CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 50-781

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

NOV 21 2000

Clinical Pharmacology/Biopharmaceutics Review

Submission:	NDA 50-781
Product Trade Name:	Minocycline PTS
Indication:	An adjunct treatment of moderate to severe adult periodontitis
Submission Date:	February 17, 2000
Type of Submission:	Original NDA (3S)
Sponsor:	OraPharma, Inc, Warminster, PA 18974
Reviewer:	Tapash K. Ghosh, Ph.D.
Team Leader:	Dennis Bashaw, Pharm. D.

Background: In this submission, the sponsor seeks approval of minocycline periodontal therapeutic system or minocycline PTS which is a tetracycline derivative microencapsulated in a bioresorbable polymer, poly (glycolide-co-dl-lactide) or PGLA. It is supplied in a unit dose dispenser. Each unit dose of minocycline PTS is designed to deliver 1mg of minocycline and is administered subgingivally into periodontal pockets.

Synopsis: The intended use of minocycline PTS is as an adjunct to periodontal therapy involving scaling and root planing (S/RP) for reduction of pocket depth in patients with adult periodontitis. Local administration of minocycline PTS, an antibiotic specific for periodontal pathogens combined with the sustained release properties of the medication, will improve the treatment of moderate to severe adult periodontitis. One unit dose (1 mg) is recommended to be used per affected site of each affected tooth following scaling and root planing. A pharmacokinetic study was conducted with 18 patients (10 men and 8 women) with moderate to advanced chronic periodontitis. Patients were treated with a mean dose of 46.2 mg (25-112 unit doses) of MPTS . After fasting for at least 10 hours, patients received subgingival application of MPTS (1 mg per treatment site) following scaling and root planing at a minimum of 30 sites on at least eight teeth. The treatment clinician administered investigational drug until all eligible sites ≥5 mm in probing depth were treated. Serum and saliva samples were collected for minocycline concentration analysis prior to dosing and at post dose hours 0.5, 1, 2, 3, 6, 9, 18, 24, 48, 72, 168 (7 days) and 336 (14 days). It was found that the described method of administration of MPTS provided minocycline concentrations in saliva and gingival crevicular fluid (GCF) sufficient (defined as > 1 μg/mL minocycline) to kill bacteria associated with periodontal disease *in vitro*. These levels lasted up to 14 days without significant systemic exposure (details inside).

Recommendation: Based on the review, NDA 50-781 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. A review of the PK data in this submission resulted in certain changes that are included in the "Labeling Comments" and have been conveyed to the reviewing division.

Dated 11/21/00

Tapash K. Ghosh, Ph.D.
OCPB, DPE III

Dated 11/21/00

Team Leader: E. Dennis Bashaw, Pharm.D.

CC: NDA 50-781 (Orig), HFD-540/Div File, HFD-540/CSO/Bhatt, HFD-880 (Bashaw/Ghosh)
HFD-880 (Lazor), HFD-344 (Viswanathan), CDR ATTN: B. Murphy

Table of Contents

I. BACKGROUND

Minocycline periodontal therapeutic system or minocycline PTS is a tetracycline derivative microencapsulated in a bioresorbable polymer, poly (glycolide-co-dl-lactide) or PGLA. It is supplied in a unit dose dispenser. Each unit dose of minocycline PTS is designed to deliver 1mg of minocycline and is administered subgingivally into periodontal pockets.

The active ingredient in minocycline PTS, minocycline HCl, has been shown to be safe and effective for oral and parenteral use through both extensive nonclinical testing and data obtained from over 15 years of clinical use. Treatment with minocycline HCl has been shown to control the growth of oral microflora associated with periodontitis.

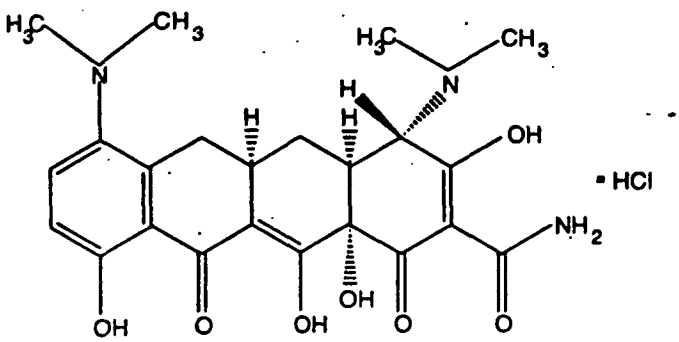
Tetracyclines and metronidazole have been used adjunctively to treat periodontitis. Oral administration of these antibiotics can lead to therapeutic drug levels within periodontal pockets, alteration of the flora, and clinical improvement; however, systemic delivery may be hampered by patient compliance, systemic side effects, and resistance selection with chronic dosing. Local delivery of antibiotics with polymer formulations professionally placed directly into periodontal pockets will decrease total exposure and associated risks for systemic complications and minimize patient compliance issues.

The intended use of minocycline PTS is as an adjunct to periodontal therapy involving scaling and root planing (S/RP). Local administration of minocycline PTS, an antibiotic specific for periodontal pathogens combined with the sustained release properties of the medication, will improve the treatment of moderate to severe adult periodontitis.

