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BEST POSSIBLE

Table ~~30~~ 0.4.1

Subgroup Analysis of Headache Relief Rates at 240 Minutes Post First Dose in the Placebo-Controlled Parallel Efficacy Studies In Adult Patients [1]

		Placebo		Naratriptan 1.0mg		Naratriptan 2.5mg		Homogeneity of Differences Across Subgroups Between: [2] Placebo vs. Naratriptan 1.0mg	Placebo vs. Naratriptan 2.5mg	Naratriptan 1.0mg vs. 2.5mg
Intent-to-Treat Population No of Patients		485		574		579				
Gender	**Female**	146	(34%)	263	(53%)	320	(64%)	0.169	0.266	0.784
	Male	13	(26%)	48	(59%)	51	(66%)			
Ethnic Origin	**Caucasian Other**	153	(33%)	294	(54%)	355	(63%)	0.909	0.212	0.201
		6	(35%)	17	(59%)	16	(84%)			
Age (years)	**18-30**	33	(39%)	49	(44%)	70	(64%)	0.059	0.394	0.384
	31-40	45	(32%)	94	(56%)	110	(64%)			
	41-50	65	(33%)	121	(58%)	116	(63%)			
	51-65	16	(25%)	47	(55%)	75	(67%)			
Weight (kg)	**<75**	111	(32%)	204	(51%)	269	(64%)	0.192	0.736	0.083
	≥75	48	(34%)	106	(62%)	101	(64%)			
Time from onset to first dose	**≤4 Hours**	122	(35%)	209	(52%)	263	(63%)	0.038	0.191	0.422
	>4 Hours	37	(28%)	101	(60%)	105	(66%)			

[1] Analysis includes data from studies S2WB2004, S2WA3001, S2WB3002 (first attack data only) and S2WA3003 (First attack data only). Headache relief is defined as a reduction of headache severity from score 2 or 3 (moderate or severe) to score 1 or 0 (mild or none). Percentages are the percent of patients in each subgroup who achieved headache relief at 240 minutes post first dose.

[2] P-values are based on the Breslow-Day test, comparing across subgroup factors.

[3] Smoking/Tobacco Use was not recorded in S2WB3002.

Table 30 ~~continued~~ 0.4.2

Subgroup Analysis of Headache Relief Rates at 240 Minutes Post First Dose in the Placebo-Controlled Parallel Efficacy Studies in Adult Patients [1]

		Placebo		Naratriptan 1.0mg		Naratriptan 2.5mg		Homogeneity of Differences Across Subgroups Between: [2]		
								Placebo vs. Naratriptan 1.0mg	Placebo vs. Naratriptan 2.5mg	Naratriptan 1.0mg vs. 2.5mg
Intent-to-Treat Population No of Patients		485		574		579				
Migraine Prophylactic Use	**Absent**	122	(33%)	240	(55%)	275	(65%)	0.678	0.664	0.985
	Present	37	(32%)	71	(51%)	96	(62%)			
Smoking/Tobacco Use [3]	**Never Smoked**	84	(36%)	129	(56%)	151	(67%)	0.643	0.016	0.126
	Former	21	(22%)	39	(46%)	55	(58%)			
	Current	26	(52%)	34	(67%)	33	(57%)			
Current Migraine Type	**Without Aura**	132	(33%)	263	(55%)	317	(64%)	0.330	0.697	0.555
	With Aura	27	(35%)	46	(49%)	53	(63%)			
Oral Contraceptive Use	**No**	119	(34%)	218	(55%)	256	(64%)	0.758	0.580	0.362
	Yes	27	(31%)	48	(48%)	64	(65%)			

[1] Analysis includes data from studies S2WB2004, S2WA3001, S2WB3002 (first attack data only) and S2WA3003 (First attack data only). Headache relief is defined as a reduction of headache severity from score 2 or 3 (moderate or severe) to score 1 or 0 (mild or none). Percentages are the percent of patients in each subgroup who achieved headache relief at 240 minutes post first dose.

[2] P-values are based on the Breslow-Day test, comparing across subgroup factors.

[3] Smoking/Tobacco Use was not recorded in S2WB3002.

Naratriptan Tablets - Integrated Summary of Efficacy
Intent-to-Treat Population

Table # 0.4.3

Subgroup Analysis of Headache Relief Rates at 240 Minutes Post First Dose in the Placebo Controlled Parallel Efficacy Studies in Adult Patients

				Homogeneity of Differences Across Subgroups Between:		
	Placebo	NARATRIPTAN 1.0MG	NARATRIPTAN 2.5MG	Placebo vs NARATRIPTAN 1.0MG	Placebo vs NARATRIPTAN 2.5MG	NARATRIPTAN 1.0MG vs NARATRIPTAN 2.5MG
Intent-to-Treat Population						
No. of Patients	485	574	579			
Baseline HA Severity						
Moderate	44 (40%)	95 (55%)	119 (73%)	0.026	0.968	0.011
Severe	19 (22%)	67 (56%)	67 (54%)			

Note: Includes data from studies S2WA3001, S2WA3003 (first attack only), S2WB2004 and S2WB3002 (first attack only).
P-values are based on the Breslow-Day test, comparing across subgroup factors.
Headache relief is defined as a reduction of headache severity from grade 2 or 3 (moderate or severe pain) to grade 1 or 0 (mild or no pain). Percentages are the percent of patients in each subgroup who achieved headache relief at 240 minutes post first dose.

Naratriptan Tablets - Protocol S2WA3001
Intent-to-Treat Population

Table 12 1.3.1

Headache Relief Rates Within 240 Minutes Post First Dose - Intent-to-Treat Population

		NARATRIPTAN (mg/dose)				Between-Treatment Comparison P-values[1]					Linear Trend Test P-Value[2]	
	Placebo	0.1	0.25	1.0	2.5	PBO vs 1.0	PBO vs 2.5	0.1 vs 1.0	0.1 vs 2.5	0.25 vs 2.5	With Placebo	Without Placebo
Intent-to-Treat Population												
No. of Patients	122	128	119	117	127							
No. of Patients with Headache Relief at Post-Dose Time:												
30 minutes	5 (4%)	4 (3%)	4 (3%)	9 (8%)	10 (8%)	NS	NS	NS	NS	NS	0.048	0.064
60 minutes	19 (16%)	13 (10%)	10 (8%)	17 (15%)	25 (20%)	NS	NS	NS	0.056	0.015	0.027	0.006
90 minutes	31 (25%)	24 (19%)	15 (13%)	31 (26%)	40 (31%)	NS	NS	0.093	0.028	<0.001	0.006	<0.001
120 minutes	37 (30%)	32 (25%)	24 (20%)	49 (42%)	51 (40%)	0.106	0.112	0.001	0.013	0.002	0.001	<0.001
180 minutes	43 (35%)	41 (32%)	38 (32%)	58 (50%)	66 (52%)	0.035	0.004	0.008	0.003	0.004	<0.001	<0.001
240 minutes	42 (34%)	41 (32%)	42 (35%)	59 (50%)	76 (60%)	0.022	<0.001	0.004	<0.001	<0.001	<0.001	<0.001
No. of Patients with Headache Relief within 240 Minutes	51 (42%)	47 (37%)	47 (39%)	68 (58%)	79 (62%)							
Median Minutes to First Relief[3]	90	90	120	120	94							

Note: Headache severity is defined on a four-point scale (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain). Headache relief is defined as a reduction in headache severity from grade 3 or 2 (severe or moderate) to grade 1 or 0 (mild or no pain). Patients who took rescue medication or a second dose of study medication are considered to have headache severity grade 3 from that point forward.

[1] P-values are based on the Cochran-Mantel-Haenszel test adjusted for investigator. P-values > 0.15 are denoted as NS. ND indicates that, due to the small number of events, a statistical test was not done.

[2] P-values are based on a logistic regression model to test for linear trend.

[3] Among patients who report headache relief within 240 minutes.

