Among the categories (Appendix A[56]) in which substantial excess of discontinuation related events occurred in the total cilostazol relative to placebo group were:

•"Body As A Whole"-5.8% for total cilostazol versus 3.2% for placebo. The majority of this difference is due to headache 3.3% versus 0.3%.

•"Cardiovascular"- 7.8% for total cilostazol versus 4.9% for placebo. The majority of the difference was due to palpitations 1.1% versus 0.1%; tachycardia 0.6% versus 0.1%; angina pectoris 0.8% versus 0.4%; and myocardial infarctions 1.1% versus 0.7%.

•"Digestive"- 2.8% for total cilostazol versus 1.7% for placebo. The majority of the difference is due to diarrhea 1.1% versus 0.4%.

•"Musculoskeletal"- 0.6% for total cilostazol versus 0.1% for placebo. The adverse events were well scattered over various manifestation of bone and joint pain.

•"Nervous"- 1.5% for total cilostazol versus 1.2% for placebo. The adverse events were well scattered. Perhaps dizziness with a 0.6% versus 0.3% is the strongest signal.

Mortality:

In the placebo controlled data base (12 trials), there were 7 placebo (N=1032) and 12 pooled cilostazol (N=1441) deaths which include patients who died on therapy or within 30 days of the cessation of treatment (Dr. Rodin's Table 43, summarized as Table 9). Although the crude relative risk of mortality (per 100 patient year exposure), comparing treatment to placebo is 1.3: 1, there were so few patients who died that the confidence intervals of cilostazol and placebo treatments overlap. Similarly, any dose relationship to mortality is skewed by the small number of events, particularly in the 150 mg BID dose group. Dr. Rodin's review contains a Kaplan-Meir plot (Figure 13 of his review) which graphs the time dependence of the mortal events.

Assuming that these point estimates are accurate, in order to confirm a difference in mortality between placebo and cilostazol, a study of approximately 20,000 patients with follow-up for 1 year would be required (the power calculations assumed an alpha=0.05 and (1-beta)=0.8; calculated by Dr. Mahjoob). To rule out a 50% increase in mortality, a study of approximately 8,000 patients, equally divided between treatment and placebo would be

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56 This table is derived only from seven studies, and excludes study 21-90-201 per sponsor because the CRFs were designed differently. There were 27 placebo and 54 cilostazol patients enrolled for 16 weeks. The reasons for discontinuation from this study were as follows :

Placebo 2 patients : #1= MI, death; and #2= headache leg swelling diarrhea

Cilostazol 10 patients: #1= Diarrhea; #2= esophageal hemorrhage, esophageal stenosis; #3= subclavian artery stenosis; #4= anemia, NPN increased; #5= unstable angina, CHF; #6= bacterial pneumonia ,# 7= MI (on ECG); #8= Pneumonia, CHF; #9= TIA ; #10= nausea, headache anorexia and diarrhea.

needed. To rule out a doubling of deaths, i.e. 100 % increase in deaths, a study with 2100 patients equally-divided would be needed.

Please note that the average patient exposure duration for this data base was approximately 4 months for cilostazol, so that even with the relatively large number of treated patients, the at-risk exposure time is far from sufficient to come to any conclusions with respect to mortality comparisons between treatment and placebo.

Table 12. Deaths During the Study or Within 30 days of Discontinuation of Treatment (Adapted From Dr. Rodin's Review)

			Cilostazol			
Dose	PBO	Pentox	Pooled	50 BID	100 BID	150 BID
N=	1032	355	1441	303	1048	90
# died	7	2	12	2	9	1
Crude Rate	0.68%	0.56%	0.83%	0.66%	0.86%	1.11%
Adjusted Mortality : Deaths/ 100 patients exposure years (95% CI)	1.90 0.77-3.90	1.48 ?-?	2.47 1.28-4.30	1.58 0.19-5.64	2.63 1.20-4.97	6.30 0.16-34.2

Hospitalizations: There was no clear listing of hospitalizations either in the briefing booklet or in Dr. Rodin's review. Hospitalizations were, however, to be captured and subsumed under the heading of "Serious Adverse Events", but were not further separately listed.

Serious Adverse Events: Serious Treatment-Emergent Events, for which the event rate on Cilostazol exceeded those of placebo, were listed by Dr. Rodin (Table 45 of his review). There was no listing of "All" Serious Adverse Events", either in the sponsor's briefing booklet or in Dr. Rodin's review. The designation of an event as Treatment Emergent requires a decision by someone, and not necessarily someone blinded to treatment, to define the index event as Treatment Emergent.