Minocycline periodontal therapeutic system (minocycline PTS) has not been marketed in any country. NDA 50-781 is the first application for this product.

II. PHARMACOLOGY

Minocycline hydrochloride (Molecular Formula: $C_{23}H_{27}N_3O_7 \bullet HCl$, Molecular Weight: 493.94) is a yellow crystalline powder. It has four ionizable groups with pKa's of 2.8, 5.0, 7.8, and 9.5. Thus its solubility in water is a complex function of pH. The aqueous solubility is minimum at pH 4.0 with a solubility of approximately 16 mg/ml.



Minocycline HCl, being a semi-synthetic derivative of tetracycline, is thought to inhibit bacterial protein synthesis by binding to the 30S bacterial ribosome and preventing access to aminoacyl tRNA to the acceptor site on the mRNA-ribosome complex. Minocycline has a much higher partition coefficient (39.4) than tetracycline (0.102). The greater lipophilicity allows easier penetration of biological membranes, thus facilitating penetration into the body tissues. Absorption of minocycline is between 95% and 100% and occurs in the stomach as well the duodenum and jejunum. Absorption is not influenced by food or milk. Minocycline has been found in the saliva at 30% to 65% of serum concentrations. These observed concentrations (obtained with usual therapeutic doses) are higher than the minimal inhibitory concentrations, which may be of therapeutic value in stomatological infections. The elimination half-life of minocycline is 16 hours. Minocycline elimination is not altered in patients with renal failure, which is expected because of the small fraction normally eliminated by this route. Furthermore, in cases of long term administration, no accumulation is observed.

III. COMPOSITION AND DOSAGE FORM

Minocycline PTS consists of the antibiotic minocycline microencapsulated in bioresorbable polymer microspheres composed of poly(glycolide-co-dl-lactide)(PGLA) which is an ester linked copolymer of glycolic and lactic acids. This polymer has been used extensively as suture material in humans and animals. PGLA is resorbed through a non-enzymatic process in which the ester bonds are hydrolyzed to lower molecular weight units and ultimately to its constituent acid which is water soluble.

Minocycline PTS is administered into the periodontal pocket as a dry powder using a unit dose dispenser designed specifically for this purpose. Each unit dose delivers 1 mg of minocycline encapsulated in approximately 3 mg of PGLA. It is a sustained release dosage form. The bioresorbable polymer confers sustained-release characteristics that allow for prolonged antibiotic release. Minocycline PTS consists of microspheres with diameters ranging from ———— . The active ingredient makes up approximately —% by weight of the product and exists as particles distributed throughout the interior of the microspheres. Exposure to moisture in the periodontal pocket triggers release of the active ingredient and hydrolysis of the polymer. Composition of minocycline PTS and minocycline PTS microspheres are shown in Tables I and II.

Table I: Composition of Minocycline PTS, 1mg

Component	Label Claim (mg minocycline per unit dose)[1]	Content per Dosage Unit (mg minocycline per dosage unit)[1]
Minocycline PTS microspheres	1.00	—

[1]Minocycline PTS, 1 mg contains — mg of minocycline per unit dose dispenser. An overage of —s included to allow for incomplete delivery from the dispenser.

Table II: Composition of Minocycline PTS microspheres

Component	Quantity (%)	Quantity per Batch (grams)*
Minocycline Hydrochloride USP		
Poly(glycolide-co-dl-lactide) G.A. Initiated		

[ ]

Applied Analytical Industries, Inc, (AAI) manufactures minocycline PTS microspheres and Packaging Coordinators, Inc. (PCI) fills the bulk microspheres into unit-dose dispensers which are then placed in re-sealable aluminum foil pouches along with desiccant packets.

IV. CLINICAL PHARMACOKINETICS OF MINOCYCLINE PTS

One Phase 1 and two Phase 2 studies were conducted by Lederle Laboratories primarily to confirm minocycline release from MPTS into the gingival crevicular fluid (GCF). These studies were four weeks (Phase 1) to six months (Phase 2) in duration with a total of 137 evaluable patients. Each patient had one or more teeth with a pocket depth (PD) of at least 5 mm. Scaling and root planing (S/RP) were performed on all but 25 patients; 58 patients received MPTS in addition to S/RP, 42 received a saline sham treatment in addition to S/RP, 12 patients received MPTS alone, and 13 received no treatment. Each application of MPTS delivered minocycline 1 mg to the affected subgingival pocket.

Immediate release of minocycline into the crevicular fluid was observed with concentrations in some cases exceeding the range for the assay calibration (0.5 µg/mL - 15,000 µg/mL). A therapeutic concentration was defined as >1 µg/mL minocycline.

There were large variations within and between patients, as evidenced by the large standard deviations at each collection interval. Therapeutic concentrations of minocycline were observed in the vast majority of patients at Day 3, and in some patients were maintained as long as 28 days.

The results also suggest that, at the untreated sites, migration of the minocycline dose from treated to untreated sites occurred and resulted in bacteriostatic activity for at least 14 days after dose deposition.