Naratriptan Tablets - Protocol S2WA3001
Intent-to-Treat Population

Table 1.4.1
Post-dose Rescue Medications

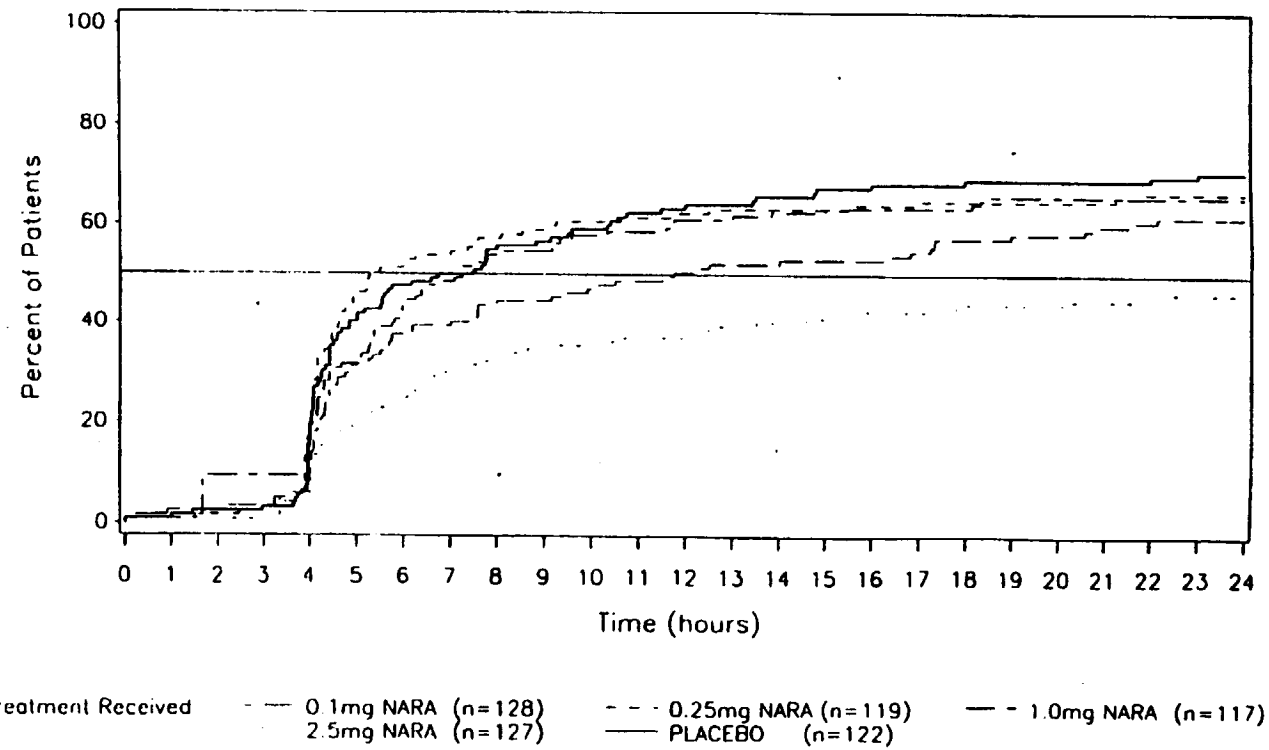
	Placebo	NARATRIPTAN (mg/dose) 0.1	0.25	1.0	2.5	Between-Treatment Comparison P-values[1] PBO vs 1.0	PBO vs 2.5	0.1 vs 1.0	0.1 vs 2.5	0.25 vs 2.5	Linear Trend Test[2] P-Value
Intent-to-Treat Population No. of Patients	122	128	119	117	127						
No. of Patients Taking Post-dose Rescue Meds[3]	68 (56%)	68 (53%)	62 (52%)	45 (38%)	39 (31%)	NS	<0.001	0.062	<0.001	0.014	<0.001
No. of Patients Taking Either 2nd Dose of Study Med or Post-dose Rescue Meds[3]	85 (70%)	84 (66%)	80 (67%)	72 (62%)	60 (47%)	NS	0.005	NS	0.006	0.005	<0.001

[1] P-values are based on the Cochran-Mantel-Haenszel test adjusted for investigator. P-values > 0.15 are denoted as NS.
[2] P-values are based on a logistic regression model to test for linear trend. P-values > 0.15 are denoted as NS.
[3] Includes medications taken by the patient for acute migraine pain or symptoms within 24 hours after taking study treatment.

Naratriptan Tablets
Protocol S2WA3001

Figure 1.5.1

Time to Retreatment (2nd Dose or Rescue)
(Kaplan – Meier estimates)



Naratriptan Tablets - Protocol S2WA3001
Intent-to-Treat Populati n

Table 08 (6)
Headache Recurrence Rates

	Placebo	NARATRIPTAN (mg/dose) 0.1	0.25	1.0	2.5
Intent-to-Treat Population No. of Patients	122	128	119	117	127
No. of Patients with Headache Relief at 4 Hours	42 (34%)	41 (32%)	42 (35%)	59 (50%)	76 (60%)
No. of Patients with Recurrence of Headache	16 (38%)	16 (39%)	16 (38%)	23 (39%)	21 (28%)
Time to Recurrence of Headache (hours)					
N	16	16	16	23	21
Mean	11.2	10.0	9.0	12.6	11.4
Std.Dev.	1.6	1.4	1.7	1.3	1.3
Median	9.2	7.4	5.5	11.8	10.4
Minimum	4.8	4.3	4.1	4.2	4.0
Maximum	25.3	23.0	23.9	22.1	22.1
No. of Patients with Recurrence of Headache Who Took 2nd Dose	15 (94%)	14 (88%)	16 (100%)	21 (91%)	21 (100%)

Note: Headache severity is defined on a four-point scale (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain). Headache recurrence is defined as a headache that gets significantly worse [increase to grade 2 or 3 (moderate or severe)] between 4 and 24 hours post first dose after achieving headache relief (grade 0/1) at 240 minutes post first dose. The time to recurrence of headache is calculated from the time of first dose.

Note: Patients may have taken rescue medications before headache recurrence. The number of patients in each treatment group doing so was: 0.1MG, 2; 0.25MG, 0; 1.0MG, 1; 2.5MG, 0; Placebo, 1.

Naratriptan Tablets - Protocol S2WA3003
Randomized Population

Table # 2.2.1.

Patient Accountability

Attack Number		NARATRIPTAN (mg/dose)									
		Placebo		0.25		1.0		2.5		Total	
All Attacks	Total No. of Patients	606		593		600		590		740	
	Patients Withdrawn from Study	43	(7%)	41	(7%)	43	(7%)	42	(7%)	227	(31%)
	Reason for Withdrawal										
	Lack of Efficacy	6	(1%)	2	(<1%)	2	(<1%)	4	(1%)	14	(2%)
	Adverse Event	5	(1%)	4	(1%)	3	(1%)	1	(<1%)	13	(2%)
	Failed to Return	6	(1%)	4	(1%)	7	(1%)	3	(1%)	28	(4%)
	Never Treated Headache									50	(7%)
	Sponsor Ended Study	18	(3%)	24	(4%)	23	(4%)	26	(4%)	91	(12%)
	Other	8	(1%)	7	(1%)	8	(1%)	8	(1%)	31	(4%)
Attack 1	Total No. of Patients	172		174		167		169		682	
	Patients Withdrawn from Study	13	(8%)	11	(6%)	12	(7%)	14	(8%)	50	(7%)
	Reason for Withdrawal										
	Lack of Efficacy	2	(1%)	1	(1%)	0		2	(1%)	5	(1%)
	Adverse Event	2	(1%)	3	(2%)	1	(1%)	0		6	(1%)
	Failed to Return	2	(1%)	3	(2%)	1	(1%)	1	(1%)	7	(1%)
	Sponsor Ended Study	4	(2%)	4	(2%)	7	(4%)	6	(4%)	21	(3%)
	Other	3	(2%)	0		3	(2%)	5	(3%)	11	(2%)
Attack 2	Total No. of Patients	164		156		158		154		632	
	Patients Withdrawn from Study	21	(13%)	16	(10%)	17	(11%)	17	(11%)	71	(11%)
	Reason for Withdrawal										
	Lack of Efficacy	3	(2%)	1	(1%)	1	(1%)	2	(1%)	7	(1%)
	Adverse Event	2	(1%)	1	(1%)	1	(1%)	0		4	(1%)
	Failed to Return	4	(2%)	1	(1%)	3	(2%)	2	(1%)	10	(2%)
	Sponsor Ended Study	7	(4%)	8	(5%)	8	(5%)	11	(7%)	34	(5%)
	Other	5	(3%)	5	(3%)	4	(3%)	2	(1%)	16	(3%)

Note: In the TOTAL column for ALL ATTACKS, the relevant population is those patients who were randomized to (but did not necessarily treat with) study drug. For all other values in this table, the relevant population is those patients who treated with the indicated study drug.

Note: Patients 2655 and 2665 did not treat four attacks (assigned study medication for the second attack was skipped) but were not considered withdrawals by the investigator.

continued

Naratriptan Tablets · Protocol S2WA3003
Randomized Population

Table 2.2.1 continued
Patient Accountability

Attack Number		Placebo		NARATRIPTAN (mg/dose) 0.25		1.0		2.5		Total	
Attack 3	Total No. of Patients	142		134		145		140		561	
	Patients Withdrawn from Study	9	(6%)	14	(10%)	12	(8%)	10	(7%)	45	(8%)
	Reason for Withdrawal										
	Lack of Efficacy	1	(1%)	0		1	(1%)	0		2	(<1%)
	Adverse Event	1	(1%)	0		1	(1%)	1	(1%)	3	(1%)
	Failed to Return	0		0		1	(1%)	0		1	(<1%)
	Sponsor Ended Study	7	(5%)	12	(9%)	8	(6%)	9	(6%)	36	(6%)
	Other	0		2	(1%)	1	(1%)	0		3	(1%)
Attack 4	Total No. of Patients	128		129		130		127		514	
	Patients Withdrawn from Study	0		0		2	(2%)	1	(1%)	3	(1%)
	Reason for Withdrawal										
	Lack of Efficacy	0		0		0		0		0	
	Adverse Event	0		0		0		0		0	
	Failed to Return	0		0		2	(2%)	0		2	(<1%)
	Sponsor Ended Study	0		0		0		0		0	
	Other	0		0		0		1	(1%)	1	(<1%)

Note: Patients 2655 and 2665 did not treat four attacks (assigned study medication for the second attack was skipped) but were not considered withdrawals by the investigator.

