medication listing had omitted uses that were continuing when the patients ended the study. A new listing was therefore submitted. In addition, specific information on the use of antibiotics in the following patients was provided:

DL6027-9510

DL6027-9516

Out of these patients, patients [redacted] in DL6027-9510 and [redacted] in DL6027-9516 did not use antibiotics. The protocol violation for patient [redacted] was for dropout due to worsening of rosacea even though the reason of stopping treatment was burning and itching. This should have been classified as an adverse event. For patient [redacted] protocol violation was for use of propranolol started during the study (beta-blockers not allowed).

Some patients used antibiotics and yet were included in the efficacy population. For 3 of these patients, the Applicant rationalized this by stating that all patients who completed 7 weeks of therapy and made the final visit were included in the efficacy population irrespective of antibiotic use after the seventh week. The patients who used antibiotics and included in efficacy analysis were:

DL6027-9510

(vehicle qd) - one dose of ciprofloxacin 500 mg on day 34

(vehicle qd) - amoxicillin 500 mg tid from day 59 to day 65

DL6027-9516

(metronidazole qd) - Augmentin 500 mg tid on days 55 through 65

(metronidazole qd) - amoxicillin 500 mg bid on days 52 through 61

(metronidazole qd) - Bactroban ung on excised basal cell carcinoma of the nose

(vehicle qd) - polysporin ung on a wound on the forehead resulting from nevi removal

Comment It is undesirable to include patients who used antibiotics, especially those who used them near the endpoint evaluation (week-10). However, since the primary endpoint data appear to be robust, it is unlikely that exclusion of these patients will have a significant impact. Nevertheless, analyses of these two studies should have been made by removing these patients who violated protocol [Dr. Shahla Farr of Biometrics is of the opinion that as the number of patients to be further excluded is small (2 vehicle subjects in DL6027-9510 and 3 metronidazole and 1 vehicle subjects in

DL6027-9516), reanalysis is not necessary].

4. In DL6027-9510, the adverse event "application site reaction" has not been defined. There are five cases. Details on what exactly occurred in each one were requested.

The Applicant defines "application site reaction" as any adverse event resulting from or in response to the application of the cream to the facial area, i.e. burning, stinging and itching. In this response, 6 cases were provided, one of which was not listed as "application site reaction" but as "burning" in the original submission. Details are as follows:

<u>Case</u>	<u>Event</u>	<u>Severity</u>	<u>Discontinuation</u>
218	burning after application	mild	no
338	burning after application	mild	no
062	burning after application	mild	no
095	burning after application	mild	no
080	burning/itching after application	severe	yes
213	burning/itching after application	mild	no

Comment Application site reaction is not the best description for adverse events. An actual description would be preferable.

5. Information for the following in both pivotal studies DL6027-9510 and DL6027-9516 was requested: the number of patients (1) who used any metronidazole treatment before entry and (2) who used topical metronidazole treatment before entry. Since the protocols excluded patients who were known non-responders to metronidazole, were patients asked about whether they had ever used metronidazole, not just for the washout period?

The data on previous metronidazole use in the last 2 years prior to entry (not including the washout period, in which patients were not to use metronidazole) are shown in the following Table. Patients were asked about use in the last 2 years, not whether they ever used metronidazole.

	<u>metronidazole qd</u>	<u>metronidazole bid</u>	<u>vehicle qd</u>	<u>vehicle bid</u>
<u>DL6027-9510</u> Metrogel use Oral met use	45/97=46% 0/97	38/98=39% 1/98= 1%	16/50=32% 0/50	23/48=48% 1/48= 2%
<u>DL6027-9516</u> Metrogel use Oral met use	56/104=54% 0/104		22/52=42% 0/52	

met=metronidazole

Comment Since these studies only enrolled responders to metronidazole, it would be important to know if there is a bias introduced in enrollment if there are more known responders in a particular arm of the study. In both studies, the data show that there is a 12% to 14% difference between the metronidazole qd and vehicle qd treatment groups in favor of the metronidazole qd arm. Interestingly, for the bid treatment

groups, the metronidazole bid arm enrolled 10% fewer known responders than the vehicle arm and the primary variables between these two groups did not show statistically significant differences. An analysis of the above data by Biometrics for significance in differences in enrollment is therefore needed. [Drs. S. Farr and R. Srinivasan have subsequently analyzed the enrollment in the two pivotal studies with respect to previous metronidazole use. There were no significant differences between treatment groups in previous metronidazole use.]

6. The Sponsor of the studies provided a specific sunscreen for use. Information on: a) name and directions for use of the sunscreen and b) a listing of all patients who used sunscreen was requested.

The Applicant states that no patient required use of sunscreen.

7. Baseline erythema score and overall rosacea severity score. The number of patients in each category (mild, moderate and severe) for each arm in each study for both (a) the efficacy and (b) the intent-to-treat analyses was requested.

The following Table shows the information in this response.

Baseline Erythema and Overall Rosacea Scores in Pivotal Studies DL6027-9510 and DL6027-9516

	metronidazole qd			metronidazole bid			vehicle qd			vehicle bid		
	Subjects with baseline score of			Subjects with baseline score of			Subjects with baseline score of			Subjects with baseline score of		
	2.0	2.5	3.0	2.0	2.5	3.0	2.0	2.5	3.0	2.0	2.5	3.0
DL6027-9510												
ITT: Erythema	56	32	9	59	28	9	33	14	3	29	16	2
	58%	33%	9%	61%	29%	9%	58%	28%	6%	62%	34%	4%
ORS	60	34	3	66	22	8	33	16	1	32	14	1
	62%	35%	3%	69%	23%	8%	58%	32%	2%	68%	30%	2%
Eff: Erythema	52	31	9	56	28	8	32	14	3	27	15	2
	57%	34%	10%	61%	30%	9%	58%	29%	6%	61%	34%	5%
ORS	56	33	3	65	21	6	32	16	1	29	14	1
	61%	36%	3%	71%	23%	7%	58%	33%	2%	66%	32%	2%
DL6027-9516												
ITT: Erythema	75	17	11				42	3	7			
	73%	17%	11%				58%	6%	13%			
ORS	83	16	3				41	6	5			
	81%	16%	3%				58%	12%	10%			
Eff: Erythema	66	13	10				40	3	7			
	74%	15%	11%				58%	6%	14%			
ORS	73	12	3				39	6	5			
	83%	14%	3%				58%	12%	10%			

ITT=Intent-to-treat population, Eff=Efficacy population, ORS=overall rosacea score.

Comment Most patients enrolled had moderate to severe disease activity at baseline as shown by erythema and overall rosacea scores. Only 2 to 10% of patients had "severe" disease as judged on the overall rosacea score system, and the majority had "moderate" disease. This is acceptable.

Labeling as Revised by the Applicant as of 7/1/97

3 pages (7-9)

Deleted

Comments

1. The Applicant does not want to list the conditions excluded in pivotal trials under the _____ section. Such exclusions may be listed under the clinical studies.
2. The Applicant wants to put _____ in the _____ section. As the data on pustules did not support efficacy, it would be misleading to use the word _____ in that section. Stating _____ would be adequate.
3. The Applicant wishes to use percentages in the ADVERSE REACTIONS section. This would have been acceptable if the percentages gave meaningful information. However, many of the percentages are given as <1%. Giving absolute numbers in combination with the total patient numbers in the studies would be more informative.
4. One of the patients who discontinued treatment due to adverse events did so because of rosacea aggravated. The Applicant substituted this patient in the label with another who did not use metronidazole qd. This should be corrected.

Conclusions

1. Most of the responses by the Applicant appear to be acceptable.
2. One of the deficiencies previously recognized but not conveyed to the Applicant was:

This issue has been addressed by Dr. S. Farr in Biometrics, who found that the primary efficacy data for that study did reveal superiority of metronidazole qd over vehicle bid.

3. The only current outstanding clinical issue is on labeling. The label should be revised to accommodate the changes as given above (page 6 to the top of current page).

Information to be Conveyed to the Applicant by CSO

Changes to be made to the label as shown above (page 6 to the top of current page).

Recommendations

1. The Applicant should further revise the label as shown (see above under section "Labeling as Revised by the Applicant as of 7/1/97", pp 6-10).
2. This application may be approved when the Applicant has addressed the outstanding issues from all disciplines.