The study designs of these four clinical pharmacokinetics trials are outlined in **Table III**. OraPharma Study OPI-105 is the pharmacokinetic trial of primary significance to the reviewer. It evaluates both serum and salivary concentrations of minocycline following minocycline PTS subgingival administration. Additional information concerning gingival crevicular fluid (GCF) concentrations of minocycline is available from three early trials conducted by Lederle, 15-16-1, 15-18-1, and 15-20-2. However, because the studies were conducted more than 10 years ago and OraPharma Study OPI-105 appeared more relevant and significant from clinical pharmacology aspect, these are not reviewed thoroughly. Therefore, outcomes of these studies are not included in the label.

Table III: Study Designs of Pharmacokinetic Trials

Study Number /Title *Phase, (Start Date) Status* Investigators	Design -- Study Area, Dosing -- Possible Minocycline Dose Per Treatment (Min/Max) -- End Points	Inclusion Criteria -- Treatment Criteria	Treatment Groups -- Patients Entered Each Treatment	Age Range Gender Race (Cauc./Black/Other)	Duration
OPI-105 - A Pharmacokinetic Trial of Minocycline Periodontal Therapeutic System (PTS) in Subjects With Adult Periodontitis. *Phase 2, (Apr. 1999) Complete* Dr. David Paquette University of North Carolina at Chapel Hill, School of Dentistry Clinical Research Unit, Chapel Hill NC	Open-label -- All Teeth - Single Subgingival Application (1 mg per treatment site) following scaling and root planing at a minimum of 30 sites on at least eight teeth. -- Possible M Dose per treatment: Min. = 30 mg, Max.=168 mg (Actual doses administered ranged from 25 mg-112 mg) -- Pharmacokinetics (salivary and serum minocycline conc.), and assessment of microbial resistance (fecal)	4 sites ≥ 5 mm with BOP + ≥ 30 sites ≥ 5 mm on ≥ 8 teeth -- All pockets ≥ 5 mm	S/RP + MPTS 18	36-62 yrs 10M / 8F (10/8/0)	8 weeks
15-16-1 – Tissue Response and Release of Minocycline After Subgingival Deposition by Use of a Resorbable Polymer. *Phase 1, (Jul. 1988) Complete*	Randomized, evaluator blind, open-label, 2-arm parallel -- 1 tooth - single subgingival treatment -- Possible M Dose per Tx: Min. = 1 mg, Max.=1 mg -- Safety, Mino conc. in GCF	1 site ≥ 5 mm -- 1 site ≥ 5 mm	S/RP + MPTS 16 S/RP + S 16 Non Study Teeth Tx: S/RP Pre-Tx	27-66 yrs 32M / 0F (29/2/3)	4 weeks

15-18-1 - Clinical and Microbiological Responses to Minocycline with Resorbable Polymer after Subgingival Deposition in Patients with Periodontitis *Phase 2, (Feb. 1989) Complete*	Randomized, evaluator blind, open-label, parallel -- 2 teeth - single subgingival treatment -- Possible M Dose per Tx: Min. = 2 mg, Max.=12 mg -- PD, CAL, Micro, Mino conc. in GCF	1 site ≥ 7 mm -- All pockets ≥ 5 mm	S/RP + MPTS 30 S/RP + S 26 *Non Study Teeth Tx:* S/RP 1-2 mo. Pre-Tx	24-65 yrs 35M / 21F (38/13/5)	6 months
15-20-2 – Parallel Study of Clinical and Microbiological Response in Patients with Periodontitis to Minocycline with Resorbable Polymer after Subgingival Deposition *Phase 2, (Nov. 1989) Complete* Dr. Thomas Van Dyke Emory University School of Dentistry Department of Periodontology 1462 Clifton Road, NE Atlanta GA 30322	Randomized, open-label, evaluator blind, 4-arm parallel group -- 2 teeth - single subgingival treatment -- Possible M Dose per Tx: Min. = 2 mg, Max.=12 mg -- PD, CAL, Micro, Mino conc. in GCF	2 sites ≥ 6 mm with PGE_2 > 66.2 ng/mL -- All pockets ≥ 5 mm	S/RP + MPTS 12 S/RP 12 MPTS 12 No Tx 13 (evaluable data) *Non Study Teeth Tx:* S/RP Post-Tx	> 21 yrs 23M / 26F (32/17/0) *(evaluable data)*	6 months

BOP = Bleeding on probing
CAL = clinical attachment level
M = minocycline
Micro = microbiological assessments
Mino conc = concentration of minocycline in GCF
MPTS = minocycline 1mg in 4 mg PGLA polymer
PD = pocket depth
PGE_2 = prostaglandin E_2
S = saline
S/RP = scaling and root planing
Tx = treatment
V = Vehicle (PGLA polymer vehicle

OraPharma Study OPI-105

Title:

A Pharmacokinetic Trial of Minocycline Periodontal Therapeutic System (PTS) in Subjects With Adult Periodontitis. This was a two-center, 56-day, open-label, single-dose trial in adult patients with generalized moderate to advanced adult periodontitis.