Naratriptan Tablets - Protocol S2WA3003
Intent-to-Treat Population

Table 2.3.1

Headache Relief Rates Within 240 Minutes Post First Dose - Intent-to-Treat Population - All Attacks

	Placebo	NARATRIPTAN (mg/dose) 0.25	1.0	2.5	Between-Treatment Comparison P-values[1] PBO vs 1.0	PBO vs 2.5	0.25 vs 1.0	0.25 vs 2.5	Linear Trend Test[2] P-Value
Intent-to-Treat Population									
No. of Patients	602	591	595	586					
No. of Patients with Headache Relief at Post-Dose Time:									
30 minutes	34 (6%)	33 (6%)	35 (6%)	43 (7%)	NS	NS	NS	NS	0.129
60 minutes	76 (13%)	101 (17%)	120 (20%)	133 (23%)	<0.001	<0.001	0.146	0.012	<0.001
90 minutes	130 (22%)	141 (24%)	196 (33%)	215 (37%)	<0.001	<0.001	<0.001	<0.001	<0.001
120 minutes	160 (27%)	175 (30%)	253 (43%)	289 (49%)	<0.001	<0.001	<0.001	<0.001	<0.001
180 minutes	184 (31%)	210 (36%)	309 (52%)	354 (60%)	<0.001	<0.001	<0.001	<0.001	<0.001
240 minutes	197 (33%)	233 (39%)	338 (57%)	396 (68%)	<0.001	<0.001	<0.001	<0.001	<0.001
No. of Patients with Headache Relief within 240 Minutes	245 (41%)	270 (46%)	359 (60%)	409 (70%)					
Median Minutes to First Relief[3]	90	90	90	90					

Note: Headache severity is defined on a four-point scale (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain). Headache relief is defined as a reduction in headache severity from grade 3 or 2 (severe or moderate) to grade 1 or 0 (mild or no pain). Patients who took rescue medications or a second dose of study medication are considered to have headache severity grade 3 from that point forward.

[1] P-values are based on the logistic regression cross-over model to test for active versus placebo treatment differences and for linear trend. P-values > 0.15 are denoted as NS.

[2] Among patients who report headache relief within 240 minutes.

Figure 9.3.2 Headache Relief Rates at 240 Minutes Post First Dose, by Attack

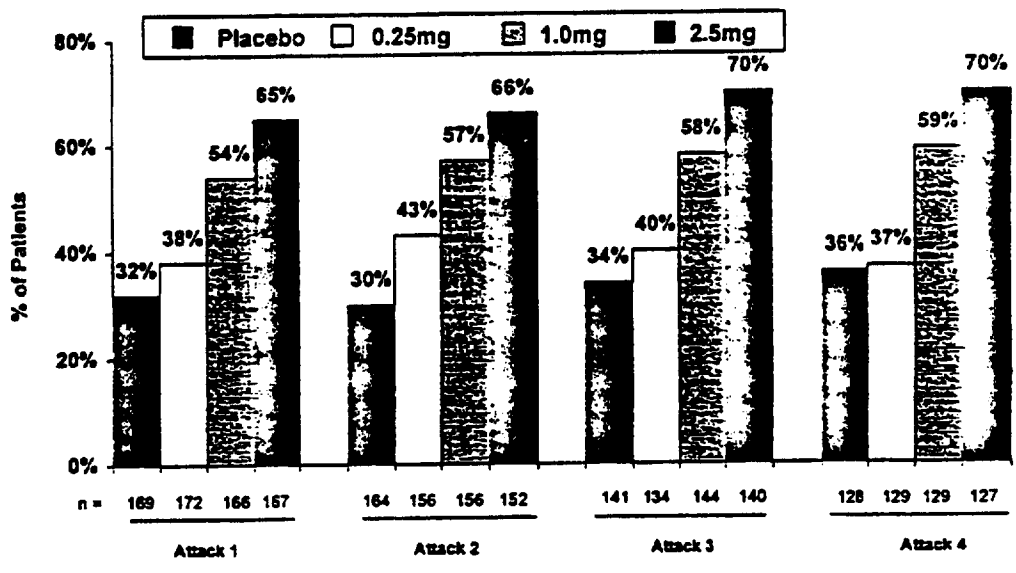


Table 19

Naratriptan Tablets - Protocol S2WA3003
Intent-to-Treat Population

Table 2.4.1
Post-dose Rescue Medications - All Attacks

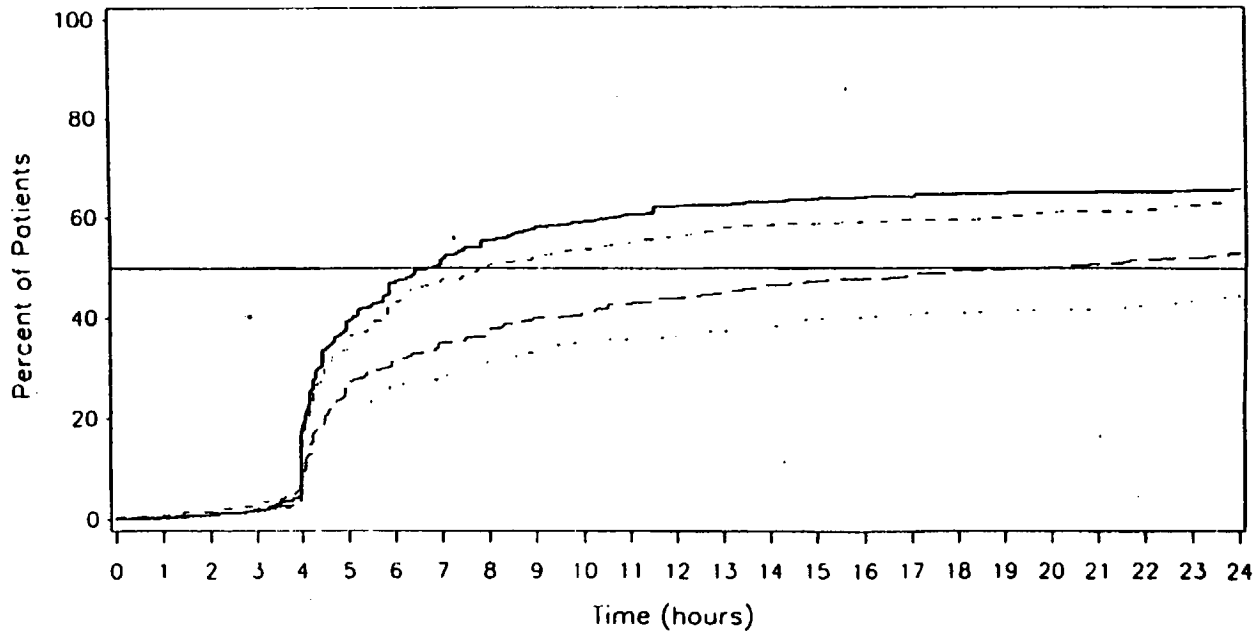
		NARATRIPTAN (mg/dose)			Between-Treatment Comparison P-values[1]				
	Placebo	0.25	1.0	2.5	PBO vs 1.0	PBO vs 2.5	0.25 vs 1.0	0.25 vs 2.5	Linear Trend Test P-Value
Intent-to-Treat Population No. of Patients	602	591	595	586					
No. of Patients Taking Post-dose Rescue Meds[2]	312 (52%)	285 (48%)	200 (34%)	155 (26%)	<0.001	<0.001	<0.001	<0.001	<0.001
No. of Patients Taking Either 2nd Dose of Study Medication or Post-dose Rescue Meds[2]	395 (66%)	374 (63%)	316 (53%)	264 (45%)	<0.001	<0.001	<0.001	<0.001	<0.001

[1] P-values are based on the logistic regression cross-over model to test for active versus placebo treatment differences and for linear trend. P-values > 0.15 are denoted as NS.
[2] Includes medications taken by the patient for acute migraine pain or symptoms within 24 hours after taking study treatment.

Naratriptan Tablets
Protocol S2WA3003

Figure 2.5.1

Time to Retreatment (2nd Dose or Rescue) – All Attacks
(Kaplan – Meier estimates)



Naratriptan Tablets - Protocol S2WA3003
Intent-to-Treat Population

Table 2.6.1
Headache Recurrence Rates - All Attacks

		NARATRIPTAN (mg/dose)		
	Placebo	0.25	1.0	2.5
Intent-to-Treat Population				
No. of Patients	602	591	595	586
No. of Patients with Headache Relief at 4 Hours	197 (33%)	233 (39%)	338 (57%)	396 (68%)
No. of Patients with Recurrence of Headache	70 (36%)	79 (34%)	111 (33%)	105 (27%)
Time to Recurrence of Headache (hours)				
N	70	79	111	104
Mean	8.5	10.0	11.0	11.2
Std.Dev.	0.5	0.6	0.6	0.6
Median	6.8	7.9	8.3	9.0
Minimum	4.0	4.0	4.0	4.0
Maximum	22.3	23.8	28.4	27.8
No. of Patients with Recurrence of Headache Who Took 2nd Dose	62 (89%)	69 (87%)	98 (88%)	96 (91%)

Note: Headache severity is defined on a four-point scale (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain). Headache recurrence is defined as a headache that gets significantly worse [increase to grade 2 or 3 (moderate or severe)] between 4 and 24 hours post first dose after achieving headache relief (grade 0/1) at 240 minutes post first dose. The time to recurrence of headache is calculated from the time of first dose.

Note: Patients may have taken rescue medications before headache recurrence. The number of patients in each treatment group doing so was: 0.25MG, 5; 1.0MG, 9; 2.5MG, 4; Placebo, 5.

Patient 184 (2.5MG) had missing data for time to recurrence.

