TABLE 1

NARATRIPTAN TABLETS

TABLE OF CONTROLLED CLINICAL STUDIES IN MIGRAINE PATIENTS (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
1. Placebo-Controlled US Studies (Cont'd)									
S2WA1007/ RM1996/ 00021/00	A Study to Evaluate the Pharmacokinetics and Pharmacodynamics of Oral Naratriptan in Migraine Subjects	Part 2: To describe the pharmacokinetics and pharmacodynamics (safety / efficacy)of single doses of Naratriptan tablets 0.25mg, 1.0mg and 2.5mg during a migraine attack.	Part 2: Double-blind, randomized, placebo-controlled, single-period, parallel design	Part 2 0.25mg: 34/34 1.0mg: 39/39 2.5mg: 35/35 Placebo: 19/19 Total completed: 127	22-66	M: 15% F: 85%	Completed (Jan 24, 1996)	USA C	[1] 102/1 (F)[2] [103/219]

[1] Report also included in Clinical Data Section

[2] Report also included in Human Pharmacokinetics and Bioavailability Section

* Investigators are listed, by protocol, in Appendix 1 to this table

** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

*** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl), E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as prefilled syringes (mannitol), H. Nasal solution

\# Date of first treatment

Nov 14, 1996

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CONTROLLED CLINICAL STUDIES IN MIGRAINE PATIENTS (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
2. Placebo-Controlled, Non-US Studies									
S2WB2003 (S2WT50) GCV/95/017	A Double Blind, Placebo-Controlled, Randomized, Parallel Group Study to Evaluate the Safety and Efficacy of Oral Naratriptan (5mg and 10mg) Following Dosing During a Migraine Attack	To compare the blood pressure changes following oral naratriptan (5mg & 10mg) with placebo over the 4, 8, and 24-hour periods following dosing during a migraine attack. Also to compare the efficacy, safety, and tolerability of these two doses of oral naratriptan.	Double-blind, placebo-controlled, parallel-group, randomized. The randomization is on a 2:2:1 ratio (5mg:10mg:placebo)	5mg: 29/29 10mg: 33/33 Placebo: 18/18 Total completed: 80	19-55	M: 6% F: 94%	Completed (Dec 21, 1993)	Finland France Germany Netherlands Norway Sweden B	161/1 (F) [163/1]
S2WB2004 (S2WT51) GCV/95/015	A Double Blind, Randomized, Placebo-Controlled, Parallel Group Study to Compare the Efficacy and Safety of Oral Naratriptan (1mg-10mg) with that of Oral Sumatriptan (100mg) and Placebo in the Acute Treatment of Migraine Headache	To compare safety, efficacy and tolerability of five doses of oral naratriptan (1.0, 2.5, 5.0, 7.5, 10.0mg) with that of placebo in the acute treatment of migraine headache.	Randomized, double-blind, placebo-controlled, active-controlled, parallel-group, dose-ranging study	1.0mg: 85/85 2.5mg: 87/87 5.0mg: 93/93 7.5mg: 93/93 10mg: 96/96 Sumatriptan 100mg: 98/98 Placebo: 91/91 Total completed: 638 Total for interim analysis = 419	18-61	M: 12% F: 88%	Completed (Oct 14, 1993)	Austria Belgium Denmark Finland France Germany Holland Israel New Zealand Poland Portugal Sweden B	165/1 (F) [169/1]

1 Report also included in Clinical Data Section
2 Report also included in Human Pharmacokinetics and Bioavailability Section
* Investigators are listed, by protocol, in Appendix 1 to this table
** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.
*** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl), E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as prefilled syringes (mannitol), H. Nasal solution
# Date of first treatment
Nov 14, 1996

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CONTROLLED CLINICAL STUDIES IN MIGRAINE PATIENTS (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
2. Placebo-Controlled, Non-US Studies (cont'd)									
S2WB2005 GCN/96/015	A Double-Blind Crossover Study to Rechallenge Patients with Oral Naratriptan who Previously Experienced an Adverse Event Involving Discomfort or Pain in the Chest Following Oral Naratriptan Administration	To assess the safety and tolerability of Naratriptan by rechallenging patients who previously experienced at least one adverse event involving discomfort or pain in the chest. Patients will be rechallenged during two separate migrane attacks, with both placebo and oral Naratriptan.	Placebo-controlled, double-blind, crossover	Initial dose patient received in the previous study			Ongoing	Europe B	177/1 (S)

1 Report also included in Clinical Data Section
2 Report also included in Human Pharmacokinetics and Bioavailability Section
* Investigators are listed, by protocol, in Appendix 1 to this table
** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.
*** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl), E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as prefilled syringes (mannitol), H. Nasal solution
# Date of first treatment
Nov 14, 1996

TABLE 1

NARATRIPTAN TABLETS

TABLE OF CONTROLLED CLINICAL STUDIES IN MIGRAINE PATIENTS (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
2. Placebo-Controlled, Non-US Studies (Cont'd)									
S2WB3002 GCV/96/006	A Randomized, Double-Blind, Placebo-Controlled, Sumatriptan-Controlled (100mg), Three Attack, Parallel Group Study to Compare the Efficacy, Safety and Tolerability of Oral Naratriptan 0.1mg, 0.25mg, 1mg and 2.5mg in the Acute Treatment of Migraine	To determine the incidence of headache relief at 4 hours for 0.1mg, 0.25m, 1mg, 2.5mg of oral naratriptan in the acute treatment of migraine headache.	Double-blind, randomized, placebo-controlled, active-controlled, parallel design	0.1mg: 251/221 0.25mg: 254/224 1mg: 259/219 2.5mg: 246/209 Sumatriptan 100mg: 260/241 Placebo: 130/108 Total completed: 942	18-35	F = 84% M = 16%	Completed (Jul,13 1995)	Austria Belgium Canada Denmark Finland Iceland Italy Norway Portugal South Africa Spain Sweden Switzerland United Kingdom C	148/1 (F) [153/1]

! Report also included in Clinical Data Section

2 Report also included in Human Pharmacokinetics and Bioavailability Section

* Investigators are listed, by protocol, in Appendix 1 to this table

** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

*** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl), E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as prefilled syringes (mannitol), H. Nasal solution

Date of first treatment

Nov 14, 1996

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CONTROLLED CLINICAL STUDIES IN PATIENTS (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
3. Active-Controlled, Non-US Studies									
S2WB3011 GCV/96/009	A Randomized, Double-Blind, Two Attack, Cross-Over Study to Compare the Efficacy, Safety, and Tolerability of Oral Naratriptan (2.5mg) with Oral Sumatriptan (100mg) in the Acute Treatment of Migraine in Patients Susceptible to Headache Recurrence	To determine the 24 hour overall efficacy of oral naratriptan 2.5mg. To determine the incidence of headache recurrence following treatment with oral naratriptan 2.5mg in the acute treatment of migraine. To compare the above with oral sumatriptan 100mg.	Randomized, double-blind, two-attack, crossover	2.5mg Naratriptan: 100mg Sumatriptan: 264/239 Total completed: 225	18-65	F = 91% M = 9%	Completed (14 Sep 1995)	Canada Denmark France Germany The Netherlands Norway C	183/1 (F) [185/1]

[1] Report also included in Clinical Data Section
[2] Report also included in Human Pharmacokinetics and Bioavailability Section
* Investigators are listed, by protocol, in Appendix 1 to this table
** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.
*** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl), E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as prefilled syringes (mannitol), H. Nasal solution
# Date of first treatment
Nov 14, 1996