Objectives:

The objectives were:

- To document the pharmacokinetic profile of minocycline in serum and in saliva following subgingival delivery of MPTS, 1 mg;
- To assess the development of minocycline resistance in gastrointestinal (fecal) flora;
- To evaluate the safety of MPTS, 1 mg in subjects with generalized moderate to advanced adult periodontitis.

Only the results relating to the pharmacokinetics of MPTS are presented here.

Experimental Design:

Eighteen patients (10 men and 8 women) were enrolled in and completed the study. Demographic information is summarized in **Table IV.**

Table IV: Demographic Summary

	Site A	Site B	Sites A & B
Age (yr) (mean ± SD)	45.7 ± 8.91	42.0 ± 8.55	44.1 ± 8.70
Gender			
Male	6	4	10
Female	4	4	8
Race			
Caucasian	3	7	10
Black	7	1	8
Smoking Status			
Smoker	5	6	11
Non-smoker	5	2	7

After fasting for at least 10 hours, patients received subgingival application of MPTS (1 mg per treatment site) following scaling and root planing at a minimum of 30 sites on at least eight teeth. The treatment clinician administered investigational drug until all eligible sites ≥5 mm in probing depth were treated. Doses ranged from 25 mg to 112 mg.

Blood and saliva samples for pharmacokinetic analyses were collected prior to dosing (within 15 minutes or immediately prior to scaling and root planing), and at 0.5, 1, 2, 3, 6, 9, 18, 24, 48, 72, 168 and 336 hours post-dosing. Protocol Amendment No. 2, in which the collection of saliva samples was added, was implemented for Patients A-006 onward. Therefore, no saliva samples were collected for Patients A-001 to A-005. Concentrations of minocycline in serum and in saliva were determined at PPD Development using validated HPLC methods with a lower limit of quantification of 0.0200 µg/mL.

Noncompartmental pharmacokinetic parameters for minocycline were calculated from serum and saliva concentrations of the drug. The pharmacokinetic parameters AUC0-t (zero to the last measurable concentration), AUCinf (from zero to infinity), $AUCinf_{sal}$ (salivary concentrations from zero to infinity) and Cmax were also estimated following dose-normalization.

An analysis of variance (ANOVA) was performed on the pharmacokinetic parameters AUC 0-t, AUCinf, $AUCinf_{sal}$ and Cmax to test for a site effect. The ANOVA model included "site" as a factor. A 5% level of significance was used.

Analytical:

[redacted]

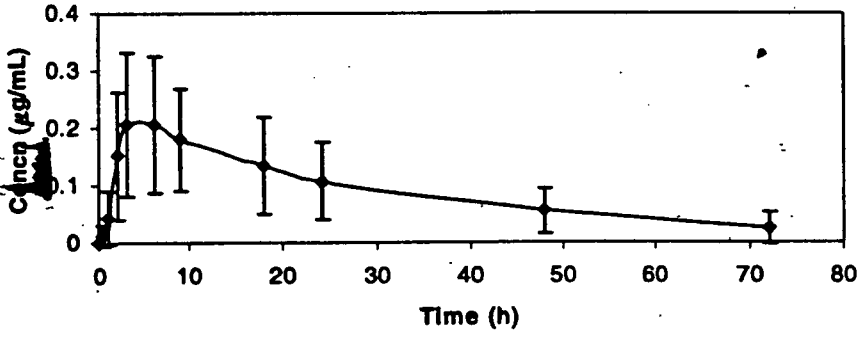
Comments:

[redacted]

Results:

Serum Data: Serum concentration of minocycline at different time points are shown in Table V. For all patients, serum minocycline concentrations were not detectable by 168 hours (7 days) post-dose. A

Figure 1: Serum Minocycline Concentration vs Time



maximum concentration of —— µg/mL was observed in patient # 15 at – hrs. Pharmacokinetic parameters in Serum, derived from the noncompartmental analysis are presented in Tables VI. The mean serum minocycline concentration versus time profile is presented in Figure 1.

Table V: Serum Minocycline Concentration vs Time Profile

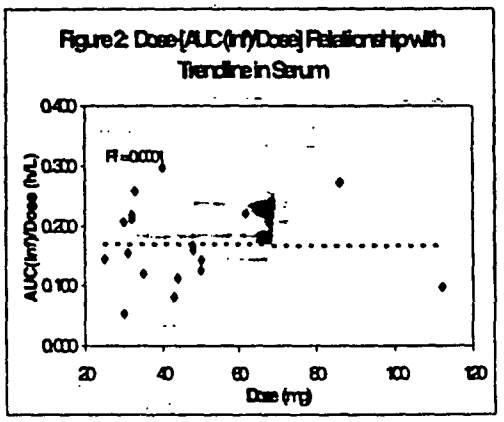
ID	Time (h)												
	0	0.5	1	2	3	6	9	18	24	48	72	168	336
	Concentration (µg/mL)												
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													
13													
14													
15													
16													
17													
18													
Mean	0	0.01218	0.04309	0.15182	0.20544	0.20678	0.18045	0.1342	0.10698	0.05535	0.02551	0	0
SD	0	0.01971	0.04676	0.11162	0.12475	0.11822	0.08831	0.08509	0.06765	0.0389	0.02841	0	0
CV%	0	161.814	108.53	73.519	60.7199	57.1745	48.9388	63.4085	63.2407	70.2736	111.365	0	0
n	18	18	18	18	18	18	18	18	18	18	17	18	18

