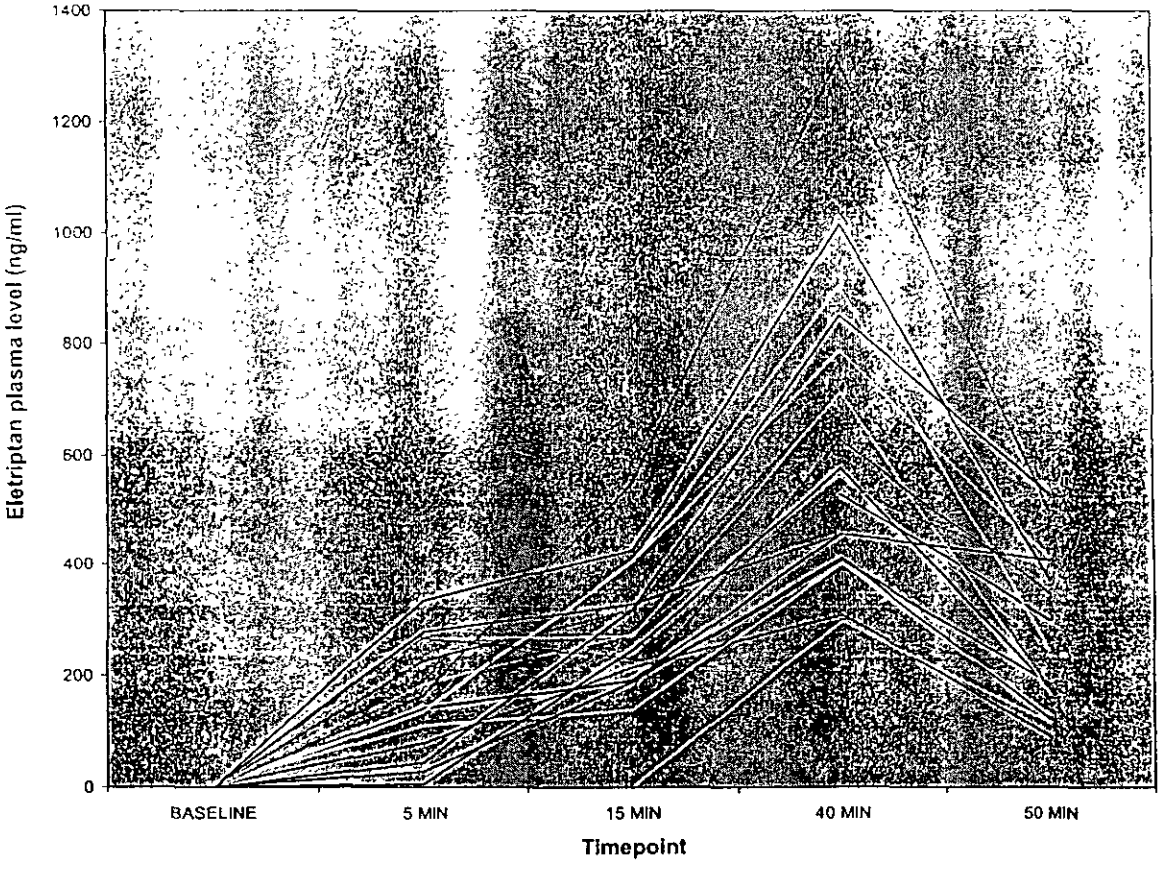
Subjects randomized to eletriptan with $C_{max} \geq 264$ ng/ml

I created a dataset combining all subjects with eletriptan $C_{max} \geq 264$ ng/ml (n=20). This combined group corresponds to the Sponsor-defined MITT population, since all subjects also exceeded the eletriptan plasma level required for the MITT population (299 ng/ml). The maximum vasoconstriction was achieved at 40 and 50 minutes post-baseline respectively in 13 and 8 subjects in this subgroup. Patient 50 reached the peak concentration at 25 minutes post-baseline and was discontinued at that timepoint. Thirteen subjects had $\geq$ 20% vasoconstriction in the LAD territory, and 8 subjects had $\geq$ 20% vasoconstriction in the PCA territory. Two subjects (19 and 50) exceeded 30% vasoconstriction in the LAD.

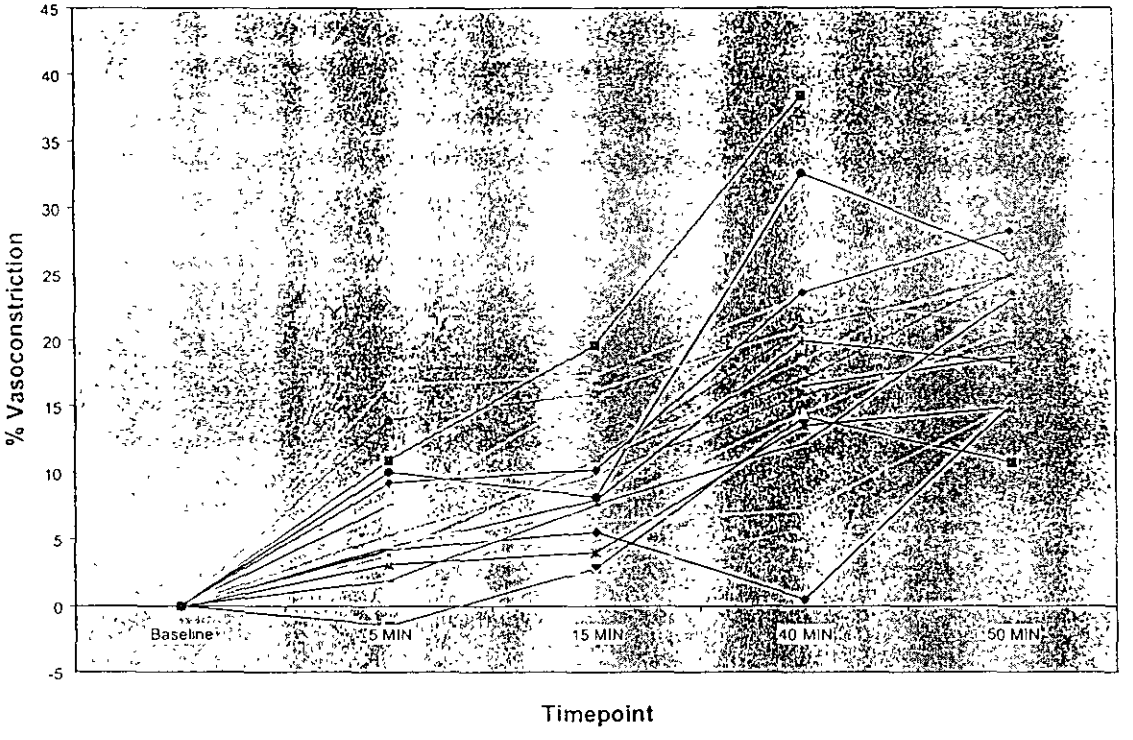
Figure 3 shows that, as expected, eletriptan plasma level peaked at 40 minutes post-baseline and fell sharply by 50 minutes post-baseline (10 minutes after infusion end).

Figure 3: Eletriptan plasma level over time in subjects with eletriptan Cmax $\geq$ 264 ng/ml (n=20)



However, Figure 4 shows that in 14/20 subjects, vasoconstriction was still on the rise at the 50 minutes post-baseline, so that the actual maximum level of vasoconstriction may have ben missed in these subjects. This is potentially problematic, but must be interpreted in a context of increasing vasoconstriction over time even in patients randomized to placebo (see below).

Figure 4: Vasoconstriction over time in the LAD territory for subjects with eletriptan Cmax ≥ 264 ng/ml.



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Subjects randomized to sumatriptan

In this subgroup, all subjects had their peak vasoconstriction for both the LAD and the PCA territories at 50 minutes post-baseline, whereas sumatriptan C_{max} occurred at 5 or 15 minutes post-baseline (subcutaneous injection). This may explain why the Sponsor amended the protocol to select sumatriptan-induced vasoconstriction at the timepoint where this was maximum. This creates some imbalance between study groups, with subjects randomized to sumatriptan with an earlier T_{max} than subjects randomized to eletriptan, and then having more time available for the full pharmacodynamic effect to develop (in case there is a time lag between T_{max} and the maximum pharmacodynamic effect). Eight subjects had ≥ 20% vasoconstriction in the LAD territory, and six subjects had ≥ 20% vasoconstriction in the PCA territory. No patient had ≥ 30% vasoconstriction in any territory.

Table 25: Maximum vasoconstriction at any timepoint in subjects randomized to sumatriptan

Patient ID	Peak plasma concentration (time)	LAD % vasoconstriction	PCA % vasoconstriction	Time (PCA and LAD)
30				
27				
20				
36				
47				
14				
38				
41				
22				
1				
16				
53				
33				
44				
51				
5				
11				
9				
Average	68.3 ± 18	19.2 ± 5.8	17 ± 7.1	

Figure 5 and Figure 6 show the changes in vasoconstriction and sumatriptan plasma level in patients randomized to sumatriptan. The maximum vasoconstriction level was seen long after T_{max}, at the last timepoint, so that it remains unclear if these subjects reached their maximum level of vasoconstriction by the end of the study (50 minutes after baseline).

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Subjects randomized to placebo

Here also, most subjects had their peak vasoconstriction at 50 minutes post-baseline. Average maximum vasoconstriction in the LAD territory was 16.1% ± 7.8%, and average maximum vasoconstriction in the PCA territory was 13% ± 7.2% (Table 26).

Four subjects had ≥ 20% vasoconstriction in the LAD territory, and 1 subject had ≥ 20% vasoconstriction in the PCA territory. One patient each in the LAD and PCA territories exceeded 30% vasoconstriction.

Table 26: Maximum vasoconstriction at any timepoint in subjects randomized to placebo

Patient ID	LAD change	PCA change
39		
43		
29		
32		
23		
12		
34		
54		
49		
15		
17		
40		
26		
46		
3		
21		
7		
4		
Average	16.1±7.8	13±7.2

The degree of vasoconstriction increased over time even for patients randomized to placebo, as shown in Figure 7 , Figure 8, and in Table 27.

Figure 7: Vasoconstriction over time in the LAD territory for patients randomized to placebo

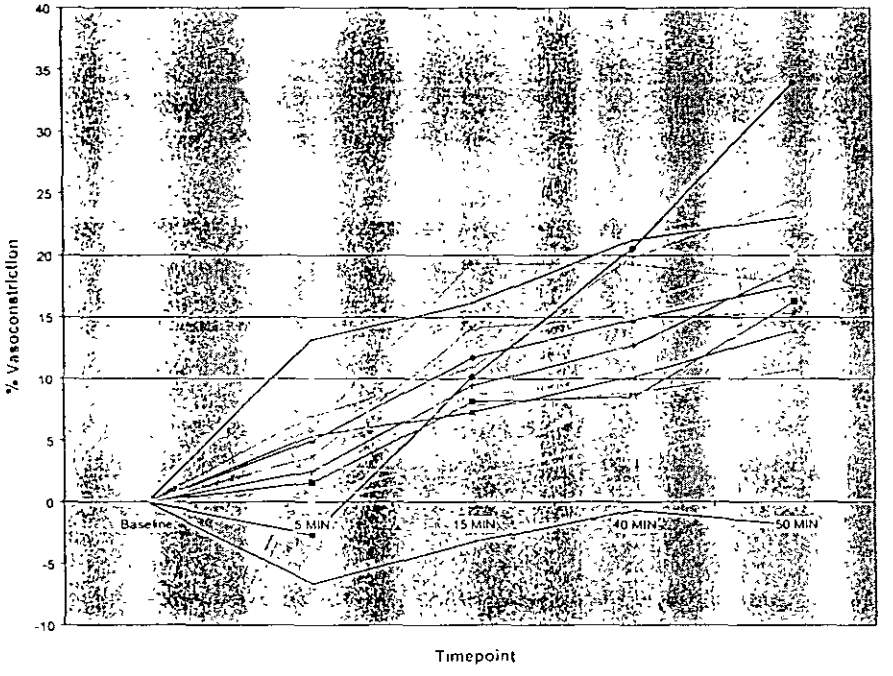


Figure 8: Vasoconstriction over time in the PCA territory for patients randomized to placebo

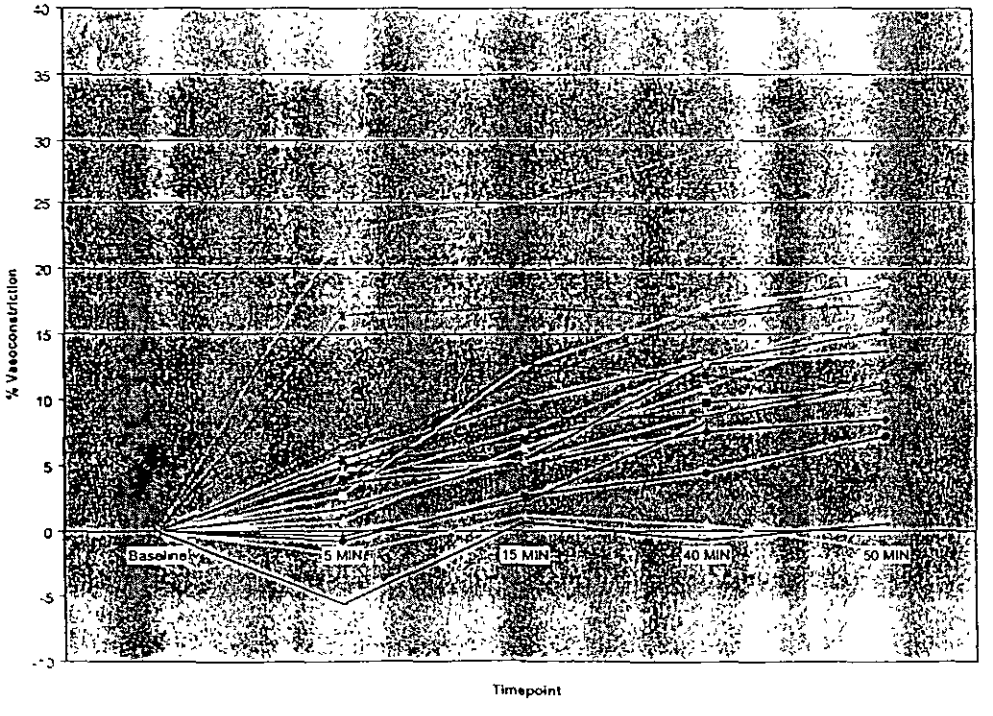


Table 27: Maximum vasoconstriction in any subject and average vasoconstriction for the group in the LAD and PCA territories for subjects randomized to placebo

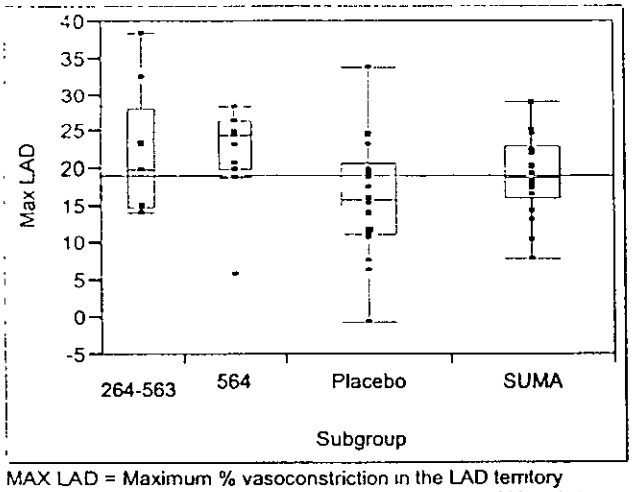
	5 min	15 min	40 min	50 min
LAD max vasoconstriction (%)	13.1	19 3	21.7	33.9
LAD avg vasoconstriction (%)	3.7 ± 4 4	9 3 ± 5.6	12.7 ± 6.4	15.9 ± 8 0
PCA max vasoconstriction (%)	22.8	25 0	29.3	33.1
PCA avg.vasoconstriction (%)	4 3 ± 4.4	8.1 ± 5.6	10.9 ± 6.4	12.8 ± 8 0

Group comparisons

In the following sections, I refer to the subgroup of patients randomized to eletriptan who had a C_{max} 264-563 ng/ml as "eletriptan 264-563", and to the subgroup of patients randomized to eletriptan who had a $C_{max} \geq 564$ ng/ml as "eletriptan 564". First, I verified if data were normally distributed. The distribution of the percent vasoconstriction in the left anterior descending artery (LAD) territory in the "eletriptan 564" subgroup was not normal (Shapiro-Wilk p=0.01; skewness p=0.006). Therefore, to compare data across groups, I first looked at the quantiles distribution. In Figure 9 and in the following box plots, the median is shown with the red horizontal bar in the middle of the box. The red box shows the limits of the 25% quartile and of the 75% quartile. The upper and lower red horizontal bars show the maximum and minimum values.