TABLE 1

SUBCUTANEOUS NARATRIPTAN

TABLE OF CONTROLLED CLINICAL STUDIES IN MIGRAINE PATIENTS

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
1. Placebo-Controlled, Non-US Studies									
S2WB2001 (S2WT01) GCV/92/007	A Double-Blind, Ascending Dose, Dose-Ranging Study to Compare the Efficacy and Safety of Subcutaneous Naratriptan and of Subcutaneous Sumatriptan with that of Subcutaneous Placebo Injection in the Acute Treatment of Migraine	To compare the safety, efficacy, & tolerability of five doses of subcutaneous naratriptan (0.5mg, 1mg, 2.5mg, 5mg and 10mg) with subcutaneous placebo & 6mg subcutaneous sumatriptan in the acute treatment of migraine.	Double-blind, parallel-group, randomized, placebo-controlled, active controlled.	0.5mg: 60/60 1.0mg: 55/55 2.5mg: 42/42 5.0mg: 34/34 10mg: 34/34 Placebo: 63/63 Sumatriptan 6.0mg: 47/47 Total completed: 335	18-64	M: 14% F: 86%	Completed (Dec 17, 1991)	Belgium Denmark France Germany Netherlands Sweden D	177/4 (F)
S2WB2002 (S2WT02) GCV/93/012	A Double-Blind, Parallel Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Subcutaneous Naratriptan 2.5mg and 5mg in the Acute Treatment of Three Separate Migraine Attacks	To compare the efficacy and safety of 2.5mg and 5.0mg naratriptan with placebo in the treatment of the first migraine attack. To look at the consistency of response of treating 3 attacks with 2.5mg & 5.0mg of naratriptan. To obtain efficacy and safety data on the use of a second dose of naratriptan (placebo-controlled) in the treatment of recurrence.	Double-blind, parallel group, randomized, placebo-controlled.	2.5mg: 300/266 5.0mg: 283/248 Placebo: 149/130 Total completed: 549	18-65	M: 13% F: 87%	Completed (Mar 5, 1993)	Belgium Denmark Finland France Germany Netherlands Norway Spain Sweden South Africa United Kingdom G	179/1 (F)

[1] Report also included in Clinical Data Section

[2] Report also included in Human Pharmacokinetics and Bioavailability Section

* Investigators are listed, by protocol, in Appendix 1 to this table

** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

*** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl), E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as prefilled syringes (mannitol), H. Nasal solution

Date of first treatment

Nov 14, 1996

TABLE 1

NARATRIPTAN TABLETS

TABLE OF UNCONTROLLED CLINICAL STUDIES IN MIGRAINE PATIENTS

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
1. Open-Label									
S2WB3004 GCV/96/005	An Open Study of the Long Term Safety and Efficacy of Oral Naratriptan 2.5mg in the Acute Treatment of Migraine	To assess the long-term safety and tolerability of naratriptan.	open-label	2.5mg: 451/414 Total completed: 385	18-65	F: 82% M: 18%	Ongoing (Jun 26, 1995)	Europe C	187/12 (S)
S2WA1007/ RM 1996/00021/00	A Study to Evaluate the Pharmacokinetics and Pharmacodynamics of Oral Naratriptan in Migraine Subjects	Part I: To evaluate the pharmacokinetics of a 2.5mg single dose of naratriptan tablets during a migraine and non-migraine period.	Part I - Open-label, two-period, cross-over	Part I 2.5mg: 15/15 Total completed: 15	22-66	F: 100%	Completed (Jan 24, 1996)	USA C	83/1 (F)[1] [84/156]

[1] Report also included in Clinical Data Section

[2] Report also included in Human Pharmacokinetics and Bioavailability Section

* Investigators are listed, by protocol, in Appendix 1 to this table

** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

*** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl), E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as prefilled syringes (mannitol), H. Nasal solution

Date of first treatment

Nov 14, 1996

TABLE 2

DEMOGRAPHICS SUMMARY - ORAL NARATRIPTAN

		Age							Sex			Race				Migraine type			
	Total	12-17	18-30	31-40	41-50	51-65	>65	Unk	M	F	Unk	Caucasian	Black	Other	Unk	Without Aura	With Aura	Both	Unk
LINICAL PHARMACOLOGY STUDIES [1]	312	0	136	71	49	34	10	12	115	197	0	283	9	8	12				
IIGRAINE STUDIES																			
LACEBO-CONTROLLED STUDIES																			
COMPLETED STUDIES																			
SINGLE ATTACK STUDIES																			
Clinic-based Single Dose [2]	850	0	212	228	312	98	0	0	104	746	0	826	11	13	0	748	77	25	0
Home-based Multiple Dose [3]	913	300	108	202	204	99	0	0	218	695	0	839	45	29	0	748	165	0	0
MULTIPLE ATTACK STUDIES																			
Home-based Multiple Dose [4]	1904	0	336	555	690	323	0	0	263	1641	0	1846	21	37	0	1491	389	0	24
'TIVE CONTROLLED STUDIES																			
COMPLETED STUDIES [5]	253	0	24	52	112	65	0	0	23	230	0	250	1	2	0	207	43	0	3
NCONTROLLED STUDIES																			
COMPLETED STUDIES [6]	429	0	81	91	160	97	0	0	74	355	0	425	2	2	0	356	66	2	5

1] C94-034, C93-006, C92-055, C93-060, S2WA1002, C93-070, C94-071, S2WA1003, C94-007, C93-081, S2WB1004, C93-087, S2WB1003, S2WA1010, S2WA1011, S2WB1002, C94-036, C94-045, S2WB1006 and S2WA1004.
2] S2WA1007 (Part II), S2WB2003 and S2WB2004.
3] S2WA3001 and S2WA3012.
4] S2WB3002 and S2WA3003.
5] S2WB3011.
6] S2WB3004 completed interim data and S2WA1007 (Part I).

ura presence or absence relates to first attack only except for study S2WA1007 (Parts I and II) where it relates to patient's general migraine history.

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TABLE 3

DEMOGRAPHICS SUMMARY - SUBCUTANEOUS NARATRIPTAN

	Total	Age							Sex			Race				Migraine type			
		12-17	18-30	31-40	41-50	51-65	>65	Unk	M	F	Unk	Caucasian	Black	Other	Unk	Without Aura	With Aura	Both	Unk
CLINICAL PHARMACOLOGY STUDIES [1]	51	0	21	15	9	5	1	0	33	18	0	50	0	1	0				
MIGRAINE STUDIES																			
PLACEBO-CONTROLLED STUDIES																			
COMPLETED STUDIES																			
SINGLE ATTACK STUDIES																			
Clinic-based Single Dose [2]	335	0	100	88	103	44	0	0	47	288	0	322	5	8	0	273	28	34	0
MULTIPLE ATTACK STUDIES																			
Home-based Multiple Dose [3]	644	0	110	191	219	124	0	0	87	557	0	628	5	11	0	469	87	88	0

[1] S2WB3009, S2WB3010, W91-013, W91-023
[2] S2WB2001
[3] S2WB2002

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ATTACHMENT 5

TABLE 6

EXTENT OF EXPOSURE TO STUDY TREATMENTS

		Number of Administrations									
		Naratriptan									
	Number of Patients	IN	SC	PO	IV	Sumatriptan	DHE	Ergotamine	Codeine	Placebo	Multiple doses
..INICAL PHARMACOLOGY STUDIES [1]	393	24	91	823	75	24	42	33	36	358	1113
GRAINE STUDIES											
ACEBO-CONTROLLED STUDIES											
COMPLETED STUDIES											
SINGLE ATTACK STUDIES											
Clinic-based Single Dose [2]	1185	0	225	624	0	145	0	0	0	191	0
Home-based Multiple Dose [3]	913	0	0	891	0	0	0	0	0	235	213
MULTIPLE ATTACK STUDIES											
Home-based Multiple Dose [4]	2548	0	1893	5019	0	857	0	0	0	1509	6730
TIVE CONTROLLED STUDIES											
COMPLETED STUDIES [5]	253	0	0	340	0	371	0	0	0	0	458
CONTROLLED STUDIES											
COMPLETED STUDIES [6]	429	0	0	10396	0	0	0	0	0	0	9967

] S2WB1001, S2WB3009, S2WB3010, W91-013, W91-023, C93-006, C94-034, W91-004, W91-019, WHP:90:06, C94-036, C94-045, C92-055, C93-060, S2WA1002, C93-070, C94-071, S2WA1003, C94-007, C93-081, S2WB1004, C93-087, S2WB1003, S2WA1010, S2WA1011, S2WB1002, S2WB1006 and S2WA1004.
] S2WB2001, S2WA1007 (Part II), S2WB2003 and S2WB2004.
] S2WA3001 and S2WA3012.
] S2WB2002, S2WB3002 and S2WA3003.
] S2WB3011.
] S2WB3004 completed interim data and S2WA1007 (Part I).