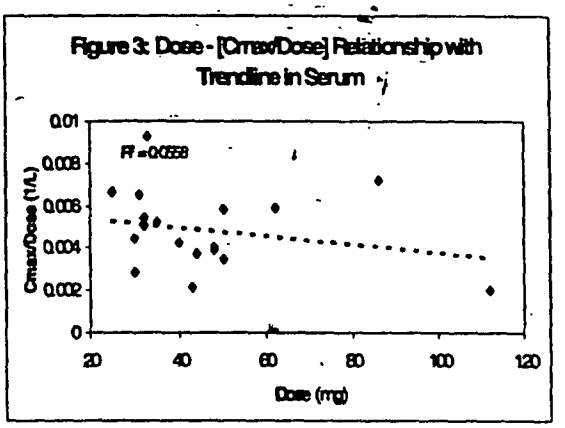
N - No Sample. Value set to missing
t - Time adjusted based on late or early blood draw
BLQ - Below Limit of Quantitation, values set to zero for PK and statistical analyses

Table VI: Pharmacokinetic Parameters of Minocycline in Serum

ID	Dose (mg)	AUC(0-t) (mg.h/mL)	AUC(0-t)/Dose (h/L)	AUC (inf) (mg.h/mL)	AUC(inf)/Dose (h/L)	Cmax (mg/mL)	Cmax/Dose (1/L)	Tmax (h)	Kel (1/h)	t(1/2) (h)	CL/F (L/h)	Varea/F (L)
1	48	5.45	0.114	7.66	0.160	0.192	0.00400	6	0.0282	24.6	6.27	223
2	40	7.68	0.192	11.92	0.298	0.169	0.00423	3	0.0142	48.9	3.36	237
3	50	5.56	0.111	6.26	0.125	0.172	0.00344	3	0.0315	22	7.99	254
4	33	7.7	0.233	8.48	0.257	0.308	0.00933	3	0.0324	21.4	3.89	120
5	32	5.7	0.178	6.76	0.211	0.162	0.00506	6	0.0264	26.2	4.74	179
6	62	11.45	0.185	13.72	0.221	0.365	0.00589	6	0.0261	26.6	4.52	173
7	30	5.09	0.170	6.18	0.206	0.133	0.00443	9	0.0246	28.2	4.85	197
8	31	3.96	0.128	4.83	0.156	0.202	0.00652	3	0.0367	18.9	6.42	175
9	32	6.21	0.194	6.98	0.218	0.173	0.00541	6	0.033	21	4.58	139
10	25	3.18	0.127	3.63	0.145	0.167	0.00668	6	0.0447	15.5	6.89	154
11	44	4.33	0.098	4.96	0.113	0.166	0.00377	3	0.0442	15.7	8.86	200
12	112	8.9	0.079	11.11	0.099	0.226	0.00202	6	0.023	30.1	10.08	438
13	30	1.2	0.040	1.63	0.054	0.0844	0.00281	3	0.0618	11.2	18.43	298
14	48	6.36	0.133	8.04	0.168	0.187	0.00390	6	0.0229	30.3	5.97	261
15	86	19.74	0.230	23.38	0.272	0.621	0.00722	3	0.0268	25.9	3.68	137
16	35	3.58	0.102	4.22	0.121	0.183	0.00523	6	0.0412	16.8	8.3	202
17	43	2.64	0.061	3.51	0.082	0.0923	0.00215	6	0.0301	23.1	12.25	408
18	50	5.88	0.118	7.15	0.143	0.292	0.00584	3	0.0327	21.2	6.99	214
Mean	46.2	6.367	0.138	7.8	0.1693	0.2164	0.0049	4.8333	0.0323	23.7556	7.1150	222.7222
SD	21.9	4.108	0.055	5.0	0.0677	0.1229	0.0019	1.8231	0.0107	8.1900	3.6879	86.4202
CV%	47.5	64.517	39.952	63.5	39.9608	56.7793	38.2061	37.7184	33.2295	34.4760	51.8326	38.8018
n	18	18	18	18	18	18	18	18	18	18	18	18

The relationships between dose-normalized AUC 0-t, AUCinf (or AUCinfsal) and Cmax versus dose were investigated. Relationship between Dose and Dose normalized AUC and between Dose and Dose normalized Cmax in Serum are presented in Figures 2 and 3 respectively.





Saliva Data: Saliva concentration of minocycline at different time points are shown in Table VII. Saliva minocycline concentrations were detectable in 7 out of 13 patients even by 168 hours (14 days) post-dose. A maximum concentration of ——μg/mL was observed in patient # 14 at—— hrs. Pharmacokinetic parameters in Saliva, derived from the noncompartmental analysis are presented in Tables VIII. The mean serum minocycline concentration versus time profile is presented in Figure 4.