Figure 9 shows that the median % vasoconstriction in the "eletriptan 564" subgroup was the highest, but that the maximum and 75th quantile were higher in the "eletriptan 264-563" subgroup. Subjects randomized to placebo had the lowest median vasoconstriction, and subjects randomized to sumatriptan had mostly values between those of the eletriptan subgroups and those of the placebo group.

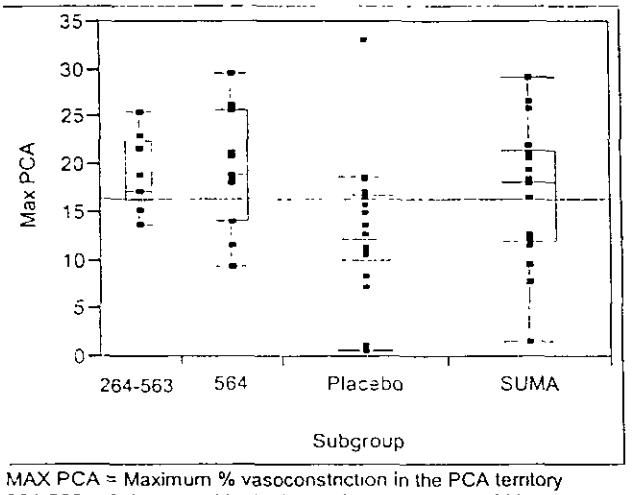
Figure 9: Quintile distribution for % LAD vasoconstriction



MAX LAD = Maximum % vasoconstriction in the LAD territory
264-563 = Subgroup with eletriptan plasma level 264-563 ng/ml
564 = Subgroup with eletriptan plasma level ≥ 564 ng/ml
Placebo = Placebo group
Suma = Sumatriptan group

Figure 10 shows the same comparison for percent vasoconstriction in the posterior circumflex artery (PCA) territory

Figure 10: Quantile distribution for % vasoconstriction in the PCA territory



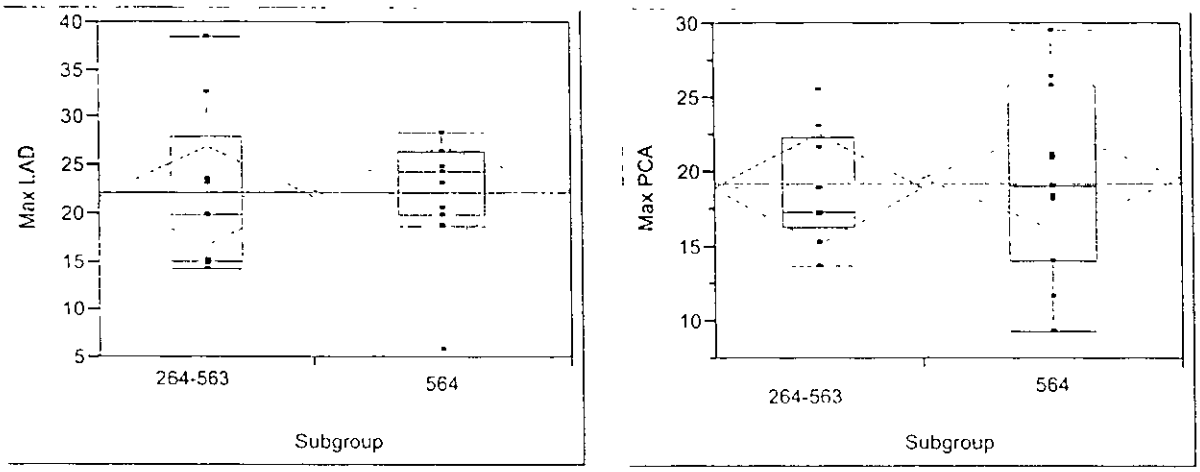
MAX PCA = Maximum % vasoconstriction in the PCA territory
264-563 = Subgroup with eletriptan plasma level 264-563 ng/ml
564 = Subgroup with eletriptan plasma level ≥ 564 ng/ml
Placebo = Placebo group
Suma = Sumatriptan group

Figure 9 and Figure 10 suggest that % vasoconstriction was similar in both eletriptan subgroups ("264-563" and "564"). The median vasoconstriction in both eletriptan subgroups was close to that of the sumatriptan group. The placebo group had a lower vasoconstriction than the active treatment groups.

Non parametric testing showed a trend for a statistically significant difference in the means between the "eletriptan 264-563" subgroup, the "eletriptan 564" subgroup, the placebo group and the sumatriptan group (p=0.051). I therefore tested subgroups by pairs. I did not correct for multiple comparisons since this testing was exploratory.

Figure 11 compares both subgroups of eletriptan subjects ("264-563" and "564"). The red lines have the same meaning as above. The green diamond show the 95% confidence interval, and the green horizontal line in the middle of the diamond shows the mean value.

Figure 11: Comparison of eletriptan subjects for LAD and PCA % vasoconstriction



MAX LAD = Maximum % vasoconstriction in the LAD territory
MAX PCA = Maximum % vasoconstriction in the PCA territory
264-563 = Subgroup with eletriptan plasma level 264-563 ng/ml
564 = Subgroup with eletriptan plasma level ≥ 564 ng/ml

LAD: The "eletriptan 264-563" and "eletriptan 564" subgroups were not significantly different (p=0.43, Wilcoxon rank sum test). The "eletriptan 564" subgroup was significantly different from the placebo group (p=0.01). The "eletriptan 264-563" subgroup was not significantly different from the placebo group (p=0.12). The "eletriptan 564" subgroup and the "eletriptan 264-563" subgroup were not significantly different from the sumatriptan group (respectively p=0.09 and p=0 68).

I also considered the entire population of subjects randomized to eletriptan who had a C_{max} ≥264 ng/ml (which includes the combined population of the "eletriptan 264-563" subgroup and of the "eletriptan 564" subgroup). This group was not significantly different from the sumatriptan group (p=0.18, Wilcoxon rank sum test), but was statistically different from the placebo group (p=0 01). The sumatriptan group was not different from the placebo group (p=0.15).

PCA: Again, the "eletriptan 264-563" and "eletriptan 564" subgroups were not significantly different (p=0.62). Both "eletriptan 264-563" and "eletriptan 564" subgroups were significantly different from the placebo group (respectively p=0.009 and p=0.01). The "eletriptan 264-563" and "eletriptan 564" were not significantly different from sumatriptan (respectively p=0.42 and p=0.54). For the combined "eletriptan 264-563" and "eletriptan 564" subgroups, there was no significant difference from the sumatriptan group (p=0.38, Wilcoxon rank sum test), but there was a significant difference from the placebo group (p=0.002). The sumatriptan group was not different from the placebo group (p=0.06).

Overall, as shown in Figure 11, both eletriptan subgroups were very similar, with the exception of outliers. Given the small sample size, the lack of significant difference between the eletriptan and sumatriptan groups has limited meaning.

I also conducted non-inferiority analysis after logarithmic transformation. I first calculated the geometric means to compare patient groups. Table 28 shows the ratios of geometric means of the differences in coronary artery diameter between the minimum measurement and the baseline measurement. Sponsor's estimates are shown in brackets. My analysis essentially reproduced the results reported by the Sponsor for the geometric means ratio. The "264-563" and "564" eletriptan subgroups had almost identical results.

Table 28: Geometric means of LAD and PCA vasoconstriction

	LAD min/base diameter geometric mean ratio (Sponsor's estimate)	LAD 95% CI	PCA min/base diameter geometric mean ratio (Sponsor's estimate)	PCA 95% CI
Eletriptan (all ≥ 264)	0.78 (0 78)	0.75-0.81	0 81 (0.81)	0.78-0.83
Eletriptan 264-563	0.78	0.71-0.85	0 81	0.78-0 84
Eletriptan ≥ 564	0.78 (ND)	0 74-0.82	0 80 (ND)	0.78-0 84
Placebo	0.84	0.80-0.88	0.92	0 89-0.95
Sumatriptan	0.81 (0 81)	0.78-0 84	0 83 (0 83)	0.79-0 87

I also recalculated the ratio of the geometric means of eletriptan versus sumatriptan, which was the study primary outcome. This is shown along with other ratios in Table 29 for the LAD and Table 30 for the PCA.

Table 29:Ratios of geometric means for the LAD

	/Placebo	/Sumatriptan (95%CI)
Eletriptan (all ≥ 264)	0.927	**0.961 (0.93-1.01)**
Eletriptan 264-563	0 929	0.963 (0.88-1 05)
Eletriptan ≥ 564	0.926	0.960 (0 91-1.01)
Sumatriptan	0.964	

Table 30: Ratios of geometric means for the PCA

	/Placebo	/Sumatriptan
Eletriptan (all ≥ 264)	0.879	**0.974 (0.94-1.00)**
Eletriptan 264-563	0.884	0.979 (0.94-1.02)
Eletriptan ≥ 564	0.875	0.970 (0.91-1.01)
Sumatriptan	0.903	

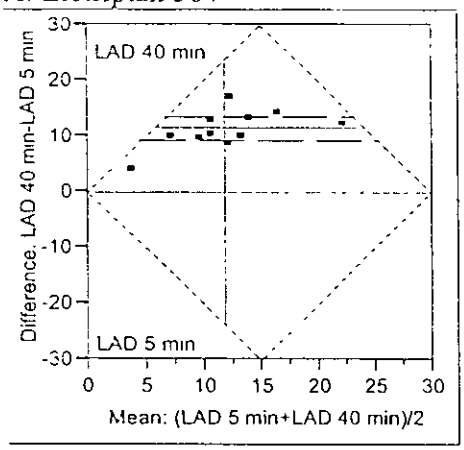
For the LAD and the PCA, the non-inferiority criteria (eletriptan effect ≥ 0.9 sumatriptan effect) was met for all subgroups, except for a borderline value for the "eletriptan 264-563" subgroup in the LAD territory (0.88). The issue of power of analysis and assay sensitivity remains, given the small sample size.

Intra-subject comparison of vasoconstriction at low eletriptan concentration versus high eletriptan concentration

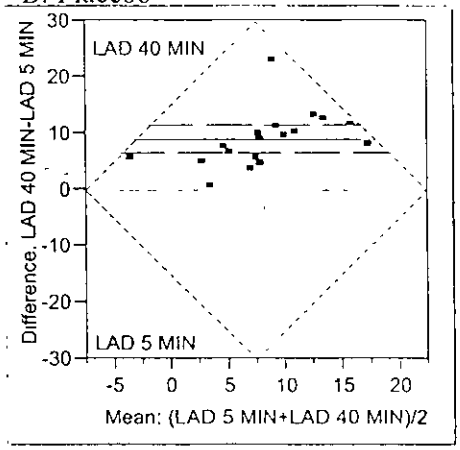
For the "eletriptan 564" subgroup, I made paired comparisons of the % vasoconstriction at the 5 minutes timepoint (eletriptan avg. concentration 155.1 ng/l), to % vasoconstriction at the 40 minutes timepoint (eletriptan avg. concentration 833.6 ng/ml). My objective was to use subjects as their own control, to determine if the high eletriptan concentrations expected with CYP3A4 inhibition induced higher vasoconstriction than concentration closer to the range expected without CYP3A4 inhibition, in the same subjects. Figure 12 shows the matched pairs difference between % vasoconstriction at 40 min and % vasoconstriction at 5 min in the "eletriptan 564" subgroup . Mean difference was 11.3%.

Figure 12: Matched pairs difference of % vasoconstriction at 40 min versus % vasoconstriction at 5 min in the "eletriptan 564" subgroup (A) and placebo group (B)

A: Eletriptan 564



B: Placebo



LAD 5 min = % vasoconstriction at 5 min
LAD 40 min = % vasoconstriction at 40 min

However, there are 2 caveats in the interpretation of these data. First, there may be a time lag between eletriptan T_{max} and the time of maximum pharmacodynamic effect. Second, vasoconstriction increased over time even in the placebo group (see Figure 12 B), so that the increased vasoconstriction at 40 minutes may be related not to eletriptan, but to other factors. Mean difference in placebo subjects was 8.98 %.

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Concomitant medications

I looked at the use of concomitant medications with potential effect on the coronary circulation in the Condrug.xpt dataset. I identified the overall use of concomitant medications in Table 31.

Table 31: Concomitant medication occurrences

Drug	Eletriptan	Sumatriptan	Placebo
Amlodipine	1	6	3
Atenolol	4	11	9
Atropine	1	1	0
Irbesartan/HCTZ	3	0	0
Doxazosin	3	0	0
Fosinopril	0	0	3
Gemfibrozil	3	3	0
Isosorbide Mononitrate	2	4	3
Lisinopril	9	12	0
Losartan	0	0	9
Metoprolol	17	20	28
Nitroglycerin	25	17	17
Propanolol	3	0	3
Ramipril	0	0	2
Timolol	0	0	3
Valsartan	3	3	0

Overall, there was no major imbalance across therapeutic classes. The actual doses of nitrates given to subjects during the procedure were unfortunately not available. I identified a subset of procedure related drugs susceptible to have an effect on vasoconstriction or vital signs (Table 32).

Table 32: Procedure-related concomitant medications

Drug	Eletriptan (n=18)	Sumatriptan (n=18)	Placebo (n=18)
Atropine	1 (4%)	3 (17%)	0 (0%)
Nitroglycerin	9 (38%)	4 (22%)	1 (6%)

There was an imbalance between the groups, with more nitroglycerin use in the eletriptan group. This may be related to the higher incidence of "vasoconstriction" adverse events in the eletriptan group (see below).