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TABLE 7

EXTENT OF EXPOSURE TO ORAL NARATRIPTAN

	Number of Patients Exposed to Naratriptan	Number of Attacks Treated with Naratriptan	Average Number of Attacks per Patient Treated with Naratriptan	Average Time # Between Attacks (Days)		
				Mean	STD	Range
GRAINE STUDIES						
ACEBO-CONTROLLED STUDIES						
COMPLETED STUDIES						
SINGLE ATTACK STUDIES						
Clinic-based Single Dose [1]	624	624	1.0	N/A	N/A	N/A
Home-based Multiple Dose [2]	717	717	1.0	N/A	N/A	N/A
MULTIPLE ATTACK STUDIES						
Home-based Multiple Dose [3]	1544	4079	2.6	22.0	18.5	0-167
TIVE CONTROLLED STUDIES						
COMPLETED STUDIES [4]	239	239	1.0	N/A	N/A	N/A
CONTROLLED STUDIES						
COMPLETED STUDIES [5]	429	7873	18.4	7.7	9.0	0-109

] S2WA1007 (Part II), S2WB2003 and S2WB2004.
] S2WA3001 and S2WA3012.
] S2WB3002 and S2WA3003.
] S2WB3011.
] S2WB3004 completed interim data and S2WA1007 (Part I).

= For consecutive attacks treated with Naratriptan.

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TABLE 8

EXTENT OF EXPOSURE TO ORAL NARATRIPTAN BY DOSE

	Placebo	0.1mg	0.25mg	1mg	2.5mg	5mg	7.5mg	10mg	Suma #
GRAINE STUDIES									
ACEBO-CONTROLLED STUDIES									
OMPLETED STUDIES									
INGLE ATTACK STUDIES									
Clinic-based Single Dose [1]									
Number of patients exposed	128	0	34	124	122	122	93	129	98
Number of attacks treated	128	0	34	124	122	122	93	129	98
Number of attacks treated with 1 dose	128	0	34	124	122	122	93	129	98
Number of attacks treated with 2 doses	0	0	0	0	0	0	0	0	0
Number of attacks treated with 3 doses	0	0	0	0	0	0	0	0	0
Total number of doses given	128	0	34	124	122	122	93	129	98
Number of patients treating only 1 attack	128	0	34	124	122	122	93	129	98
Number of patients treating 2 attacks	0	0	0	0	0	0	0	0	0
Number of patients treating 3 - 5 attacks	0	0	0	0	0	0	0	0	0
Number of patients treating > 5 attacks	0	0	0	0	0	0	0	0	0
Average time between attacks (days)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SINGLE ATTACK STUDIES									
Home-based Multiple Dose [2]									
Number of patients exposed	196	128	197	195	197	0	0	0	0
Number of attacks treated	196	128	197	195	197	0	0	0	0
Number of attacks treated with 1 dose	157	92	150	143	158	0	0	0	0
Number of attacks treated with 2 doses	39	36	47	52	39	0	0	0	0
Number of attacks treated with 3 doses	0	0	0	0	0	0	0	0	0
Total number of doses given	235	164	244	247	236	0	0	0	0
Number of patients treating only 1 attack	196	128	197	195	197	0	0	0	0
Number of patients treating 2 attacks	0	0	0	0	0	0	0	0	0
Number of patients treating 3 - 5 attacks	0	0	0	0	0	0	0	0	0
Number of patients treating > 5 attacks	0	0	0	0	0	0	0	0	0
Average time between attacks (days)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Suma = Sumatriptan 100mg
| S2WA1007 (Part II), S2WB2003 and S2WB2004.
| S2WA3001 and S2WA3012.
| S2WB3002 and S2WA3003.
| S2WB3011.
| S2WB3004 and S2WA1007 (Part 1).

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TABLE 8 (Continued)

EXTENT OF EXPOSURE TO ORAL NARATRIPTAN BY DOSE

	Placebo	0.1mg	0.25mg	1mg	2.5mg	5mg	7.5mg	10mg	Suma #
ULTIPLE ATTACK STUDIES									
ome-based Multiple Dose [3]									
Number of patients exposed	716	222	819	822	802	0	0	0	271
Number of attacks treated	888	564	1176	1185	1154	0	0	0	686
Number of attacks treated with 1 dose	740	458	908	878	895	0	0	0	515
Number of attacks treated with 2 doses	148	106	268	307	259	0	0	0	171
Number of attacks treated with 3 doses	0	0	0	0	0	0	0	0	0
Total number of doses given	1036	670	1444	1492	1413	0	0	0	857
Number of patients treating only 1 attack	623	40	628	624	613	0	0	0	51
Number of patients treating 2 attacks	14	24	25	34	28	0	0	0	27
Number of patients treating 3 - 5 attacks	79	158	166	164	161	0	0	0	193
Number of patients treating > 5 attacks	0	0	0	0	0	0	0	0	0
Average time between attacks (days)	23.5	22.9	21.7	22.5	21.5	N/A	N/A	N/A	21.7
IVE CONTROLLED STUDIES									
OMPLETED STUDIES [4]									
Number of patients exposed	0	0	0	0	239	0	0	0	239
Number of attacks treated	0	0	0	0	239	0	0	0	239
Number of attacks treated with 1 dose	0	0	0	0	138	0	0	0	107
Number of attacks treated with 2 doses	0	0	0	0	101	0	0	0	132
Number of attacks treated with 3 doses	0	0	0	0	0	0	0	0	0
Total number of doses given	0	0	0	0	340	0	0	0	371
Number of patients treating only 1 attack	0	0	0	0	239	0	0	0	239
Number of patients treating 2 attacks	0	0	0	0	0	0	0	0	0
Number of patients treating 3 - 5 attacks	0	0	0	0	0	0	0	0	0
Number of patients treating > 5 attacks	0	0	0	0	0	0	0	0	0
Average time between attacks (days)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

uma = Sumatriptan 100mg
S2WA1007 (Part II), S2WB2003 and S2WB2004.
S2WA3001 and S2WA3012.
S2WB3002 and S2WA3003.
S2WB3011.
S2WB3004 and S2WA1007 (Part I).

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TABLE 8 (Continued)

EXTENT OF EXPOSURE TO ORAL NARATRIPTAN BY DOSE

	Placebo	0.1mg	0.25mg	1mg	2.5mg	5mg	7.5mg	10mg	Suma #
CONTROLLED STUDIES									
COMPLETED STUDIES [5]									
Number of patients exposed	0	0	0	5	429	0	0	0	0
Number of attacks treated	0	0	0	23	7850	0	0	0	0
Number of attacks treated with 1 dose	0	0	0	19	5346	0	0	0	0
Number of attacks treated with 2 doses	0	0	0	4	2504	0	0	0	0
Number of attacks treated with 3 doses	0	0	0	0	0	0	0	0	0
Total number of doses given	0	0	0	27	10354	0	0	0	0
Number of patients treating only 1 attack	0	0	0	0	22	0	0	0	0
Number of patients treating 2 attacks	0	0	0	1	8	0	0	0	0
Number of patients treating 3 - 5 attacks	0	0	0	2	43	0	0	0	0
Number of patients treating > 5 attacks	0	0	0	2	356	0	0	0	0
Average time between attacks (days)	N/A	N/A	N/A	14.1	7.7	N/A	N/A	N/A	N/A

Suma = Sumatriptan 100mg
] S2WA1007 (Part II), S2WB2003 and S2WB2004.
] S2WA3001 and S2WA3012.
] S2WB3002 and S2WA3003.
] S2WB3011.
] S2WB3004 and S2WA1007 (Part I).