H. S. Ko 8-6-97

Hon-Sum Ko, M.D.

cc: NDA 20-743
HFD-540
HFD-340
HFD-540/CSO/Cintron
HFD-540/CHEM/Higgins
HFD-540/PHARM/Alam
HFD-520/BIOPHARM/Kumi
HFD-715/BIOMETRICS/Farr
HFD-540/MO/Ko

I agree with the review preceding labeling.
This ^{labeling} is superseded by later revisions
of labeling on which I have
concurred. JW 8/29/97

Medical Officer's Review of NDA 20-743

1. General Information

NDA #20-743

Original

Submission date: September 30, 1996

Received date: October 2, 1996

Assigned date: October 7, 1996

Review completed: June 9, 1997

Review revised: July 7, 1997

JUL 8 1997

Drug name: metronidazole 1% topical cream

Generic name: metronidazole

Proposed trade name: NORITATE® Cream

Chemical name : 2-methyl-5-nitroimidazole-1-ethanol

Applicant: Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

Pharmacologic category: Antiprotozoal/antibacterial

Proposed Indication: topical treatment of rosacea including inflammatory papules, pustules and erythema

Dosage Form(s) and Route(s) of Administration: topical cream

NDA Drug Classification: 3 S

Related NDAs:

NDA 19-737 MetroGel® (metronidazole 0.75% gel) for the treatment of inflammatory papules and pustules of rosacea

NDA 20-531 MetroCream® (metronidazole 0.75% cream) for the treatment of inflammatory papules and pustules of rosacea

Studies done by the Applicant for this NDA were conducted under IND

Related Reviews: **Statistical Review dated:** 2/19/97
Biopharm Review dated: 5/5/97

Table of Contents

1	Title and General Information	1
2	Table of Contents	2
3	Material Reviewed	3
4	Chemistry/Manufacturing Controls	3
5	Animal Pharmacology/Toxicology	3
6	Clinical Background	3
7	Description of Clinical Data Sources	5
8	Clinical Studies	9
8.1	Indication # 1 Rosacea	9
8.1.1	Trial#1: Study# <u>DL6027-9510</u> Double-blind, multicenter study to evaluate the efficacy and safety of metronidazole cream 1% applied once daily vs. vehicle applied once daily vs. metronidazole cream 1% applied twice daily vs. vehicle applied twice daily in the treatment of rosacea	9
8.1.2	Trial#2: Study# <u>DL6027-9516</u> Double-blind, multicenter study to evaluate the efficacy and safety of a once daily application of metronidazole cream 1% vs. vehicle in the treatment of rosacea	19
8.1.3	Trial#3: Study# <u>CMT 1286</u> Comparison of metronidazole 1% cream versus placebo in the treatment of rosacea	26
8.1.4	Trial#4: Study# <u>CMT 1487</u> Comparison of metronidazole 1% cream versus oral tetracycline in rosacea	29
9	Overview of Efficacy	33
10	Overview of Safety	41
11	Labeling Review	53
12	Conclusions	58
13	Recommendations	58
Appendix 1	All/treatment-related Adverse Events in DL6027-9510	
Appendix 2	All/treatment-related Adverse Events in DL6027-9516	
Appendix 3	All/treatment-related Adverse Events in Phase 3 Trials with Metronidazole 1% Cream (Including DL6027-9510, DL6027-9516, CMT 1286 & CMT 1487)	

3 Material Reviewed

This review is based on material submitted by the Applicant in volumes 1.13 through 1.25 of NDA 20-743. In addition, the Applicant submitted requested material as follows:

Data listings for dermal safety studies and pivotal U.S. trials	12/2/96
Data listings for pivotal U.S. trials	12/13/96
Reanalysis of adverse event data with pooling of phase 3 U.S. and Canadian trials	2/5/97
Worldwide adverse event data	4/9/97

In the 120-day Safety Update dated 2/14/97, the Applicant states that there is no new information with human use of NORITATE® cream.

4 Chemistry/Manufacturing Controls see review by Chemist.
NORITATE® (metronidazole 1% cream) has the following formulation:

<u>Ingredient</u>	<u>Percent</u>
✓ Metronidazole, USP, micronized	1.00
✓ Stearic acid, NF	
✓ Glyceryl monostearate, NF (Myverol 18-07)	
✓ Glycerin, USP	
✓ Methylparaben, NF	
✓ Propylparaben, NF	
✓ Triethanolamine, NF	
✓ Purified water, USP	

Comment The phase 3 clinical trials done in the U.S. used this formulation, which is being proposed for marketing. In addition, there was an "old Canadian formulation" whose composition has not been described. It is not clear whether the two phase 3 studies done in Canada used the current or the "old Canadian" formulation.

5 Animal Pharmacology/Toxicology

The Pharm/Tox Reviewer, Dr. S. Alam has recommended that this application be approvable. Although no new studies have been performed with the proposed 1% cream formulation, the existing published and unpublished database for the safety evaluation of metronidazole appears to be satisfactory. However, the issue of possible enhanced photocarcinogenicity would need to be addressed in labeling. In addition, the PREGNANCY subsection of the label would need to be expanded to include data present in the label for Flagyl® 375 capsules.

6 Clinical Background

6.1 Relevant Human Experience

Metronidazole is an antibacterial/antiprotozoal agent approved since 1963 in oral dosage form for the treatment of trichomoniasis and amebiasis. It has since become available in an intravenous form for serious anaerobic bacterial infections, such as infected decubitus or diabetic ulcers. A vaginal cream at 10% concentration has been available in Canada since 1970 and a gel preparation at 0.75% was approved in the U.S. in 1992 for the treatment of bacterial vaginitis. Topical formulations including a

0.75% gel and a 0.75% cream have been approved in 1988 and 1995 respectively for the treatment of rosacea. The current indication of these two drug products is for topical application in the treatment of inflammatory papules and pustules of rosacea. NORITATE® (Metronidazole 1% cream) has been available in Canada for the treatment of rosacea with a bid dosing regimen.

Rosacea is a syndrome characterized in its most severe form by flushing, erythema, telangiectasia, facial edema, papules, pustules, ocular lesions and rhinophyma. It may be considered as a cutaneous vascular disorder which, in combination with multiple provocation factors, leads to a low-grade, sterile dermal cellulitis due to extravascular fluid accumulation. Treatment has been with oral antibiotics including tetracycline and clindamycin. Topical metronidazole 0.75% gel and 0.75% cream are now also available for the treatment of papules and pustules of rosacea (see above). More recently, Kligman *et al* have published data on the successful use of topical tretinoin or low dose oral isotretinoin in treating papules, pustules and erythema in rosacea (*Arch Dermatol* 130: 319, 1994).

6.2 Important Information from related INDs and NDAs

Studies performed by the Applicant on metronidazole 1% cream in the treatment of rosacea were conducted under IND Topical metronidazole has been approved under NDA 19-737 for METROGEL® 0.75% and, as a line extension, under NDA 20-531 for METROCREAM® 0.75% for the twice-daily treatment of rosacea (Galderma Laboratories, Inc.).

6.3 Foreign Experience

Metronidazole 1% cream has been approved for marketing in Canada and in the U.K. since 1995 and 1996 respectively. At the time of filing for this original NDA, NORITATE® has not been withdrawn from the market in any country.

6.4 Human Pharmacology, Pharmacokinetics and Pharmacodynamics

Human pharmacology and pharmacodynamics data have been submitted in the Clinical Section of this NDA and will be the subject of this review. Human PK data for NORITATE® were submitted in Item 6 (Human Pharmacokinetics and Bioavailability Section) of this NDA and reviewed by Biopharm. Dr. K.A. Kumi, the Biopharm Reviewer, has concluded that after topical application of NORITATE® cream, the plasma or serum levels of metronidazole are very low, about 1% of that reported after a single 250 mg dose of oral metronidazole.

6.5 Other Relevant Background Information

The development program of NORITATE® started in May, 1995 with filing of IND for the first phase 3 trial of metronidazole 1% cream in the treatment of rosacea. A second phase 3 trial was started in the last quarter of 1995. The Applicant and the Agency held a pre-NDA meeting in April, 1996 upon completion of phase 3 studies. The

Agency recommended that dermal safety studies and a PK study to clarify percutaneous absorption of metronidazole from the current formulation be performed prior to submission of an NDA. These studies were subsequently performed and NDA 20-743 submitted on September 30, 1996.

6.6 Directions for Use

Clinical Studies Included in Analysis for NDA 20-743

Study No. Investigators, Publications	Duration of drug Tx	Study Design	MET Formulation	Tx dose(s)	Control Tx	No. entered	Age range (yrs) (Mean)	M/F
CLINICAL PHARMACOLOGY (PHARMACOKINETICS)								
DL-6027-9620 Laurent Hunt	single dose	Open label, absorption and PK	Dermik's 1% cream	1g	none	16	≥18	8/8
#63/0003 Darragh Branagan Hallinan Claffey Lambe Kenny	12 hr (cream left in place, uncovered for 12 hrs after applic.)	Open study of percutaneous absorption using ¹⁴ C tagged material	2% cream	Single applic. of 100 mg	none	16	20-45	16/0
Nielsen Gamborg <i>Br J Dermatol</i> 1983a; 108: 327-332	1 mo	D-B, randomized, placebo- controlled; MET blood levels were determined after 1 mo (n=40) of a 2-month clinical study	1% cream	QD 3.75 mg	Placebo	81	26-87 (47)	32/49
Aronson Rumsfield West Alexander Fischer Paloucek <i>Drug Intell Clin Pharm</i> 1987;21:346-351	single dose	Crossover, randomized, bioavailability (Note: These investigators also conducted a D-B clinical study, which is reported in the same publication)	0.75% gel	1 g gel (= 7.5 mg MET)	MET oral sol.	10	25-74 (50.5)	5/5
ICP#63/0001 Darragh Branagan Elegant Lambe Kenny	44 days	Randomized, third-party blinded, intraindividual, study of acute and cumulative irritation potential and photosensitivity. Plasma MET blood levels were evaluated after 44 days.	0.5%, 1%, 2% cream	0.2 g of each was applied daily to intact skin; 0.2 g of 2% cream applied daily to stripped skin	Placebo cream	24	≥18	7/17
CLINICAL DERMAL SAFETY								
DL-6027-9611 Berger Mills	3 wks + 48 hrs	Jordan-King modification of Draize procedure	Dermik's 1% cream	0.2 mL repetitive	cream vehicle	258	≥18	68/190
DL-6027-9617 Kaidbey	24 hrs	Phototoxicity Bioassay	Dermik's 1% cream	80mg	cream vehicle	21	18-29	11/10
DL-6027-9618 Kaidbey	3 wks: six 24-hr exposures	Photocontact allergy assay	Dermik's 1% cream	80mg	none	29	18-23	14/15