It is also unclear how many subjects sustained a Serious Adverse Event. For example, if a subject was hospitalized for chest pain, which progressed to angina, followed by evidence that the event was a myocardial infarction, the event could be tabulated three times, i.e. chest pain, angina and myocardial infarction. The number of events, therefore, exceeds the number of patients with these events.

Any interpretation of the relationship of dose to Serious Adverse Events should take into account the different durations of exposure to each dose. A Kaplan-Meir plot reflecting the different exposure times would have been useful, but was not supplied.

Adverse Events:

The sponsor did not tabulate Total Adverse Events. instead, the sponsor supplied only the Treatment-Emergent Adverse Events. (Table 4.9-8 of the Briefing Document). This table should also be interpreted with full knowledge that there were different durations of

observations for the treatment groups. Below is a abbreviated table of adverse events (at a frequency of >3% in any of the cilostazol groups).

Table 13. Selective Overall Treatment Emergent Adverse Events (> 3% in any cilostazol group)

	Cilostazol				PBO	PTX
	Total	50 mg BID	100 mg BID	150 mg BID		
Randomized	1374	303	998	73	973	355
Completed	1073 (78%)	250 (83%)	775 (78%)	48 (66%)	835 (86%)	258 (73%)
Days Exposure (days)	127	153	123	62	134	139
Headache	443 (32%)	78 (26%)	333 (34%)	32 (44%)	127 (13%)	40 (11%)
Diarrhea	233 (17%)	34 (11%)	185 (19%)	14 (9%)	65 (7%)	29 (8%)
Abnormal Stools	193(14%)	37(12%)	146(15%)	10(14%)	40(4%)	19(5%)
Infection	127 (9%)	35 (12%)	88 (9%)	4 (6%)	72 (7%)	26 (7%)
Dizziness	127 (9%)	25 (8%)	98 (10%)	4 (6%)	60 (6%)	29 (8%)
Palpitations	118 (9%)	15 (5%)	96 (10%)	7 (10%)	10 (1%)	8 (2%)
Pharyngitis	112 (8%)	21 (7%)	84 (8%)	7 (10%)	60 (6%)	46 (13%)
Rhinitis	101 (7 %)	32 (11 %)	(11 %)	2 (3 %)	45 (5 %)	2 (1 %)
Peripheral Edema	97 (7%)	23 (8%)	23 (8%)	8 (11%)	37 (4%)	14 (4%)
Nausea	89 (7 %)	16 (5 %)	16 (5 %)	9 (12 %)	56 (6 %)	41 (12 %)
Dyspepsia	77 (7 %)	18 (6 %)	18 (6 %)	4 (6 %)	40 (4 %)	33 (9 %)
Chest Pain	76 (6 %)	18 (6 %)	18 (6 %)	5 (7 %)	53 (5 %)	19 (5 %)
Periph Vasc Disorder	61 (4 %)	17 (6 %)	17 (6 %)	1 (1 %)	75 (8 %)	34 (10 %)
Tachycardia	61 (4 %)	11 (4 %)	11 (4 %)	7 (10 %)	7 (1 %)	2 (1 %)
Abdominal Pain	60 (4 %)	11 (4 %)	11 (4 %)	4 (6 %)	27 (3 %)	15 (4 %)
Asthenia	47 (3 %)	9 (3 %)	9 (3 %)	5 (7 %)	31 (3 %)	10(3 %)
Cough Increased	47 (3 %)	9 (3 %)	9 (3 %)	1 (1 %)	27 (3 %)	10 (3 %)
Dyspnea	41 (3%)	6 (2 %)	6 (2 %)	1 (1 %)	36 (4%)	13(4 %)

The overall treatment emergent adverse event profile generally fits into three basic categories:

1) Palpitation and tachycardia, consistent with the inotropic effect of the drug.
2) Vasodilator effects such as headache, dizziness and peripheral edema.
3) Gastrointestinal dysfunction such as diarrhea, abnormal stools, dyspepsia and(perhaps nausea).

Vital Signs: It is unclear if the vital signs were recorded at peak, trough or randomly relative to drug concentrations.

There was a dose dependent increase in heart rate in the pooled eight-placebo controlled studies; 5.1, 7.4 and 10.5 BPM in the 50, 100 and 150 mg BID doses, respectively (based on ECG readings). Similar 24-hour mean rate increases were detected during Holter monitoring. There, however, did not appear to be major changes in blood pressures.