Table 3.2.1

TABLE 4. ATTENDANCE AT CLINIC VISITS: SAFETY POPULATION

	Sumatriptan		Naratriptan				
	Placebo (+100mg)	100mg (+100mg)	0.1mg (+0.1mg)	0.25mg (+0.25mg)	1.0mg (+1.0mg)	2.5mg (+2.5mg)	Total
Number of patients in safety population	108	241	221	224	219	209	1222
Number of patients who attended at:							
Visit 1	108 (100%)	241 (100%)	221 (100%)	224 (100%)	219 (100%)	209 (100%)	1222 (100%)
Visit 2	106 (98%)	239 (99%)	219 (99%)	221 (99%)	214 (98%)	208 (100%)	1207 (99%)
Visit 3	94 (87%)	222 (92%)	205 (93%)	198 (88%)	203 (93%)	193 (92%)	1115 (91%)

Table 3.2.2

GCV/96/006
Protocol No. S2WB3002

TABLE 5. NUMBER OF PATIENTS WITHDRAWN FROM THE STUDY: SAFETY POPULATION

	Sumatriptan		Naratriptan				
	Placebo (+100mg)	100mg (+100mg)	0.1mg (+0.1mg)	0.25mg (+0.25mg)	1.0mg (+1.0mg)	2.5mg (+2.5mg)	Total
Number of patients in safety population	108	241	221	224	219	209	1222
Number of patients withdrawn from the study	29 (27%)	44 (18%)	61 (28%)	56 (25%)	49 (22%)	41 (20%)	280 (23%)
Reason for withdrawal							
Lack of efficacy	12 (41%)	3 (7%)	20 (33%)	15 (27%)	6 (12%)	5 (12%)	61 (22%)
Adverse event	4 (14%)	8 (18%)	4 (7%)	1 (2%)	1 (2%)	3 (7%)	21 (8%)
Failure to return	0	5 (11%)	3 (5%)	5 (9%)	5 (10%)	3 (7%)	21 (8%)
Failure to treat attack	7 (24%)	24 (55%)	31 (51%)	27 (48%)	23 (47%)	24 (59%)	136 (49%)
Other	6 (21%)	4 (9%)	3 (5%)	8 (14%)	14 (29%)	6 (15%)	41 (15%)

Table 3-3-1

TABLE 12. IMPROVEMENT IN HEADACHE SEVERITY 0.5, 1, 1.5, 2, 3, 4, 12 AND 24 HOURS AFTER FIRST DOSE ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 3 OR 2 (ATTACK 1): INTENT-TO-TREAT POPULATION (Continued)

		Sumatriptan		Naratriptan		
Improvement at 4 hours	Placebo	100mg	0.1mg	0.25mg	1.0mg	2.5mg
Number of patients in intent-to-treat population	107	240	220	224	219	209
Number with initial headache severity grade 3 or 2	104	229	207	214	208	199
Number improved after 4 hours to grade 1 or 0	28 (27%)	173 (76%)	75 (36%)	78 (36%)	109 (52%)	132 (66%)
Number not improved after 4 hours	76 (73%)	56 (24%)	132 (64%)	136 (64%)	99 (48%)	67 (34%)

67 patients had headache severity grade 3 carried forward due to taking rescue or second treatment prior to this assessment: 11 on placebo, 9 on sumatriptan, 21 on naratriptan 0.1mg, 10 on 0.25mg, 12 on 1mg and 4 on 2.5mg

Headache relief is defined as a change in headache severity from grade 3 or 2 pre-treatment to grade 1 or 0 post-treatment

Table 3.3.2

TABLE 12. IMPROVEMENT IN HEADACHE SEVERITY 0.5, 1, 1.5, 2, 3, 4, 12 AND 24 HOURS AFTER FIRST DOSE ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 3 OR 2 (ATTACK 1): INTENT-TO-TREAT POPULATION (Continued)

Four hour comparisons

Mantel-Haenszel Analysis (stratified for country)

Comparison	Odds Ratio	95% Confidence Interval	P-value
Naratriptan 0.1mg/Placebo	1.57	0.94, 2.60	0.083
Naratriptan 0.25mg/Placebo	1.59	0.95, 2.66	0.079
Naratriptan 1.0mg/Placebo	2.93	1.78, 4.82	< 0.001
Naratriptan 2.5mg/Placebo	5.41	3.25, 9.00	< 0.001
Naratriptan 0.1mg/Sumatriptan	0.18	0.12, 0.28	< 0.001
Naratriptan 0.25mg/Sumatriptan	0.19	0.13, 0.28	< 0.001
Naratriptan 1.0mg/Sumatriptan	0.35	0.24, 0.53	< 0.001
Naratriptan 2.5mg/Sumatriptan	0.64	0.42, 0.97	0.036
Naratriptan 2.5mg/Naratriptan 0.25mg	3.37	2.26, 5.01	< 0.001
Naratriptan 2.5mg/Naratriptan 1.0mg	1.79	1.19, 2.68	0.005

Logistic Regression Analysis*

Comparison	Odds Ratio	95% Confidence Interval	P-value
Naratriptan 0.1mg/Placebo	1.51	0.89, 2.56	0.124
Naratriptan 0.25mg/Placebo	1.48	0.88, 2.50	0.139
Naratriptan 1.0mg/Placebo	2.96	1.76, 4.99	< 0.001
Naratriptan 2.5mg/Placebo	5.27	3.09, 8.99	< 0.001
Naratriptan 0.1mg/Sumatriptan	0.18	0.12, 0.28	< 0.001
Naratriptan 0.25mg/Sumatriptan	0.18	0.12, 0.27	< 0.001
Naratriptan 1.0mg/Sumatriptan	0.36	0.24, 0.54	< 0.001
Naratriptan 2.5mg/Sumatriptan	0.64	0.41, 0.98	0.039
Naratriptan 2.5mg/Naratriptan 0.25mg	3.55	2.35, 5.37	< 0.001
Naratriptan 2.5mg/Naratriptan 1.0mg	1.78	1.18, 2.68	0.006

* Allowing for effects due to treatment, migraine type, duration of migraine prior to treatment and country

Headache relief is defined as a change in headache severity from grade 3 or 2 pre-treatment to grade 1 or 0 post-treatment

Table 3.3.3

TABLE 12. IMPROVEMENT IN HEADACHE SEVERITY 0.5, 1, 1.5, 2, 3, 4, 12 AND 24 HOURS AFTER FIRST DOSE ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 3 OR 2 (ATTACK 1): INTENT-TO-TREAT POPULATION (Continued)

		Sumatriptan		Naratriptan		
Improvement at 1 hour	Placebo	100mg	0.1mg	0.25mg	1.0mg	2.5mg
Number of patients in intent-to-treat population	107	240	220	224	219	209
Number with initial headache severity grade 3 or 2	104	229	207	214	208	199
Number improved after 1 hour to grade 1 or 0	18 (17%)	76 (33%)	30 (14%)	33 (15%)	38 (18%)	44 (22%)
Number not improved after 1 hour	86 (83%)	153 (67%)	177 (86%)	181 (85%)	170 (82%)	155 (78%)

2 patients had headache severity grade 3 carried forward due to taking rescue or second treatment prior to this assessment: 1 on placebo, 0 on sumatriptan, 0 on naratriptan 0.1mg, 0 on 0.25mg, 0 on 1mg and 1 on 2.5mg

Headache relief is defined as a change in headache severity from grade 3 or 2 pre-treatment to grade 1 or 0 post-treatment

Table 3.3.4

TABLE 12. IMPROVEMENT IN HEADACHE SEVERITY 0.5, 1, 1.5, 2, 3, 4, 12 AND 24 HOURS AFTER FIRST DOSE ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 3 OR 2 (ATTACK 1): INTENT-TO-TREAT POPULATION (Continued)

One hour comparisons

Logistic Regression Analysis*

Comparison	Odds Ratio	95% Confidence Interval	P-value
Naratriptan 0.1mg/Placebo	0.86	0.45, 1.67	0.665
Naratriptan 0.25mg/Placebo	0.90	0.47, 1.71	0.742
Naratriptan 1.0mg/Placebo	1.12	0.59, 2.13	0.723
Naratriptan 2.5mg/Placebo	1.34	0.71, 2.52	0.366
Naratriptan 0.1mg/Sumatriptan	0.34	0.21, 0.56	< 0.001
Naratriptan 0.25mg/Sumatriptan	0.36	0.22, 0.57	< 0.001
Naratriptan 1.0mg/Sumatriptan	0.45	0.28, 0.70	< 0.001
Naratriptan 2.5mg/Sumatriptan	0.53	0.34, 0.83	0.006
Naratriptan 2.5mg/Naratriptan 0.25mg	1.49	0.90, 2.49	0.124
Naratriptan 2.5mg/Naratriptan 1.0mg	1.19	0.72, 1.96	0.488

* Allowing for effects due to treatment, migraine type, duration of migraine prior to treatment and country

Headache relief is defined as a change in headache severity from grade 3 or 2 pre-treatment to grade 1 or 0 post-treatment

Table 3.3.5
~~12.2~~

TABLE 12. IMPROVEMENT IN HEADACHE SEVERITY 0.5, 1, 1.5, 2, 3, 4, 12 AND 24 HOURS AFTER FIRST DOSE ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 3 OR 2 (ATTACK 1): INTENT-TO-TREAT POPULATION (Continued)

		Sumatriptan		Naratriptan		
Improvement at 2 hours	Placebo	100mg	0.1mg	0.25mg	1.0mg	2.5mg
Number of patients in intent-to-treat population	107	240	220	224	219	209
Number with initial headache severity grade 3 or 2	104	229	207	214	208	199
Number improved after 2 hours to grade 1 or 0	23 (22%)	135 (59%)	62 (30%)	62 (29%)	79 (38%)	100 (50%)
Number not improved after 2 hours	81 (78%)	94 (41%)	145 (70%)	152 (71%)	129 (62%)	99 (50%)

8 patients had headache severity grade 3 carried forward due to taking rescue or second treatment prior to this assessment: 1 on placebo, 2 on sumatriptan, 1 on naratriptan 0.1mg, 3 on 0.25mg, 0 on 1mg and 1 on 2.5mg

Headache relief is defined as a change in headache severity from grade 3 or 2 pre-treatment to grade 1 or 0 post-treatment

Table 3.3.6

TABLE 12. IMPROVEMENT IN HEADACHE SEVERITY 0.5, 1, 1.5, 2, 3, 4, 12 AND 24 HOURS AFTER FIRST DOSE ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 3 OR 2 (ATTACK 1): INTENT-TO-TREAT POPULATION (Continued)