Clinical Studies Included in Analysis for NDA 20-743 (Cont'd)

Study No., Investigators, Publications	Duration of drug Tx	Study Design	MET Formulation	Tx dose(s)	Control Tx	No. entered	Age range (yrs) (Mean)	M/F
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PHASE 3 CONTROLLED U.S. CLINICAL TRIALS WITH DERMIK'S METRONIDAZOLE 1% CREAM

DL-6027-9510 Eisen Jacobson Jorizzo Kang Katz Lebwohl Medansky Monroe Pariser Savin Weiss Stough Asarch	10 wks	D-B, parallel, randomized, placebo (vehicle) controlled, evaluator regimen-blind	Dermik's 1% cream	QD BID	cream vehicle	293	19-83 (50)	103/190
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DL-6027-9516 Breneman Hevia Hino Stewart Stiller	10 wks	D-B, parallel, randomized, placebo (vehicle) controlled	Dermik's 1% cream	QD	cream vehicle	156	25-82 (48)	50/106
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PHASE 3 CONTROLLED CANADIAN CLINICAL TRIALS WITH DERMIK'S METRONIDAZOLE 1% CREAM

CMT 1286 Bitar Dore Dubuc Giroux Landry Roy Panzini* Mathieu-Serra	2 mo	D-B, parallel, randomized, placebo controlled, fixed dose	1% cream	0.25cm ² BID	placebo cream	100	26-73 (51)	41/59
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CMT 1487 Schachter Schachter Long Schiffman Lester Miller Bargman Haber Taradash	2 mo	D-B, parallel, randomized, double- dummy, fixed dose	1% cream	≈ 0.25 cm ² BID	250mg tetra- cycline capsule tid	101**	22-81 (45)	40/61
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*Dr. Panzini recruited six patients. None of the six patients signed consent and patients were listed as dropouts and none of their data were included in the analysis.

**Data available only for 101 patients in efficacy population, 125 patients enrolled

Clinical Studies Included in Analysis for NDA 20-743 (Cont'd)

Study No. Investigators, Publications	Duration of drug Tx	Study Design	MET Formulation	Tx dose(s)	Control Tx	No. entered	Age range (yrs) (Mean)	M/F
SUPPORTIVE STUDIES								
Nielsen <i>Br J Dermatol</i> 1983a;108:327-332	2 mo		1% cream	3.75 mg QD	placebo	81	26-87 (47)	32/49
Nielsen <i>Br J Dermatol</i> 1983b;109:63-65	2 mo	D-B, randomized	1% cream	QD	oxytetra- cycline, PO	51	(44)	17/34
Nielsen <i>Br J Dermatol</i> 1983c;109:122	-	6-month follow- up	1% cream	QD	none	33	(48)	14/19
Veien VK <i>et al</i> <i>Cutis</i> 1986;38: 209-210	2 mo	D-B, randomized	1% cream	-	tetra- cycline, PO	76	22-90 (52)	36/39
Bjerke JR <i>et al</i> <i>Clin Trial J</i> 1989;26:187-194	8 wks	D-B, multicenter	1% cream	BID	placebo cream	101 (97 eval)	18-77 (47)	44/53
Eriksson G, Nord CE <i>Infection</i> 1987; 15:8-10	1 mo	Open	1% cream	BID	none	20	(51)	6/14
Aronson IK <i>et al</i> <i>Drug Intell Clin</i> <i>Pharm</i> 1987;21: 346-351	9 wks	Randomized, D-B, split face	0.75% gel	BID	placebo gel	60	25-74 (51)	29/31
Aikén G <i>Presse Med</i> 1983; 12: 1490-1491	3 mo	D-B, active control	5% cream	BID	chlortetra- cycline, PO	85	-	-
Dupont C <i>Br J Dermatol</i> 1984; 111: 499-502	3 mo	Open	5% topical suspension	QD	none	15	-	4/11
Bleicher PA <i>et al</i> <i>Arch Dermatol</i> 1987;123: 609-614	9 wks	D-B, split face, paired comparison	0.75% gel	BID	placebo gel	40	30-70 (49)	16/24
Lowe NJ <i>et al</i> <i>Cutis</i> 1989;43: 283-286	8 wks	-	0.75% gel	BID	none	19	33-79 (51)	8/11
Pye RJ, Burton JH <i>Lancet</i> 1976;1: 1211-1212	6 wks	D-B	oral	200 mg PO+1% hc*cream BID	placebo PO+1% hc* cream BID	29	24-86	-
Kurkcuoğlu N Atakan N <i>Arch Dermatol</i> 1984;120:837	3 wks	Open, BID	oral	250mg BID	none	10	-	0/10
Saihan EM, Burton JL <i>Br J Dermatol</i> 1980;102:443-445	12 wks	Randomized, D-B	oral	200mg BID	oxytetra- cycline, PO	40	-	-
Nasir MA <i>JPMA</i> 1985;35 148-149	8 wks	Open	oral	200mg BID	tetra cycline, PO	19	25-40	8/11
Guilhou JJ <i>et al</i> <i>Ann Dermatol</i> <i>Venerol</i> 1979; 106:127-129	2-6 mo (mean 2-3)	Open	oral	500mg/d 1st mo; 250 mg/d 2nd mo & after	none	62	21-78	26/36

*hc=hydrocortisone.

8 Clinical Data

8.1 Indication#1 Treatment of Rosacea

8.1.1 Trial#1: Study#DL6027-9510 Double-blind, multicenter study to evaluate the efficacy and safety of metronidazole cream 1% applied once daily vs. vehicle applied once daily vs. metronidazole cream 1% applied twice daily vs. vehicle applied twice daily in the treatment of rosacea

8.1.1.1 Objective/Rationale The objectives were (1) to compare the efficacy and safety of metronidazole cream 1% and vehicle when administered qd or bid for 10 weeks in the treatment of moderate to severe rosacea, and (2) to compare the metronidazole 1% cream dosing regimens qd and bid.

8.1.1.2 Design Randomized, parallel-group, treatment double-blind, evaluator regimen-blind, placebo-controlled, multicenter study. Study procedures are as shown below:

	<u>Baseline</u>	<u>Wk 2</u>	<u>Wk 4</u>	<u>Wk 7</u>	<u>Wk 10</u>
Baseline Procedures*	X				
Urine Pregnancy Test	X				X
Record Concomitant Medications	X	X	X	X	X
Check for Use of Prohibited Meds	X	X	X	X	X
Dispense Test Treatment	X	X	X	X	
Retrieve Test Treatment		X	X	X	X
<u>Evaluations</u>					
Number of Papules/Pustules	X	X	X	X	X
Severity Score of Sign/Symptom	X	X	X	X	X
Overall Rosacea Severity Score	X	X	X	X	X
Physician's Global Evaluation Score		X	X	X	X
Patient's Global Evaluation Score					X
Check for Adverse Events		X	X	X	X

*written informed consent, inclusion/exclusion criteria, medical and rosacea history, physical exam, baseline photography, record previous medications and confirmation of washout periods.

8.1.1.3 Protocol

8.1.1.3.1 Population/Procedures

Patient Selection

Either sex, ≥ 18 years of age, in good general health and free from conditions that might affect or interfere with the study, having stage II rosacea according to the Plewig and Kligman classification system (persistent erythema, numerous telangiectases, papules and pustules), and with the following disease activity:

- (1) a total of 8 to 50 combined papules/pustules on the face,
- (2) baseline severity of erythema ≥ 2 (moderate) on the 0 to 3 scale.
- (3) baseline overall rosacea severity score ≥ 2 (moderate) on the 0 to 3 scale.

Females had to be post-menopausal for ≥ 1 year, or have a hysterectomy or tubal ligation, or be abstinent, or have been using oral/systemic contraceptives, the double-

barrier method, an intrauterine device or Norplant® for ≥28 days prior to entry. Females of child-bearing potential had to have a negative pregnancy test at baseline.