Adverse events.

Adverse event (AE) data were provided in the adverse.xpt dataset. I first looked at the distribution of AEs across the 3 treatment groups (eletriptan, sumatriptan and placebo).

Table 33 confirms the imbalance in the number of vasoconstriction events reported, with all 8 events occurring in eletriptan subjects. Chest tightness, frequent PVCs and left bundle branch block were also reported only in 2 eletriptan subjects each. One case of exacerbated transient ST elevation (ECG) occurred in one eletriptan patient. On the other hand, one case of exacerbated chest pain and one case of chest pain were reported in placebo subjects only,

and 2 cases of mild chest heaviness in sumatriptan subjects only. Overall, chest symptoms were similar across drug groups. I concentrated my analysis on the cases of vasoconstriction.

Table 33: Adverse events list in study 1072

ADVERSE EVENT	Total (n=60)	Eletriptan (n=24)	Sumatriptan (n=18)	Placebo (n=18)
VASOCONSTRICTION	8	8	0	0
CHEST TIGHTNESS	2	2	0	0
FREQUENT PVC'S	2	2	0	0
LEFT BUNDLE BRANCH BLOCK	2	2	0	0
RIGHT FEMORAL ARTERY DISSECTION (TRAUMATIC)	2	2	0	0
RIGHT FEMORAL ARTERY THROMBUS	2	2	0	0
DIMINISHED PULSES RIGHT FOOT	1	1	0	0
EXACERBATED TRANSIENT ST ELEVATION (ECG)	1	1	0	0
LIGHT HEADED X 2 DAYS	1	1	0	0
NAUSEA	2	1	1	0
NAUSEA AT HOME AFTER DISCHARGE	1	1	0	0
RIGHT FEMORAL ARTERIAL PUNCTURE SITE BLEEDING	1	1	0	0
TIRED X 2 DAYS	1	1	0	0
URTICARIAL LESIONS ON FACE & CHEST	1	1	0	0
CHEST PAIN	1	0	0	1
EXACERBATED CHEST PAIN	1	0	0	1
EXACERBATION BRADYCARDIA	1	0	1	0
FAST HEART RATE	1	0	0	1
GROIN BURNING AT SHEATH INSERTION SITE	1	0	0	1
HEADACHE	1	0	1	0
INCREASE IN FEMORAL ARTERY SYSTOLIC BP	2	0	2	0
LEFT WRIST PAIN	1	0	0	1
MILD CHEST HEAVINESS	2	0	2	0
PATIENT SITTING IN CHAIR FEELING CLAMMY	1	0	1	0
PATIENT SITTING IN CHAIR FEELING FAINT	1	0	1	0
PREGNANCY	2	0	2	0
SPONTANEOUS ABORTION	1	0	1	0
UNUSUAL BODY ODOR SINCE PROCEDURE	2	0	0	2

In all eight cases, vasoconstriction was attributed to the study drug (mild in seven cases, and moderate in one case). Duration ranged from 5 minutes to 5 days, 23h and 59 minutes (?). Treatment was given in 5/8 cases, and study drug was discontinued in one case. AE was not considered serious in any case (Table 34).

Table 34: Subjects with vasoconstriction AE

Patient ID	Eletriptan dose	Severity	Duration	Treatment given?
2	36 MG	mild	5 min	Yes
6	36 MG	mild	44min	Yes
19	36 MG	mild	5 d 23 h 59min	No

25	36 MG	mild	10 min	No
35	52 MG	mild	12 min	Yes
42	72 MG	mild	46 min	Yes
48	72 MG	mild	45 min	No
50	72 MG	moderate	15 min	Yes.

* Patient discontinued

I also used the FDAeff.xpt dataset to identify if the reported vasoconstriction AE was associated to a high degree of vasoconstriction at any time during the study period, or to a high eletriptan blood level. Table 35 shows that there was not clear pattern in the peak eletriptan plasma level or peak % vasoconstriction (as evaluated by the blinded Quantitative Coronary Angiography (QCA)) in these patients, except for patient 50. Patient 50 had the highest % vasoconstriction of any patient at 15 minutes and 25 minutes post-baseline. Patient 19 has the second highest peak % vasoconstriction. The other six subjects were within the range of % vasoconstriction observed in the eletriptan group. Observations were similar for the PCA territory. COMMENT: this lack of correlation raises questions about the validity of the study, since there is no clear relationship between AE reports of vasoconstriction and coronary artery diameter measurements by the QCA lab.

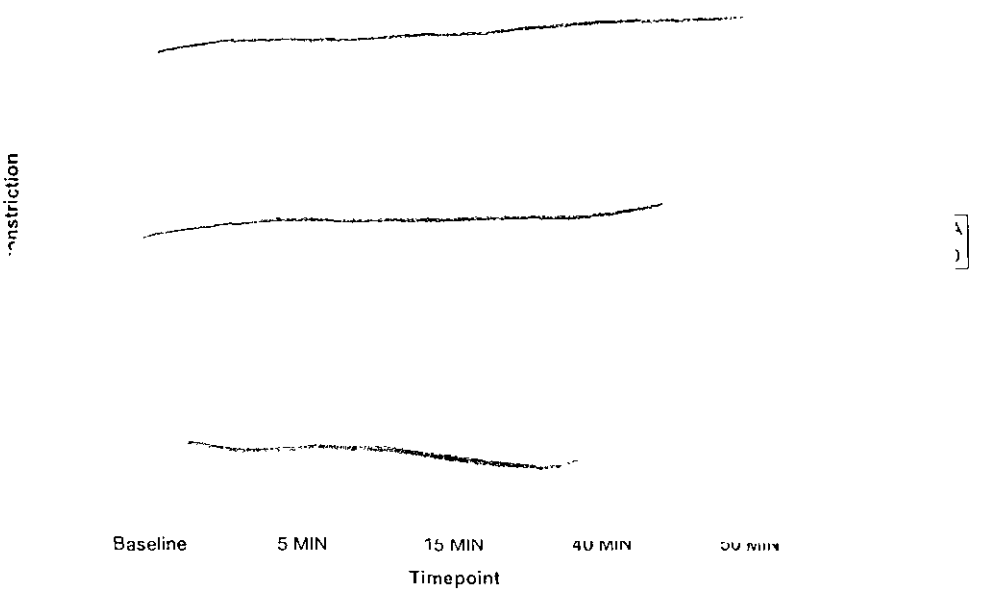
Table 35: Characteristics of subjects with vasoconstriction adverse event

Patient ID	Eletriptan level (ng/ml)	LAD max vasoconstriction (%)	PCA max Vasoconstriction (%)
2			
6			
19			
25			
35			
42			
48			
50			
Average	662±348	23.5±8.8	19.9±5.9

Because of the apparent discrepancy between AE reports and peak % vasocosntriction, I reviewed the case report forms of all 8 subjects who had a vasoconstriction AE.

Subject 2 (Dr. Goldstein investigator) was a 52 year old white female with a history of hypertension and hyperlipidemia. Eletriptan infusion started at 12:15. The AE of vasoconstriction was reported at 12:55 (40 minutes timepoint). The AE was initially reported as "vasospasm >30% per attending at 40 minutes. Resolved once drug stopped. Resolved with IC nitrates." This was later crossed and replaced by "vasoconstriction." The patient received nitroglycerin at 13:00. The AE was reported as resolved at 13:00.

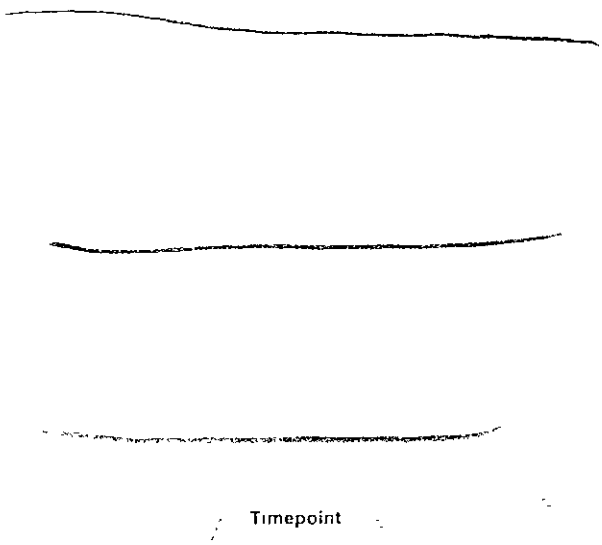
Figure 13: % Vasoconstriction in Subject 2



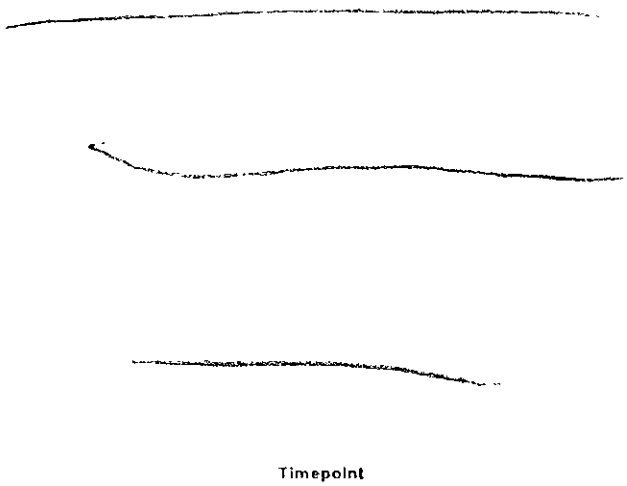
The blinded QCA is in disagreement with the AE description. In this patient, the % vasoconstriction was not remarkably high at 40 minutes post-baseline (time of the AE), but increased rather dramatically by 50 minutes post-baseline, when the AE was deemed "resolved" by the investigator.

Subject 6 (Dr. Goldstein investigator) was a 44 year old white male with a history of angina and systolic heart murmur. The patient had several ECGs during the procedure relative to the patient experiencing vasospasm (per investigator). Infusion was started at 08:05. The AE of vasoconstriction was reported as occurring at 08:20 (15 minutes post-baseline). It was described as "vasoconstriction." Patient received nitroglycerin at 09:04. AE was resolved at 09:04. Again, there is a discrepancy between the time of AE and QCA (Figure 14).

Figure 14: % Vasoconstriction in Subject 6



Subject 19 (Dr. Goldstein investigator) was a 35 year old white male with a history of abnormal stress test and chest pain. AE was first reported as "narrowing of the left anterior descending artery and narrowing of circumflex artery." This was replaced by "vasoconstriction." Infusion started at 11:34. Time of AE was reported "unknown."



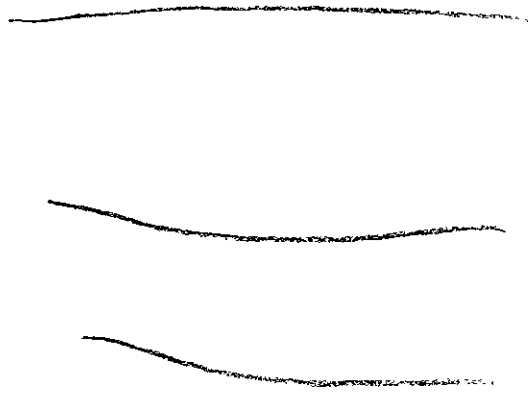
Subject 25 (Dr. Goldstein investigator) was a 42 year old white male with a history of angina, hyperlipidemia and abnormal stress imaging (inferior/posterior ischemia). This patient had an AE of "exacerbated transient ST elevation" and "transient vasospasm in proximal LAD." ECG was normal at baseline. ECG post-procedure (10:15) had ST elevation in II, III, AVF and ST depression in AVF. Eletriptan infusion started at 09:35. AE of vasoconstriction was reported at 10:15 (40 minutes post-baseline). No action was taken. AE was reportedly resolved at 10:25 (50 minutes post-baseline). ECG at 11:36 was reportedly normal.

Figure 16: % Vasoconstriction in Subject 25

Figure 16 shows a discrepancy between the reported improvement at 50 minutes post-baseline and the observations of the blinded evaluator (QCA).

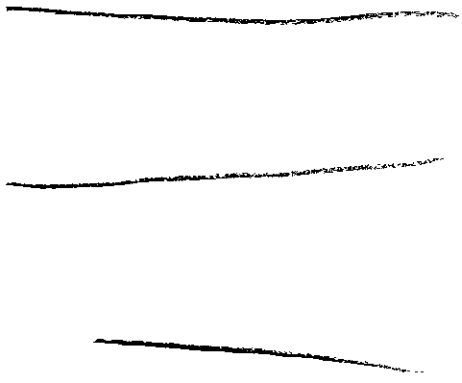
Subject 35 (Dr. Goldstein investigator) was a 54 year old white male with a history of recurrent tension type headache, hyperlipidemia, chest pain and positive stress test. Eletriptan infusion started at 15:45. AE vasoconstriction onset was reported at 16:25 (40 minutes post-baseline). The original event description was crossed and is essentially unreadable. It was replaced by "vasoconstriction." IC nitroglycerin was administered at 16:36 (41 minutes post-baseline). AE was reported as resolved at 16:37 (42 minutes post-baseline). Again, there is a discrepancy between the adverse event report and the blinded QCA (Figure 17).

Figure 17: % Vasoconstriction in Subject 35



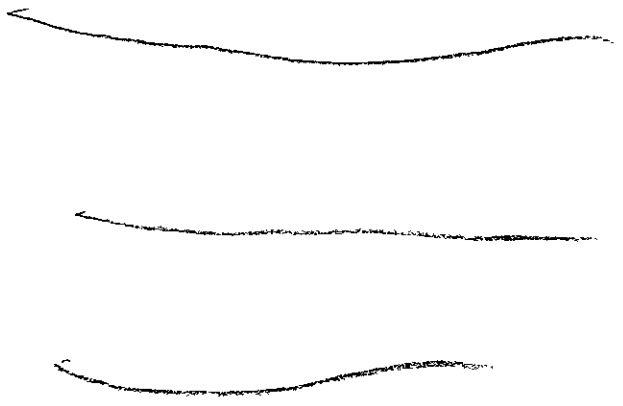
Subject 42 was a 46 year old white female with a history of chest pain, and abnormal myocardial perfusion scan. Eletriptan infusion started at 14:05. AE was first reported as "diffuse 50% ? ?". Onset was at 14:10 (5 minutes post-baseline). This was crossed and replaced by "vasospasm." Patient received nitroglycerin at 14:56 (50 minutes post-baseline). AE was reported as resolved at 14.56. Again, I found a discrepancy between AE description and QCA evaluation (Figure 18).