Two hour comparisons

Logistic Regression Analysis*

Comparison	Odds Ratio	95% Confidence Interval	P-value
Naratriptan 0.1mg/Placebo	1.49	0.85, 2.60	0.165
Naratriptan 0.25mg/Placebo	1.38	0.79, 2.42	0.253
Naratriptan 1.0mg/Placebo	2.18	1.26, 3.78	0.006
Naratriptan 2.5mg/Placebo	3.55	2.04, 6.16	< 0.001
Naratriptan 0.1mg/Sumatriptan	0.29	0.19, 0.43	< 0.001
Naratriptan 0.25mg/Sumatriptan	0.27	0.18, 0.40	< 0.001
Naratriptan 1.0mg/Sumatriptan	0.42	0.29, 0.63	< 0.001
Naratriptan 2.5mg/Sumatriptan	0.69	0.46, 1.02	0.064
Naratriptan 2.5mg/Naratriptan 0.25mg	2.56	1.69, 3.89	< 0.001
Naratriptan 2.5mg/Naratriptan 1.0mg	1.63	1.09, 2.44	0.019

* Allowing for effects due to treatment, migraine type, duration of migraine prior to treatment and country

Headache relief is defined as a change in headache severity from grade 3 or 2 pre-treatment to grade 1 or 0 post-treatment

Table 3.3.7

Consistency of Response - Percentage of Patients with Headache Relief at 240 Minutes Post First Dose Across Repeated Attacks in the Placebo-Controlled Multiple Attack Efficacy Study[1] (S2WB3002)

	S2WB3002				
		Naratriptan (mg/dose)			
	Placebo (n=78)	0.1 (n=156)	0.25 (n=166)	1.0 (n=163)	2.5 (n=159)
0 of 3 Attacks	45%	36%	34%	21%	12%
1 of 3 Attacks	33%	35%	25%	29%	16%
2 of 3 Attacks	17%	21%	31%	28%	38%
3 of 3 Attacks	5%	8%	11%	22%	34%

[1] Includes data on patients who treated at least 3 attacks with the same dose of study drug. The 13 patients who were inadvertently given different doses of study medication for at least one attack were excluded from this table.

Table # 33.8

Consistency of Response Between Attacks (S2WB3002)
(Number / Percentage of Patients with a Pattern of Response)

PATTERN(Response pattern) TMTGR(Treatment group)

Frequency Col Pct	Placebo	Naratrip tan 0.1mg	Naratrip tan 0.25mg	Naratrip tan 1mg	Naratrip tan 2.5mg	Sumatrip tan 100mg	Total
NNN	28 41.79	45 31.91	42 29.17	25 17.24	13 8.97	13 7.60	166
NNY	6 8.96	17 12.06	13 9.03	13 8.97	6 4.14	6 3.51	61
NYN	5 7.46	15 10.64	13 9.03	14 9.66	8 5.52	7 4.09	62
NYY	6 8.96	6 4.26	18 12.50	14 9.66	17 11.72	15 8.77	76
YNN	12 17.91	16 11.35	11 7.64	14 9.66	8 5.52	7 4.09	68
YNY	4 5.97	16 11.35	13 9.03	16 11.03	17 11.72	11 6.43	77
YYN	2 2.99	12 8.51	16 11.11	12 8.28	21 14.48	16 9.36	79
YYY	4 5.97	14 9.93	18 12.50	37 25.52	55 37.93	96 56.14	224
Total	67	141	144	145	145	171	813

3.4.1.

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TABLE 29. USE OF RESCUE MEDICATION 0-24 HOURS POST FIRST DOSE ADMINISTRATION (ATTACK 1): INTENT-TO-TREAT POPULATION

		Sumatriptan	Naratriptan			
	Placebo	100mg	0.1mg	0.25mg	1.0mg	2.5mg
Number of patients in intent-to-treat population	107	240	220	224	219	209
Number of patients who (<4 hours) required rescue medication	11 (10%)	9 (4%)	23 (10%)	12 (5%)	12 (5%)	4 (2%)
Number of patients who (4-24 hours) required rescue medication	64 (60%)	96 (40%)	127 (58%)	136 (61%)	113 (52%)	84 (40%)
Total number requiring rescue 0-24 hours	75 (70%)	105 (44%)	150 (68%)	148 (66%)	125 (57%)	88 (42%)

9 patients recorded use of rescue but had missing time to rescue, hence excluded here: 2 on placebo, 1 on sumatriptan, 1 on naratriptan 0.1mg, 3 on 0.25mg, 1 on 1mg and 1 on 2.5mg

Rescue medication is defined as any additional acute migraine medication taken for the treatment of ongoing headache including use of the second dose of study medication, i.e. use of the second dose to treat the original headache instead of treatment of recurrence

TABLE 29: USE OF RESCUE MEDICATION 0-24 HOURS POST FIRST DOSE ADMINISTRATION (ATTACK 1): INTENT-TO-TREAT POPULATION (Continued)

Logistic Regression Analysis of 0-24h Responses*

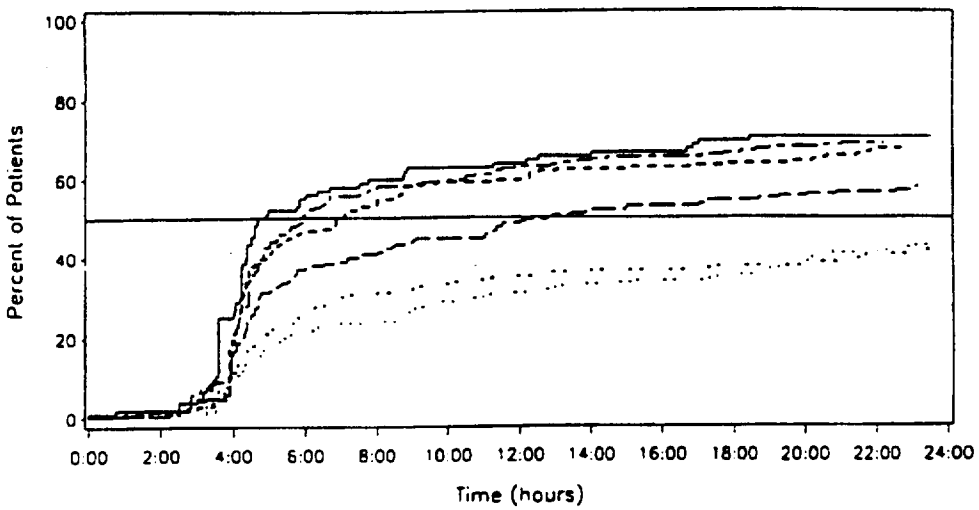
Comparison	Odds Ratio	95% Confidence Interval	P-value
Naratriptan 0.1mg/Placebo	0.99	0.59, 1.64	0.955
Naratriptan 0.25mg/Placebo	0.91	0.55, 1.51	0.714
Naratriptan 1.0mg/Placebo	0.59	0.36, 0.97	0.037
Naratriptan 2.5mg/Placebo	0.33	0.20, 0.55	< 0.001
Naratriptan 0.1mg/Sumatriptan	2.91	1.97, 4.30	< 0.001
Naratriptan 0.25mg/Sumatriptan	2.69	1.83, 3.94	< 0.001
Naratriptan 1.0mg/Sumatriptan	1.73	1.19, 2.53	0.004
Naratriptan 2.5mg/Sumatriptan	0.98	0.67, 1.44	0.924
Naratriptan 2.5mg/Naratriptan 0.25mg	0.37	0.25, 0.54	< 0.001
Naratriptan 2.5mg/Naratriptan 1.0mg	0.57	0.38, 0.84	0.004

* Allowing for effects due to treatment, migraine type, duration of migraine prior to treatment and country

Naratriptan Tablets
Protocol S2WB3002 –

Figure 3.5.1

Time to Retreatment (2nd Dose or Rescue) (Attack 1)
(Kaplan – Meier estimates)



TRT
Placebo (n=104)
0.1mg Naratriptan (n=207)
0.25mg Naratriptan (n=214)
1.0mg Naratriptan (n=208)
2.5mg Naratriptan (n=199)
100mg Sumatriptan (n=229)

Table 3 6.1

TABLE 22. HEADACHE RECURRENCE BETWEEN 4 AND 24 HOURS POST FIRST DOSE ADMINISTRATION IN PATIENTS WHO IMPROVED FROM INITIAL SEVERITY GRADE 3 OR 2 TO 1 OR 0 AT 4 HOURS (ATTACK 1): INTENT-TO-TREAT POPULATION

		Sumatriptan	Naratriptan			
	Placebo	100mg	0.1mg	0.25mg	1.0mg	2.5mg
Number of subjects in intent-to-treat population	107	240	220	224	219	209
Number with initial headache severity grade 3 or 2	104	229	207	214	208	199
Number improved after 4 hours to grade 1 or 0	28	173	75	78	109	132
Headache Recurrence						
Yes*	2 (10%)	53 (36%)	24 (39%)	30 (43%)	39 (42%)	22 (19%)
No	18 (90%)	96 (64%)	37 (61%)	40 (57%)	54 (58%)	94 (81%)
Not Recorded	8	24	14	8	16	16
Median time to recurrence (hours)	17	12	9	9	9	10
n	1	52	21	29	37	22

* Includes 5 patients who used rescue medication or second dose prior to reporting recurrence, but after improvement: 0 on placebo, 1 on sumatriptan, 0 on naratriptan 0.1mg, 2 on 0.25mg, 1 on 1mg and 1 on 2.5mg