• **Exclusion criteria were:**

- (1) Disease activity:
 - a) >2 nodules (defined as papule/pustule ≥ 5 mm), presence of moderate or severe rhinophyma, dense telangiectases, plaque-like facial edema, or
 - b) ocular involvement, such as conjunctivitis, episcleritis, iritis, and keratitis.
- (2) Treatment with topical antibiotics or topical anti-acne drugs within two weeks; or systemic antibiotics, systemic anti-acne drugs, topical retinoids and systemic, inhaled or topical corticosteroids on the face within four weeks; or oral retinoids within the past year prior to baseline. Patients who started hormonal therapy within 6 months of entry were also excluded. Such therapy started ≥6 months previously needed continuation throughout study period.
- (3) Known hypersensitivity to metronidazole (in any dose form) or any of the ingredients in the vehicle.
- (4) Anticoagulant, vasodilator or beta-blocker therapy, except low dose prophylactic aspirin.
- (5) Unwillingness to minimize external factors that might produce exacerbation, including, but not limited to, hot (temperature) and/or spicy foods, very hot beverages, hot environments, and/or alcoholic beverages.
- (6) Unwillingness to minimize recreational or occupational activities frequently exposing the subject to the sun.
- (7) Any condition that might interfere with evaluation, i.e. conditions with signs/symptoms similar to those of rosacea (including seborrheic dermatitis, acne vulgaris, corticoid-induced rosacea, carcinoid syndrome and mastocytosis).
- (8) Known non-responders to metronidazole in any dose form for rosacea.
- (9) Participated in a trial of an investigational drug within 30 days of entry.
- (10) Alcohol or drug abuse.
- (11) Pregnancy or lactation.

Concomitant Medications, Application of Study Medication, Visits and Evaluations

- The following restrictions applied during the study period:

A. Prohibited drugs and preparations: (1) any treatment for rosacea other than the test treatment, (2) antibiotics, anti-acne drugs, topical and oral retinoids, systemic corticosteroids, topical corticosteroids on the face, (3) alcoholic toners, astringents, medicated topical preparations (including medicated make-up), (4) abrasive cleansers or washes.

B. Patients were to avoid exposure to the sun. If sun exposure was unavoidable, then the patient was to be counseled by the investigator to use a sunscreen designated for this study.

C. Patients were not to wear make-up at the visits so as not to interfere with evaluations.

Comments

1. Limiting the study to patients with Stage II disease only would result in limitation on the indication sought.
2. It is probably not practical for the patients to avoid sun exposure for 10 weeks. Metronidazole is radiosensitizing but there is no clear evidence of photosensitization. The sunscreen to be used has not been identified in the study report. The extent of its use has not been further commented on either.
3. The protocol excluded patients who were known responders to metronidazole.

- **Application of test material:** Patients were randomly assigned with equal chance into one of the following three main treatment groups: metronidazole 1% cream qd, metronidazole cream 1% b.i.d., and vehicle. The vehicle group was subdivided into qd and b.i.d. groups in order to match the active treatment regimens. At the baseline visit, each patient was instructed on how to use the test treatment and provided a detailed instruction sheet. This task was performed by a person other than the one who performed or assisted in efficacy evaluations. Ten minutes prior to applying treatment,

the patient washed the face. Rinsing was to be thorough and drying done. The test treatment was applied in a thin film and massaged into the skin over the entire face (defined as the hairline superiorly, the mandibular angle inferiorly, and the tragus laterally) but avoiding the eyes.

• **Evaluations:**

A. Efficacy - At each visit, the current overall rosacea severity score and the global evaluation were made prior to other evaluations:

1. Number of papules and pustules – counted separately,
2. Sign/symptom scores – erythema, telangiectases, burning, dryness, scaling/peeling and pruritus: 0=none, 1=mild, 2=moderate, 3=severe [burning and pruritus were subjective symptoms estimated for the 3 days up to each visit],
3. Overall rosacea severity score – 0=none, 1=mild, 2=moderate, 3=severe,
4. Global by physician – determined by comparison with baseline photograph:

6=Cleared:	100% improvement
5=Excellent:	90-99% improvement
4=Very good:	75-89% improvement
3=Good:	50-74% improvement
2=Fair:	25-49% improvement
1=Slight:	1-24% improvement
0=No change:	No detectable improvement
-1=Slightly Worse:	1-24% deterioration
-2=Mildly Worse:	25-49% deterioration
-3=Moderately Worse:	50-74% deterioration
-4=Severely Worse:	≥75% deterioration
5. Patient's Global Evaluation Score – at the final visit: 3=much better, 2=better, 1=somewhat better, 0=no change, -1=somewhat worse, -2=worse and -3=much worse.

B. Safety - data on adverse events.

8.1.1.3.2 Subject Disposition and Endpoints

Patients were followed to endpoint unless dropped out due to: treatment failure, adverse event, noncompliance, lost to follow up or voluntary discontinuation. Endpoint was defined as visit at week-7 or week-10, whichever was later.

Primary Variables There were 3 primary variables at week 10 or endpoint:

- (1) percent change from baseline in the number of papules, pustules and their sum,
- (2) percent change from baseline in the current severity score for erythema, and
- (3) physician's global evaluation score.

Comment Although these primary variables are acceptable, the primary disorder in rosacea, which is vascular in nature, is not being addressed. Thus, this study is examining the effect of metronidazole on relief of certain symptoms (lesional reduction and erythema), and this may be considered as a form of palliation rather than definitive treatment of a disease. It is noted that relief from flushing, one of the most common and annoying symptoms, is not being explored.

Secondary Variables

All other efficacy data were treated as secondary variables.

8.1.1.3.3 Statistical Considerations

Power Calculation The sponsor assumed a 50% standard deviation for the percent change from baseline in erythema based on previous metronidazole studies for rosacea and desired to detect a difference of 30% between treatment groups for this parameter, using a 2-tailed t-test with 80% power at 0.05 level of significance. This would require 76 evaluable patients for metronidazole cream and 38 for vehicle for each regimen.

Populations Analyzed

Safety population included any subject who took at least one dose of study medication. Intent-to-treat patients took at least one dose of medication and had at least one postbaseline visit efficacy datum.

Efficacy subjects were to (1) have completed ≥ 7 weeks of study; (2) have gone through a "final" visit and (3) not be in the "non-compliance" or "lost to follow up" category.

Comment This study has incorporated an "endpoint" analysis which includes only those subjects who stayed up to or beyond week-7. It is not clear whether this was only used in the intent-to-treat analysis. In efficacy analysis, the week-10 and endpoint analysis results were identical, suggesting that all "endpoint" patients in this analysis had adhered protocol and been followed to week-10.

Analytic Methodology

Descriptive statistics was used for comparison between treatment groups and regimens for efficacy data and rates of dropout due to treatment failure. In addition, global scores were studied for frequency distributions. Safety data comparison was made using adverse event incidences.

8.1.1.4 Results

8.1.1.4.1 Patient Disposition/Comparability

Enrollment and Disposition Thirteen investigators enrolled 293 subjects:

Drore Eisen, M.D.	Dermatology Associates, 7961 Five Mile Rd, Suite 312, Cincinnati, OH 45230
Coleman Jacobson, M.D.	Dallas Associated Dermatologists, 3600 Gaston Ave, Suite 1051, Dallas, TX 75246
Joseph L. Jorizzo, M.D.	Dept of Dermatology, Bowman Gray Sch of Medicine, Medical Ctr Blvd, Winston-Salem, NC 27157
Sewon Kang, M.D.	Dept of Dermatology, Univ of Michigan Medical Center, 1618 Taubman Ctr, Ann Arbor, MI 48109
H. Irving Katz, M.D.	Minnesota Clinical Study Ctr, 7205 University Ave, N.E., Fridley, MN 55432
Mark G. Lebwohl, M.D.	Dept of Dermatology, Mount Sinai Medical Ctr, 5 East 98th Street, New York, NY 10029
Roland S. Medansky, M.D.	7447 West Talcott Rd, Chicago, IL 60631
Eugene W. Monroe, M.D.	Milwaukee Medical Clinic, S.C., 3003 West Good Hope Rd, Milwaukee, WI 53217
David M. Pariser, M.D.	Virginia Clinical Research, Inc., 601 Medical Tower, Norfolk, VA 23507
Ronald C. Savin, M.D.	Savin Dermatology Ctr, P.C., 134 Park St, New Haven, CT 06511
Jonathan S. Weiss, M.D.	Gwinnett Clinical Research Ctr, 2366 Lenora Church Rd, Snellville, GA 30278
Dow Stough, M.D.	The Stough Clinic, One Mercy Lane, Suite 304, Hot Springs, AR 71913
Richard G. Asarch, M.D.	Clinical Research Group of Colorado, 3601 South Clarkson, Suite 220, Englewood, CO 80110

Enrollment and Discontinuation Information*

<u>Center and Code</u>		<u>Met qd</u>	<u>Met bid</u>	<u>Vehicle qd</u>	<u>Vehicle bid</u>
Eisen	01	7 (-3)	7 (-2)	4 (-1)	3
Jacobson	02	9	8	4 (-1)	4
Jorizzo	03	8	8 (-1)	5	4 (-1)
Kang	04	8	8 (-1)	3 (-1)	4 (-2)
Katz	05	8	8 (-2)	4	4 (-1)
Lebwohl	06	10	10	5 (-1)	5
Medansky	07	8	8	4	4 (-1)
Monroe	08	10 (-1)	10(-1)	5	5 (-1)
Pariser	09	3	4	2	2 (-1)
Savin	10	8	8	4	4
Weiss	11	4	5 (-1)	3	3
Stough	12	10 (-1)	10	5	5
Asarch	13	4	4	2	1 (-1)
TOTAL		97 (-5)	98 (-8)	50 (-4)	48 (-8)

*Numbers in parentheses indicate discontinuations from study. Met=metronidazole 1%.