Figure 18: % Vasoconstriction in Subject 42



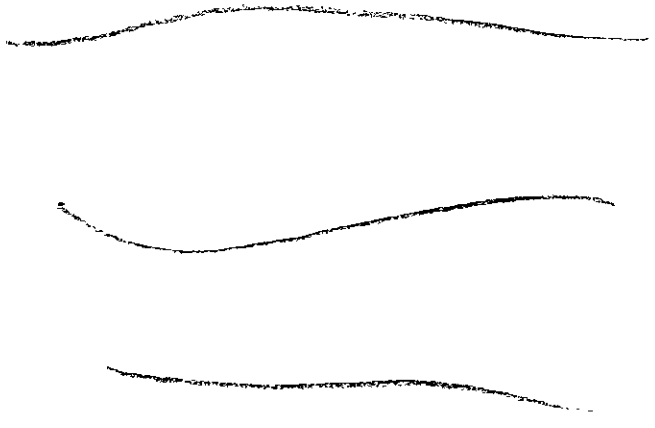
Subject 48 (Dr. Goldstein investigator) was a 54 year old white male, with a history of hypertension, hyperlipidemia, positive stress test, and mild polyvalvular insufficiency. Eletriptan infusion started at 13:00 AE onset was at 13:05 (5 minutes post-baseline). It was first reported as "mild diffuse ? spasm." This was crossed and replaced by "vasoconstriction." AE was reported as resolved at 13:50 (50 minutes post-baseline). Again, there was a discrepancy between the AE description and QCA assessments (**Figure 19**).

Figure 19: % Vasoconstriction in Subject 48



Subject 50 was a 53 year old black female with a history of migraine headache, and chest pain. Eletriptan infusion started at 12:01. AE onset was at 12:16 (15 minutes post-baseline). AE was first reported as ">50% increase in narrowing of diameter of previous 20% vasospasm". This was crossed, and replaced by "vasoconstriction." Patient received nitroglycerin at 12:28. AE was reported as resolved at 12:31 (30 minutes). There is no evidence of resolution from the QCA (Figure 20).

Figure 20: % Vasoconstriction in Subject 50



In an effort to reconciliate the discrepancies seen in several subjects with a vasoconstriction AE between the QCA and narratives of AEs by investigators, I requested the source documents for these subjects. Unfortunately, source documents did not provide the investigator estimates of the degree of vasoconstriction at timepoints across the study, so that they were not helpful.

These eight cases were also discussed by the Sponsor at the pre-NDA meeting. The following paragraph is an excerpt from the Sponsor's meeting minutes of the pre-NDA meeting. *"Dr. Goldstein, the principal investigator for Study 1072, explained that the subjects he enrolled were either from his own practice or from other colleagues who wanted to be certain that their subjects would not be subjected to any undue risk from that which they were informed when signing the Patient Consent Form. Although initially cautious as to the size of the unknown effects, he gradually became reassured with the triptans as he could not discern any clinical effect that seemed to distinguish between any of the treatment groups Dr Goldstein adopted a conservative approach suggesting that nitroglycerin be administered in any situation where the operator felt any concern about subjects who demonstrated a vasoconstrictive response. He was not aware of any significant vasoconstriction being reported during his attendance at any angiographic procedures and was surprised to see them in the study database. He confirmed that angiographers were not routinely queried to describe such an effect as it was anticipated that this information would be collected by the blinded angiographic assessment. He emphasized that there was no relationship between the Quantitative Coronary Angiography (QCA) and the subjective observations on these eight subjects and that none of these subjects were discontinued from the study. He concluded that the disparity of these eight subjects compared to the others in the study emphasizes the limitations of subjectively assessing mild change in the coronary arteries in comparison to QCA. Dr. Jackson added that there was no difference in the symptoms described by these subjects nor in their hemodynamic variables such as blood pressure, that distinguished them from other subjects in the study Drs. Katz and Temple noted that some of the extremely small objective changes from baseline (.01mm, .35mm, .08mm, etc) described as vasoconstriction in these eight subjects would seem impossible to visually identify by inspection alone. Dr. Rankin stated that angiograms from all eight subjects had been subsequently reviewed by the core laboratory, which was unable to discern any specific notable features of the angiograms. While agreeing that the vasoconstrictor effects in Study 1072 were small, Dr. Temple noted that when viewing the effect of ergonovine on the coronary artery, vasoconstriction is dramatic. Dr. Goldstein concurred and suggested that the triptans appeared to produce an effect within the physiologic range of coronary dynamic constriction."* COMMENT: this explanation does not justify why all events of vasocontriction occurred in the eletriptan subgroup, with sometimes large percentages of vasoconstriction reported by the angiographer, such as in Subject 50 or in Subject 42..

2.6.3.5.2 Cardiology consult

A cardiology consult was requested about study 1072. The full consult report (Dr. Marciniak) is copied in section 2.11.1.1. I share the concerns of Dr. Marciniak. The key conclusions of his consult are:

1. Most aspects of the methodology were excellent In retrospect there appear to be major flaws: variations in coronary artery tone were not controlled, and multiple segments measurements were not done.
2. This study failed to show a drug effect for the primary endpoint either with eletriptan or with the active control sumatriptan, so no information is provided by the primary endpoint results. The methodology failed for the primary endpoint.
3. The primary endpoint may fail to detect localized spasm. The interpretation of small changes in artery diameter is difficult.
4. While myocardial bridging might partially account for the event in Subject 50, Dr Marciniak is not reassured. If similar events occurred in the one-third of adults with myocardial bridges taking eletriptan and CYP3A4 inhibitors, Dr. Marciniak would worry about an increased risk of ischemic events.
5. The vasoconstrictive adverse events occurring only in one-third of eletriptan patients are cause for concern. They suggest, but do not prove conclusively, that eletriptan may lead to increased rates of cardiac ischemic events.
6. This study does not answer the question of what is the risk of cardiac ischemic events in patients exposed to high levels of eletriptan when taken concomitantly with a CYP3A4 inhibitor. Answering the latter question is difficult and the Cardio-renal Division has no suggestion for additional studies.

2.6.3.5.3 Study 160-039

2.6.3.5.3.1 Study protocol

Study 160-309 "a double-blind randomized, placebo-controlled, single-dose, parallel group study to compare the effects of intravenous eletriptan and subcutaneous sumatriptan on the coronary circulation in subjects undergoing percutaneous transluminal coronary angioplasty for single vessel disease" was not requested by FDA, but was conducted on the Sponsor's initiative.

The study was conducted in 46 subjects in one center in Portugal, and in 5 centers in the United Kingdom. The study had a general design similar to Study 1072. The major difference was the patient population (subjects candidate for angioplasty with angina pectoris and documented ischemia, unstable angina pectoris and documented ischemia or documented silent ischemia), eletriptan dose used (6 mg instead of up to 72 mg) and duration of administration (15 minutes infusion instead of 40 minutes). Subjects also were administered 200 µg intracoronary glyceryl trinitrate to determine if this could reverse drug effects if any. The dose of sumatriptan was the same as in study 1072 (6 mg sc).

In this study, investigators directly measured coronary artery diameter, instead of using a blinded central reading Investigators took measurements at five minutes pre-dose, at the

start of dosing (baseline), at 15 and 30 minutes post-baseline, and two minutes after glyceryl trinitrate administration (defined as 32 minutes post-baseline). Measurements were also made if chest symptoms occurred prior to angioplasty. In contrast to study 1072, one single vessel was studied. Investigators also measured intracoronary blood pressure, systemic blood pressures, ECGs and heart rate up to 30 minutes post-infusion start and two minutes later after an intracoronary bolus of glyceryl trinitrate 200mg. An independent expert assessed and wrote narratives for each ECG without knowledge of study drug treatment. Investigators took blood samples up to 30 minutes post-dose for assay of plasma eletriptan and sumatriptan and calculation of pharmacokinetic parameters.

The study analyzed an intention to treat (ITT) group, of subjects who received study drug and had some on-study drug data and an evaluable (EVAL) group who satisfied the ITT criteria plus other inclusion criteria. The main primary analysis was based on the % change from baseline to 15 minutes post-baseline in coronary artery diameter (CAD) at the focal point of stenosis. This time point was chosen as it was expected to coincide with the peak drug concentration and therefore maximum coronary effects. The comparison of interest was between eletriptan 6mg iv and sumatriptan 6mg sc. The Wilcoxon-Mann-Whitney test was used and a corresponding non-parametric 95% confidence interval (CI) calculated.

The secondary objectives analysis concerned:

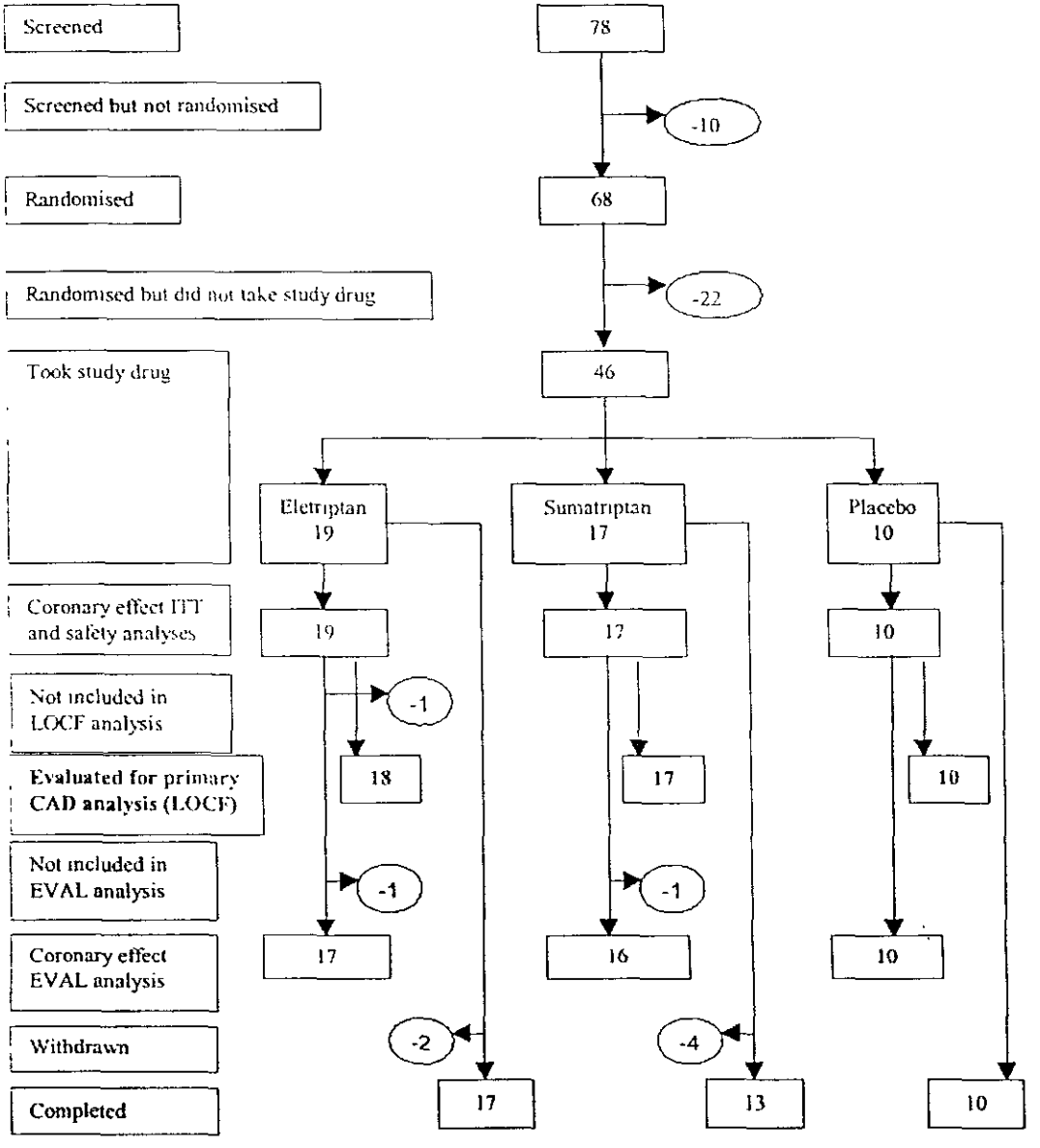
1. Median % change in coronary artery diameter (CAD) from baseline at 15, 30 and 32 minutes post-baseline.
2. Maximum % CAD decrease at any time after study drug administration, and maximum % CAD decrease observed in each group.
3. Mean intracoronary pressure proximal and distal to the stenosis.
4. Mean arterial pressure, calculated as DBP + [1/3 x (SBP minus DBP)], at baseline, 15, 30 and 32 minutes post-baseline.
5. % change from baseline in the intracoronary pressure gradient and ratio at 15, 30 and 32 minutes post-baseline.
6. Intracoronary pressure and CAD whenever a subject had a chest symptom episode
7. Mean heart rate, SBP, DBP, 12-lead ECG data and plasma concentrations of eletriptan and sumatriptan.

2.6.3.5.3.2 Study Results

Patient disposition

Patient disposition is summarized in Figure 21. Six subjects were discontinued from the study, all because of adverse events; 2 in the eletriptan group and 4 in the sumatriptan group. Both withdrawals of subjects of the eletriptan group were considered to be unrelated to study drug.

Figure 21: Patient disposition (pages 29, study 160-309 report)



Coronary artery diameter (CAD) results (Sponsor's analysis with reviewer's comments)

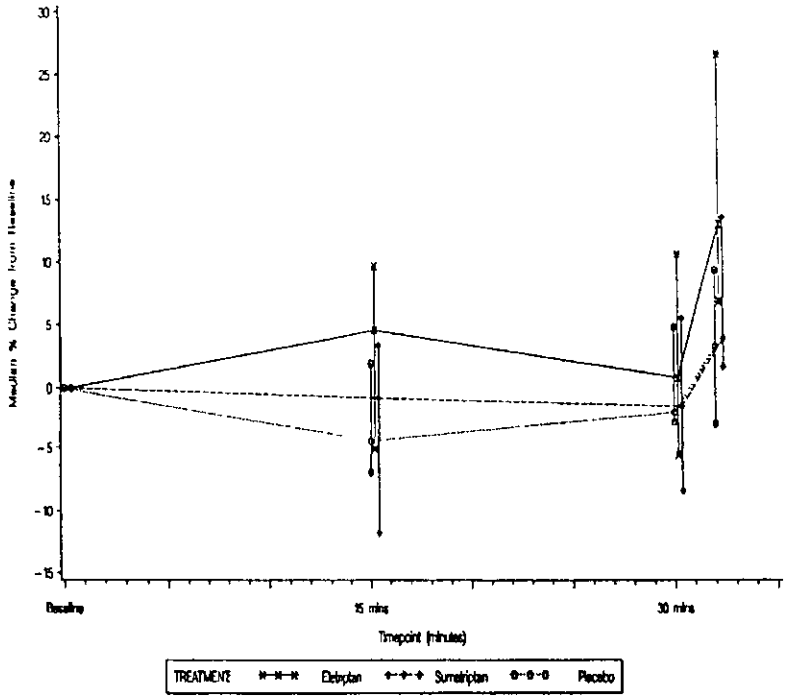
The Sponsor performed a pre-planned blinded interim analysis of the baseline variability after the first 20 subjects were treated. The standard deviation of the baseline variability was 15.16%, which was 8.26% higher than the estimate of 6.9% and would have required a

sample size of 190 subjects to produce 80% power for the primary analysis. The Sponsor decided that it was not practical to recruit 190 subjects but that recruitment would continue up to 45 evaluable subjects as specified in the protocol.