ECG data: ECG information was available for the eight-placebo controlled studies. Again it is unclear whether the ECG measurements correspond to peak, trough or random drug effects. Given the increase in heart rate in the cilostazol treated group, it is not surprising that the PR intervals and QT intervals decrease. The effect of cilostazol on repolarization is markedly dependent on which rate-correction calculation is used. Applying the Bazzett's

correction, the QTc appears to increase. Applying the method of Fredericia, there did not appear to be a change in repolarization. Applying the linear correction, there appeared to be a small dose-related effect to repolarization. Aside, from the correction of Bazzett, pentoxifylline had a greater effect on repolarization than cilostazol. None of the rate corrections for reoplarization are entirely accurate, in particular at the extremes of heart rate changes. The increase in the QTc as corrected by the method of Bazzett's method, therefore, is not by itself definitive that repolarizatin is increased.

There is no *in vivo* or *in vitro* animal systems which further defines the effect of cilostazol on repolarization.

Holter: Holter information was available for a total of 180 cilostazol-treated patients and 80 placebo patients. The sponsor claims there were no differences in VT beats/hour or ventricular premature beats/hour when comparing placebo to cilostazol. These Holters were also analyzed by Dr. J. Morganroth, for proarrhythmic events using previously published criteria[57]. Proarrhythmic events were more frequent in cilostazol than placebo treated patients. One subject patient # 116 (study #21-95-201) who had 373 runs of NSVT while on cilostazol 150 mg.

Table 14. Proarrhythmic Events per Criteria of Morganroth[57]

	Cilostazol BID in mg (n=number with Holters)				Placebo (n=84)
	50 (n=18)	100 (n=92)	150 (n=70)	Total (n=180)	
VPB*	0 (0%)	5 (5.4%)	3 (4.3%)	8 (4.4%)	1 (1.3%)
NSVT**	3 (33%)	11 (12.0%)	9 (12.8%)	23 (12.8%)	6 (7.1%)
*VPB criteria: if Baseline 0 an increase to ≥ 10/hr; if baseline >0<100 an 10-fold increase; if Baseline > 100 a > 3-fold increase					
**NSVT: If Baseline =0 then any post baseline event; if baseline > 1 at baseline a 10-fold increase in events					

Laboratory Assessment: Cilostazol has no major effect on hepatic function. Shift tables, among the truncated population who had both on-therapy and baseline measurements, suggest a dose-related increase in the number of patients with increased creatinine.

Open Label Exposure

There is a second data base which consists of those who were treated open label with cilostazol. This data base consisted almost entirely of both placebo and treated patients who completed the original protocols. There were a total of 1105 such patients. Among these patients were 439 patients who were initially treated with placebo during the double-blind studies. The data base cut-off was 2 September 1996.

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[57]Morganroth, J.; Borland, M.; and Chao, G. "Application of Frequency Definition of Ventricular Proarrhythmia" Am. J. Cardiol, 1987, 59 (1) 97-99.

This data base needs to be taken with some degree of skepticism. It is unclear how compulsively patients were followed and whether patients were lost to follow up by the end of the study. The mortality rate, therefore must be considered a lower limit estimate of the true effect. Estimates of other serious events must also be interpreted with caution. It is strongly likely that such events were incompletely captured.

There is no analysis of the naive cilostazol patients (n=439) with respect to mortality or serious adverse events i.e. the patients who were treated with placebo during the clinical trials and were then switched cilostazol for the open-label portion of the study.

The demographics of the entire open-label cohort is not that dissimilar from those who entered the controlled studies (see sponsor's table 4.9-4). The mean (median) duration of exposure was 450 (239) days. The median dose/patients, that is the average daily dose during the study was generally between 100 to $\leq$ 200 mg/day. (A subject who was treated for 100 mg BID for the vast majority of the study but received a short term exposure to 150 mg BID would be classified under the 200 to $\leq$ 300 mg dose group).

Dr. Rodin indicates 14 patients died during treatment and an additional 13 patients who died 1-157 days post exposure (a total of 27 patients). The sponsor notes there were 18 patients in this data base died on therapy or within 30 days of cessation of therapy.

In summary, the safety data base is underpowered to rule-in or rule-out a potentially harmful effect of cilostazol on overall mortality. Since those who enrolled and who had cardiovascular disease at baseline had to have their exercise limited by their claudication, it appears that any concurrent cardiovascular disease was only mild-moderate in severity.

Serious adverse events in the cilostazol group are consistent with expected effects of a PDE-inhibitor.