Reasons for Discontinuation

<u>Reason</u>	<u>Met* qd</u>	<u>Met bid</u>	<u>Vehicle qd</u>	<u>Vehicle bid</u>
Non-compliance	4	3	1	3
Treatment failure	1	2	0	2
Adverse event	0	2	1	2
Did not wish to continue	0	1	1	1
Lost to follow up	0	0	1	0
TOTAL	5	8	4	8

*Met=metronidazole 1%.

Over 90% of patients received ≥ 10 weeks of treatment with test material. Adverse events leading to discontinuation were: -

Metronidazole 1% bid: contact dermatitis of face ; burning
 Vehicle qd: burning
 Vehicle bid: contact dermatitis (site unspecified) ; redness, burning & rosacea exacerbation

Populations for Analysis

<u>Population</u>	<u>Met qd</u>	<u>Met bid</u>	<u>Vehicle qd</u>	<u>Vehicle bid</u>	<u>Total</u>
Safety	97	98	50	48	293
Intent-to-treat*	97	96	50	47	290
Efficacy**	92	92	49	44	277

*Intent-to-treat group excluded three patients without postbaseline data. Met=metronidazole 1%.

** Efficacy group exclusions were:	<u>Met qd</u>	<u>Met bid</u>	<u>Vehicle qd</u>	<u>Vehicle bid</u>	<u>Total</u>
Baseline violation (telangiectases score=3)	1	3	0	0	4
Protocol violation (prohibited drugs/non-compliance)	4	3	1	3	11
Lacking efficacy data	0	0	0	1	1

Comments

1. The Applicant states that because the intent-to-treat population had more patients than the efficacy population at certain time points and with certain variables, some differences showing statistical significance were observed in the intent-to-treat population but not in the efficacy population. Both analyses have been submitted. Only the efficacy population data will be discussed here. Results of the intent-to-treat analysis has also been reviewed. They closely resemble the efficacy analysis.

2. The Applicant also states that treatment-investigator interactions were sporadic and not seen at endpoint for the changes from baseline variables. Pooled data across centers will be discussed here.

Baseline Comparability

Baseline Data for Enrolled Patients

Characteristics	Met* qd	Met bid	Vehicle qd	Vehicle bid
	(N=97)	(N=98)	(N=50)	(N=48)
Mean age and range	49	51	49	50
Male: females	34: 63	44: 54	13: 37	12: 36
Race: White/Hispanic/Black	95/0/2	97/1/0	49/0/1	47/0/1
Mean duration of rosacea (months)	108	84	113	107
Mean rosacea severity score	2.2	2.2	2.2	2.2
Mean number of papules	17	17	15	14
Mean number of pustules	2	2	2	2
Mean erythema score	2.2	2.2	2.2	2.2

*Met=metronidazole 1%.

Comment Although none of these parameters show significant differences among the treatment groups, it is noted that the sex ratios in both vehicle groups are approximately 1:3 (male: female), lower than that in either active group.

8.1.1.4.2 Efficacy Parameters

Primary Variables at Endpoint

• Lesion Counts

	Met qd		Met bid		Vehicle qd		Vehicle bid		Paired Comparisons (p values)	
	N	Mean	N	Mean	N	Mean	N	Mean	Met qd vs Veh qd	Met bid vs Veh bid
Papules										
Baseline	92	17	92	17	49	15	44	15	0.127	0.354
Week-10*	82	7	79	7	41	11	38	9	0.117	0.216
% ↓	82	55	79	59	41	28	38	39	0.004	0.012
Pustules										
Baseline	92	2	92	2	49	2	44	2	0.593	0.144
Week-10	82	<1	79	<1	41	1	38	<1	0.202	0.458
% ↓	82	76	79	66	41	64	38	70	0.958	0.017
Papules+Pustules										
Baseline	92	19	92	19	49	17	44	17	0.133	0.715
Week-10	82	8	79	8	41	12	38	10	0.098	0.202
% ↓	82	58	79	58	41	30	38	40	<0.001	0.019

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole 1%, Veh=vehicle.

Comments

- At endpoint, no significant differences between the two metronidazole regimens (qd vs bid) were observed (data not shown), except for percent reduction in pustule counts (p=0.011).
- Percent reductions in papule counts and in papule+pustule counts showed highly significant differences between the qd regimens (metronidazole vs vehicle).
- Analysis of percent reductions of pustules did not show significance between the qd regimens (metronidazole vs vehicle). It would be misleading to have a claim that metronidazole 1% qd is superior to vehicle for reduction of papules plus pustules even though the combined lesion counts did show significance. This significance is primarily based on the data from papules, since the small number of pustules (1-2) would not be expected to have made much difference.

• Erythema

	Met qd		Met bid		Vehicle qd		Vehicle bid		Paired Comparisons (p values)	
	N	Mean	N	Mean	N	Mean	N	Mean	Met qd vs Veh qd	Met bid vs Veh bid
Erythema										
Baseline	92	2.3	92	2.2	49	2.2	44	2.2	0.280	0.940
Week-10*	82	1.4	79	1.4	40	1.8	38	1.6	0.006	0.377
% ↓	82	40	79	36	40	19	38	28	0.002	0.362

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Veh=vehicle. Score 0=none, 1=mild, 2=moderate, 3=severe.

Comments

1. Significant differences are noted between the qd regimens (metronidazole and vehicle) in mean scores for erythema reduction and mean percentage reduction in erythema at endpoint.
2. Metronidazole 1% bid and qd regimens did not show significant difference in erythema reduction (p=0.759). However, the bid regimen was not superior to vehicle because of substantial vehicle effect.

• Investigator's Global

	Met* qd		Met bid		Vehicle qd		Vehicle bid		Paired Comparisons (p values)	
	N	Mean	N	Mean	N	Mean	N	Mean	Met qd vs Veh qd	Met bid vs Veh bid
≥25% improvement	65/82	(79%)	57/79	(72%)	16/41	(39%)	17/38	(45%)	<0.01	0.01
≥50% improvement	42/82	(51%)	40/79	(51%)	8/41	(20%)	15/38	(39%)	<0.01	0.32
≥75% improvement	18/82	(22%)	27/79	(34%)	3/41	(7%)	10/38	(26%)	0.05	0.52

*Met=metronidazole, Veh=vehicle. Week-10 and Endpoint analyses gave identical results.

Comments

1. At endpoint, metronidazole 1% cream qd was superior to vehicle qd in the analysis of success rates using three different cutoffs (≥25%, ≥50% and ≥75% improvement) in the treatment for rosacea.
2. Between-group comparisons using "90% or greater improvement" or "cleared" have not been performed.

Secondary Variables All efficacy data other than the endpoint/week-10 results for (1) percent reduction in papules, pustules and their sum, (2) percent reduction in erythema and (3) global were treated as secondary variables.

1. Reductions in lesion counts during course of study

	Met qd		Met bid		Vehicle qd		Vehicle bid		Paired Comparisons (p values)	
	N	Mean	N	Mean	N	Mean	N	Mean	Met qd vs Veh qd	Met bid vs Veh bid
Papules										
Baseline	92	17	92	17	49	15	44	15	0.127	0.354
wk-2 % ↓	88	26	83	20	43	17	42	9	0.176	0.080
wk-4 % ↓	87	41	85	40	43	25	39	29	0.012	0.163
wk-7 % ↓	84	50	78	47	39	26	36	28	0.011	0.200
wk-10/EP* % ↓	82	55	79	59	41	28	38	39	0.004	0.012
Pustules										
Baseline	92	2	92	2	49	2	44	2	0.593	0.144
wk-2 % ↓	52	33	48	42	22	5	20	52	0.515	0.219
wk-4 % ↓	53	51	50	53	21	17	17	56	0.043	0.041
wk-7 % ↓	48	65	46	66	19	51	17	62	0.504	0.205
wk-10/EP* % ↓	51	76	46	66	19	64	17	70	0.958	0.017
Papules+Pustules										
Baseline	92	19	92	19	49	17	44	17	0.133	0.715
wk-2 % ↓	88	27	83	21	43	16	42	14	0.093	0.329
wk-4 % ↓	87	43	85	40	43	21	39	30	0.001	0.269
wk-7 % ↓	84	51	78	48	39	26	36	28	0.008	0.109
wk-10/EP* % ↓	82	58	79	58	41	30	38	40	<0.001	0.019

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Veh=vehicle. Reductions in nodules not shown (baseline <1 in each group and only ≤10 patients per arm had nodules)