The median CAD changes for eletriptan and sumatriptan were small and in opposite directions. There was a 2.6% dilatation after eletriptan and a 6.85% constriction after sumatriptan. This difference was not statistically significant (p=0.062). Placebo reduced CAD more than eletriptan but less than sumatriptan at the focal point of the stenosis 15 minutes post-baseline. COMMENT: this result is somewhat counter-intuitive, given the known pharmacological effect of triptans, and raises some questions about the study validity. It probably represents a random variation in the placebo group.

There was no evidence that eletriptan causes coronary constriction in this small population. In all groups, subsequent nitrates administration reversed the vasoconstriction at the focal point of the stenosis.

Figure 22: % change from baseline in coronary artery diameter at focal point of stenosis (from figure 1.7, Sponsor study report)



Placebo reduced CAD numerically more than eletriptan but less than sumatriptan at the focal point of the stenosis 15 minutes post dose. In all groups, nitrates produced a significant vasodilatation at the focal point of the stenosis. There was no association between chest pain

and CAD reductions COMMENT: placebo induced much less vasoconstriction in this study than in Study 1072.

Figure 23 shows the distribution of maximum % CAD changes post-baseline for all ITT subjects in each study drug group. The Sponsor defined the maximum % CAD change in this context as either the largest decrease or, in the case of there being no decrease, the smallest increase.

Figure 23: Maximum % change post baseline in coronary artery diameter at focal point of stenosis in ITT population (from page 42, study 160-309 report)

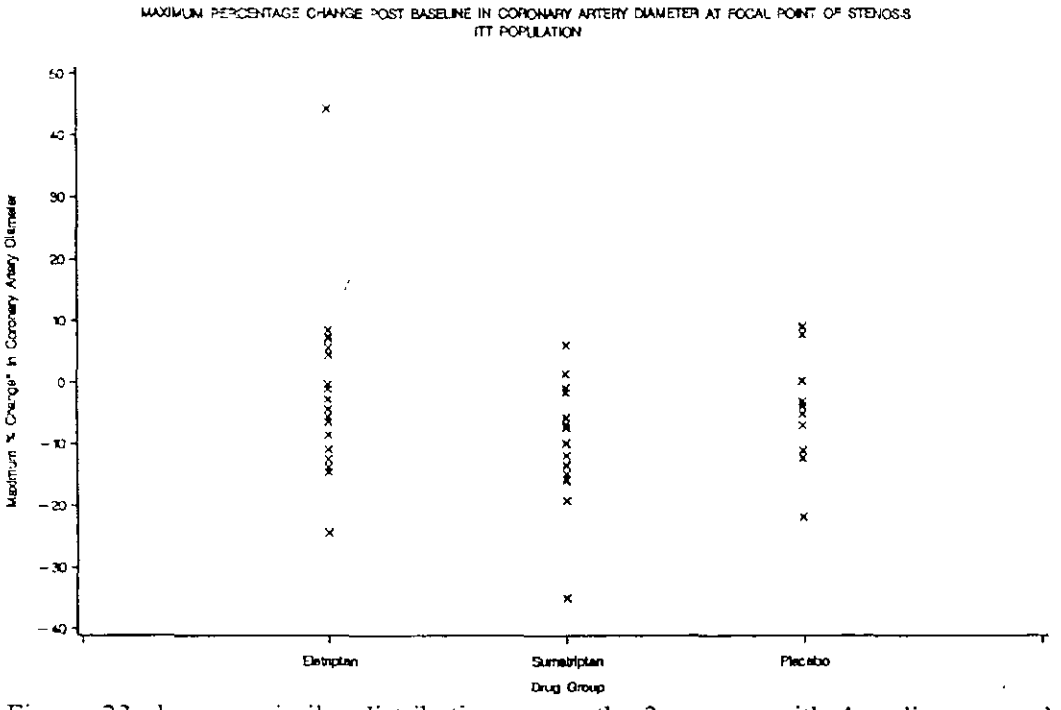


Figure 23 shows a similar distribution across the 3 groups, with 4 outliers: one eletriptan patient with very large vasodilation, and one patient of each group with somewhat larger vasoconstriction, most extreme in the sumatriptan group.

There were 13 subjects, 4 in the eletriptan group (21%), 8 in the sumatriptan group (47%) and 1 in the placebo group (10%), who experienced chest pain. 5/13 subjects had focal CAD reductions post-dose of >10% (2 and 3 after eletriptan and sumatriptan, respectively). 1/4 eletriptan subjects had ischemic ECG changes (Subject 03430301). This subject had no ischemic sign at baseline ECG, with sinus rate of 108 bpm. 8 minutes post-infusion, patient had a 1mm ST segment depression of V5 – V6, with sinus rate of bpm. 11 minutes post-infusion during chest pain, patient had 2mm ST segment depression in V5, 2.5mm ST segment depression in V6 at a heart rate of 134 bpm. Nitrates were not administered to this

patient. 3/8 sumatriptan subjects had ischemic ECG changes emerging or worsening post-dose.

Systemic Blood Pressure

Mean systemic blood pressure increased after each treatment until returning to near baseline levels after nitrates administration. The sumatriptan group had the highest mean at baseline and the largest mean increase. Mean baseline and post-dose heart rate were similar for each study group but were raised after nitrates, most likely as a reaction to the SBP reduction.

Table 36: Blood pressure and heart rate changes in the 3 dosage groups

Time	Eletriptan 6mg iv		Sumatriptan 6mg sc		Placebo	
(min)	N=17 to 19		N=11 to 17		N=10	
	Blood pressure (mmHg)	Heart rate (bpm)	Blood pressure (mmHg)	Heart rate (bpm)	Blood pressure (mmHg)	Heart rate (bpm)
0	144/79	79	162/79	69	148/76	65
+5	153/84	74	184/87	70	153/78	65
+10	157/84	74	191/91	70	157/78	64
+15	158/84	70	187/87	68	155/78	64
+20	155/83	70	182/85	66	156/79	66
+25	153/82	70	180/85	66	156/79	64
+30	150/83	71	175/80	65	155/79	64
+32	135/84	81	160/87	75	129/80	75

ECG Parameters:

The PR, QRS, QT and QTc intervals were unaffected by the study drugs. Some subjects had ischemic ECG abnormalities at baseline. Eight subjects had evidence of ischemic ECG changes, 3 and 5 after eletriptan and sumatriptan, respectively. None of the four subjects who reported chest pain after eletriptan had ischemic ECG changes attributed to the study drug.

Pharmacokinetic Results:

The eletriptan infusion produced a plasma concentration of 102 ng/ml at 15 minutes post-baseline, which was consistent with the C_{max} obtained after an oral 80mg dose in subjects with a migraine attack. This peak level was much lower than in study 1072. This means that data of this study are not relevant to the issue of the higher eletriptan levels seen with CYP3A4 inhibition. This study addresses only the safety of a single dose of eletriptan 80 mg (or 2 doses of eletriptan 40 mg) in the cardiac population.

Adverse events

Table 37 lists all treatment-emergent adverse events. The adverse events reported in this study were mostly mild or moderate. 22/46 subjects (47.8%) reported at least one adverse event, comprising 9/19 subjects in the eletriptan group (47.4%), 10/17 subjects in the sumatriptan group (58.8%) and 3/10 subjects in the placebo group (30.0%). Chest pain and rash were the only events reported by more than one subject in any study drug group.

Table 37: Treatment emergent adverse events (from table 6.1.1, Study 160-309 report)

TREATMENT EMERGENT ADVERSE EVENTS (ALL CAUSALITIES)

NUMBER OF:	ELETRIPTAN (6.0 MG)	(%)	SUMATRIPTAN (6.0 MG)	(%)	DOUBLE BLIND PLACEBO	(%)
Subjects Treated	19		17		10	
Subjects-DAYS of Drug Exposure	19		17		10	
Subjects with Adverse Events	9	(47.4)	10	(58.8)	3	(30.0)
Adverse Events	14		15		6	
Subjects with Serious Adverse Events	1	(5.3)	2	(11.8)	0	
Subjects with Severe Adverse Events	2	(10.5)	3	(17.6)	0	
Subjects discontinued due to Adverse Events	2	(10.5)	4	(23.5)	0	
Subjects with dose reduced or temporary discontinuation due to Adverse Events	0		0		0	

8/46 subjects (19.6%) had at least one treatment related adverse event, comprising 2/19 eletriptan subjects (10.5%) and 6/17 sumatriptan subjects (41.2%). Chest pain was the only treatment related event reported by more than one subject in any study drug group. There was one subject (5.3%) with moderate chest pain after eletriptan. There were 6 subjects with chest pain after sumatriptan (2 severe).

Serious adverse events

There were five serious adverse events in this study, none of which were related to study drug. Two occurred after eletriptan infusion. Subject 01410054 was a 64-year-old male who was hospitalized for a GI bleed lasting for 7 days from 3 days after eletriptan. The investigator considered the event related to aspirin. Subject 01410065 was a 72-year-old female who had unstable angina from 24 days after eletriptan and was hospitalized. The investigator gave the diagnosis of musculo-skeletal pain.

Adverse dropouts

Six subjects discontinued because of adverse events. The four discontinuations in the sumatriptan group were due to chest pain or chest pain and headache and were study drug related. Both discontinuations in the eletriptan group were considered not to be treatment related; one was related to chest pain and intra-coronary thrombus, and the other to chest pain. I can not rule out that there was no treatment causality in either case.

Subject 03250010 had the eletriptan infusion stopped after 10 minutes because of severe chest pain, associated with slight ST elevation. The angiography suggests intra-coronary thrombus proximal to the lesion. The LAD lesion was treated by primary stenting, with improvement in distal flow. However, angiography showed filling defects in the distal LAD, related by the Sponsor to thrombus possibly embolised during stent deployment. The patient subsequently had residual chest discomfort associated with minor enzyme and ECG changes the following day, interpreted as myocardial necrosis. The investigator considered the chest

pain and myocardial infarction to be related to a thrombus, possibly embolised during stent deployment. The subject also had a rash considered related to taking antibiotics.

Subject 03430301 (randomized to eletriptan) discontinued due to chest pain. He also had a hematoma over the femoral artery. The investigator study drug related considered neither event. The investigator considered the tachycardia (140 bpm) and the associated chest pain to be related to the subject's anxious state, and the hematoma to be related to the angioplasty procedure itself. This subject had rate dependent (?) ischemic ECG changes.

Clinical Laboratory Test Results

Given the nature of the study, clinical laboratory abnormalities were not expected, and did not occur.

2.6.3.5.3 3 Sponsor's conclusions:

Eletriptan at a plasma concentration consistent with the C_{max} obtained after an oral 80mg dose in subjects with a migraine attack produced negligible effects on the coronary arteries of subjects with severe coronary artery stenosis The effects were similar to those seen with placebo. Although the vasoconstrictive effect on the coronary arteries after sumatriptan was small, it was different from eletriptan and approached statistical significance. Systemic blood pressure, heart rate and ECG measurements raised no particular concerns. There was no evidence of ischemic ECG changes attributable to study drug. The adverse events produced no safety concerns but the incidence of treatment related events and discontinuations due to adverse events were higher in the sumatriptan group Coronary effect and safety data show that eletriptan and placebo groups respond in a similar way and the angiographic procedure itself, or spontaneous dynamic variation, could be responsible for any vasoconstriction seen.

2.6.3 5.3.4 Reviewer's analysis

For this study, I analyzed the angiography data contained in the c_artery.xpt dataset. I identified records for a total of 46 subjects (19 eletriptan; 17 sumatriptan; 10 placebo). Six subjects (2 eletriptan – 4 sumatriptan) had missing data at 15 min and 30 min. All 6 subjects had a measurement at an earlier timepoint corresponding to the time of an AE (3-10 minutes after baseline). I used a LOCF approach and I took the earlier timepoint data to fill the missing data.

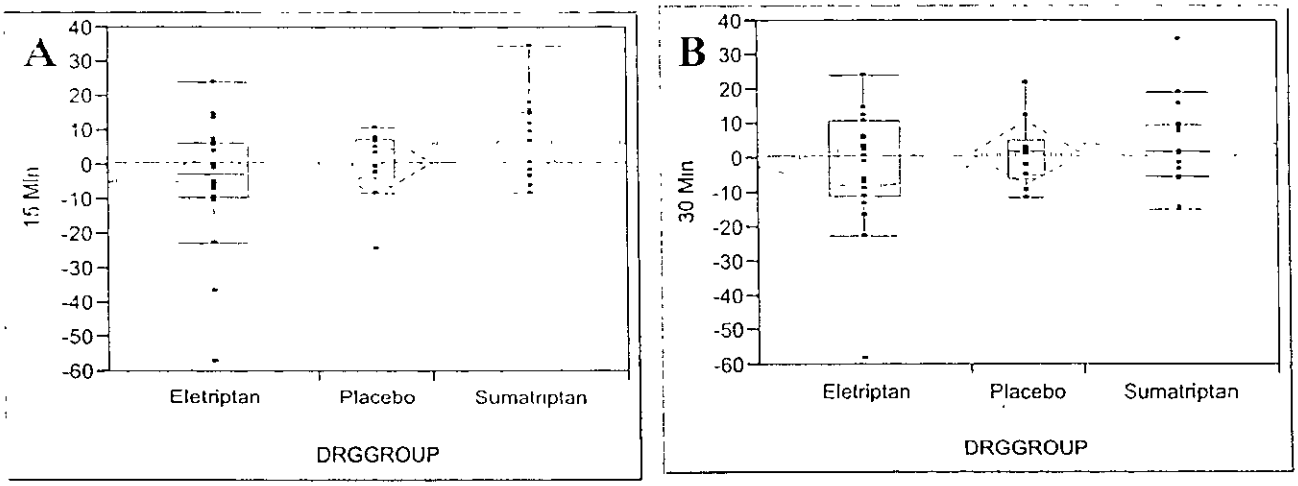
Coronary artery diameter was the smallest at the 30 minutes post-baseline timepoint (15 minutes after discontinuation of the eletriptan infusion or 30 minutes after sumatriptan injection) respectively in 8/19 subjects of the eletriptan group, 4/17 subjects of the sumatriptan group, and 4/10 subjects of the placebo group .

Table 38: vasoconstriction (%) at stenosis location (negative values represent vasodilation)

	15 Min	30 Min	32 Min
Eletriptan	-2 6	-1 0	-1 3
Sumatriptan	6.8	2 2	-3.9
Placebo	4.5	1.6	-3.2

I calculated the maximum vasoconstriction or minimum vasodilation at the 15 or 30 minutes timepoint for each patient. Since subjects received nitrates prior to the 32 minutes timepoint, I consider this timepoint less relevant in assessing the issue of eletriptan-induced vasoconstriction. In Figures 25-26, the median is shown with the red horizontal bar in the middle of the box. The red box shows the limits of the 25% quartile and of the 75% quartile. The upper and lower red horizontal bars show the maximum and minimum values. The green diamond show the 95% confidence interval, and the green horizontal line in the middle of the diamond shows the mean value. Negative values represent vasodilation, and positive values vasoconstriction.

Figure 24: Quantiles, mean and 95% confidence interval for % coronary artery diameter reduction at 15 min post-baseline (A) and 30 min post-baseline (B).