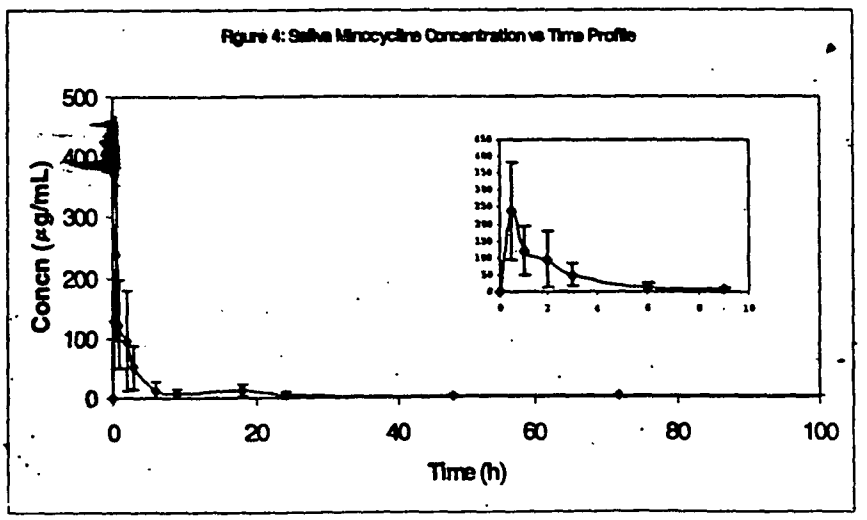


Table VII :Saliva Minocycline Concentration vs Time Profile

ID	Time (h)												
	0	0.5	1	2	3	6	9	18	24	48	72	168	336
	Concentration (µg/mL)												
6													
7													
8													
9													
10													
11													
12													
13													
14													
15													
16													
17													
18													
Mean	0.047	239.831	122.131	95.7462	51.6462	13.5462	7.683	11.7815	4.49062	3.06585	1.30169	0.34462	0.03962
SD	0.162	143.552	73.3078	82.2853	35.7106	12.8943	7.13229	10.3598	4.91067	2.46139	1.05743	0.54336	0.05485
CV %	347.2	59.8554	60.024	85.9411	69.1448	95.1875	92.8321	87.9327	109.354	80.2842	81.2351	157.668	138.455
n	13	13	13	13	13	13	13	13	13	13	13	13	13

N - No Sample. Value set to missing

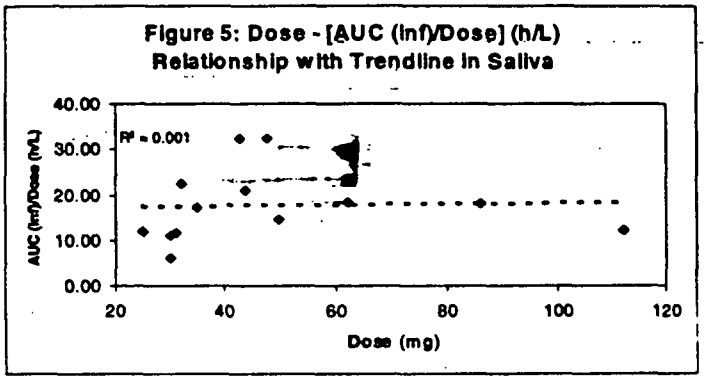
T - Time adjusted based on late or early blood draw

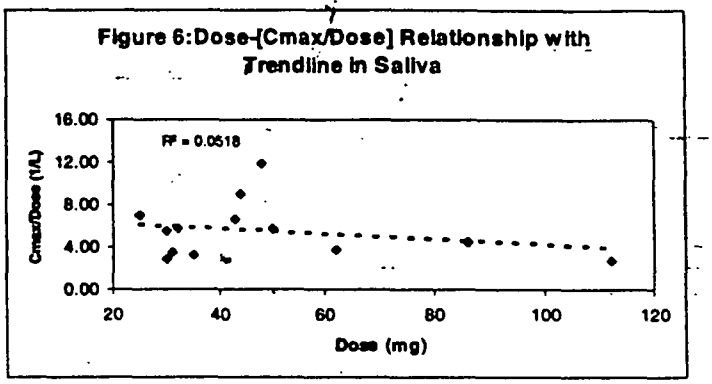
BLQ - Below Limit of Quantitation, values set to zero for PK and statistical analyses