2. Sign/symptom scores

	Met qd		Met bid		Vehicle qd		Vehicle bid		Paired Comparisons (p values)	
	N	Mean	N	Mean	N	Mean	N	Mean	Met qd vs Veh qd	Met bid vs Veh bid
Erythema										
Baseline	92	2.3	92	2.2	49	2.2	44	2.2	0.280	0.940
wk-2 % ↓	88	17	83	14	43	4	42	10	0.033	0.344
wk-4 % ↓	87	27	85	25	43	10	39	18	0.001	0.103
wk-7 % ↓	84	33	78	33	39	19	36	28	0.025	0.407
wk-10/EP* % ↓	82	40	79	36	40	19	38	28	0.002	0.362
Telangiectases										
Baseline	92	1.4	92	1.5	49	1.4	44	1.4	0.671	0.712
wk-2 % ↓	81	4	80	(<1)	40	1	38	<1	0.295	0.552
wk-4 % ↓	80	3	80	7	39	(3)	35	5	0.004	0.422
wk-7 % ↓	78	5	73	7	35	(<1)	33	5	0.002	0.807
wk-10/EP* % ↓	75	8	74	13	37	(5)	35	7	<0.001	0.874
Burning										
Baseline	92	0.4	92	0.5	49	0.4	44	0.4	0.959	0.707
wk-2 % ↓	32	67	28	54	11	68	15	51	0.738	0.104
wk-4 % ↓	32	81	29	80	12	56	14	82	0.102	0.644
wk-7 % ↓	29	91	25	84	10	90	13	87	0.940	0.633
wk-10/EP* % ↓	29	84	28	89	10	64	13	92	0.178	0.685
Dryness										
Baseline	92	0.7	92	0.6	49	0.7	44	0.7	0.637	0.532
wk-2 % ↓	43	60	41	51	22	17	24	56	0.025	0.988
wk-4 % ↓	43	75	41	67	22	37	22	59	0.033	0.483
wk-7 % ↓	40	75	40	57	18	51	21	46	0.164	0.535
wk-10/EP* % ↓	41	78	39	60	21	57	22	69	0.065	0.790
Scaling/Peeling										
Baseline	92	0.5	92	0.5	49	0.5	44	0.5	0.995	0.560
wk-2 % ↓	41	71	37	48	18	13	21	49	0.024	0.740
wk-4 % ↓	41	75	37	63	19	11	19	62	0.024	0.676
wk-7 % ↓	38	74	35	44	17	9	19	74	0.058	0.342
wk-10/EP* % ↓	39	84	36	45	18	36	19	76	0.009	0.631
Pruritus										
Baseline	92	0.5	92	0.6	49	0.6	44	0.4	0.865	1.000
wk-2 % ↓	37	69	36	56	15	56	16	41	0.410	0.601
wk-4 % ↓	35	65	37	76	16	54	14	68	0.313	0.412
wk-7 % ↓	32	77	34	63	15	86	13	46	0.662	0.242
wk-10/EP* % ↓	32	80	34	86	16	54	13	35	0.352	0.005

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Veh=vehicle. Score 0=none, 1=mild, 2=moderate, 3=severe. Percent increases are shown in parentheses.

3. Overall rosacea severity score

	Met qd		Met bid		Vehicle qd		Vehicle bid		Paired Comparisons (p values)	
	N	Mean	N	Mean	N	Mean	N	Mean	Met qd vs Veh qd	Met bid vs Veh bid
Baseline	92	2.2	92	2.2	49	2.2	44	2.2	0.274	0.649
wk-2 % ↓	82	16	83	13	43	5	42	9	0.019	0.239
wk-4 % ↓	87	27	85	25	43	10	39	21	<0.001	0.342
wk-7 % ↓	84	32	78	31	39	20	36	25	0.008	0.340
wk-10/EP* % ↓	82	39	79	39	41	19	38	30	0.001	0.127

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Veh=vehicle. Score 0=none, 1=mild, 2=moderate, 3=severe.

Comment Most of the secondary variable data support those of primary variables at endpoint. However, the percent reductions in the following clinical signs and symptoms only showed sporadic or no significant differences between the qd regimens (metronidazole vs vehicle) and comparison of the differences at endpoint did not reveal significance: pruritus, burning and dryness. The two bid regimens (metronidazole vs vehicle) were not significantly different for any of the 6

signs/symptoms except for pruritus at endpoint.

4. Global scores assessed by Investigator
Distributions of global scores are as follows:

	-4	-3	-2	-1	0	1	2	3	4	5	6	p
Week-2												
Met qd	0	0	0	5	13	39	24	4	2	1	0	Met qd vs
Veh qd	0	1	1	6	13	14	4	4	0	0	0	<u>Veh qd <0.01</u>
Met bid	1	1	1	9	12	31	18	7	3	0	0	Met bid vs
Veh bid	0	0	0	5	13	16	4	3	1	0	0	<u>Veh bid 0.28</u>
Week-4												
Met qd	0	0	0	8	6	21	29	14	7	2	0	Met qd vs
Veh qd	0	1	1	5	6	19	6	5	0	0	0	<u>Veh qd <0.01</u>
Met bid	0	1	1	8	9	18	17	19	11	1	0	Met bid vs
Veh bid	0	0	0	3	7	12	11	4	1	1	0	<u>Veh bid 0.22</u>
Week-7												
Met qd	0	0	3	0	4	20	24	16	12	4	1	Met qd vs
Veh qd	0	0	1	5	4	14	7	4	4	0	0	<u>Veh qd <0.01</u>
Met bid	0	0	2	3	7	18	12	16	13	7	0	Met bid vs
Veh bid	0	1	0	2	9	6	6	7	2	3	0	<u>Veh bid 0.24</u>
Week-10/EP*												
Met qd	0	0	2	3	3	9	23	24	11	5	2	Met qd vs
Veh qd	0	0	2	3	8	12	8	5	2	1	0	<u>Veh qd <0.01</u>
Met bid	0	0	0	2	8	12	17	13	17	9	1	Met bid vs
Veh bid	0	1	1	0	10	9	2	5	9	1	0	<u>Veh bid 0.16</u>

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Veh=vehicle. 6=Cleared: 100% improvement, 5=Excellent: 90-99% improvement, 4=Very good: 75-89% improvement, 3=Good: 50-74% improvement, 2=Fair: 25-49% improvement, 1=Slight: 1-24% improvement, 0=No change: no detectable improvement, -1=Slightly worse: 1 - 24% deterioration, -2=Mildly worse: 25-49% deterioration, -3=Moderately worse: 50-74% deterioration. -4=Severely worse: ≥75% deterioration.

Analyses of global scores with different levels of cutoff are shown below:

	Met* qd	Met bid	Vehicle qd	Vehicle bid	Paired Comparisons (p values)	
					Met qd vs Veh qd	Met bid vs Veh bid
Week-2						
	N=88	N=83	N=43	N=42		
≥25% improvement	35%	34%	19%	19%	0.07	0.10
≥50% improvement	8%	12%	9%	10%	0.75	0.77
≥75% improvement	3%	4%	0%	2%	0.55	1.00
Week-4						
	N=87	N=85	N=43	N=39		
≥25% improvement	60%	56%	26%	44%	<0.01	0.25
≥50% improvement	26%	36%	12%	15%	0.07	0.02
≥75% improvement	10%	14%	0%	5%	0.03	0.22
Week-7						
	N=84	N=78	N=39	N=36		
≥25% improvement	68%	62%	38%	50%	<0.01	0.31
≥50% improvement	39%	46%	21%	33%	0.04	0.23
≥75% improvement	20%	26%	10%	14%	0.21	0.22
Week-10						
(See under Primary Variables)						

*Met=metronidazole, Veh=vehicle.

Comment Between-group comparisons using "90% or greater improvement" or "cleared" have not been performed.

5. Patient's global evaluation scores at final visit

	Patient Numbers				Paired Comparisons (p values)	
	Met* qd	Met bid	Vehicle qd	Vehicle bid	Met qd vs Veh qd	Met bid vs Veh bid
Final Visit	N=82	N=79	N=41	N=38		
Score 3	34	25	3	5	<0.01	0.02
Score 2	18	20	12	8		
Score 1	15	17	10	9		
Score 0	10	15	9	13		
Score -1	4	1	3	2		
Score -2	1	1	2	0		
Score -3	0	0	2	1		
Score 1 or better	82%	78%	61%	58%	0.02	0.03

*Met=metronidazole, Veh=vehicle. Score 3=much better, 2=better, 1=somewhat better, 0=no change, -1=somewhat worse, -2=worse and -3=much worse.

Comment Patient's global showed significant differences between metronidazole and vehicle treatment for both the qd and bid regimens at endpoint.

8.1.1.4.3 Safety Comparison

Adverse Events See Appendix 1. There were no deaths or serious adverse events. The majority of adverse events were mild and did not result in discontinuation of treatment. Discontinuations due to adverse events are shown above (8.1.1.4.1).

Laboratory Studies There were no samples taken for Clinical Laboratory studies.

Comments

1. Adverse events related to treatment were primarily local and included application site reactions, aggravation of rosacea, paresthesia, dry skin, pruritus and conjunctivitis. The term "application site reaction" remains to be defined.
2. As some of the adverse events are also symptoms which may be related to rosacea, their significance can only be clarified with dermal safety studies in healthy volunteers (see Section 10.2.3).