Patients are considered to have experienced migraine recurrence if: they achieved headache relief at 4 hours after taking study medication (reduction in headache severity 3 or 2 to 1 or 0 without taking rescue medication, and they experienced a significant worsening of their headache (as defined by the patient) between 4 and 24 hours of taking the study medication

Table 14.3.1

~~TABLE 32:~~ HEADACHE RELIEF AT 60 MINUTES AFTER TREATMENT ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 2 OR 3: INTENT-TO-TREAT POPULATION

	Placebo	GR85548A 5mg	GR85548A 10mg
Number of patients in safety population	18	29	33
Number of patients in intent-to-treat population	18	29	33
Number with initial headache severity grade 2 or 3	18	28	33
Headache relief at 60 minutes (grade 2/3 to 0/1)	1 (6%)	11 (39%)	10 (31%)
No headache relief after 60 minutes (grade 2/3 to 2/3)	17 (94%)	17 (61%)	22 (69%)
Number not recorded	0	0	1

	Odds Ratio	95%CI	p-value
GR85548A (5mg) vs Placebo -	11.0	#	0.015
GR85548A (10mg) vs Placebo -	7.8	#	0.072

#: Fisher's Exact test was used since Mantel-Haenszel was not appropriate

TABLE 33. HEADACHE RELIEF AT 120 MINUTES AFTER TREATMENT ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 2 OR 3: INTENT-TO-TREAT POPULATION

	Placebo	GR85548A 5mg	GR85548A 10mg
Number of patients in safety population	18	29	33
Number of patients in intent-to-treat population	18	29	33
Number with initial headache severity grade 2 or 3	18	28	33
Headache relief at 120 minutes (grade 2/3 to 0/1)	5 (28%)	20 (71%)	15 (47%)
No headache relief after 120 minutes (grade 2/3 to 2/3)	13 (72%)	8 (29%)	17 (53%)
Number not recorded	0	0	1

	Odds Ratio	95%CI	p-value(M-H)
GR85548A (5mg) vs Placebo -	6.5	1.8-23.3	0.004
GR85548A (10mg) vs Placebo -	2.3	0.7- 7.9	0.190

Table 4.5.1

~~TABLE 41.~~ NEED FOR RESCUE MEDICATION WITHIN 24 HOURS OF TREATMENT ADMINISTRATION: INTENT-TO-TREAT POPULATION

	Placebo	GR85548A 5mg	GR85548A 10mg
Number of patients in safety population	18	29	33
Number of patients in intent-to-treat population	18	29	33
Number requiring rescue medication before 4 hours	0	0	0
Number requiring rescue medication at or after 4 hours and before 24 hours	12	3	10
Total number of patients requiring rescue medication before 24 hours	12	3	10

~~TABLE 89.~~ PATIENTS WHOSE HEADACHE SEVERITY GRADE BECAME 0 WHILST IN CLINIC: INTENT-TO-TREAT POPULATION

	Placebo	GR85548A 5mg	GR85548A 10mg
Number of patients in safety population	18	29	33
Number of patients in intent-to-treat population	18	29	33
Number of patients whose headache became 0 whilst in clinic	0	18	15
Median time to headache becoming 0 (minutes)	-	146	128

TABLE 11. HEADACHE RELIEF AT 60 MINUTES AFTER TREATMENT ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 2 OR 3: INTENT-TO-TREAT POPULATION

	Placebo	Sumatriptan 100mg	GR85548A 1.0mg	GR85548A 2.5mg	GR85548A 5.0mg	GR85548A 7.5mg	GR85548A 10.0mg
Number of patients in safety population	91	98	85	87	93	93	96
Number of patients in intent-to-treat population	91	98	85	87	93	93	96
Number with initial headache severity grade 2 or 3	91	97	83	86	93	93	96
Number improved after 60 minutes (grade 2/3 to 0/1)	18 (20%)	34 (35%)	21 (25%)	26 (30%)	32 (34%)	40 (43%)	38 (40%)
Number not improved after 60 minutes (grade 2/3 to 2/3)	73 (80%)	63 (65%)	62 (75%)	60 (70%)	61 (66%)	53 (57%)	58 (60%)
p value *		0.024					

* Logistic Regression Models (p value is adjusted for country)

Odds Ratio and 95% Confidence Limits:

Sumatriptan (100mg)	vs Placebo - 2.2	(1.1 -	4.4)
GR85548A (1.0mg)	vs Placebo - 1.4	(0.7 -	2.9)
GR85548A (2.5mg)	vs Placebo - 1.8	(0.9 -	3.6)
GR85548A (5.0mg)	vs Placebo - 2.1	(1.1 -	4.2)
GR85548A (7.5mg)	vs Placebo - 3.2	(1.6 -	6.1)
GR85548A (10mg)	vs Placebo - 2.7	(1.4 -	5.2)

2 patient(s) on treatment GR85548A 2.5mg group had their headache severity data carried forward as they took rescue medication prior to this assessment

Table 5.3.2

GCV/95/015
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TABLE 12. HEADACHE RELIEF AT 120 MINUTES AFTER TREATMENT ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 2 OR 3: INTENT-TO-TREAT POPULATION

	Placebo	Sumatriptan 100mg	GR85548A 1.0mg	GR85548A 2.5mg	GR85548A 5.0mg	GR85548A 7.5mg	GR85548A 10.0mg
Number of patients in safety population	91	98	85	87	93	93	96
Number of patients in intent-to-treat population	91	98	85	87	93	93	96
Number with initial headache severity grade 2 or 3	91	97	83	86	93	93	96
Number improved after 120 minutes (grade 2/3 to 0/1)	28 (31%)	58 (60%)	48 (58%)	45 (52%)	50 (54%)	63 (68%)	66 (69%)
Number not improved after 120 minutes (grade 2/3 to 2/3)	63 (69%)	39 (40%)	35 (42%)	41 (48%)	43 (46%)	30 (32%)	30 (31%)
p value *		<0.001					

* Logistic Regression Models (p value is adjusted for country)

TABLE 12. HEADACHE RELIEF AT 120 MINUTES AFTER TREATMENT ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 2 OR 3: INTENT-TO-TREAT POPULATION (CONTINUED)

Odds Ratio and 95% Confidence Limits:

Sumatriptan (100mg) vs Placebo	- 3.5	(1.9 - 6.4)
GR85548A (1.0mg) vs Placebo	- 3.2	(1.7 - 6.1)
GR85548A (2.5mg) vs Placebo	- 2.5	(1.3 - 4.6)
GR85548A (5.0mg) vs Placebo	- 2.7	(1.5 - 5.0)
GR85548A (7.5mg) vs Placebo	- 4.9	(2.6 - 9.3)
GR85548A (10mg) vs Placebo	- 5.2	(2.8 - 9.8)
GR85548A (1.0mg) vs Sumatriptan (100mg)	- 0.9	(0.5 - 1.7)
GR85548A (2.5mg) vs Sumatriptan (100mg)	- 0.7	(0.4 - 1.3)
GR85548A (5.0mg) vs Sumatriptan (100mg)	- 0.8	(0.4 - 1.4)
GR85548A (7.5mg) vs Sumatriptan (100mg)	- 1.4	(0.8 - 2.6)
GR85548A (10mg) vs Sumatriptan (100mg)	- 1.5	(0.8 - 2.7)

1 patient(s) on treatment Placebo group
1 patient(s) on treatment Sumatriptan 100mg group
2 patient(s) on treatment GR85548A 1.0mg group
2 patient(s) on treatment GR85548A 2.5mg group
1 patient(s) on treatment GR85548A 10.0mg group
had their headache severity data carried forward as they took rescue medication prior to this assessment

1 patient(s) on treatment GR85548A 2.5mg group
had their headache severity data carried forward as they withdrew from the study and took rescue prior to this assessment

Table 5.3.4

TABLE 13. HEADACHE RELIEF AT 240 MINUTES AFTER TREATMENT ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 2 OR 3: INTENT-TO-TREAT POPULATION

	Placebo	Sumatriptan 100mg	GR85548A 1.0mg	GR85548A 2.5mg	GR85548A 5.0mg	GR85548A 7.5mg	GR85548A 10.0mg
Number of patients in safety population	91	98	85	87	93	93	96
Number of patients in intent-to-treat population	91	98	85	87	93	93	96
Number with initial headache severity grade 2 or 3	91	97	83	86	93	93	96
Number improved after 240 minutes (grade 2/3 to 0/1)	35 (39%)	78 (80%)	53 (64%)	54 (63%)	60 (65%)	74 (80%)	76 (80%)
Number not improved after 240 minutes (grade 2/3 to 2/3)	55 (61%)	19 (20%)	30 (36%)	32 (37%)	33 (35%)	18 (20%)	19 (20%)
Number not recorded	1	0	0	0	0	1	1
p value *		<0.001					

* Logistic Regression Models (p value is adjusted for country)

Table 5.3.5

TABLE 13. HEADACHE RELIEF AT 240 MINUTES AFTER TREATMENT ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 2 OR 3: INTENT-TO-TREAT POPULATION (CONTINUED)

Odds Ratio and 95% Confidence Limits:

Sumatriptan (100mg)	vs Placebo	- 7.0	(3.6 - 13.8)
GR85548A (1.0mg)	vs Placebo	- 2.9	(1.5 - 5.5)
GR85548A (2.5mg)	vs Placebo	- 2.7	(1.4 - 5.1)
GR85548A (5.0mg)	vs Placebo	- 3.1	(1.7 - 5.8)
GR85548A (7.5mg)	vs Placebo	- 7.0	(3.5 - 13.8)
GR85548A (10mg)	vs Placebo	- 6.8	(3.4 - 13.3)
GR85548A (1.0mg)	vs Sumatriptan (100mg)	- 0.4	(0.2 - 0.8)
GR85548A (2.5mg)	vs Sumatriptan (100mg)	- 0.4	(0.2 - 0.8)
GR85548A (5.0mg)	vs Sumatriptan (100mg)	- 0.4	(0.2 - 0.9)
GR85548A (7.5mg)	vs Sumatriptan (100mg)	- 1.0	(0.5 - 2.1)
GR85548A (10mg)	vs Sumatriptan (100mg)	- 1.0	(0.5 - 2.0)

10 patient(s) on treatment Placebo group
3 patient(s) on treatment Sumatriptan 100mg group
6 patient(s) on treatment GR85548A 1.0mg group
5 patient(s) on treatment GR85548A 2.5mg group
9 patient(s) on treatment GR85548A 5.0mg group
4 patient(s) on treatment GR85548A 7.5mg group
4 patient(s) on treatment GR85548A 10.0mg group
had their headache severity data carried forward as they took rescue medication prior to this assessment

1 patient(s) on treatment Placebo group
1 patient(s) on treatment GR85548A 2.5mg group
had their headache severity data carried forward as they withdrew from the study and took rescue prior to this assessment

5.4.1.