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ON ORIGINAL

Figure 25: Quantiles, mean and 95% confidence interval for maximum vasoconstriction (15 or 30 minutes)

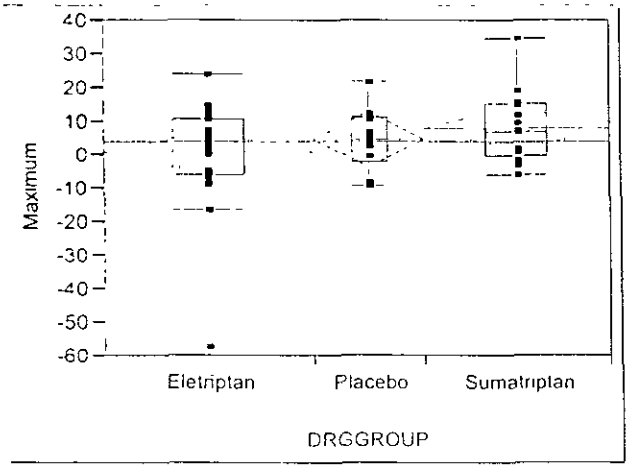

Figure 24 and Figure 25 show a similar distribution of data for all 3 groups, with numerically lower values (more vasoconstriction) in the sumatriptan group, and minimal vasoconstriction in the eletriptan group Also, no patient in the eletriptan group exceeded 25% vasoconstriction (in addition to the pre-existing anatomic stenosis).

2.6.3.5.3 5 Reviewer's conclusion:
I concur with the Sponsor that the study did not show any evidence of major coronary vasoconstriction with eletriptan at blood level equivalent to those seen after a 80 mg dose, or with sumatriptan. Eletriptan effect was not significantly different from the sumatriptan effect. This study gives a modest reassurance about the possible side effects of eletriptan in the cardiac population. Its main limits are the small population size, the small dose of eletriptan used, and the absence of central reading of angiograms.

2.6.4 Summary of Critical Safety Findings and Limitations of Data

The main issue in this response to approvable letter was the cardiovascular safety of eletriptan in case of concomitant use of CYP3A4 inhibitors. This issue was largely discussed by Dr. Oliva in his 11/1/00 review of the previous response to approvable letter (of 5/1/00). Dr Oliva commented on a small coronarography study conducted by the Sponsor with eletriptan (Study 211). This study had several limitations. The main one was the low eletriptan exposure, lower than that achieved with the maximum planned dose of the marketed product. Dr. Oliva concluded that the in vivo effect of eletriptan on coronary arteries relative to other triptans remained largely unknown, particularly at eletriptan exposures achieved when a 40mg or 80mg dose is given in association with verapamil or another more potent CYP3A4 inhibitor. He also concluded that despite the cerebroselectivity claims put forth in two expert reports provided by the Sponsor, the degree of maximum coronary vasoconstriction seen with the naratriptan and eletriptan doses studied in vivo are, at best, similar. These studies lacked a placebo arm, which limited the interpretation of the

angiograms. There was no clear association between the eletriptan plasma level and the adverse events of vasoconstriction.

The only adverse dropout in Study 1072 occurred in an eletriptan-treated patient. The investigator estimated the narrowing in the mid-LAD as 60-70%, about 50% greater than a baseline 20% narrowing, although the QCA lab estimated about 39% narrowing. In the cardiology consult, Dr. Marciniak noted that myocardial bridging (muscle overlying an epicardial coronary artery) is common, with prevalence ranging from 5% to 86% by autopsy and less by angiography. Myocardial bridges are located most frequently in the mid-LAD, as in this case. They have been associated with ischemic events. However, based on the frequency of bridges and the rarity of case reports linking them reasonably to ischemic events, ischemia is rare with bridges alone. I concur with Dr. Marciniak that while myocardial bridging might partially account for the event in this case, we are not reassured. If similar events occurred in the one-third of adults with myocardial bridges taking eletriptan and CYP3A4 inhibitors, we would worry about an increased risk of ischemic events. In addition, this patient had no QCA after discontinuation of eletriptan, when the degree of vasoconstriction may have been even more severe.

Study 309 does not provide any new information on the safety of eletriptan when administered concomitantly with CYP3A4 inhibitors. Study 309 did not show any evidence of major coronary vasoconstriction with eletriptan at blood level equivalent to those seen after a 80 mg dose, or with sumatriptan This study gives a modest reassurance about the possible side effects of eletriptan in the cardiac populations, but has several flaws, including the small population, the small dose of eletriptan used, and the absence of central reading of angiograms.

The safety update does not add any new significant finding. Study 160-1048, a large a multicenter, double-blind, placebo-controlled parallel group study completed after the safety update, showed a similar incidence of chest and cardiac symptoms in patient treated with eletriptan 40 mg (3.1%) and sumatriptan 100 mg (2.8%), compared to 1.4% in placebo-treated patients.

Pharmacovigilance data show no cardiovascular SAEs after the sale of [redacted] tablets of eletriptan. There was one spontaneous report of a SAE described as an anaphylactic reaction to eletriptan. There was also a massive MI leading to death reported (not part of this submission), in a patient who took one tablet of eletriptan 40mg and possibly two tablets of sumatriptan 50mg. Even tough both triptans should not have been taken in the same 24-hour interval, their individual dosages remain well within the allowed maximum daily dosage. Overall, the post-marketing experience gives some reassurance about eletriptan cardiovascular safety. However, maximum recommended daily dosage varied between 40mg, 80mg or 160 mg across countries, with no breakdown provided by the Sponsor. There are additional obvious issues limiting the validity of these post-marketing data, such as the fact that [redacted] tablets were sold does not mean that [redacted] tablets were used by patients, and that here can be a significant delay before post-marketing information is conveyed to the Agency.

Overall, I believe that the postmarketing experience only supports a maximum eletriptan daily dosage of 40mg.

2.7 Dosing, Regimen, and Administration Issues

The Sponsor proposes 40mg eletriptan as the recommended starting dose. The Sponsor also suggests that the 80mg dose of eletriptan represents an acceptable balance of benefit and tolerability, and that some patients who optimize their treatment to the 80mg dose, may need to treat headache recurrence by taking a second 80mg dose (after a two hour interval) within a 24 hour period. This results in a maximum daily dose of 160mg.

In his 11/1/00 review of the response to approvable letter, Dr. Oliva reviewed in detail the safety and efficacy of the 80mg eletriptan dose. Dr. Oliva concluded that "in the only study specifically designed to demonstrate a benefit of the 80mg over the 40mg dose [Study 103], the primary outcome was negative. Other studies are suggestive of a benefit, but do not establish a benefit (section 3 1, page 10, 11/10/00 review of response to approvable letter)." Regarding the safety of the 80mg dose, Dr. Oliva observed a dose dependent increases in incidence of the most common adverse events (Table 39).

Table 39: Single Attack Data – All Causality Adverse Events with Incidence of ≥3% in Any Treatment Group (from table 5, page 10, Dr. Oliva 11/10/00 review of the response to approvable letter)

AE incidence (%)	Placebo N=1235	Eletriptan 20mg N=531	Eletriptan 40mg N=2138	Eletriptan 80mg N=1518
Overall Incidence	30.0%	33.5%	42.8%	54.9%
Asthenia	2.8	4.0	5 2	12.2
Chest pain	1 2	0 9	2.4	4.7
Headache	2 5	3.2	3 6	4.5
Vasodilatation	1.9	2 1	1 9	3.5
Dry mouth	2.0	1 9	3.1	4.0
Dysphagia	0 3	0.6	1 8	3.0
Nausea	5.0	4.7	5.4	8.8
Vomiting	3.9	0 9	1.7	2.8
Dizziness	3.2	3.4	6.3	8.3
Hypertonia	0.5	1.5	1.6	3.4
Paresthesia	1.5	3.2	2.9	4.5
Somnolence	3.4	2.8	6.0	7.8

Noticeably, there was a double incidence of chest pain with the 80mg dose as compared to the 40mg dose. As reviewed by Dr. Oliva in his 11/10/00 review, the cause of triptan-induced chest symptoms has not yet been determined although many mechanisms other than cardiovascular ischemia have been suggested. I concur with Dr. Oliva's assessment that is best to assume, from a public health perspective, that increased incidence of chest pain/pressure will likely be associated with an increased incidence of coronary vasospasm, and ultimately with adverse cardiac events such as cardiac ischemia, myocardial infarction, and cardiac death. In this regard, a doubled incidence of chest pain with the 80mg dose is not comforting.

Considering the remaining uncertainty about the effect of eletriptan on coronary arteries, particularly at eletriptan exposures achieved when a 40mg or 80mg dose is given in association with verapamil or another more potent CYP3A4 inhibitor, but also even after exposure corresponding to a 40mg tablet (as in coronary Study 211, where a case of chest pain with 60% vasoconstriction was observed in one subject), I recommend to limit the initial to the lowest effective dose: 20mg. As shown in Table 39, the 20 mg was associated with the lowest incidence of side effects In addition, the 20mg dose was clearly effective, as shown in the pooled efficacy analysis for the first attack from the seven outpatient efficacy studies part of the original NDA (Table 40), and reviewed by Dr. Oliva in section 7.3.7 of his review (page 27-29, 7/9/99 NDA review). Pairwise comparisons between doses were nominally significant for 80mg vs. 40mg (p=0.0049) and for 40mg vs. 20mg (p=0.0001), but this efficacy of the 20mg dose was clinically significant.

Table 40: Dose Response – Pooled Efficacy Analysis (from Table 20, Dr. Oliva NDA 7/9/99 NDA review).

Time point	PBO	20mg	40mg	80mg
0 5	4 3%	5.6%	8.6%	10.3%
1	13.3%	23.9%	31.7%	35.0%
2	24 4%	49.5%	60 2%	65.8%
(95% CI)		(44.6- 54.4)	(58.0- 62.4)	(63.3- 68.3)

Includes 1st attack from seven adult outpatient efficacy studies, 102, 103, 104, 305, 307, 314, 318

The 20mg dose was in several studies numerically superior to the 40mg or 80mg dose for nausea at 2 hours, as shown in Table 41.

Table 41: Nausea at Two Hours Post-Treatment (from table 23, Dr. Oliva NDA 7/9/99 NDA review).

Study	Dose	N	Nausea Present At Baseline				Nausea Absent At Baseline				p-value		
			Base line	%	2HR	%	Base line	%	2HR	%	vs. PBO	vs. low dose comparator	vs. high dose comparator
102	20mg	290	177	(65 1)	72	(40.7)	95	(34.9)	84	(88.4)	0.0001		
	40mg	296	187	(66.8)	99	(52.9)	93	(33.2)	75	(80.6)	<0.0001		
	80mg	312	190	(64 8)	83	(43.7)	103	(35.2)	81	(78.6)	0.0003		
	PBO	292	190	(69.1)	53	(27.9)	85	(30.9)	57	(67.1)			
103	40mg	507	286	(58.2)	166	(58.0)	205	(41.8)	171	(83.4)	0.0989		
	PBO	124	71	(59 2)	29	(40.8)	49	(40.8)	44	(89.8)			
104	40mg	184	68	(39 5)	38	(55.9)	104	(60.5)	89	(85.6)	0.4765	0.6357	0.9236
	80mg	180	69	(40.8)	44	(63.8)	100	(59.2)	79	(79.0)	0.5596	0.7500	0.9532
	S25mg	180	79	(47.3)	42	(53.2)	88	(52.7)	74	(84.1)			
	S50mg	181	72	(41.6)	42	(58.3)	101	(58.4)	84	(83.2)			
	PBO	93	33	(37.5)	13	(39.4)	55	(62.5)	49	(89.1)			
105	40mg	141	57	(41.3)	34	(59.6)	81	(58.7)	69	(85.2)	0.3340		
	PBO	133	62	(48.1)	38	(61.3)	67	(51.9)	62	(92.5)			
305	40mg	452	282	(65.6)	162	(57.4)	148	(34.4)	120	(81.1)	<0.0001		
	80mg	461	279	(63.4)	152	(54.5)	161	(36.6)	137	(85.1)	<0.0001		
	PBO	238	153	(66.8)	52	(34.0)	76	(33.2)	55	(72.4)			
307	40mg	210	140	(67.6)	75	(53 6)	67	(32.4)	54	(80.6)	0.0059	<0.0001	
	80mg	214	145	(69.7)	78	(53.8)	63	(30.3)	51	(81.0)	0.0050	<0.0001	

Study	Dose	N	Nausea Present At Baseline				Nausea Absent At Baseline				p-value		
			Base line	%	2HR	%	Base line	%	2HR	%	vs. PBO	vs. low dose comparator	vs. high dose comparator
	Cafergot	203	137	(69 5)	34	(24.8)	60	(30 5)	36	(60.0)			
	PBO	105	68	(67.3)	23	(33 8)	33	(32 7)	24	(72.7)			
314	20mg	144	86	(67.2)	50	(58.1)	42	(32.8)	36	(85.7)	0.0021		0.3259
	40mg	135	74	(62 2)	38	(51.4)	45	(37 8)	38	(84 4)	0.0291		0.8885
	80mg	141	85	(72.0)	59	(69 4)	33	(28 0)	30	(90.9)	<0 0001		0.0095
	S100mg	129	74	(65.5)	36	(48 6)	39	(34 5)	34	(87 2)			
	PBO	142	82	(65 6)	31	(37 8)	43	(34.4)	31	(72.1)			
318	40mg	175	108	(64 7)	67	(62.0)	59	(35 3)	52	(88.1)	0 0003	0.0160	0.0380
	80mg	164	108	(67 9)	61	(56 5)	51	(32.1)	43	(84.3)	0 0053	0.1627	0.2851
	S50mg	181	110	(63 2)	52	(47.3)	64	(36.8)	52	(81.3)			
	S100mg	169	115	(72 3)	58	(50 4)	44	(27.7)	35	(79.5)			
	PBO	84	54	67 5)	19	(35 2)	26	(32.5)	19	(73 1)			

In the two studies where the 20mg was compared to the 40mg dose, the recurrence rate was numerically lower for the 20mg dose than for the 40mg dose (Table 42). Dr Oliva noted that recurrence rates were numerically lower for eletriptan in six of the seven studies (all but 314), and reached nominal significance for almost all eletriptan doses (20, 40, 80mg) in those six studies.

Table 42: Headache Recurrence Rates (from table 22, Dr. Oliva NDA 10/27/98 NDA review).

Study	PBO	20mg	40mg	80mg
102	43.9%	28 2% *	31.6% *	23.1% *
103	39 4%	--	15.8% *	--
104	19 4%	--	6.5% *	7.5% *
305	39.6%	--	30.3%	21.0% *
307	44.4%	--	20.9% *	22.1% *
314	23.5%	28.4%	33.7%	31.7%
318	25.0%	--	19.3%	16.2%

* nominally significant vs placebo

A meta analysis of the five studies in which the second dose was randomized to drug or placebo was reviewed by Dr. Oliva in section 7.3.14 of his 7/9/99 NDA review. This analysis showed that a second dose (40 or 80mg) was effective in the treatment of a headache recurrence. The second eletriptan dose was also associated with a greater proportion of patients with no nausea, vomiting, photophobia, or phonophobia. The efficacy of a second dose to treat persistent pain was not demonstrated by this analysis. The 20mg dose was not examined for treatment of persistent or recurrent pain.