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TABLE 9

EXTENT OF EXPOSURE TO SUBCUTANEOUS NARATRIPTAN

	Number of Patients Exposed to Naratriptan	Number of Attacks Treated with Naratriptan	Average Number of Attacks per Patient Treated with Naratriptan	Average Time Between Attacks (Days)		
				Mean	STD	Range
MIGRAINE STUDIES						
PLACEBO-CONTROLLED STUDIES						
COMPLETED STUDIES						
SINGLE ATTACK STUDIES						
Clinic-based Single Dose [1]	225	225	1.0	N/A	N/A	N/A
MULTIPLE ATTACK STUDIES						
Home-based Multiple Dose [2]	589	1508	2.6	24.0	21.4	1-162

[1] S2WB2001
[2] S2WB2002

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TABLE 10

EXTENT OF EXPOSURE TO SUBCUTANEOUS NARATRIPTAN BY DOSE

	Placebo	0.5mg	1mg	2.5mg	5mg	10mg	Sumatriptan 6mg
GRAINE STUDIES							
ACEBO-CONTROLLED STUDIES							
OMPLETED STUDIES							
SINGLE ATTACK STUDIES							
Clinic-based Single Dose [1]							
Number of patients exposed	63	60	55	42	34	34	47
Number of attacks treated	63	60	55	42	34	34	47
Number of attacks treated with 1 dose	63	60	55	42	34	34	47
Number of attacks treated with 2 doses	0	0	0	0	0	0	0
Number of attacks treated with 3 doses	0	0	0	0	0	0	0
Total number of doses given	63	60	55	42	34	34	47
Number of patients treating only 1 attack	63	60	55	42	34	34	47
Number of patients treating 2 attacks	0	0	0	0	0	0	0
Number of patients treating 3 - 5 attacks	0	0	0	0	0	0	0
Number of patients treating > 5 attacks	0	0	0	0	0	0	0
Average time between attacks (days)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MULTIPLE ATTACK STUDIES							
Home-based Multiple Dose [2]							
Number of patients exposed	208	0	0	307	282	0	0
Number of attacks treated	473	0	0	781	727	0	0
Number of attacks treated with 1 dose	473	0	0	574	549	0	0
Number of attacks treated with 2 doses	0	0	0	207	178	0	0
Number of attacks treated with 3 doses	0	0	0	0	0	0	0
Total number of doses given	473	0	0	988	905	0	0
Number of patients treating only 1 attack	59	0	0	51	39	0	0
Number of patients treating 2 attacks	33	0	0	39	43	0	0
Number of patients treating 3 - 5 attacks	116	0	0	217	200	0	0
Number of patients treating > 5 attacks	0	0	0	0	0	0	0
Average time between attacks (days)	26	N/A	N/A	23	25	N/A	N/A

] S2WB2001
] S2WB2002

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ATTACHMENT 6

TABLE 5. NUMBER OF ATTACKS TREATED WITH STUDY TREATMENT BY EACH CLINIC VISIT: SAFETY POPULATION

		Naratriptan 1mg (+1mg)	Naratriptan 2.5mg (+2.5mg)
Number of patients in safety population		5	414
Visit 3:			
Number of attacks *	0	2 (40%)	2 (<1%)
	1-6	3 (60%)	145 (35%)
	7-12	0	131 (32%)
	13-18	0	109 (26%)
	> 18	0	27 (7%)
Visit 4:			
Number of attacks @	0	2 (40%)	80 (19%)
	1-6	2 (40%)	92 (22%)
	7-12	1 (20%)	112 (27%)
	13-18	0	89 (21%)
	> 18	0	41 (10%)

* At or before clinic visit 3.
@ After clinic visit 3 and at or before clinic visit 4.

Due to data extraction problems, patients 3835 and 3853 have missing clinic visit 4 date but have a clinic visit 5 date available. It is assumed, however, that this is the clinic visit 4 date.

Note that for patients who withdrew from the study prior to a clinic visit with clinic visit date missing, all attacks at or before withdrawal are included as attacks treated after the last known clinic visit and at or before the next scheduled clinic visit.

Note that patient 3662 treated their last attack after they withdrew from the study and withdrawal was prior to clinic visit 3 with clinic visit 3 date missing. This attack is included as an attack treated at or before clinic visit 3.

If a patient did not withdraw from the study and a clinic visit date is missing, then all attacks treated after the last known clinic visit are included as attacks treated at or before the next scheduled clinic visit.

* 276 patients treated ≥2 attacks per month with oral naratriptan 2.5mg (+2.5mg). 196 patients treated >18 attacks in the 6 month period with oral naratriptan 2.5mg (2.5mg). Two hundred and ninety four patients treated attacks for at least 6 months with oral naratriptan 2.5mg (+2.5mg).

TABLE 13. PATIENT EXPOSURE TO ORAL NARATRIPTAN 2.5mg

Total number of patients treated with 2.5mg Naratriptan during a 12-month period	407
Total number of patients with at least 12 months treatment with 2.5mg Naratriptan*	261
Total number of patients who treated >=2 attacks/month with 2.5mg Naratriptan in 12 months	253
Total Number of patients who treated >36 attacks with 2.5mg Naratriptan in 12 months	185

The 12-month period is defined as clinic visit 2 + 366 days
* Note that patients who treated attacks at or beyond clinic visit 2 + 355.5 days are included in this total

APPEARS THIS WAY
ON ORIGINAL

TABLE 14. ADVERSE EVENTS: OVERALL INCIDENCE: NUMBER (%) OF ATTACKS WITH ASSOCIATED ADVERSE EVENTS: SAFETY POPULATION

Post-treatment by Total Dose

	Naratriptan			
	1mg	1mg + 1mg	2.5mg	2.5mg + 2.5mg
Number of attacks treated in safety population	66	17	10376	4842
Number of attacks with an associated adverse event	51 (77%)	10 (59%)	1689 (16%)	693 (14%)
Number of attacks with an adverse event considered to be drug related	42 (64%)	7 (41%)	1313 (13%)	492 (10%)
Number of attacks with an adverse event graded as moderate or severe	12 (18%)	3 (18%)	831 (8%)	306 (6%)
Number of attacks with an adverse event graded as severe	0	0	122 (1%)	42 (<1%)

Drug related = Investigator's opinion of causality of almost certainly, probably or possibly related to study treatment of unknown or missing causality.

TABLE 11

DISPOSITION AND DISCONTINUATION FROM STUDIES

ORAL NARATRIPTAN

Study	Country	Study Medication	Number Treated	Number withdrawn due to: Adverse Event	Lack of Efficacy	Other
CLINICAL PHARMACOLOGY STUDIES						
C92-055	UK	Placebo	18	1 (6%)	0	1 (6%)
		Naratriptan	18	0	0	0
C93-070	UK	Naratriptan	26	1 (4%)	0	2 (8%)
C94-034	UK	Naratriptan	24	1 (4%)	0	0
C94-036	Holland	Placebo	25	1 (4%)	0	0
		Naratriptan	27	0	0	2 (7%)
C94-071	UK	Placebo	12	0	0	0
		Naratriptan	12	1 (8%)	0	0
S2WB1002	UK	Placebo	24	0	0	0
		Naratriptan	25	1 (4%)	0	0
C93-006	UK	Naratriptan	6	0	0	0
C93-060	UK	Placebo	8	0	0	0
		Naratriptan	9	0	0	1 (11%)
C93-081	UK	Naratriptan	23	0	0	0
C93-087	UK	Naratriptan	16	0	0	0
C94-007	UK	Naratriptan	2	0	0	0
C94-045	UK	Placebo	16	0	0	0
		Naratriptan	16	0	0	0
S2WA1002	US	Placebo	12	0	0	0
		Naratriptan	12	0	0	0
S2WA1003	US	Naratriptan	20	0	0	0
S2WA1004	US	Placebo	12	0	0	0
		Naratriptan	12	0	0	0
		Codeine	12	0	0	0