Table VIII: Pharmacokinetic Parameters of Minocycline in Saliva

ID	Dose	AUC(0-t)	AUC(0-t)/Dose	AUC (inf)	AUC(inf)/Dose	Cmax	Cmax/Dose	Tmax	Kel	t(1/2)
	(mg)	(mg.h/mL)	(h/L)	(mg.h/mL)	(h/L)	(mg/mL)	(1/L)	(h)	(1/h)	(h)
6	62	1141	18.40	1143	18.44	235	3.79	2	0.0163	42.6
7	30	324	10.80	335	11.17	165	5.50	0.5	0.0152	45.5
8	31	351	11.32	360	11.61	108	3.48	0.5	0.0181	38.4
9	32	710	22.19	715	22.34	186	5.81	0.5	0.0315	22
10	25	301	12.04	302	12.08	176	7.04	0.5	0.0227	30.5
11	44	919	20.89	927	21.07	398	9.05	0.5	0.0079	87.5
12	112	1362	12.16	1368	12.21	314	2.80	0.5	0.0143	48.4
13	30	165	5.50	181	6.03	85	2.83	0.5	0.0291	23.9
14	48	1548	32.25	1549	32.27	572	11.92	0.5	0.0174	39.8
15	86	1554	18.07	1558	18.12	383	4.45	0.5	0.0136	50.9
16	35	596	17.03	600	17.14	112	3.20	0.5	0.014	49.5
17	43	1368	31.81	1388	32.28	283	6.58	2	0.0092	75.6
18	50	723	14.46	730	14.60	285	5.70	0.72	0.0263	26.4
Mean	48.31	850.92	17.46	858.15	17.64	254.00	5.55	0.75	0.02	44.69
SD	25.28	499.94	7.92	498.90	7.88	139.32	2.66	0.56	0.01	19.18
CV%	52.34	58.75	45.35	58.14	44.69	54.85	47.99	74.77	40.17	42.92
n	13	13	13	13	13	13	13	13	13	13

The relationships between dose-normalized AUC 0-t, AUCinf (or AUCinfsal) and Cmax versus dose were investigated.Relationship between Dose and Dose normalized AUC and between Dose and Dose normalized max in Saliva are presented in Figures 5 and 6 respectively.





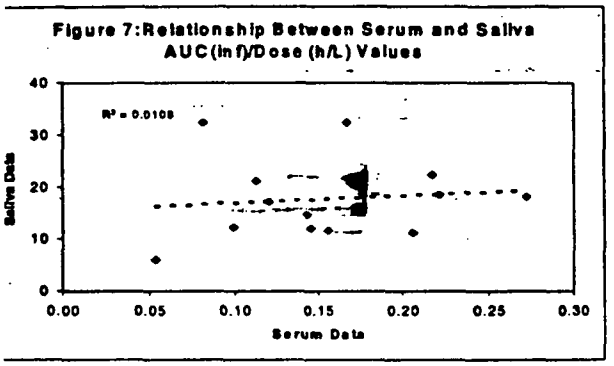
The summary table demonstrating individual sites are presented [mean (CV%)] in **Table IX**

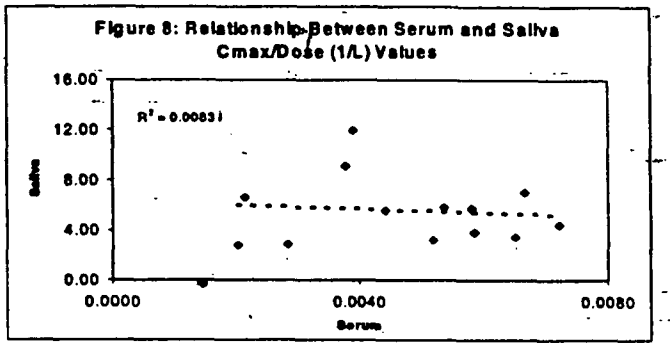
Table IX: Summary of Pharmacokinetic Results [Mean (%CV)]

Pharmacokinetic Parameter	Serum Data			Saliva Data		
	Site A (n=10)	Site B (n=8)	All Subjects (n=18)	Site A (n=5)	Site B (n=8)	All Subjects (n=13)
AUC 0-t/Dose (μg•h/mL)	0.163 (25.2)	0.108 (53.5)	0.139 (40.0)	14.9 (33.9)	19.0 (48.6)	17.5 (45.3)
AUCinf/Dose (μg•h/mL) or $AUCinf_{sal}$/Dose (μg•h/mL)	0.200 (26.9)	0.131 (50.8)	0.169 (40.0)	15.1 (33.1)	19.2 (48.0)	17.6 (44.7)
Cmax/Dose (μg/mL)	0.00550 (31.3)	0.00412 (45.0)	0.00488 (38.2)	5.13 (28.9)	5.82 (56.2)	5.55 (47.9)
tmax (h)	5.10 (39.7)	4.50 (35.6)	4.83 (37.7)	0.800 (83.9)	0.715 (73.4)	0.748 (74.8)
kel or K_{sal} (1/h)	0.0298 (27.2)	0.0353 (37.5)	0.0322 (33.2)	0.0208 (32.1)	0.0165 (46.0)	0.0181 (40.2)
Half-life (h)	25.3 (36.0)	21.8 (31.7)	23.8 (34.5)	35.8 (26.8)	50.3 (43.9)	44.7 (42.9)
CL/F (L/h)	5.35 (27.4)	9.32 (48.3)	7.12 (51.8)	NC[a]	NC	NC
V_{AREA}/F (L)	185 (23.2)	270 (39.2)	223 (38.7)	NC	NC	NC

a - NC - Not calculated

In addition, the relationship between serum and salivary pharmacokinetic parameters for minocycline were examined. Relationship between serum and salivary AUC and between serum and salivary Cmax are presented in figures 7 and 8 respectively.