APPENDIX A

Events which Led to Discontinuation in the Eight Placebo-Controlled Studies

Category		Cilost 50 BID	PCT n=303	Cilost 100 BID	PCT n=944	Cilost 150 BID	PCT n=73	Cilost Total	PCT n=1320	Placebo	PCT n=946
		49	16	197	21	25	34	272	21	122	13
Body as a Whole		12	3.96	57	6.04	8	10.96	77	5.83	30	3.17
	Abdominal Pain	0	0.00	5	0.53	0	0.00	5	0.38	3	0.32
	Accidental injury	0	0.00	3	0.32	0	0.00	3	0.23	1	0.11
	Asthenia	0	0.00	3	0.32	1	1.37	4	0.30	1	0.11
	Back Pain	0	0.00	3	0.32	0	0.00	3	0.23	0	0.00
	Carcinoma	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Chest Pain	3	0.99	4	0.42	1	1.37	8	0.61	5	0.53
	Chills	0	0.00	1	0.11	0	0.00	1	0.08	1	0.11
	Death	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	Face Edema	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Fever	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Gangrene	0	0.00	0	0.00	0	0.00	0	0.00	2	0.21
	Headache	4	1.32	35	3.71	5	6.85	44	3.33	3	0.32
	Infection	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Malaise	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Neoplasm	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	Pain	3	0.99	1	0.11	1	1.37	5	0.38	11	1.16
	Pelvic Pain	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Sepsis	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Sudden Death	0	0.00	0	0.00	0	0.00	0	0.00	2	0.21
Cardiovasc.		20	6.60	73	7.73	9	12.33	103	7.80	46	4.86
	Angina Pectoris	1	0.33	9	0.95	1	1.37	11	0.83	4	0.42
	Arrhythmia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Atrial Fibrillation	0	0.00	6	0.64	1	1.37	7	0.53	5	0.53
	Cardiovascular Disorder	0	0.00	1	0.11	0	0.00	1	0.08	1	0.11
	Cerebral Infarct	0	0.00	2	0.21	0	0.00	2	0.15	0	0.00
	Cerebral Ischemia	2	0.66	3	0.32	0	0.00	5	0.38	4	0.42
	Cerebrovascuar Accident	1	0.33	1	0.11	0	0.00	2	0.15	3	0.32
	CHF	0	0.00	2	0.21	0	0.00	2	0.15	1	0.11
	CAD	0	0.00	2	0.21	0	0.00	2	0.15	0	0.00
	Deep Thrombophlebitis	0	0.00	0	0.00	0	0.00	0	0.00	2	0.21
	Embolus	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Embolus Lower Extremity	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Heart Arrest	1	0.33	0	0.00	0	0.00	1	0.08	1	0.11
	Heart Failure	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Hemorrhage	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Hypertension	0	0.00	1	0.11	2	2.74	1	0.08	0	0.00
	MI	1	0.33	10	1.06	0	0.00	14	1.06	7	0.74

	Myocardial Ischemia	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Occlusion	0	0.00	0	0.00	2	2.74	0	0.00	0	0.00
	Palpitation	3	0.99	9	0.95	0	0.00	14	1.06	1	0.11
	Peripheral Gangrene	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	Peripheral Vascular Disorder	5	1.65	8	0.85	0	0.00	13	0.98	8	0.85
	SVT	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Syncope	1	0.33	1	0.11	1	1.37	3	0.23	0	0.00
	Tachycadia	1	0.33	6	0.64	1	1.37	8	0.61	1	0.11
	Thrombophlebitis	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	Vascular Anomaly	0	0.00	3	0.32	0	0.00	3	0.23	0	0.00
	Vascular Disorder	1	0.33	1	0.11	0	0.00	2	0.15	2	0.21
	Vasodilitation	1	0.33	2	0.21	0	0.00	3	0.23	1	0.11
	Ventricular Extrasystoles	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Ventricular Fibrillation	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Ventricular Tachycardia	0	0.00	2	0.21	1	1.37	3	0.23	2	0.21
Digestive		5	1.65	27	2.86	5	6.85	37	2.80	16	1.69
	Abnormal Stools	0	0.00	2	0.21	0	0.00	2	0.15	0	0.00
	Anorexia	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Constipation	0	0.00	1	0.11	0	0.00	1	0.08	1	0.11
	Diarrhea	1	0.33	8	0.85	5	6.85	14	1.06	4	0.42
	Duodenal Ulcer	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	Duodenitis	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	Dyspepsia	0	0.00	2	0.21	0	0.00	2	0.15	0	0.00
	Esophagitis	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Flatulence	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Gastritis	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	Gastrointestinal Carcinoma	0	0.00	1	0.11	0	0.00	1	0.08	1	0.11
	Gastrointestinal Hemorrhage	0	0.00	1	0.11	0	0.00	1	0.08	1	0.11
	Hepatic Neoplasia	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Liver Function Disorder	0	0.00	1	0.11	0	0.00	1	0.08	1	0.11
	Melena	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Nausea	0	0.00	6	0.64	0	0.00	6	0.45	4	0.42
	Rectal Disorder	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Rectal Hemorrhage	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Stomach Ulcer	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	Vomiting	0	0.00	1	0.11	0	0.00	1	0.08	1	0.11
Endocrine		0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Diabetes Melitis	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00