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TABLE 11 (continued)

DISPOSITION AND DISCONTINUATION FROM STUDIES

ORAL NARATRIPTAN

Study	Country	Study Medication	Number Treated	Number withdrawn due to: Adverse Event	Lack of Efficacy	Other
CLINICAL PHARMACOLOGY (continued)						
S2WA1010	US	Placebo	16	0	0	2 (13%)
		Naratriptan	15	0	0	0
		DHE	15	1 (7%)	0	1 (7%)
S2WA1011	US	Placebo	12	1 (8%)	0	0
		Naratriptan	11	0	0	0
		Ergotamine	12	1 (8%)	0	0
S2WB1003	UK	Placebo	12	0	0	0
		Naratriptan	12	0	0	0
		Sumatriptan	12	0	0	0
S2WB1004	UK	Naratriptan	16	0	0	0
S2WB1006	UK	Placebo	8	0	0	0
		Naratriptan	8	0	0	0
		Codeine	12	0	0	0
MIGRAINE STUDIES						
PLACEBO-CONTROLLED STUDIES						
COMPLETED STUDIES						
SINGLE ATTACK STUDIES						
Clinic-based Single Dose						
S2WA1007(II)	US	Placebo	19	0	0	0
		Naratriptan	108	0	0	0
S2WB2003	Multinational	Placebo	18	0	0	0
		Naratriptan	62	0	0	0
S2WB2004	Multinational	Placebo	91	0	1 (1%)	1 (1%)
		Naratriptan	454	0	2 (<1%)	1 (<1%)
		Sumatriptan	98	0	0	0

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TABLE 11 (continued)

DISPOSITION AND DISCONTINUATION FROM STUDIES

ORAL NARATRIPTAN

Study	Country	Study Medication	Number Treated	Number withdrawn due to: Adverse Event	Lack of Efficacy	Other
SINGLE ATTACK STUDIES						
Home-based Multiple Dose						
S2WA3001	US	Placebo	122	0	0	1 (<1%)
		Naratriptan	491	0	0	1 (<1%)
S2WA3012	US	Placebo	74	0	0	0
		Naratriptan	226	1 (<1%)	0	0
MULTIPLE ATTACK STUDIES						
Home-based Multiple Dose						
S2WB3002	Multinational	Placebo	110	4 (4%)	12 (11%)	13 (12%)
		Naratriptan	875	9 (1%)	46 (5%)	152(17%)
		Sumatriptan	271	8 (3%)	3 (1%)	33 (12%)
S2WA3003	US	Placebo	606	5 (<1%)	6 (<1%)	32 (5%)
		Naratriptan	669	8 (1%)	8 (1%)	110(16%)
TIVE CONTROLLED STUDIES						
OMPLETED STUDIES						
S2WB3011	Multinational	Naratriptan	239	1 (<1%)	0	13 (5%)
		Sumatriptan	239	0	1 (<1%)	13 (5%)
CONTROLLED STUDIES						
OMPLETED STUDIES						
S2WB3004	Multinational	Naratriptan	414	9 (2%)	59 (14%)	16 (4%)
S2WA1007(I)	US	Naratriptan	15	0	0	0

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TABLE 12

DISPOSITION AND DISCONTINUATION FROM STUDIES

SUBCUTANEOUS NARATRIPTAN

Study	Country	Study Medication	Number Treated	Number withdrawn due to: Adverse Event	Lack of Efficacy	Other
LINICAL PHARMACOLOGY STUDIES						
S2WB3009	UK	Naratriptan	10	0	0	1 (10%)
		Placebo	10	0	0	0
S2WB3010	UK	Naratriptan	19	0	0	0
		Placebo	19	0	0	0
W91-013	UK	Naratriptan	16	0	0	0
		Placebo	16	0	0	0
W91-023	UK	Naratriptan	6	0	0	0
		Placebo	6	0	0	0
IGRAINE STUDIES						
LACEBO-CONTROLLED STUDIES						
COMPLETED STUDIES						
SINGLE ATTACK STUDIES						
Clinic-based Single Dose						
S2WB2001	Multinational	Sumatriptan	47	0	0	0
		Naratriptan	225	0	0	0
		Placebo	63	0	0	0
MULTIPLE ATTACK STUDIES						
Home-based Multiple Dose						
S2WB2002	Multinational	Naratriptan	644	24 (4%)	9 (1%)	62 (10%)

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TABLE 74
SERIOUS ADVERSE EVENT PATIENT LISTING

Body System	Case ID Number	Protocol	Inv. No.	Sub. No.	Age	Sex	Study Drug, Form, Route & Daily Dose	Time/ Onset	Time/ LstDos	Adverse Events	Act ion	Dur	Outcome	Relation
CARDIOVASCULAR	A0011682	SZNA3003	2566	760	46Y	F	Placebo TAB PO Single dose GR85548A TAB PO 2.5 MG 2.5 MG Single dose	22D	6D	Palpitation(s) Pulmonary congestion Bradycardia Non cardiac chest pain Shortness of breath Dizziness	X X	3D	Resolved	Unrelated
CARDIOVASCULAR	B0004718	SZNB2004	NA	B0904	40Y	F	GR85548A TAB PO 7.5 MG 7.5 MG Single dose	2H	2H	Abnormal ECG	X		Resolved	Probable
ENDOCRINE & METABOLIC	B0035830	SZNB3002	NA	03282	43Y	M	GR85548A TAB PO 0.1 MG 0.1 MG As required			Parathyroid neoplasm	3		Resolved	Unrelated
EYE	B0012953	SZNB1002	NA	B0015	43Y	M	GR85548A TAB PO 2 MG 1 MG Twice per day	2D	26H	Ocular pain Photophobia Ocular pain Iritis	3	11D	Resolved	Unrelated
GASTROINTESTINAL	B0008352	SZNB2004	NA	B0328	31Y	F	GR85548A TAB PO 10 MG 10 MG Single dose	2D	1D	Infection of lip(s)	0	9D	Resolved	Unrelated

Time/Onset = Time to onset since first dose
Time/Last Dose = Time to onset since completion of study treatment
Action = Action taken with study drug as a result of the event: 0 = No action taken
2 = Study drug interrupted
3 = Study drug discontinue
X = Not applicable, patient completed study treatment prior to event

Dur = Duration of adverse event

TABLE 74
SERIOUS ADVERSE EVENT PATIENT LISTING

Body System	Case ID Number	Protocol	Inv. No.	Sub. No.	Age	Sex	Study Drug, Form, Route & Daily Dose	Time/ Onset	Time/ LstDos	Adverse Events	Action	Dur	Outcome	Relation
GASTROINTESTINAL	B0036234	S2NB3002	NA	03348	31Y	M	GR85548A TAB PO 1 MG As required		48D	Possible gastric obstruct Nausea Vomiting Abdominal pain Intestinal obstruction Gastric ulcer Possible partial obstruct	2	64D	Resolved	Unlikely
NEUROLOGY	A0017299	S2NA3003	9414	615	38Y	F	GR85548A TAB PO 1 MG 1 MG Single dose	1D		Exacerbation of migraine	0		Resolved	Unrelated
							GR85548A TAB PO 2.5 MG 2.5 MG Single dose	5D 57D 62D		Exacerbation of migraine Exacerbation of migraine Exacerbation of migraine	X X X		Resolved Resolved Resolved	Unrelated Unrelated Unrelated
NEUROLOGY	B0012689	S2NB3002	NA	01952	46Y	F	Placebo TAB PO 1 TAB As required	12H		Prolonged headache Nausea & vomiting	0	2D	Resolved	Unrelated
NEUROLOGY	B0037060	S2NB3011	NA	04382	40Y	F	Sumatriptan succinate TAB PO 100 MG 100 MG Single dose	37D	16D	Numbness Paralysis/7 cranial nerve	X		Unresolved	Unlikely
							GR85548A TAB PO 2.5 MG 2.5 MG Single dose				X			
NON-SITE SPECIFIC	A0039656	S2NA3003	8174	407	27Y	F	GR85548A TAB PO 2.5 MG 2.5 MG Single dose	8D	5D	Pyelonephritis Urinary tract infection Nausea Vomiting	X		Resolved	Unrelated
								25D	22D	Shunt infection Edema of face Eye infection Fever Dehydration	X		Resolved	Unrelated