8.1.1.5 Conclusions

1. At endpoint, metronidazole 1% cream qd was found to be superior to vehicle qd in the following primary parameters: percent reduction in papule counts and erythema scores and in Investigator's global. It was also superior to vehicle in secondary parameters including percent reduction in telangiectases, scaling/peeling, overall rosacea score and patient's global.
2. At endpoint, metronidazole 1% cream bid was superior to vehicle bid for percent reduction in papule counts and pruritus scores and in patient's global. The lack of success with two of the primary parameters (erythema and Investigator's global) has been attributed to the considerable beneficial effects of vehicle or the cleansing associated with a bid dosage regimen.
3. However, metronidazole 1% cream qd and bid regimens were not significantly different in efficacy, thus rendering the vehicle effect or cleansing effect hypotheses hard to sustain.
4. An analysis between the metronidazole qd and placebo bid arms would be needed.
5. Metronidazole 1% cream used in a qd regimen for the treatment of moderate to severe rosacea appears to be safe, with local irritation symptoms as the main treatment-related adverse events. The qd regimen was associated with a slightly lower

incidence of adverse events as compared to the bid regimen, both total and treatment-related (total 31% vs 35%, treatment-related 1% vs 8%). The difference was primarily due to the incidence of application site reactions and skin adverse events.

8.1.2 Trial#2: Study#DL6027-9516 Double-blind, multicenter study to evaluate the efficacy and safety of a once daily application of metronidazole cream 1% vs. vehicle in the treatment of rosacea

8.1.2.1 Objective/Rationale The objective was to compare the efficacy and safety of metronidazole cream 1% and vehicle when administered qd for 10 weeks in the treatment of moderate to severe rosacea.

8.1.2.2 Design Randomized, parallel-group, double-blind, placebo-controlled, multicenter study. Study procedures were same as in DL6027-9510.

8.1.2.3 Protocol Apart from eliminating the two arms with bid regimens, this protocol is identical to DL6027-9510.

8.1.2.4 Results

8.1.2.4.1 Patient Disposition/Comparability

Enrollment and Disposition

Five investigators enrolled 156 subjects:

- Debra L. Breneman, M.D. Dept of Dermatology, Univ of Cincinnati Med Ctr, 234 Goodman St., Pavilion A-3, Cincinnati, OH 45267
- Oscar Hevia, M.D. Dermatology Associates of Tallahassee, 1707 Riggins Rd, Tallahassee, FL 32317
- Peter D. Hino, M.D. VIP Research Inc., 8230 Walnut Hill Lane, Suite 500, Dallas, TX 17523
- Daniel Stewart, M.D. Midwest Cutaneous Research, 43900 Garfield, Suite 106, Clinton Township, MI 48038
- Matthew Stiller, M.D. Dept of Dermatology, Massachusetts general Hospital DCIU, Warren 505, Boston, MA 02114

Enrollment and Discontinuation Information*

		Met qd	Vehicle qd
Breneman	01	24 (-1)	12
Hevia	02	20/19*	10
Hino	03	24 (-7)	12
Stewart	04	22 (-7)	12 (-3)
Stiller	05	14 (-2)	6 (-1)
TOTAL		104/103*(-19)	52 (-4)

*Safety population different from enrolled population at Hevia's center. Numbers in parentheses indicate discontinuations from study. Met=metronidazole 1% cream

Reasons for Discontinuation

Reason	Met* qd	Vehicle qd
Non-compliance	12	2
Treatment failure	0	2
Adverse event	2	0
Did not wish to continue	1	0
Death	1	0
Lost to follow up	3	0
TOTAL	19	4

*Met=metronidazole 1% cream

Out of the 14 patients discontinued as a result of noncompliance, 13 used antibiotics from an intercurrent illness. Over 86% of patients received ≥ 9 weeks of treatment with test material. Adverse events leading to discontinuation were (all in metronidazole arm):
 - comedonal acne flare, exacerbation of rosacea and death from myocardial infarction

Populations for Analysis		
Population	Met qd	Vehicle qd
Safety*	103	52
Intent-to-treat	103	52
Efficacy**	89	50

*One enrolled patient did not return after baseline and was not included in any analysis including safety.

Met=metronidazole.

** Efficacy group exclusions were:

	Met qd	Vehicle qd	Total
Protocol violation (prohibited drugs/non-compliance)	12	2	14
Lost to follow up	3	0	3

Comments

1. The Applicant states that because the intent-to-treat population had more patients than the efficacy population at certain time points and with certain variables, some differences showing statistical significance were observed in the intent-to-treat population but not in the efficacy population.

2. Significant treatment-investigator interactions were observed: Dr. Hino's and Dr. Stewart's sites for reduction in papule counts, Dr. Stewart's site for mean erythema scores and Dr. Hino's site for patient's global.

Baseline Comparability

Baseline Data for Enrolled Patients		
Characteristics	Met qd (N=97)	Vehicle qd (N=50)
Mean age and range	49	46
Male: females	36: 67	14: 38
Race: White/Hispanic/Black	102/0/1	47/3/2*
Past treatment for rosacea: yes/no	32/71	14/38
Mean duration of rosacea (months)	92	98
Mean rosacea severity score	2.1	2.2
Mean number of papules	12	16*
Mean number of pustules	3	3
Mean number of nodules	<1	<1
Mean erythema score	2.2	2.2

*Significant differences between treatment arms (p value for race= <0.01 and for number of papules=0.01). Met=metronidazole

The following also showed significant baseline differences:

at Dr. Hevia's site - erythema (met vs vehicle=2.16 vs 2.00, p=0.05)
 scaling (met vs vehicle=0.26 vs 0, p=0.03) and
 pruritus (met vs vehicle=0.45 vs 0, p=0.04);
 at Dr. Stewart's site - number of papules (met vs vehicle=14.14 vs 24.50, p=0.04)
 & at Dr. Hino's site - overall rosacea severity score (met vs vehicle=2.00 vs 2.21, p=0.03),
 number of papules (met vs vehicle=11.83 vs 18.58, p=0.01) and
 erythema (met vs vehicle=2.00 vs 2.21, p=0.03).

Comment In addition to a complete analysis, the Applicant has provided analyses of the efficacy data with exclusion of Dr. Hino's as well as Dr. Stewart's sites but not with Dr. Hevia's site. Although it is noted that Dr. Hevia's subjects showed more severe disease in the metronidazole group, it would still be useful to examine the data without that site included.

8.1.2.4.2 Efficacy Parameters

Analysis using the Efficacy Population will be presented here. The intent-to-treat analysis has been reviewed and there are no major differences for the primary variables at endpoint.

Primary Variables at Endpoint

- Lesion Counts

	Met qd		Vehicle qd		Treat	p values	
	N	Mean	N	Mean		Inv	Treat-Inv
Papules							
Baseline	89	13	50	15	0.05 [0.06]	<0.01 [<0.01]	0.22
Week-10*	80	7 (7)	45	12 (12)	<0.01 [<0.01] (<0.01)	0.09 [0.17] (0.10)	0.38 (0.22)
↓ at wk-10	80	6	45	4	0.14 [0.08]	<0.01 [0.01]	0.13
% ↓	80	41	45	14	0.03	0.03	0.29
Pustules							
Baseline	89	2	50	3	0.41 [0.54]	<0.01 [<0.01]	0.06
Week-10*	80	<1 (<1)	45	3 (2)	0.01 [<0.01] (<0.01)	<0.01 [0.02] (<0.01)	0.01 (0.02)
↓ at wk-10	80	2	45	-0.3	0.01 [0.01]	<0.01 [<0.01]	0.09
% ↓	43	66	22	-14	0.02	<0.01	<0.01
Papules+Pustules							
Baseline	89	15	50	18	0.04 [0.05]	0.25 [0.54]	0.08
Week-10*	80	7 (8)	45	15 (14)	<0.01 [<0.01] (<0.01)	0.60 [0.60] (0.74)	0.54 (0.82)
↓ at wk-10	80	8	45	3	0.02 [0.01]	0.68 [0.66]	0.64
% ↓	80	49	45	17	<0.01	0.76	0.79

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Treat=between treatment comparisons, Inv= between investigator comparisons and Treat-Inv=treatment-investigator interactions; P values for ANCOVA using baseline count as covariate are shown for week-10 counts in parentheses (). P values for Friedman nonparametric ANOVA for actual counts or change in counts are shown in parentheses [].

Comments

- This study showed significant differences between treatment groups for lesion counts and percentage reduction at week-10/endpoint re: papules, pustules and their sum. In addition, the actual reduction was significantly different for pustules and the sum of papules and pustules.
- ANCOVA for actual lesion counts with baseline counts as covariate and Friedman non-parametric ANOVA for lesion counts and change in counts support the results of unadjusted ANOVA.
- About half of the patients in either treatment group had no pustules at baseline (48% in metronidazole and 54% in placebo groups) and the mean baseline counts were small (2-3). The analysis of such data may be misleading.
- Dr. Hino and Dr. Stewart's sites had significant treatment-investigator interactions for lesion counts. Papule, pustule and papule+pustule counts were analyzed with exclusion of these sites separately but not combined, using ANOVA and ANCOVA (see below under secondary variables).

- Erythema

	Met qd		Vehicle qd		Treat	p values	
	N	Mean	N	Mean		Inv	Treat*Inv
Baseline	89	2.2	50	2.2	0.76 [0.88]	<0.01 [<0.01]	0.25
Week-10*	80	1.3	45	1.7	0.01 [<0.01] (<0.01)	0.88 [0.81] (0.93)	0.13 (0.23)
↓ at wk-10	80	0.9	45	0.5	<0.01 [<0.01]	0.68 [0.37]	0.32
% ↓	80	42	45	25	<0.01	0.87	0.31

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Treat=between treatment comparisons, Inv= between investigator comparisons and Treat-Inv=treatment-investigator interactions. Score 0=none, 1=mild, 2=moderate, 3=severe. P values for ANCOVA using baseline score as covariate are shown for week-10 scores in parentheses (). P values for Friedman nonparametric ANOVA on actual scores or changes in scores are in parentheses [].