Hemic & Lymphatic		1	0.33	0	0.00	0	0.00	1	0.08	1	0.11
	Lymphoma Like RXN	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	PT increased	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
Metabolic & Nutr		2	0.66	4	0.42	0	0.00	6	0.45	3	0.32
	Alkaline Phos Inc	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Creatinine Inc	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Edema	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Gout	1	0.33	0	0.00	0	0.00	1	0.08	1	0.11
	Hyperglycemia	1	0.33	1	0.11	0	0.00	2	0.15	0	0.00
	Peripheral Edema	0	0.00	2	0.21	0	0.00	2	0.15	1	0.11
	SGOT inc	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	SGPT Incr	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Musculo-Skeletal		0	0.00	8	0.85	0	0.00	8	0.61	1	0.11
	Arthralgia	0	0.00	2	0.21	0	0.00	2	0.15	0	0.00
	Arthritis	0	0.00	2	0.21	0	0.00	2	0.15	0	0.00
	Bone Disorder	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Bone Neoplasm	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Bone Pain	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Myasthenia	0	0.00	1	0.11	0	0.00	1	0.08	1	0.11
Nervous		6	1.98	13	1.38	1	1.37	20	1.52	11	1.16
	Amnesia	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	Anxiety	0	0.00	1	0.11	1	1.37	2	0.15	0	0.00
	Dementia	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Depression	2	0.66	0	0.00	0	0.00	2	0.15	2	0.21
	Dizziness	0	0.00	6	0.64	0	0.00	6	0.45	3	0.32
	Emotional Lability	0	0.00	1	0.11	0	0.00	1	0.08	1	0.11
	Hemiplegia	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Hypesthesia	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Insomnia	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	Nervousness	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Neuralgia	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Paraestheia	0	0.00	2	0.21	0	0.00	2	0.15	0	0.00
	Somnolence	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Speech Diorder	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Thinking Abnormal	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Tremor	1	0.33	0	0.00	0	0.00	1	0.08	0	0.00
	Vertigo	1	0.33	1	0.11	0	0.00	2	0.15	0	0.00
Respiratory		2	0.66	4	0.42	2	2.74	8	0.61	8	0.85
	Apnea	0	0.00	0	0.00	1	1.37	1	0.08	0	0.00
	Asthma	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Bronchitis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Carcinoma of the Lung	0	0.00	1	0.11	0	0.00	1	0.08	4	0.42

	Cough Increased	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Dyspnea	2	0.66	2	0.21	0	0.00	4	0.30	2	0.21
	Epistaxis	0	0.00	0	0.00	1	1.37	1	0.08	0	0.00
	Pneumonia	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Respiratory Disorder	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Rhinitis	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
Skin & Appendiges		1	0.33	1	0.11	0	0.00	2	0.15	2	0.21
	Pruritis	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Rash	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Skin Disorder	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Skin Ulcer	1	0.33	0	0.00	0	0.00	1	0.08	1	0.11
Special Senses		0	0.00	3	0.32	0	0.00	3	0.23	2	0.21
	Amblyopia	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Blindness	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Eye Hemorrhage	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Eye Pain	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Visual Field Defect	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
Urogenital		0	0.00	6	0.64	0	0.00	6	0.45	2	0.21
	Bladder Carinoma	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Bladder Neoplasm	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Bladder Stenosis	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Hematuria	0	0.00	3	0.32	0	0.00	3	0.23	0	0.00
	Kidney Failure	0	0.00	0	0.00	0	0.00	0	0.00	1	0.11
	Kidney Pain	0	0.00	1	0.11	0	0.00	1	0.08	0	0.00
	Urinary Retention	0	0.00	0	0.00	0	0.00	0	0.00	0.00	0.00