In terms of dose escalation, the Sponsor only specifically examined the scenario where patients failed to respond to 40mg and received were randomized to received 80mg, 40mg or placebo at the second attack (Study 103). This was examined by Dr. Oliva in section 7.3.8 of his 7/9/99 NDA review. The two-hour pain-free response for 80mg was 26.3% (total n=156)

and for 40mg was 20.3% (total n=138) Although numerically in favor of the 80mg dose, it failed to reach statistical significance

Given the dose/response curve as shown in Table 40, patients who do not obtain satisfactory efficacy after an appropriate trial of the starting dose (20 mg), (e.g good tolerability and failure to respond in 2 out of 3 attacks), may be effectively treated with 40 mg in subsequent migraine attacks (with no supporting evidence).

If the migraine headache recurs within 24 hours of an initial response, I recommend that a second 20mg dose can be taken after 2 hours. A second dose has been shown to be effective in treating the recurrence for the 40mg dose, but it has not been specifically studied for the 20mg dose. There is however no major safety concern in allowing that second dose. If a patient does not achieve a headache response to the first dose of Relpax within 2 hours, a second dose should not be taken for the same attack as clinical trials have not adequately established efficacy with the second dose. The maximum daily dose should not exceed 40 mg (see Brief Statement of Conclusions for my Safety Review).

Of note, the minimal effective dose was not established, and it is possible that doses lower than 20mg (*e.g.* 10mg or even 5mg) are effective, but this would require additional studies, with sufficient power, in order to establish this possibility (see comment 2 of Dr. Oliva Efficacy Conclusions, section 7 6, Dr. Oliva NDA 7/9/99 review).

Because of the high eletriptan exposure achieved in case of concomitant administration of CYP3A4 inhibitors, and because of the uncertainty about the cardiovascular risk at that exposure level, I recommend to contra-indicate eletriptan in patients taking jointly CYP3A4 inhibitors.

2.8 Use in Special Populations

Use in special populations was reviewed by Dr. Oliva in his original NDA review (7/9/99). I did not repeat this analysis, and I refer the reader to specific sections of Dr. Oliva's review. I summarize here below his conclusions (sections 2.8.1 – 2.8.4).

2.8.1 Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The response rates were generally consistent group by group between genders. There was neither a statistically significant treatment by gender interaction nor a statistically significant gender effect (Dr. Oliva's NDA review section 7.3.18.2, page 36).

2.8.2 Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Among the adult population, response rates were analyzed according to age strata (18-40, 41-64, and ≥65 years). Treatment response was consistent across age groups for 20mg (47.9-51.3%), 40mg (55-62.3%), and 80mg (63.8-78.6%). Placebo responses were similar for the 18-40 and 41-64 age groups (27% and 21.5%, respectively), but was much higher in the ≥65 age group (71.4%) There was a statistically significant treatment by age interaction (p-

0.0134), likely due to the high placebo response rate in the elderly (Dr. Oliva's NDA review section 7.3.18.1, page 36).

There was no statistically significant race effect and no statistically significant treatment by race interaction among the four race groups analyzed (white, black, asian, other, Dr. Oliva's NDA review section 7.3.18.3, page 36).

2.8.3 Evaluation of Pediatric Program

Study 105 enrolled adolescent migraineurs between the ages of 12-17. It compared 40mg to placebo in the treatment of an acute migraine. As in other studies, two-thirds had a moderate headache at baseline and one-third treated a severe headache. The response rates for 40mg at one hour and two hours were similar to that seen in the adult studies (27.3% and 57.2%); however the placebo response rates were very high (26.0%, 57.4%, at 1 and 2 hours, respectively) and there appeared to be no benefit of the 40mg dose over placebo in this study population (Dr. Oliva's NDA review section 7.3.16, page 35).

The pediatric program can not be considered as complete. A full scale efficacy and safety study in pediatrics would be required if Pfizer wants pediatric labeling for eletriptan. The Division agreed to consider a Written Request for a RELPAX Pediatric Study.

2.8.4 Comments on Data Available or Needed in Other Populations

Hepatic compromised subjects: Study 220 was an open, single dose PK study of eletriptan 40mg and 80mg in 12 subjects with chronic stable hepatic cirrhosis and 12 age and weight matched healthy volunteers. Five of the 12 hepatic patients reported AE's compared with 3/12 for control. For both groups, all AE's were mild and consistent with AE's reported in the development program, except for one case of severe hypertension in a subject with hepatic cirrhosis who received eletriptan 80mg. The subject had a blood pressure reading of 220/96 mm five hours after dosing. The treatment related event persisted for seven hours and resolved without treatment. None of the other subjects with hepatic cirrhosis experienced any degree of hypertension (Dr. Oliva's NDA review section 8.14, page 89).

Renal compromised subjects: Study 229 was an open, single dose PK study of eletriptan 80mg in 16 subjects with varying degrees of renal impairment (six mild, five moderate, and five severe) and six subjects with normal renal function. Adverse events were reported for two each of the normal, mild impairment and moderate impairment subjects and for three of the subjects with severe renal impairment. All events were mild and consistent with reported during development (Dr. Oliva's NDA review section 8.14, page 89).

Use in pregnancy: during development, 21 patients became pregnant while taking active study medication and were subsequently withdrawn from the study. There were 11 pregnancies in eletriptan treated women. Eight pregnancies have resulted in six normal births, and the remaining two are progressing normally. Three other pregnancies were not carried to term: two were miscarriages (one diagnosed with Turner's syndrome). The third

pregnancy was aborted at the request of the patient, who then continued in the long-term study 317. She later became pregnant again, with a normal pregnancy. Two placebo patients had pregnancies progressing normally up until the last contact with investigators. They were subsequently lost to follow-up. There were 3 normal pregnancies in sumatriptan treated patients. In the POT groups during long-term therapy, two miscarriages were reported and one pregnant subject was lost to follow-up. In blinded patients, 2 normal pregnancies and deliveries have been recorded. The Sponsor reports published data that spontaneous abortion (miscarriage) is the outcome of 14-19% of registered pregnancies. Eletriptan is excreted in human milk, but in extremely low quantities. The mean total amount of eletriptan excreted in breast milk over 24 hours was only 0.02% of an 80mg oral dose (Dr. Oliva's NDA review section 8.16, page 89).

2.9 Conclusions and Recommendations

2.9.1 Conclusions

In the 12/01/00 approvable letter, the Agency noted that:
" In the approvable letter dated October 27, 1999, we requested that you "document that the increased exposures (Cmax and AUC) that result when eletriptan is given in conjunction with CYP3A4 inhibitors do not make the risk of such concomitant use unacceptable. This is critical because even though this concomitant use will be contraindicated in labeling, we cannot be confident that such use will not occur." We are not able to approve your application at this time because we believe that the information submitted in response to that letter fails to establish that the risk of such use is acceptable, particularly since eletriptan does not appear to offer any additional therapeutic benefit over currently approved triptans.

We note particularly that concomitant use of eletriptan with verapamil, a relatively commonly used CYP3A4 inhibitor in migraine patients, results in substantial increases in eletriptan exposure. In general, the eletriptan exposures achieved in that drug interaction study are substantially higher than the exposures that have been evaluated in the coronary angiography study (Study 211) yet that study suggests that even those plasma levels may be associated with clinically meaningful coronary vasoconstriction. We therefore remain concerned about the potential effects of eletriptan on the coronary arteries, particularly at exposures achieved during CYP3A4 inhibition, but also at exposures associated with 40 mg and 80 mg single doses without metabolic inhibition.

Before this application may be approved, therefore, it will be necessary for you to address the following: You will need to conduct a placebo-controlled study designed to assess the potential of eletriptan to constrict coronary arteries at eletriptan concentrations that are higher than those achieved in Study 211 and that are comparable to exposures seen with CYP3A4 inhibition. The study should include several active controls of available triptans. The subjects studied should be those with suspected coronary artery disease who have been selected for diagnostic coronary angiography".

Study 1072 was designed and conducted in response to the 12/01/00 approvable letter. I believe that Study 1072 has failed to establish the safety of eletriptan at exposure level expected when given in conjunction with CYP3A4 inhibitors, especially with the 80mg eletriptan dose. Study 1072 can not be regarded as positive for the primary endpoint of change in coronary artery diameter because it lacked assay sensitivity. In addition, the imbalance in vasoconstriction adverse events between eletriptan and both sumatriptan and placebo is striking and worrisome. This is particularly true for one case in which there were associated ECG changes, and one case of adverse dropout because of vasoconstriction. These adverse events suggest, but do not prove conclusively, that eletriptan may lead to increased rates of cardiac ischemic events. There were also discrepancies between narratives of adverse events and blinded quantitative coronary angiography evaluations, which questions their validity.

In my opinion, the principal information supporting eletriptan safety is the postmarketing experience (eletriptan is marketed in 46 countries). After the sale of over ——— tablets, there was one single case of reported MI, coufounded with the concomitant use of sumatriptan. This provides some reassurance about eletriptan cardiovascular safety, without clearly establishing its safety at the high exposure seen when taken jointly with CYP3A4 inhibitors. Also, maximum recommended total daily dosage varied between 40mg, 80mg or 160mg in the foreign countries where eletriptan is marketed (the breakdown of sales across countries was not provided). In my opinion, the postmarketing experience only supports safety up to a total daily dose of 40mg.

Based on the information from coronary studies and postmarketing experience, I conclude that safety has not been established at doses exceeding 40mg of total daily dosage. I believe that an excess of risk of cardiovascular adverse events and deaths should not be tolerated in the migraine population, which is a benign condition for which several other effective medications of the same class are available.

The efficacy of eletriptan 20mg, 40mg and 80mg was already well established in the original NDA. In the present submission, Study 1048 provides incomplete evidence supporting that eletriptan 40mg is superior to sumatriptan 100mg .

2.9.2 Recommendations

1. I recommend approval of eletriptan 20mg and 40mg tablets, with changes in the proposed labeling as I have described in the labeling review.
2. I recommend non approval of the 80mg dose.

2.10 Labeling review

In this section, I review the draft labeling, as proposed by the Sponsor. Dr. Oliva already reviewed labeling in the original NDA review.

16 page(s) of revised draft labeling has been redacted from this portion of the review.

2.11 Appendix

2.11.1 Other Relevant Materials

2.11.1.1 Cardiology consult

A cardiology consult regarding eletriptan and coronary vasoconstriction was requested and conducted by [redacted] The section contains is a copy of that consult.

This memo addresses the questions in your consult to us dated October 3, 2002, regarding a coronary angiography study of eletriptan and coronary vasoconstriction. For ease of reference I have included below your excellent summary of the consult request followed by our summary of the study and finally your questions (in boldface) and our responses. In the assessment of the cardiovascular safety of eletriptan, a new triptan class symptomatic treatment of migraine, the Sponsor was requested to conduct a study with high doses of eletriptan in subjects undergoing a heart catheterization and who were diagnosed with a coronary artery stenosis <20%. The issue is that eletriptan is metabolized almost exclusively by CYP3A4 and that in the presence of a CYP3A4 inhibitor, blood concentrations of eletriptan can be dramatically increased (about 300%), to a level at which cardiovascular safety needed to be evaluated.

Study 1072 was a placebo-controlled, double-blind, parallel group study to determine the effect of escalating plasma concentrations of iv eletriptan on coronary vascular responsiveness, as measured by quantitative coronary angiography, and to compare it with therapeutic doses of sc sumatriptan (as an active control) and iv and sc placebo. The investigators invited subjects who were scheduled for diagnostic coronary angiography to participate in the study. The objectives of this study were to compare the effects of eletriptan with those of sumatriptan and placebo, to determine any concentration-dependent effects of eletriptan on CAD, to assess changes, if any, in mid- left anterior descending (LAD) and proximal circumflex coronary artery mean segment diameter (MSD) resulting from eletriptan exposure; and to determine the potential effects on coronary arteries of an oral eletriptan 80mg administered in the presence of a potent CYP3A4 inhibitor.

The basics of the study are the following: Subjects who underwent coronary angiography for a clinical indication and who at catheterization had no evidence of ≥20% stenosis or other multiple luminal irregularities were randomized to double dummy placebo (n = 18), eletriptan 36, 52, or 72 mg by 40 minute infusion (n = 24), or sumatriptan 6 mg SC (n = 16). Quantitative coronary angiography (QCA) of the mid-LAD (primary endpoint) and proximal circumflex (secondary endpoint) and drug levels were done at 5, 15, 40, and 50 minutes from the start of infusion.

The eletriptan dosing was selected to achieve blood levels comparable to oral eletriptan dosing at 20, 40, and 80 mg in the presence of a potent CYP3A4 inhibitor. In a prior study the mean Cmax for oral eletriptan 80 mg in the presence of ketoconazole was 491 ng/ml, 2.7 fold higher than that obtained with oral eletriptan 80 mg alone. The infusion was stepped at

20 minutes to administer 36% of the dose in the first 20 minutes and 64% in the final 20 minutes. The sumatriptan dose is the maximum single recommended adult dose. In a similar study of the effect of sumatriptan on coronary artery diameter reported in the literature and cited by the Sponsor to support the design of this study, sumatriptan 60 mg SC produced blood levels of 124ng/ml at 10 minutes and 71 ng/ml at 30 minutes. (MacIntyre, Bhargava et al. 1993).

The primary hypothesis was an non-inferiority hypothesis that the quotient of the geometric mean ratios of the minimum post-baseline mean mid-LAD segment diameter (MSD) to the baseline MSD for eletriptan to the mean such ratios for sumatriptan is ≥0.9. In addition to an intention-to-treat (ITT), as randomized analysis set, the Sponsor defined various other analysis sets. The proposed primary efficacy analysis uses a modified ITT (MITT) set consisting of subjects who had eletriptan blood levels at the last QCA measurements greater than the minimum target concentration (599 ng/ml? MITT has 20 eletriptan subjects compared to 24 in ITT set.) Because the Sponsor's presentation of the data is complex and somewhat confusing with its multiple analysis sets and adjustments, we analyzed the raw data. The study achieved levels of eletriptan close to those projected as shown in the following table.

Table 1: Mean Drug Levels by Time in Minutes After Start

	5	15	40	60
eletriptan	152	282	625	272
sumatriptan	49	68	46	37

Sumatriptan levels appear to be slightly lower than those achieved in (MacIntyre, Bhargava et al. 1993). Changes in the ratio of mid-LAD diameter to baseline were very similar in the three groups and appear to be dominated by a time trend towards lower ratios as shown in the following table.

Table 2: Mean Mid-LAD Ratios to Baseline by Time

	5	15	40	50
eletriptan	0.93	0.90	0.82	0.80
sumatriptan	0.94	0.90	0.86	0.81
placebo	0.96	0.91	0.87	0.84
Total	0.94	0.90	0.85	0.81

Results for the proximal circumflex are similar. The Sponsor calculated a geometric mean minimum mid-LAD ratio to baseline of 0.78 for eletriptan and 0.81 for sumatriptan for quotient of eletriptan to sumatriptan ratios of 0.96, 95% confidence limits 0.91 to 1.02. The Sponsor concludes non-inferiority of eletriptan.