~~180~~ Table ~~5.8.1~~ 5.5.1

~~TABLE 53:~~ REQUIREMENT FOR RESCUE MEDICATION WITHIN 24 HOURS OF TREATMENT ADMINISTRATION: INTENT-TO-TREAT POPULATION

	Placebo	Sumatriptan 100mg	GR85548A 1.0mg	2.5mg	5.0mg	7.5mg	10.0mg
Number of patients in safety population	91	98	85	87	93	93	96
Number of patients in intent-to-treat population	91	98	85	87	93	93	96
Number with initial headache severity grade 2 or 3	91	97	83	86	93	93	96
Number requiring rescue medication before 4 hours	11	3	6	6	9	4	4
Number requiring rescue medication at or after 4 hours and before 24 hours	49	22	33	24	27	19	17
Total number of patients requiring rescue medication before 24 hours	60 (66%)	25 (26%)	39 (47%)	30 (35%)	36 (39%)	23 (25%)	21 (22%)
Total number of patients not requiring rescue medication before 24 hours	31 (34%)	72 (74%)	44 (53%)	56 (65%)	57 (61%)	70 (75%)	75 (78%)

5.4.2

Table

TABLE 53: REQUIREMENT FOR RESCUE MEDICATION WITHIN 24 HOURS OF TREATMENT ADMINISTRATION: INTENT-TO-TREAT POPULATION (CONTINUED)

Logistic Regression - Odds Ratios, 95% Confidence Limits and p-values:

GR85548A 1mg	vs Placebo	0.5	(0.2 - 0.8)	0.012
GR85548A 2.5mg	vs Placebo	0.3	(0.1 - 0.5)	<0.001
GR85548A 5mg	vs Placebo	0.3	(0.2 - 0.6)	<0.001
GR85548A 7.5mg	vs Placebo	0.2	(0.1 - 0.3)	<0.001
GR85548A 10mg	vs Placebo	0.1	(0.1 - 0.3)	<0.001
GR85548A 1mg	vs Sumatriptan	2.6	(1.4 - 4.8)	0.003
GR85548A 2.5mg	vs Sumatriptan	1.5	(0.8 - 2.9)	0.181
GR85548A 5mg	vs Sumatriptan	1.8	(1.0 - 3.4)	0.058
GR85548A 7.5mg	vs Sumatriptan	0.9	(0.5 - 1.8)	0.869
GR85548A 10mg	vs Sumatriptan	0.8	(0.4 - 1.6)	0.525

Figure 5.5.1

Naratriptan Tablets
Protocol 82WB2004

Time to Retreatment (Rescue)
(Kaplan–Meier estimates)

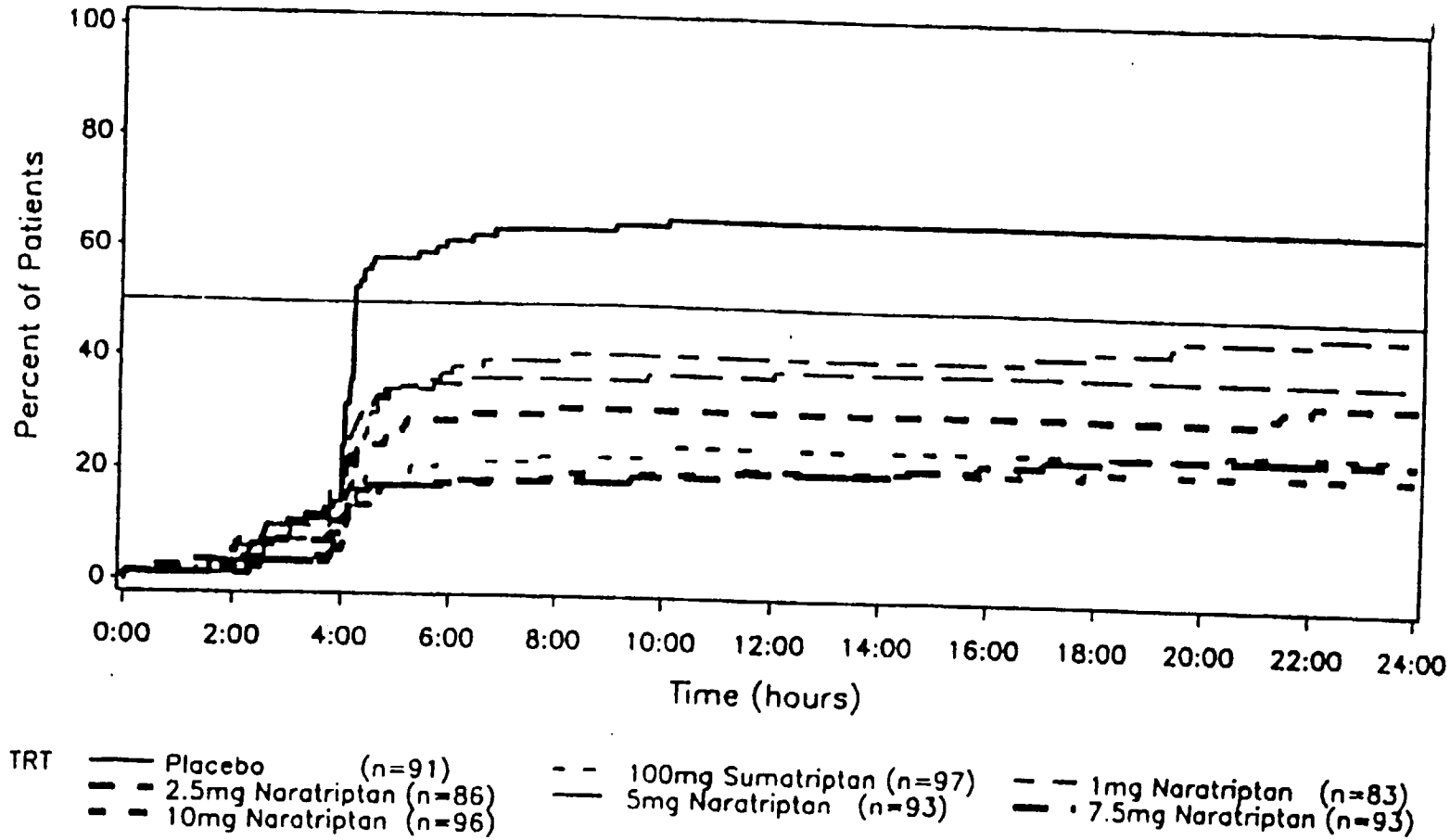

Table 2.7.1

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Table 53 HEADACHE RECURRENCE BETWEEN 4 AN 4 HOURS AFTER TREATMENT ADMINISTRATION. INTENT-TO-TREAT POPULATION

	Placebo	Sumatriptan 100mg	GR85548A 1.0mg	GR85548A 2.5mg	GR85548A 5.0mg	GR85548A 7.5mg	GR85548A 10.0mg
Number of patients in safety population	91	98	85	87	93	93	96
Number of patients in intent-to-treat population	91	98	85	87	93	93	96
Number of patients whose headache improved to Grade 0/1 within 4 hours	35	78	53	54	60	74	76
Number of patients who experienced recurrence* between 4 and 24 hours after treatment	10 (36%)	31 (44%)	14 (31%)	8 (17%)	15 (32%)	19 (30%)	20 (29%)
Number of patients who did not experience recurrence* between 4 and 24 hours after treatment	18 (64%)	40 (56%)	31 (69%)	40 (83%)	32 (68%)	44 (70%)	49 (71%)
Not recorded	7	7	8	6	13	10	7
Median time to recurrence in patients who experienced recurrence* between 4 and 24 hours (minutes)	420	720	1000	933	1035	828	1070
n	10	31	14	8	15	19	20

One patient on GR85548A 5.0mg answered Yes to experiencing recurrence but had a missing time to start of recurrence

* Recurrence: Complete or almost complete headache relief at 4 hours (grade 2/3 to grade 0/1) followed by the significant worsening of the headache between 4 and 24 hours (grade 0/1 to grade 2/3) as assessed by the patient on the diary card.

If the patient has not specifically recorded information about headache recurrence but the headache severities recorded on the diary card indicate that recurrence did occur (ie grade 0/1 to grade 2/3) then the patient is assumed to have experienced recurrence.