Discussion:

Based on serum and saliva concentration-time profiles (Figures 1 and 4 respectively), minocycline seem to display linear elimination kinetics. The mean observed terminal elimination half-life from serum in the present study is 23.8 hours and that is much longer than half life following conventional oral minocycline administration (≈ 16 hrs). Since minocycline is released in a somewhat zero-order process from the subgingival sites, the terminal slope of the concentration versus time profiles may not only reflect the terminal elimination half-life, but also the rate of minocycline release from the MPTS product.

The mean minocycline dose administered in the present study was 46.2 mg yielding mean values for Cmax and AUCinf of 0.22 µg/mL and 7.80 µg•h/mL respectively in serum. Based on these values and assuming dose proportionality, a Cmax of 0.48 µg/mL and AUC of 16.9 µg•h/mL would be expected for a 100 mg oral dose of minocycline PTS. These values are lower than those seen from an orally administered 100 mg dose (Cmax and AUC of 1.6 µg/mL and 31.6 µg•h/mL respectively). Therefore, extrapolated values at 100 mg from minocycline PTS are 2 to 3 times lower than those reported for oral minocycline. However, based on serum and saliva dose and AUC/Cmax profiles (Figures 2, 3 and 5, 6 respectively), minocycline PTS does not seem to display linear pharmacokinetics. Therefore the validity of whole extrapolation is questionable. Nevertheless, the difference may be explained in terms of a difference in route of administration and/or formulation.

Saliva minocycline concentrations from minocycline PTS were much higher than those observed in serum (approximately 1000 times). The half life of elimination from saliva (≈ 45 hrs) was also much higher than that from serum (≈ 24 hrs). Therefore, administering minocycline directly to the site of action provides higher and extended local minocycline concentration while minimizing systemic toxicity. The implication of a spike of high concentration of minocycline exposure to buccal mucosa as measured from saliva in the first few hours post application needs to be considered by the clinical reviewer. A therapeutic concentration was defined as >1 µg/mL minocycline.

In conclusion, the pharmacokinetics of minocycline PTS was assessed following single-dose administration of doses ranging from 25 mg to 112 mg. The mean maximum observed minocycline concentrations in saliva following dose-normalization were approximately 1000 times those observed in serum. The rate and extent of absorption (based on Cmax and AUCinf for serum minocycline, respectively) were approximately 3 and 2 times lower than what would be expected following systemic oral administration of a dose equivalent to that administered with the PTS formulation of minocycline.

Conclusions

The described method of administration of MPTS provides minocycline concentrations in saliva and gingival crevicular fluid (GCF) sufficient (defined as > 1 µg/mL minocycline) to kill bacteria associated with periodontal disease. These levels last up to 14 days without significant systemic exposure.

V. COMMENTS:

The following comments should be forwarded to the medical division and to the sponsor:

- The design objective for minocycline periodontal formulation was to produce a dosage form which could be administered subgingivally into the crevicular pocket and which would yield minocycline concentrations exceeding the MICs (0.05-1.56 µg/mL) for organisms associated with periodontal diseases for a period of 7 to 10 days. However, the above MIC range may be applicable for serum and MIC range of minocycline in saliva for the proposed indication has not been properly defined. It has been reported that minocycline has been found in the saliva at 30% to 65% of serum concentrations. Therefore, optimum salivary concentration to killing organisms associated with periodontal diseases needs to be evaluated. Considering saliva concentration a better marker for therapeutic effectiveness, ideally a dosage form devoid of initial spike, as observed in this application, will be better appreciated under clinical condition to avoid unnecessary dose dumping.

- No relationship was observed between dose and dose normalized AUC in either serum ((Figure 2, $R^2 = 0.0001$) or saliva (Figure 5, $R^2 = 0.001$). Similarly, no relationship was observed between dose and dose normalized Cmax in either serum ((Figure 3, $R^2 = 0.0558$) or saliva (Figure 6, $R^2 = 0.0518$). Therefore, the reviewer does not concur with the statement made by the sponsor " *Findings suggest that there is a linear relationship for serum concentrations between these pharmacokinetic parameters and dose, an expected finding for a drug with linear pharmacokinetics, and likewise suggest linear pharmacokinetics for salivary concentrations*".

- Relationship between serum and salivary AUC (Figure 7, $R^2 = 0.0108$) and between serum and salivary Cmax (Figure 8, $R^2 = 0.0083$) showed absolutely no correlation. Therefore, the reviewer does not agree with the sponsor's statement "*A statistically significant correlation was shown between serum AUC and salivary AUC ($p=0.05$, $r^2=0.4$), but not serum Cmax versus salivary Cmax.*".

- No information is available as to whether the formulation used in OPI –105 study is same or identical with the proposed to be marketed formulation.

- The units of dose normalized pharmacokinetic parameters should be corrected.

LABELING:

Following modifications have been proposed in the "Clinical Pharmacology" section of the labeling. "Strikeout" means suggested deletions and "Shading" suggests insertion of new text.

CLINICAL PHARMACOLOGY

Microbiology

WITHHOLD 1 PAGE (S)