Time/Onset = Time to onset since first dose
Time/Last Dose = Time to onset since completion of study treatment
Action = Action taken with study drug as a result of the event 0 = No action taken
2 = Study drug interrupted
3 = Study drug discontinue

Dur = Duration of adverse event

X = Not applicable, patient completed study treatment prior to event

PLACEBO CONTROLLED NARATRIPTAN TABLET STUDIES
INTERGRATED SAFETY SUMMARY

TABLE 74
SERIOUS ADVERSE EVENT PATIENT LISTING

Body System	Case ID Number	Protocol	Inv. No.	Sub. No.	Age	Sex	Study Drug, Form, Route & Daily Dose	Time/ Onset	Time/ LstDos	Adverse Events	Act ion	Dur	Outcome	Relation
NON-SITE SPECIFIC	A0039667	S2NA3003	6241	2589	35Y	F	GR85548A TAB PO 1 MG 1 MG Single dose Placebo TAB PO Single dose		8D	Virus Sialadenosis Vomiting Dehydration Fever Weakness	X X 	15D	Resolved	Unlikely
NON-SITE SPECIFIC	B0005966	S2NB2004	NA	B1182	54Y	F	GR85548A TAB PO 10 MG 10 MG Single dose	50N	50N	Pressure in chest	X	12H	Resolved	Possible
NON-SITE SPECIFIC	B0017063	S2NB3002	NA	01692	35Y	F	GR85548A TAB PO 0.25 MG 0.25 MG Single dose	24D	24D	Fever Neck pain Vomiting	0	3D	Resolved	Unrelated
NON-SITE SPECIFIC	B0035693	S2NB3002	NA	03012	32Y	F	GR85548A TAB PO 1 MG As required	67D	30D	Surgery Ovarian cyst Lower abdominal pain	0	35D	Resolved	Unrelated
NON-SITE SPECIFIC	B0036693	S2NB3002	NA	02202	33Y	M	Sumatriptan succinate TAB PO 100 MG 100 MG As required	30N	30N	Chest pain Tightness of throat Pain in arm(s) Nausea Dizziness Pain in jaw(s) Finger pain	3	10H	Resolved	Almost certain
REPRODUCTION	B0035741	S2NB3002	NA	02708	58Y	F	Sumatriptan succinate TAB PO 100 MG 100 MG Single dose	17D		Neoplasm of breast(s)	3		Unresolved	Unrelated
REPRODUCTION	B0037041	S2NB3002	NA	03124	33Y	F	Sumatriptan succinate TAB PO 100 MG 100 MG Single dose	38D	37D	Ruptured ovarian cyst Surgery Pain	0	9H	Resolved	Unrelated

Time/Onset = Time to onset since first dose
Time/Last Dose = Time to onset since completion of study treatment
Action = Action taken with study drug as a result of the event: 0 = No action taken
2 = Study drug interrupted
3 = Study drug discontinue

Dur = Duration of adverse event

X = Not applicable, patient completed study treatment prior to event

TABLE 74
SERIOUS ADVERSE EVENT PATIENT LISTING

Body System	Case ID Number	Protocol	Inv. No.	Sub. No.	Age	Sex	Study Drug, Form, Route & Daily Dose	Time/ Onset	Time/ LstDos	Adverse Events	Act ion	Dur	Outcome	Relation
SKIN	A0040262	S2N83003	2697	096	48Y	F	Placebo TAB PO Single dose	40D	5D	Malignant melanoma	0	1D	Resolved	Unrelated
							GR85548A TAB PO 0.25 MG 0.25 MG Single dose				0			
UROLOGY	A0039646	S2N83012	5981	3352	17Y	F	GR85548A TAB PO 1 MG 1 MG Single dose	3D		Lupus nephritis Nausea Vomiting Dehydration Facial rash Leukocytosis	X		Unresolved	Unrelated
UROLOGY	B0037982	S2N83002	NA	03011	31Y	F	Placebo TAB As required	33D	33D	Hydronephrosis Pain	0	22D	Resolved	Unrelated

Time/Last Dose = Time to onset since completion of study treatment
Action = Action taken with study drug as a result of the event 0 = No action taken
2 = Study drug interrupted
3 = Study drug discontinue
X = Not applicable, patient completed study treatment prior to event

Dur = Duration of adverse event

TABLE 74
SERIOUS ADVERSE EVENT PATIENT LISTING

Body System	Case ID Number	Protocol	Inv. No.	Sub No.	Age	Sex	Study Drug, Form, Route & Daily Dose	Time/ Onset	Time/ LstDos	Adverse Events	Act ion	Dur	Outcome	Relation
DRUG INTERACTION OVERDOSE & TRAUMA	B0035691	S2N83004	NA	4116	47Y	F	GR85548A TAB PO 3.7 MG 3.75 MG Single dose	1D	2H	Overdose Drowsiness	0	12H	Resolved	Probable
DRUG INTERACTION OVERDOSE & TRAUMA	B0036920	S2N83004	NA	4167	49Y	F	GR85548A TAB PO 5 MG 5 MG As required	99D		Overdose:trial medication Dreams abnormality Drowsiness Dizziness Drowsiness	0		Resolved	Possible
DRUG INTERACTION OVERDOSE & TRAUMA	B0039576	S2N83004	NA	05007	50Y	M	GR85548A TAB PO 2.5 MG 2.5 MG Per day	1D	8H	Fractured upper limb(s) Fractured upper limb(s) Back pain	3	43D	Resolved	Unlikely
GASTROINTESTINAL	B0034647	S2N83004	NA	4004	39Y	F	GR85548A TAB PO 2.5 MG 2.5 MG As required	26D	4D	Peritonitis Ovarian cyst haemorrhages Oophorectomy Postop.wound infection Hysterectomy	0	12D	Resolved	Unrelated
GASTROINTESTINAL	B0038444	S2N83004	005	3758	41Y	F	GR85548A TAB PO 2.5 MG As required	112D		Abdominal hernia	3	8D	Resolved	Unrelated
LOWER RESPIRATORY	B0038244	S2N83004	NA	4038	56Y	M	GR85548A TAB PO 2.5 MG 2.5 MG As required	124D	4D	Flu-like illness Cellulitis of leg Malaise Nausea Pain in leg(s) Swelling of leg(s)	0	14D	Resolved	Unlikely
NEUROLOGY	B0035686	S2N83004	NA	3858	41Y	F	GR85548A TAB PO 2.5 MG 2.5 MG Single dose			Migraine Vomiting	0	2D	Resolved	Unlikely

Time/Onset = Time to onset since first dose
Time/Last Dose = Time to onset since completion of study treatment
Action = Action taken with study drug as a result of the event 0 = No action taken
2 = Study drug interrupted
3 = Study drug discontinue
X = Not applicable, patient completed study treatment prior to event