The data do not show a clear drug effect of either eletriptan or sumatriptan upon coronary arterydiameter. The time trend towards lower ratios observed with placebo dominates. In the study cited (MacIntyre, Bhargava et al. 1993) sumatriptan 60 mg SC produced a significant

reduction in coronary artery diameter (17% at 30 minutes). This study was not placebo-controlled. A prior study by the same investigators of IV sumatriptan included placebo comparisons and did not show a placebo effect. (Macintyre, Bhargava et al. 1992) The methodology used by MacIntyre was similar to the present study, although MacIntyre evaluated multiple points (at least three) along each artery. If one tries to adjust for the time trend by correcting the ratios on drug with the corresponding ratio on placebo at each timepoint, one does get a significant linear trend ($p = 0.043$ for LAD, $p = 0.013$ for proximal circumflex) in decreasing diameter with increasing drug level for eletriptan by multiple regression with adjusted ratio and time as independent variables. The linear trends for the same regression analysis with sumatriptan are not significant. However, overall we conclude that the study was negative for the primary endpoint of change in coronary artery diameter because it lacked assay sensitivity due to the time trend in coronary artery diameters (see response to Question 1).

As opposed to effects upon coronary artery diameters, the blood pressure (BP) recordings show that eletriptan and sumatriptan had expected physiologic effects. Eletriptan increased mean aortic systolic BP by about 18 mm Hg at 40 minutes and mean diastolic BP by about 10 mm Hg. Sumatriptan increased mean SBP by about 10 mm Hg at 20 minutes and mean diastolic BP by about 4 mm Hg at 30-40 minutes. Placebo showed small (-2 to +2 mm Hg), mostly random changes in BP. More revealing than the primary endpoint results are the adverse events. The Sponsor's tabulation of the cardiac adverse events is shown in the following table. Note that coronary vasoconstriction was reported only in the eletriptan group while the only report of chest pain was in a placebo patient. The Sponsor emphasizes that the investigator reports of coronary vasoconstriction are unrelated to the primary endpoint QCA measurements. Rather than being reassuring, the lack of association confirms that the primary endpoint measurements are not meaningful.

Table 3: Cardiac Adverse Events by Treatment

Adverse event	Eletriptan iv	Sumatriptan 6mg sc	Placebo
Chest pain	0	0	1
ECG abnormal	1	0	0
Vasoconstriction (coronary)	8	0	0

Source: Table 6.2.3; ECG=electrocardiogram.

The one ECG abnormality was in one of the subjects with coronary vasoconstriction. The patient was a 42 year-old male with a history of angina pectoris and a family history of ischemic heart disease. He was reported to have mild asymptomatic coronary vasoconstriction in the proximal LAD after 40 minutes of eletriptan infusion that resolved within 10 minutes. He had transient ST segment elevation and T-wave inversion for the first two minutes of the vasoconstriction. (Prinzmetal's angina or a history of coronary spasm was an exclusion criterion.) The other cases of coronary vasoconstriction were asymptomatic and, with one exception, reported by the investigator as mild. The one case of vasoconstriction reported by the investigator as moderate was in a 53 year-old female with a history of migraine. She developed vasoconstriction at 15 minutes estimated by the investigator as 50%

beyond a baseline 20% constriction in the mid-LAD. The investigator discontinued the infusion at 25 minutes and the vasoconstriction resolved by 30 minutes. The patient was asymptomatic and had no ECG changes. The Sponsor notes that this patient had myocardial bridging. This case was the only discontinuation of study drug.

1. Was the methodology appropriate to achieve the study objectives (catheterization method, measurement sites and number of sites evaluated, quantitative coronary angiography technique)?

Most aspects of the methodology were excellent. In retrospect there appear to be three major flaws: a. Variations in coronary artery tone were not controlled. Contrast agents are known to dilate coronary arteries. (Jost, Hausmann et al. 1997; Baile, Pare et al. 1999) One investigator has suggested that nitrates should be administered during QCA to maximize dilation and minimize variability due to contrast agents. (Jost, Rafflenbeul et al. 1990) One can hypothesize that in this study the injection of contrast media during the scheduled coronary angiography that confirmed eligibility produced coronary vasodilation that gradually returned towards baseline during the time course of the QCA studies. B. Multiple measurements were not done as in the cited study. (MacIntyre, Bhargava et al. 1993) Multiple segment measurements should be useful in detecting effects that are localized rather than generalized. However, it is not clear whether MacIntyre et al. or this study provides the clearer picture of the effects of triptans on coronary artery diameter. This (coronary) study has some design aspects superior to Macintyre et al., such as concurrent placebo control. C. Due to the two flaws just discussed or to other unidentified problems the primary endpoint lacks assay sensitivity. This study failed to show a drug effect for the primary endpoint either with eletriptan or with the active control sumatriptan, so no information is provided by the primary endpoint results. The methodology failed for the primary endpoint.

2. What can be considered an acceptable level of vasoconstriction induced by a coronary procedure of this type?

The most relevant reference for this question is the American College of Cardiology/American Heart Association guidelines on coronary angiography, in particular this statement on coronary spasm: "Although vasomotion can result in as much as a 20% change in lumen diameter, coronary spasm is considered to be present when a reduction in lumen caliber of 50% occurs during a provocative test and reversal is achieved with intracoronary nitroglycerin." (Scanlon, Faxon et al. 1999) No patient in this study had a minimum artery diameter of <50%, although one eletriptan patient was discontinued after 25 minutes of infusion and had a maximum reduction of 38%. However, the primary endpoint may fail to detect localized spasm. The interpretation of small changes in artery diameter, such as were possibly shown in the Macintyre et al. study, is difficult. Such changes have not been linked to cardiac events.

3. After unblinding, the Sponsor modified the protocol in order to perform a placebo correction "to eliminate a pronounced placebo effect" from the comparisons between eletriptan and sumatriptan at individual timepoints. Was this acceptable in your sense,

since the effect related to the procedure and not to the study drug (as evaluated by the placebo group) was presumably similar in the eletriptan and sumatriptan groups?

The Sponsor did not perform the placebo correction for the primary endpoint analysis. For some secondary analyses by time, the Sponsor did correct for the placebo effect. For comparisons of eletriptan to sumatriptan we agree with you that correcting for a placebo effect is not appropriate. For estimating a dose-response relationship it is critical to try to adjust for the placebo effect. However, because of probable noise introduced by the adjustment, the post-hoc nature of it, and the secondary status of the analyses, interpretation is more difficult than that of the unadjusted primary endpoint.

4. Subject 50 was discontinued after 15 minutes of eletriptan infusion because of a 20% vasoconstriction, which peaked at 38% at 25 minutes post-start of the infusion. The Sponsor argued that an anatomical aberration of myocardial bridging could partially account for this observation. Is this explanation justified? How frequent is that type of abnormality in the general population?

The investigator estimated the narrowing in the mid-LAD as 60-70%, about 50% greater than a baseline 20% narrowing, although the reference lab estimated about 39% narrowing from the QCA. By coincidence Circulation has a mini-review about myocardial bridging in the current issue. (Mohlenkamp, Hort et al. 2002) Myocardial bridging is muscle overlying an epicardial coronary artery. It is common, with prevalence ranging from 5% to 86% by autopsy and less by angiography—the recent review concludes that myocardial bridges are present in about one-third of adults. Myocardial bridges are located most frequently in the mid-LAD, as in this case. They have been associated with ischemic events. However, based on the frequency of bridges and the rarity of case reports linking them reasonably to ischemic events, ischemia is rare with bridges alone as the review notes. While myocardial bridging might partially account for the event in this case, we are not reassured. If similar events occurred in the one-third of adults with myocardial bridges taking eletriptan and CYP3A4 inhibitors, we would worry about an increased risk of ischemic events.

5. In this study, there is a large imbalance between the number of treatment related adverse events in the eletriptan group (n=8) versus the sumatriptan group (n=0). These adverse events were related to the observation of vasoconstriction, deemed clinically insignificant by the Sponsor. However, the imbalance between both groups is striking. What is your impression about this observation?

The imbalance in vasoconstriction adverse events between eletriptan and both sumatriptan and placebo is striking and worrisome. The event rate with eletriptan is high (33%). While most of the events were mild, two of the events are concerning: the event associated with ECG changes and the moderately severe narrowing associated with the myocardial bridge. That symptoms or ischemic events did not develop is not completely reassuring: The subjects in this study were selected because they had relatively clean coronary angiograms. One would be concerned about ischemic event rates in the more vulnerable general population,

particularly older individuals with no history of ischemic heart disease but with diseased coronaries.

6. What is your perceived risk of eletriptan to cause coronary vasoconstriction?

The lack of difference in the primary endpoint among eletriptan, sumatriptan, and placebo is not informative. The vasoconstrictive adverse events occurring only in one-third of eletriptan subjects are cause for concern. They suggest, but do not prove conclusively, that eletriptan may lead to increased rates of cardiac ischemic events. This study does not answer the question of what is the risk of cardiac ischemic events in subjects exposed to high levels of eletriptan when taken concomitantly with a CYP3A4 inhibitor—answering the latter question is difficult and we do not have suggestions for additional studies. We did not review the rest of the NDA data in detail, but we note that your original NDA review lists chest tightness in 4.3% of subjects treated with eletriptan 80 mg, 2.3% of subjects treated with 40 mg, 0.9% with 20 mg, and 0.8% with placebo. Your NDA review also commented that triptan-related myocardial infarctions are rarely seen during the development program but have been observed after approval. Restrictive labeling may be sufficient, but you will have to weigh the potential increased risk of ischemic events with this drug against its established benefits

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/s/

Eric Bastings
12/9/02 12:08:31 PM
MEDICAL OFFICER

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12/10/02 11:49:39 AM
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DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Brand Name:	eletriptan hydrobromide
Generic Name:	Relpax
Sponsor:	Pfizer
Indication:	migraine
NDA Number:	21-016
Original Receipt Date:	10/27/98
Clinical Reviewers:	Armando Oliva, MD
Review Author:	Armando Oliva, MD
Review Completed:	7/9/99

Table of Contents

1. Review Sources

The NDA was submitted entirely in electronic format and placed on a network server on CDERnet: [redacted]. I used these electronic files to conduct my review. I used the NDA summary, integrated summaries of efficacy and safety, individual study reports, patient profiles, case report forms, and datasets from clinical studies and pooled datasets which the sponsor used for its overall clinical safety (OCS) analyses.

2. Background

Eletriptan is a selective $5HT_{1B/1D}$ agonist.

2.1 Indication

The proposed indication is the acute treatment of migraine with or without aura in adults.

2.2 Important Information from pharmacologically related agents

Eletriptan is pharmacologically similar to sumatriptan. Because of the potential for 5-$HT_{1D/1B}$ agonists to cause coronary vasospasm, they should not be used in patients with coronary artery disease (CAD) or in patients in whom unrecognized CAD is likely without a prior evaluation.

2.3 Administrative History

The following administrative history is summarized by the sponsor in the NDA. IND [redacted] for oral eletriptan was submitted on 12/8/94. The end of phase 2 (EOP2) meeting was held on 5/20/96. The Division recommended that the eletriptan NDA contain 2 efficacy studies and one long term safety study. The Division considered the design and power of Study 314 sufficient to qualify this study as potentially pivotal. Study 314 and possibly Study 302 would provide sufficient data for the minimum effective eletriptan dose of 20mg. The 40 and 80mg doses were acceptable for use in the Phase 3 program. The Division anticipated that eletriptan would have the same cardiovascular safety labeling as sumatriptan. Long term treatment, in accordance with ICH guidelines, requires the treatment of 300 subjects for 6 months and 100 subjects (with the 80mg dose) for 1 year. The Division recommended that subjects treat a minimum of two headaches per month, although this could be negotiable.

The Division accepted the study design, statistical methodology and safety analysis proposed to support the claims for treatment of acute migraine, treatment of non-responders, and treatment of migraine recurrence. It was agreed that a step-down procedure for comparing treatment groups would be performed in the statistical evaluation of the primary efficacy endpoint (2 hour response rate) for studies involving several eletriptan dosage groups. It was also agreed that a prospectively defined meta-analysis would be acceptable in the evaluation of the ability of a second dose to treat non-responders and recurrence during each treated migraine attack across the clinical program (subsequently Pfizer decided to prospectively include Studies 102, 104, 305, 307 and 318 in the meta-analysis).

At Pfizer's request, a conference call was held with the FDA on 8/22/96 to discuss the FDA's 8/12/96 EOP2 follow-up correspondence. During this conference call, the Agency confirmed that Studies 314 and 102 (for which the protocol had recently been submitted) would provide adequate data on the 20mg eletriptan dose. The Division clarified that we did not consider migraine to be the same disease in pediatrics and adults and therefore, a full scale efficacy and safety study in pediatrics would be required if Pfizer wanted pediatric labeling for eletriptan.

At the FDA's request, a teleconference was held on 4/18/97 to discuss a treatment sequence alteration which the Division thought could potentially enhance the dosing and administration information generated from Study 103, a study designed to explore the efficacy, safety and toleration of the administration of an eletriptan 80mg dose in subjects who did not achieve a pain free response to 40mg eletriptan by 2 hours. The Division suggested that replacement of one of the two placebo arms in Dose 1 of Attack 1 with a 40mg eletriptan dose might serve to further enhance the quality of the information generated from this study by enabling Pfizer to best characterize a subject's response to a second dose. Pfizer informed the FDA that subject dosing had already been initiated in 3/97. This teleconference also served as an opportunity to address the FDA faxes of 3/24/97 and 4/1/97 concerning the eletriptan meta-analysis protocol and the eletriptan pediatric Protocol 160-105. The FDA further clarified the prognostic factors which should be included in the eletriptan meta-analysis and reconfirmed that six month safety data in 300 adolescent subjects was a suggestion and not a filing requirement for the 3Q98 eletriptan NDA.

On 1/21/98, the eletriptan pre-NDA meeting was held to discuss specific labeling, clinical, statistical and pharmacological issues essential in the preparation and submission of a cohesive eletriptan NDA. Consensus was reached with the Division on the presentation of efficacy and safety data; the adequacy of the eletriptan human hepatocyte induction study results in negating the need for a drug interaction study of eletriptan with oral contraceptives; the format of the clinical and statistical components of the eletriptan electronic submission, and format and content issues concerning the NDA and the NDA Safety Update. Discussions with the Division indicate that the eletriptan NDA filing would receive a Standard Review by the Agency.

2.4 Proposed Labeling

2.4.1 Description

Eletriptan is a water soluble white to pale powder. It is available as 20mg, 40mg, and 80mg tablets for oral administration.

2.4.2 Clinical Pharmacology

Eletriptan is a potent and selective $5HT_{1B/1D}$ receptor agonist. It also exhibits high affinity for the $5HT_{1F}$ receptor. Animal studies suggest that eletriptan has some degree of cranioselectivity with regards to its vasoconstrictive properties.

2.4.3 Pharmacokinetics

Gastrointestinal absorption is at least 81%. Absolute bioavailability in males and females is 50%. T_{max} is 1.5 hours. Pharmacokinetics are linear over the clinical dose range (20-