TABLE 6.3: TWENTY-FOUR HOUR OVERALL EFFICACY ASSESSMENT FOLLOWING FIRST DOSE ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 2 OR 3 ON AT LEAST ONE ATTACK: INTENT-TO-TREAT POPULATION

By sequence group

	Sequence 1		Sequence 2	
	Naratriptan 2.5mg	Sumatriptan 100mg	Naratriptan 2.5mg	Sumatriptan 100mg
Number of patients in intent-to-treat population	115		110	
Number with initial severity 2/3	109	109	106	107
Number with 24 hour overall efficacy achieved	34 (31%)	40 (37%)	49 (46%)	34 (32%)
Number with 24 hour overall efficacy not achieved	75 (69%)	69 (63%)	57 (54%)	73 (68%)

Summary over sequence groups

	Naratriptan 2.5mg	Sumatriptan 100mg
Number of patients in intent-to-treat population	225	
Number with initial severity 2/3	215	216
Number with 24 hour overall efficacy achieved	83 (39%)	74 (34%)
Number with 24 hour overall efficacy not achieved	132 (61%)	142 (66%)

Patients who improved at 4 hours after first dose (pre-treatment grade 2/3 to grade 0/1 at 4 hours) with no significant deterioration in headache severity between 4-24 hours after first dose and with no rescue medication are defined as having achieved '24 hour overall efficacy'

Treatment Sequence 1 = Naratriptan for attack 1; Sumatriptan for attack 2
Treatment Sequence 2 = Sumatriptan for attack 1; Naratriptan for attack 2

TABLE: TWENTY-FOUR HOUR OVERALL EFFICACY ASSESSMENT FOLLOWING FIRST DOSE ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 2 OR 3 ON BOTH ATTACKS: INTENT-TO-TREAT POPULATION

Sequence 1

		Sumatriptan 100mg		
		24hr overall efficacy achieved	24hr overall efficacy not achieved	Total
Naratriptan 2.5mg	24hr overall efficacy achieved	13	21	34 (33%)
	24hr overall efficacy not achieved	25	44	69 (67%)
	Total	38 (37%)	65 (63%)	103

Sequence 2

		Sumatriptan 100mg		
		24hr overall efficacy achieved	24hr overall efficacy not achieved	Total
Naratriptan 2.5mg	24hr overall efficacy achieved	20	29	49 (47%)
	24hr overall efficacy not achieved	14	41	55 (53%)
	Total	34 (33%)	70 (67%)	104

Patients who improved at 4 hours after first dose (pre-treatment grade 2/3 to grade 0/1 at 4 hours) with no significant deterioration in headache severity between 4-24 hours after first dose and with no rescue medication are defined as having achieved '24 hour overall efficacy'

Treatment Sequence 1 = Naratriptan for attack 1; Sumatriptan for attack 2
Treatment Sequence 2 = Sumatriptan for attack 1; Naratriptan for attack 2

TABLE 14.2 TWENTY-FOUR HOUR OVERALL EFFICACY ASSESSMENT FOLLOWING FIRST DOSE ADMINISTRATION IN PATIENTS WITH INITIAL HEADACHE SEVERITY GRADE 2 OR 3 ON BOTH ATTACKS: INTENT-TO-TREAT POPULATION (Continued)

Summary over sequence groups

		Sumatriptan 100mg		
		24hr overall efficacy achieved	24hr overall efficacy not achieved	Total
Naratriptan 2.5mg	24hr overall efficacy achieved	33	50	83 (40%)
	24hr overall efficacy not achieved	39	85	124 (60%)
	Total	72 (35%)	135 (65%)	207

	Odds Ratio	95% C.I.	P-value
Naratriptan 2.5mg vs Sumatriptan 100mg	1.257	0.856, 1.846	0.242

Patients who improved at 4 hours after first dose (pre-treatment grade 2/3 to grade 0/1 at 4 hours) with no significant deterioration in headache severity between 4-24 hours after first dose and with no rescue medication are defined as having achieved '24 hour overall efficacy'

POSSIBLE

Table 6.4.1

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~~TABLE 38~~ HEADACHE RECURRENCE BETWEEN 4 AND 24 HOURS POST FIRST DOSE ADMINISTRATION IN PATIENTS WHO IMPROVED FROM INITIAL SEVERITY GRADE 2/3 TO 0/1 AT 4 HOURS ON AT LEAST ONE ATTACK: INTENT-TO-TREAT POPULATION

By sequence group

	Sequence 1		Sequence 2	
	Naratriptan 2.5mg	Sumatriptan 100mg	Naratriptan 2.5mg	Sumatriptan 100mg
Number of patients in intent-to-treat population	115		110	
Number with initial severity 2/3	109	109	106	107
Number improved after 4 hours	78	97	86	84
Number who experienced recurrence*	39 (51%)	52 (55%)	35 (41%)	49 (58%)
Number who did not experience recurrence	38 (49%)	42 (45%)	51 (59%)	35 (42%)
Not recorded	1	3	0	0
Median time to recurrence (hours)	11.8	11.7	15.3	10.2
n	38	52	35	49

* Includes 4 sequence 1 attacks (2 on Naratriptan, 2 on Sumatriptan) and 1 sequence 2 attack (0 on Naratriptan, 1 on Sumatriptan) where rescue medication or second dose was used prior to recurrence, but after improvement

A patient is considered to have experienced migraine recurrence if: they achieved headache relief at 4 hours after taking study medication (reduction in headache severity 3/2 to 1/0) without taking rescue medication and they experienced a significant worsening of their headache (as defined by the patient) between 4 and 24 hours of taking the study medication

Treatment Sequence 1 = Naratriptan for attack 1; Sumatriptan for attack 2
Treatment Sequence 2 = Sumatriptan for attack 1; Naratriptan for attack 2

TABLE 6.6.2 – HEADACHE RECURRENCE BETWEEN 4 AND 24 HOURS POST FIRST DOSE ADMINISTRATION IN PATIENTS WHO IMPROVED FROM INITIAL SEVERITY GRADE 2/3 TO 0/1 AT 4 HOURS ON AT LEAST ONE ATTACK: INTENT-TO-TREAT POPULATION (Continued)

Summary over sequence groups

	Naratriptan 2.5mg	Sumatriptan 100mg
Number of patients in intent-to-treat population	225	
Number with initial severity 2/3	215	216
Number improved after 4 hours	164	181
Number who experienced recurrence*	74 (45%)	101 (57%)
Number who did not experience recurrence	89 (55%)	77 (43%)
Not recorded	1	3
Median time to recurrence (hours)	12.5	10.5
n	73	101

* Includes 5 attacks (2 on Naratriptan, 3 on Sumatriptan) where rescue medication or second dose was used prior to recurrence, but after improvement

A patient is considered to have experienced migraine recurrence if: they achieved headache relief at 4 hours after taking study medication (reduction in headache severity 3/2 to 1/0) without taking rescue medication and they experienced a significant worsening of their headache (as defined by the patient) between 4 and 24 hours of taking the study medication

6.4.3
Table 6.6.3

TABLE 6.6.3 HEADACHE RECURRENCE BETWEEN 4 AND 24 HOURS POST FIRST DOSE ADMINISTRATION IN PATIENTS WHO IMPROVED FROM INITIAL HEADACHE SEVERITY GRADE 2/3 TO 0/1 AT 4 HOURS ON BOTH ATTACKS: INTENT-TO-TREAT POPULATION

Sequence 1

		Sumatriptan 100mg			
		No Recurrence	Recurrence	Not Recorded	Total
Naratriptan 2.5mg	No recurrence	15	20	1	36 (54%)
	Recurrence	13	18	0	31 (46%)
	Not recorded	1	0	0	1
	Total	29 (43%)	38 (57%)	1	68

Sequence 2

		Sumatriptan 100mg			
		No Recurrence	Recurrence	Not Recorded	Total
Naratriptan 2.5mg	No recurrence	21	22	0	43 (64%)
	Recurrence	7	17	0	24 (36%)
	Not recorded	0	0	0	0
	Total	28 (42%)	39 (58%)	0	67

A patient is considered to have experienced migraine recurrence if: they achieved headache relief at 4 hours after taking study medication (reduction in headache severity 3/2 to 1/0) without taking rescue medication and they experienced a significant worsening of their headache (as defined by the patient) between 4 and 24 hours of taking the study medication

Treatment Sequence 1 = Naratriptan for attack 1; Sumatriptan for attack 2
Treatment Sequence 2 = Sumatriptan for attack 1; Naratriptan for attack 2

TABLE 14: HEADACHE RECURRENCE BETWEEN 4 AND 24 HOURS POST FIRST DOSE ADMINISTRATION IN PATIENTS WHO IMPROVED FROM INITIAL HEADACHE SEVERITY GRADE 2/3 TO 0/1 AT 4 HOURS ON BOTH ATTACKS: INTENT-TO-TREAT POPULATION (Continued)

Summary over sequence groups

		Sumatriptan 100mg			
		No Recurrence	Recurrence	Not Recorded	Total
Naratriptan 2.5mg	No recurrence	36	42	1	79 (59%)
	Recurrence	20	35	0	55 (41%)
	Not recorded	1	0	0	1
	Total	57 (43%)	77 (57%)	1	135

	Odds Ratio	95% C.I.	P-value
Naratriptan 2.5mg vs Sumatriptan 100mg	1.974	1.236, 3.153	0.005

Note: the treatment comparison results may be biased due to baseline imbalances arising from loss of randomisation in sequence groups

A patient is considered to have experienced migraine recurrence if: they achieved headache relief at 4 hours after taking study medication (reduction in headache severity 3/2 to 1/0) without taking rescue medication and they experienced a significant worsening of their headache (as defined by the patient) between 4 and 24 hours of taking the study medication

Naratriptan Tablets
Protocol 82WB3011

Figure 6.5-1

Time to Retreatment (2nd Dose or Rescue)
(Kaplan–Meier estimates)