Dur = Duration of adverse event

TABLE 74
SERIOUS ADVERSE EVENT PATIENT LISTING

Body System	Case ID Number	Protocol	Inv. No.	Sub. No.	Age	Sex	Study Drug, Form, Route & Daily Dose	Time/ Onset	Time/ LstDos	Adverse Events	Act ion	Dur	Outcome	Relation
NEUROLOGY	B0036499	S2NB3004	NA	4061	52Y	F	GR85548A TAB PO 2.5 MG 2.5 MG As required			Migraine Migraine	0	2D	Resolved	Unrelated
NON-SITE SPECIFIC	B0013081	S2NB3004	011	3882	46Y	F	GR85548A TAB PO 2.5 MG As required		30H	Chest pain Pain in arm(s)	3	3H	Resolved	Possible
NON-SITE SPECIFIC	B0038459	S2NB3004	NA	04008	49Y	F	GR85548A TAB PO 2.5 MG As required	119D		Substernal chest pain Sweating	3	1D	Resolved	Unlikely
PSYCHIATRY	B0014312	S2NB3004	NA	3757	57Y	F	GR85548A TAB PO 2.5 MG 2.5 MG As required	35D		Psychiatric depression Insomnia Fatigue Incr.frequency:migraine Increased anxiety	3		Unknown	Unrelated
PSYCHIATRY	B0039480	S2NB3004	011	49001	33Y	F	GR85548A TAB PO 2.5 MG As required			Psychiatric depression	0		Unknown	Unknown
PSYCHIATRY	B0040598	S2NB3004	002	03727	42Y	F	GR85548A TAB PO 2.5 MG As required			Anxiety	0		Resolved	Unknown
REPRODUCTION	B0036854	S2NB3004	NA	05002	45Y	F	GR85548A TAB PO 2.5 MG 2.5 MG As required	187D	4D	Abdominal hysterectomy Salpingectomy	0	1D	Resolved	Unrelated

Time/Onset = Time to onset since first dose
Time/Last Dose = Time to onset since completion of study treatment
Action = Action taken with study drug as a result of the event 0 = No action taken
2 = Study drug interrupted
3 = Study drug discontinue
X = Not applicable, patient completed study treatment prior to event

Dur = Duration of adverse event

TABLE 74

SERIOUS ADVERSE EVENT PATIENT LISTING

Body System	Case ID Number	Protocol	Inv. No.	Sub. No.	Age	Sex	Study Drug, Form, Route & Daily Dose	Time/ Onset	Time/ LstDos	Adverse Events	Act ion	Dur	Outcome	Relation
CARDIOVASCULAR	B0003679	SZMB2002	NA	1525	53Y	F	GR85548A INJ SC 5 MG 5 MG Single dose			Extrasystole(s) Heat sensation Pressure in chest Dyspnea	0		Improved	Possible
HEPATOBILIARY TRACT & PANCREAS	B0002718	SZMB2002	NA	1025	34Y	F	GR85548A INJ SC 2.5 MG 2.5 MG Single dose	104D		Cholecystitis Cholecystectomy	0	70D	Resolved	Unrelated
NEUROLOGY	B0000414	SZMB2002	NA	1833	47Y	F	GR85548A INJ SC 5 MG 5 MG Single dose	30N		Decreased consciousness Increased sleep Fear Detached feeling	0	4H	Resolved	Almost certain
NEUROLOGY	B0001241	SZMB2002	NA	1743	51Y	F	Placebo INJ SC Single dose GR85548A INJ SC 5 MG 5 MG Single dose	10H		Exacerbation of migraine Nausea & vomiting	3 3	4D	Resolved	Unrelated
NEUROLOGY	B0036321	SZMB3009	NA	01417	51Y	F	GR85548A INJ SC 1.5 MG 1.5 MG Single dose Placebo INJ	170N	170N	Headache	0	9H	Resolved	Possible

Time/Onset = Time to onset since first dose
Time/Last Dose = Time to onset since completion of study treatment
Action = Action taken with study drug as a result of the event: 0 = No action taken
3 = Study drug discontinue
X = Not applicable, patient completed study treatment prior to event

Dur = Duration of adverse event

TABLE 74
SERIOUS ADVERSE EVENT PATIENT LISTING

Body System	Case ID Number	Protocol	Inv. No.	Sub. No.	Age	Sex	Study Drug, Form, Route & Daily Dose	Time/ Onset	Time/ LstDos	Adverse Events	Act ion	Dur	Outcome	Relation
NON-SITE SPECIFIC	B0001978	S2MB2002	NA	1429	51Y	F	GR85548A INJ SC 2.5 MG 2.5 MG Single dose	2N	2N	Weakness Sweating	3	4H	Resolved	Probable
REPRODUCTION	B0001879	S2MB2002	NA	1801	47Y	F	GR85548A INJ SC 5 MG 5 MG Single dose			Breast cancer Dysphagia Neck pain Dizziness Weakness Lethargy Sensitive eyes Sensitivity to noises Hyperesthesia	X		Unresolved	Unrelated
REPRODUCTION	B0006564	S2MB2002	NA	1515	53Y	F	GR85548A INJ SC 2.5 MG 2.5 MG Single dose			Excessive menstruation	0	69D	Resolved	Unrelated

Time/Onset = Time to onset since first dose
Time/Last Dose = Time to onset since completion of study treatment
Action = Action taken with study drug as a result of the event 0 = No action taken
3 = Study drug discontinue
X = Not applicable, patient completed study treatment prior to event

Dur = Duration of adverse event

SERIOUS ADVERSE EVENTS
COMPLETED NARATRIPTAN CLINICAL TRIALS FILED UNDER IND
AUGUST 20,1996 - MARCH 17,1997

Body System	Protocol Inv Nb	Case ID Number	Sub.ID/ Tr. Nb.	Age	Sex	Study Drug/ Form, Route & Daily Dose/ Unit Dose & Frequency	Time/ Onset	Time/ LstDos	Adverse Events	Act ion	Dur	Outcome	Relation
DRUG INERACTION OVERDOSE & TOXIC	62MX3004	20042766	04074 OPEN	50Y	F	Naratriptan hydrochloride TAB PO 7.5 MG 7.5 MG	11HD		Overdose Heaviness in limb(s) Pain in limb(s)	0	2H	Resolved	Probable
DRUG INERACTION OVERDOSE & TOXIC	62MX3004 004	20043210	03741 OPEN	51Y	F	Naratriptan hydrochloride TAB PO 2.5 MG As required	35ZD		Fractured lower limb(s) Falling	0		Resolved	Unrelated
DRUG INERACTION OVERDOSE & TOXIC	62MX3004	20043283	04094 OPEN	50Y	F	Naratriptan hydrochloride TAB PO 7.5 MG 7.5 MG	44SD		Overdose Cracked lip(s) Xerostomia	0		Resolved	Possible
DRUG INERACTION OVERDOSE & TOXIC	62MX3004	20043449	03641 OPEN	44Y	F	Naratriptan hydrochloride TAB PO 7.5 MG 7.5 MG	9HD	2SN	Overdose:atrial medication Heartburn	0	30N	Resolved	Almost certain
DRUG INERACTION OVERDOSE & TOXIC	62MX3004	20043665	03639 OPEN	34Y	F	Naratriptan hydrochloride TAB PO 7.5 MG 7.5 MG	14SD		Overdose Vomiting	0	10H	Resolved	Possible
GASTROINTESTINAL	62MX3004 004	20043062	03752 OPEN	51Y	F	Naratriptan hydrochloride TAB PO 2.5 MG As required	20ED		Adenocarcinoma of colon	3		Unresolved	Unrelated
NEUROLOGY	62MX3004 3178	20041334	04155 OPEN	41Y	F	Naratriptan hydrochloride TAB PO 2.5 MG As required	22ZD		Ehcumb:carpal tunnel syn Carpal tunnel surgery	0	22D	Resolved	Unrelated
NEUROLOGY	62MX3004	20043593	03641 OPEN	45Y	F	Naratriptan hydrochloride TAB PO 2.5 MG As required	26ED		Acute migraine	0	12D	Resolved	Unlikely
NON-SITE SPECIFIC	62MX3004	20043412	04130 OPEN	49Y	F	Naratriptan hydrochloride TAB PO 2.5 MG As required	27ZD		Exacerbation of pain Arthroscopy Rotator cuff tendonitis	0		Unresolved	Unrelated
NON-SITE SPECIFIC	62MX3004 018	20041372	03874 OPEN	62Y	F	Naratriptan hydrochloride TAB PO 2.5 MG As required	23ED	8D	Inflammation of toe(s) Pain in toe(s) Inflammation of toe(s)	0	58D	Resolved	Unrelated