Comments

- Significant differences are noted between metronidazole and vehicle in mean scores for erythema, erythema reduction and percentage reduction at endpoint.

2. Dr. Stewart's site had significant treatment-investigator interaction for erythema. Erythema was analyzed, using ANOVA and ANCOVA (baseline scores and papule+pustule counts as covariate) with exclusion of this site and with Dr. Hino's site, which had other treatment-investigator interactions (see below under secondary variables).

• **Investigator's Global**

	Met qd	Vehicle qd	p values
≥25% improvement	44/80=55%	16/45=36%	0.04
≥50% improvement	35/80=44%	7/45=16%	<0.01
≥75% improvement	20/80=25%	1/45= 2%	<0.01

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Veh=vehicle.

Comments

1. At endpoint, metronidazole 1% cream qd was superior to vehicle qd in the analysis of success rates using three different cutoffs (≥25%, ≥50% and ≥75% improvement) in the treatment for rosacea.
2. Between-group comparisons using "90% or greater improvement" or "cleared" have not been performed.

Secondary Variables All efficacy data other than the endpoint/week-10 results for (1) percent reduction in papules, pustules and their sum, (2) percent reduction in erythema and (3) global were treated as secondary variables.

1. Reductions in lesion counts during course of study

The following two Tables show the data on lesion counts and their percent reduction that reveal *significant differences* during the course of the study. As Dr. Hino's and Dr. Stewart's centers had significant treatment-investigator interactions, the data were also analyzed by excluding these centers individually.

I. Analysis with Data Pooled Across Centers

	Papules			Pustules			Papules + Pustules		
	Time	Met vs Veh	p	Time	Met vs Veh	p	Time	Met vs Veh	p
ANOVA-1	wk 2	Count 9.0 vs 13.1	<0.01	wk 4	Count 1.0 vs 2.8	<0.01	wk 0	Count 15.1 vs 18.1	0.04
	wk 4	Count 8.2 vs 11.7	0.01	wk10	Count 0.7 vs 2.7	0.01	wk 2	Count 10.6 vs 15.9	<0.01
	wk 7	Count 7.1 vs 12.5	<0.01	wk10	%! 66 vs 14	0.02	wk 2	%! 28 vs 8	0.01
	wk 7	%! 40 vs 8	0.01				wk 4	Count 9.2 vs 14.6	<0.01
	wk10	Count 6.6 vs 12.3	<0.01				wk 4	%! 35 vs 20	0.03
	wk10	%! 41 vs 14	0.03				wk 7	Count 8.0 vs 14.2	<0.01
						wk 7	%! 46 vs 15	<0.01	
						wk10	Count 7.3 vs 15.0	<0.01	
						wk10	%! 49 vs 17	<0.01	
ANOVA-2	wk 2	Count 9.0 vs 13.1	<0.01	wk 4	Count 1.0 vs 2.8	<0.01	wk 2	Count 10.6 vs 15.9	<0.01
	wk 4	Count 8.2 vs 11.7	<0.01	wk 7	Count 0.8 vs 1.7	0.03	wk 4	Count 9.2 vs 14.6	<0.01
	wk 7	Count 7.1 vs 12.5	<0.01	wk10	Count 0.7 vs 2.7	<0.01	wk 7	Count 8.0 vs 14.2	<0.01
	wk10	Count 6.6 vs 12.3	<0.01				wk10	Count 7.3 vs 15.0	<0.01
ANCOVA-1	wk 2	Count 9.4 vs 12.1	0.01	wk 4	Count 1.1 vs 2.6	<0.01	wk 2	Count 11.2 vs 14.3	0.01
	wk 4	Count 8.4 vs 10.8	0.03	wk10	Count 0.7 vs 2.5	<0.01	wk 4	Count 9.6 vs 13.3	<0.01
	wk 7	Count 7.2 vs 12.8	<0.01				wk 7	Count 8.0 vs 14.4	<0.01
	wk10	Count 7.2 vs 11.6	<0.01				wk10	Count 8.0 vs 13.9	<0.01
ANCOVA-2	wk 2	Count 9.3 vs 12.1	0.01	wk 4	Count 1.1 vs 2.6	0.02	SAME AS ANCOVA-1		
	wk 7	Count 7.1 vs 12.9	<0.01	wk10	Count 0.9 vs 2.2	0.04			
	wk10	Count 7.1 vs 11.7	<0.01						

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Veh=vehicle. Only actual counts and percent reductions showing significant differences between treatment groups are shown. %!=percent reduction in score. ANOVA-1: using parametric analysis. ANOVA-2: Friedman's nonparametric analysis. ANCOVA-1: using baseline counts as covariate. ANCOVA-2: using baseline papule+pustule counts as covariate.

II. Analysis excluding Centers with Significant Treatment-Investigator Interactions

	Papules			Pustules			Papules + Pustules		
	Time	Met vs Veh	p	Time	Met vs Veh	p	Time	Met vs Veh	p
ANOVA	wk 2	Count 9.1 vs 13.5	<0.01	wk 4	Count 1.2 vs 2.1	<0.01	wk 2	Count 11.2 vs 15.3	0.02
(minus Dr. Hino)	wk 2	%I 25 vs <1	0.03				wk 2	%I 26 vs <1	0.03
	wk 4	Count 8.5 vs 12.0	0.03				wk 4	Count 9.7 vs 14.1	0.01
	wk 7	Count 7.7 vs 13.0	<0.01				wk 4	%I 35 vs <1	0.03
	wk 7	%I 37 vs 3	0.02				wk 7	Count 8.7 vs 15.1	<0.01
	wk10	Count 7.0 vs 13.8	<0.01				wk 7	%I 44 vs <1	<0.01
	wk10	%I 39 vs 2	0.01				wk10	Count 7.7 vs 12.0	<0.01
							wk10	%I 48 vs <1	<0.01
ANOVA	wk 2	Count 9.6 vs 15.1	<0.01	wk 0	Count 1.1 vs 2.2	0.02	wk 0	Count 15.0 vs 19.7	0.01
(minus Dr. Stewart)	wk 2	%I 27 vs 3	<0.01	wk 4	Count 0.5 vs 2.7	<0.01	wk 2	Count 10.4 vs 17.7	<0.01
	wk 4	Count 8.8 vs 12.6	0.02	wk10	Count 0.4 vs 2.8	<0.01	wk 2	%I 27 vs 3	<0.01
	wk 7	Count 6.8 vs 12.9	<0.01				wk 4	Count 9.3 vs 5.3	<0.01
	wk 7	%I 48 vs 20	0.01				wk 7	Count 7.3 vs 4.4	<0.01
	wk10	Count 6.1 vs 12.8	<0.01				wk 7	%I 49 vs 20	<0.01
	wk10	%I 51 vs 21	0.02				wk10	Count 6.5 vs 5.6	<0.01
							wk10	%I 52 vs 19	0.01
ANCOVA	wk 2	Count 9.2 vs 12.8	<0.01	wk 4	Count 1.2 vs 2.2	<0.01	wk 2	Count 11.3 vs 14.4	0.04
(minus Dr. Hino)	wk 4	Count 8.3 vs 11.5	0.02				wk 4	Count 9.5 vs 13.6	<0.01
	wk 7	Count 7.3 vs 13.9	<0.01				wk 7	Count 8.2 vs 15.4	<0.01
	wk10	Count 7.5 vs 12.7	<0.01				wk10	Count 8.2 vs 14.3	<0.01
ANCOVA	wk 2	Count 10.1 vs 13.8	<0.01	wk10	Count 0.7 vs 2.2	0.03	wk 2	Count 11.3 vs 15.3	<0.01
(minus Dr. Stewart)	wk 7	Count 6.7 vs 13.2	<0.01				wk 4	Count 10.0 vs 13.3	0.02
	wk10	Count 6.8 vs 12.0	<0.01				wk 7	Count 7.4 vs 14.3	<0.01
							wk10	Count 7.4 vs 14.1	<0.01

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Veh=vehicle. Only actual counts and percent reductions showing significant differences between treatment groups are shown. %I=percent reduction in score. ANOVA: using parametric analysis. ANCOVA: using baseline counts as covariate.

2. Sign/symptom scores and Overall rosacea severity scores

Six clinical signs and symptoms were studied in this protocol, in addition to an "overall rosacea severity score", which were all graded on a scale of 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe):

- Burning and dryness did not show any significant differences between the treatment groups during any time in the study.
- Telangiectasia scores were greater at week-2 in metronidazole treated-patients using Friedman nonparametric ANOVA (metronidazole 1.3 vs vehicle 1.1, p=0.03).
- Scaling/peeling scores were lower in metronidazole-treated patients at week-7 using ANCOVA with baseline scaling/peeling scores as covariate (metronidazole 0.13 vs vehicle 0.25, p=0.04) when Dr. Hino's center was excluded from analysis.
- The following Tables show significant differences between treatment arms for erythema, pruritus and overall rosacea severity: