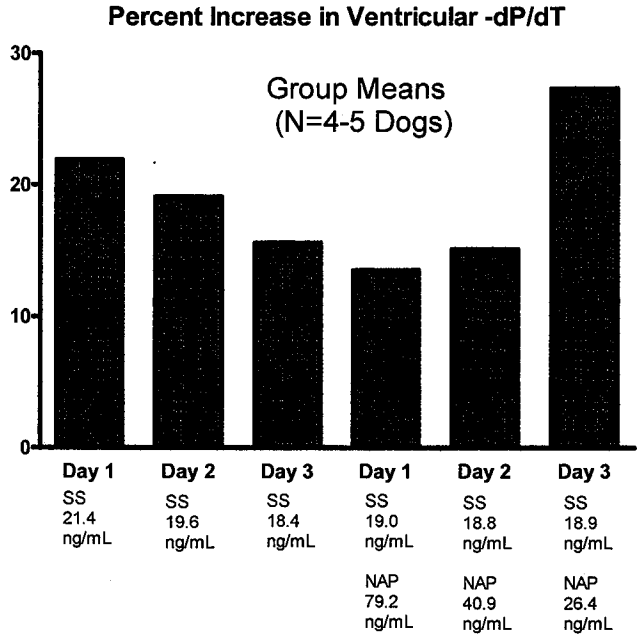
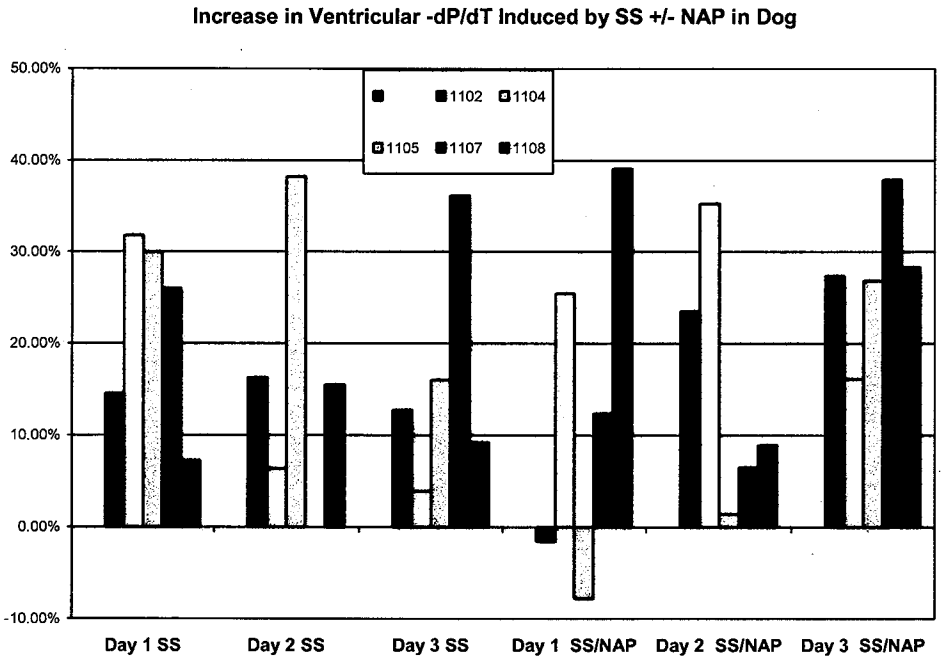
Left Ventricular -dP/dT:

The mean increase in -dP/dT induced by SS was not statistically significantly affected by coadministration of 20 mg/kg IV NAP on Day 1 (p=0.4386), Day 2 (p=0.9855), or Day 3 (p=0.1455).





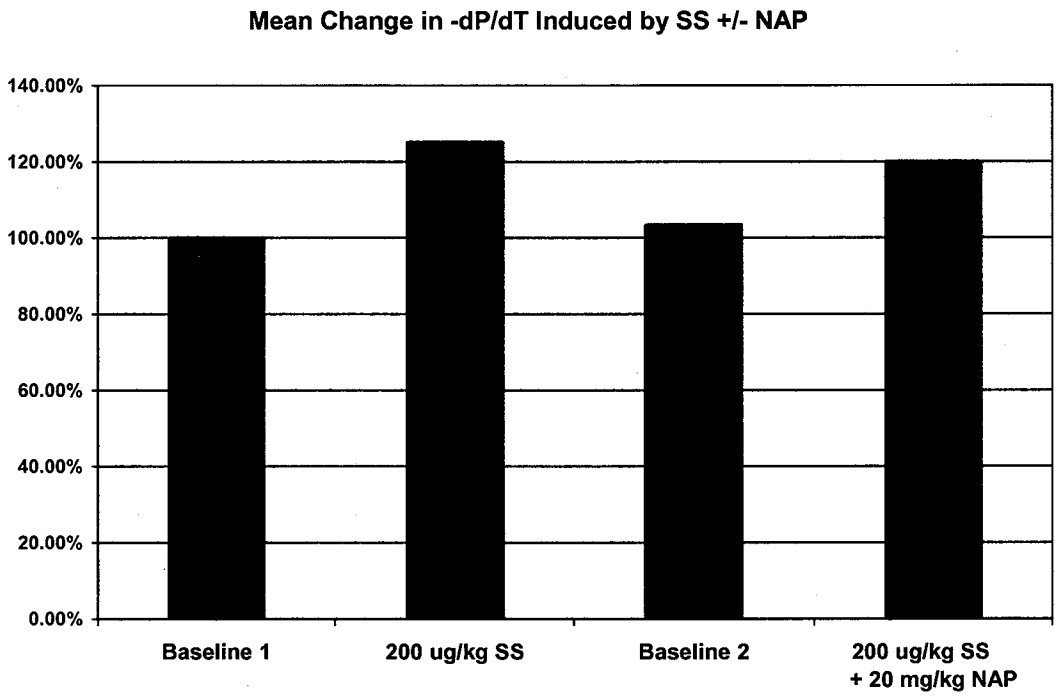
In Phase III, the mean increase in -dP/dT induced by 200 ug/kg IV SS was not statistically significantly different with coadministration of 20 mg/kg IV NAP (p=0.3097).

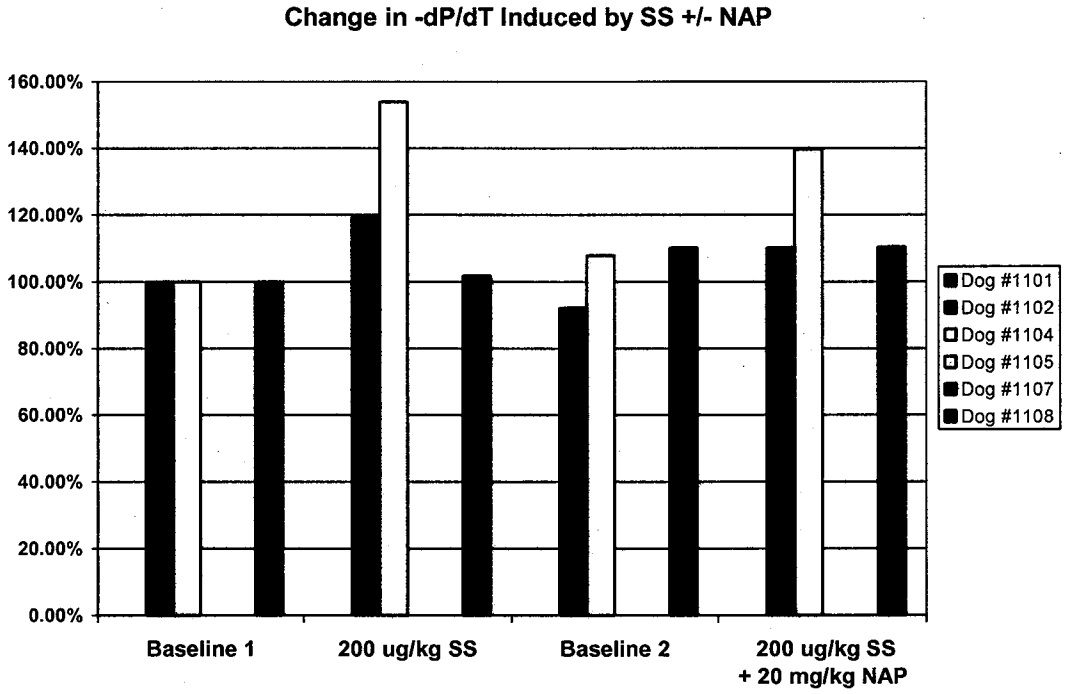
PHASE III

Study QCBW 106
Table 20
Maximum Increases in
-dP/dT (mmHg/sec)

	200 µg/kg Sumatriptan			20 mg/kg Naproxen + 200 µg/kg Sumatriptan			
Dog ID	Baseline [a]	Maximum -dP/dT [b]	Change From Baseline [c]	Baseline [a]	Maximum -dP/dT [b]	Change From Baseline [c]	(Nap+Suma) - Suma
1101[d]	.	.	.	.	.	.	.
1102	5464.8	6531.0	1066.2	5034.6	6019.0	984.4	-81.8
1104	2683.8	4130.0	1446.2	2893.0	3749.0	856.0	-590.2
1105[d]	.	.	.	.	.	.	.
1107[d]	.	.	.	.	.	.	.
1108	2610.2	2657.0	46.8	2874.4	2879.0	4.6	-42.2
						Mean	-238.1
						STD	305.6
						95% CI	(-997.2, 521.1)
						p-value	0.3097

[a] The baseline values were obtained by taking the mean of the data collected during the 5 minute interval immediately preceeding sumatriptan (sumatriptan only) or naproxen (naproxen + sumatriptan).
[b] Maximum -dP/dT during the first hour after sumatriptan administration.
[c] Maximum -dP/dT - Baseline -dP/dT.
[d] Period (.) denotes a missing value.





Deviations from Protocol:

- The LCX flow probe malfunctioned for Dog #1107 preventing collection of data on blood flow and other parameters dependent upon blood flow during all 3 phases.
- The carotid flow probe malfunctioned for Dog #1104 preventing collection of data on blood flow and other parameters dependent upon blood flow during Phase III only.
- Signal was lost from both LCX and carotid flow probes and [redacted] catheters, and from the LCX crystals (measuring diameter) in Dog #1105, so no assessments were made in Phase III for this animal.

Sponsor's Conclusions:

- **"There were no statistically significant c**hanges to the SS-induced response of the coronary and carotid arteries observed during Phase I as a result of combined **administration of naproxen sodium (NAP) with SS during Phase II."**
- **"There were no statistically** significant, biologically relevant changes to the responses of the coronary and carotid arteries as a result of combined administration of NAP **with SS," during Phase III (200 ug/**kg IV SS + 20 mg/kg IV NAP).
- **"In conclusion, co-administrat**ion of NAP with SS did not alter the vasoconstrictive effect of SS on the coronary arteries of conscious, chronically instrumented female beagle dogs, nor did it alter any of the other cardiovascular parameters measured in **this study."**

Reviewer's Conclusions:

The Sponsor's conclusion that Phases I and II showed no statistically significant changes is technically accurate, based on the paired t-test analyses of the differences between the SS-induced reductions in coronary and carotid artery diameter in the presence and absence of NAP. However, review of the group mean and individual animal data from Day 1 treatments revealed apparent trends toward NAP-related enhancement of SS-induced effects on coronary artery diameter, carotid artery diameter, mean arterial blood pressure (MAP), and coronary artery resistance. The importance of such trends is questionable, though, in the context of the wide inter-individual and intra-individual variation observed and the design flaws noted several paragraphs below.

Four out of six dogs showed substantially (2- to 7-fold) greater SS-induced reductions in LCX coronary artery diameter in the presence (7-10%) vs. the absence (1-4%) of NAP on Day 1. The group average difference (~2-fold) did not reach statistical significance because one dog showed only a small change (~5.0% SS→ ~5.5% SS/NAP) and one (#1107) showed a change in the opposite direction (~8% SS→ ~3.5% SS/NAP). However, it is difficult to argue that these data demonstrate a consistent NAP effect when both the intra-individual (day to day) and inter-individual variation are so great.

The mean SS-induced reduction in LCX coronary artery resistance was ~4-fold greater with NAP than without on Day 1, yet this difference was not statistically significant, due to the high inter-individual variability in the SS alone group (from ↑10% to ↓23%). In this case, a hint of a possible NAP effect comes from the much lower variability among individuals in the Day 1 SS/NAP group (↓17-26% in all 5 dogs).

The mean SS-induced reduction in carotid artery diameter was 2-fold greater with NAP than without on Day 1, yet, again, this difference was not statistically significant, due to the wide variability among individuals in the SS group (↓2-24%) and in the SS/NAP group (↓7-34%). Variation was also quite wide from day to day within each individual, arguing against the reliability of these data.

The mean SS-induced increase in MAP was ~1.5-fold greater with NAP than without on Day 1, but this difference was not statistically significant, due to variability. One anomalous dog showed an increase in MAP of 29% with SS and -1% with SS/NAP, and two others showed little or no extra increase in MAP with NAP. The two dogs showing the greatest increase in SS-induced MAP increase with NAP (~3-fold), showed similar large increases on Day 3, when NAP levels had decreased 3-fold, and no increases on Day 2. These data suggest that the increases in MAP were due to technical problems, or unknown factors, rather than to the presence of SS/NAP.

The Sponsor's conclusions regarding Phase III are invalidated by the design flaws described in the third paragraph below.

Study MT400-T15 was inappropriately designed. The N of 6 dogs was chosen to provide a power of > 80% to detect the mean reduction in external coronary arterial diameter (eCAD) of 1.37 um ± 21 (↓5.3% from baseline) induced by 100 ug/kg IV SS in conscious dogs *(Carel et al., 2001, Br J Pharmacol 132:1071-1083)*. However, the present study was intended to detect a *change* in that level of reduction (by NAP), not just the SS-induced reduction itself. Therefore a larger N would have been needed to provide a power of > 80% to detect an effect of NAP on SS-induced coronary artery vasoconstriction.

It is not clear to this reviewer that the data derived from Days 2 and 3 of Phase II are informative, since having plasma levels of NAP still on board from an injection 24 or 48 hrs before the fresh injection of SS is quite different pharmacologically from the clinical condition of having rapidly rising plasma concentrations of both SS and NAP in the absence of recent prior exposure. Compensatory responses to the prolonged NAP exposure may even interfere with the SS-induced vasoconstriction. If lower doses of NAP are considered desirable to evaluate, they should be administered to a separate group of animals, or to the same animals after a sufficient washout period (at least 5 days, since the half-life of NAP in dogs is ~35-40 hrs). Also, given the variability observed, repeated measures at each dose, with appropriate washout intervals, would improve the reliability of the results.

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