Action taken with study drug: 0 = no action taken, 3 = discontinued

Time codes: N = Minutes, H = Hours, D = Days

SERIOUS ADVERSE EVENT REPORTS
COMPLETED NARATRIPTAN CLINICAL TRIALS FILED UNDER IND
AUGUST 20,1996 - MARCH 20,1997
(CONTINUED)

Body System	Protocol Inv No	Case ID Number	Sub.ID/Age Tx. No.	Sex	Study Drug/ Form, Route & Daily Dose/ Unit Dose & Frequency	Time/ Onset	Time/ Letdos	Adverse Events	Act Dur ion	Outcome	Relation
REPRODUCTION	E2003004	80041587	04126 47Y OPEN	F	Naratriptan hydrochloride TAB PO 2.5 MG As required	306D		Breast cancer Breast mass excision	0	Unresolved	Unrelated
REPRODUCTION	E2003004	80041945	04097 50Y OPEN	F	Naratriptan hydrochloride TAB PO 2.5 MG As required	367D		Breast mass excision Breast biopsy Breast biopsy	0 1D	Resolved	Unrelated

ATTACHMENT 9

APPENDIX 11

LINE LISTING OF PATIENTS TAKING SSRIs WHO EXPERIENCED SEROTONIN SYNDROME-LIKE* ADVERSE EVENTS

Protocol number	Randomised group per attack	Patient number	Age (y)	Sex	Dose at Event	Attack Number	Time to onset	Adverse event code text Adverse event Investigator text	Severity	Causality
S2WA3003	1(+1)	S2W0000067	55	F	1	1	69 day(s)	Muscle cramps & spasms MUSCLE SPASM	Moderate	Unrelated
S2WA3003	2.5(+2.5)	S2W0000098	45	F	1	1	270 min(s)	Muscle atrophy weakness & tiredness LEGS WEAK	Mild	Unrelated
					1	1	270 min(s)	Cold sensation COLD SWEATS	Mild	Unrelated
S2WA3003	P(+P)	S2W0000118	26	F	1	4	30 min(s)	Muscle cramps & spasms BODY CRAMPS	Moderate	Possible
S2WA3003	1(+1)	S2W0000475	55	M	1	1	55 min(s)	Cold sensation BODY FELT COLD	Mild	Possible
					1	1	55 min(s)	Malaise & fatigue FATIGUE	Mild	Possible
S2WA3003	1(+1)	S2WC0025R2	31	F	2	2	3 day(s)	Malaise & fatigue WEAKNESS	Moderate	Unrelated
S2WA3003	P(+P)	S2W0002589	35	F	1	4	8 day(s)	Malaise & fatigue WEAKNESS	Severe	Unlikely
S2WA3003	P(+P)	S2W0002757	32	F	1	1	25 day(s)	Mood disorders DYSPHORIA	Moderate	Probable
S2WA3003	2.5(+2.5)	S2W0002908	33	F	1	3	30 min(s)	Malaise & fatigue FATIGUE	Severe	Probable
					1	4	29 day(s)	Muscle cramps & spasms LEG CRAMPS	Mild	Unrelated

For studies S2WA3003 and S2WA3012 Time to Onset has been calculated from treatment date/time and adverse event onset date/time.
* SEROTONIN SYNDROME-LIKE SYMPTOMS : Mental confusion, euphoria, agitation, sedation, difficulties in concentration, dysarthria, myoclonus, chills, shivering, dystonia, muscle cramping and weakness, diarrhea, sweating, malaise and fatigue, cognitive function disorder, and fever (Cephalalgia 1996;16:323-7).

Date : 12NOV96

Safety Review of Clinical Data

Application Information:

NDA 20-763

Sponsor: Glaxo Wellome Inc

Supplemental Submission Date: September 2, 1997
Supplemental Submission Content: Analyses of ECG Interval Data

Generic Name (Code Name): Naratriptan Hydrochloride (GR85548)

Drug Characteristics:

Pharmacologic Category: 5-hydroxytryptamine$_1$ (5-HT$_1$) receptor agonist

Proposed Indication: Acute treatment of migraine attacks

Safety Review Conducted By: Michael J. Sevka, M.D.

cc: Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products

Background: During the review of the original NDA submission, it was noted that examination of the ECG data by the sponsor did not include statistical analyses of ECG intervals. Because tabulations in the ISS of descriptive changes in ECGs included PR and QTc prolongations, the sponsor was asked to conduct statistical analyses for 6 trials (5 clinical pharmacology; 1 clinical - S2WB2001). These trials were selected because the systemic exposure was expected to be the greatest with doses up to 10mg+10mg (oral) and 10mg (Sub Q) or longest, consecutive exposure (5 days). These trials in general were designed as tolerability, pharmacodynamic, or pharmacokinetic studies and monitored subjects with serial post- dosing ECGs. Although these trials were not ideally designed to detect small changes in ECG intervals, they do provide screening for this purpose, which is comparable to that conducted for other drugs.

Protocols Analyzed					
Protocol	Design	Route	Naratriptan Dose (Bolded Doses Are the Doses Analyzed)	No. Subjects Randomized/ Treated (As presented in Table 1 of the ISS)	Length of Post Exposure Monitoring
W91-023	Cross-Over	Sub Q	**5mg** **10mg** **Placebo**	6/6 6/6 6/6	5 Hours
C92-055	Incomplete Cross-Over Double-Blind (Each subject received 2 or 3 doses of naratriptan and placebo)	Oral	0.5mg 1mg 2.5mg **5mg** **10mg** **15mg** 20mg 25mg Placebo	2/2 2/2 4/4 10/10 16/16 13/13 4/4 1/1 18/18	8 Hours
C93-060	Cross-Over Double-Blind	Oral	**5+5mg** **7.5+7.5mg** **10+10mg** **Placebo+Placebo**	9/9 9/8 9/8 9/8	12 Hours
C93-070	Cross-Over Open-Label	Oral	**2.5mg** **5mg** **7.5mg** **10mg**	26/24 26/25 26/25 26/23	8 Hours
C94-071	Cross-Over Double-Blind	Oral	**5mg X5 days** **10mg X5 days** **Placebo X5 days**	12/12 12/11 12/12	12 Hours each day
S2WB2001	Parallel Double-Blind	Sub Q	**0.5mg** **1mg** **2.5mg** **5mg** **10mg** **Placebo** **Sumatriptan**	60/60 55/55 42/42 34/34 34/34 63/63 47/47	2 Hours

All these studies recorded actual interval lengths except S2WB2001 which recorded interval lengths as ranges. All these studies obtained 3 baseline ECGs 5 minutes apart at the beginning of each dosing period except S2WB2001 which obtained only one baseline ECG at the beginning of each dosing period and except C94-071 which obtained only one baseline ECG at the beginning of each dosing period and subsequent baselines each day throughout the period before each daily dose. All the clinical pharmacology studies used machine-read data. Details of machine type and the evaluation of ECGs in S2WB2001 are not available since this is a muti-center and multi-national study (25 European sites). The number of cardiac cycles used in computing the mean ECG interval for a specific time-point was dependent on heart rate since the mean was computed from the number of cardiac cycles recorded on a 10 second ECG strip.

Analysis Methods:
ECG data for the clinical study S2WB2001 were not subjected to statistical analysis since only interval groups (interval ranges) were recorded. Instead the number of patients with abnormal ECG intervals (PR >200msec; QRS >120msec; QTc ≥440msec) were listed in a table and in a listing of ECG data by patient.

For the other studies (clinical pharmacology studies), the PR, QRS, and QTc intervals were analyzed by the sponsor as changes from baseline to each post-dosing time-point comparing each active treatment to placebo and each active treatment to other active treatments using a paired t-test. For studies where more than one baseline measurement was obtained, the average of the 3 values obtained immediately before dosing was used as the baseline value. For study C94-071, were each dosing period was 5 days long, the baseline used in the analysis of each 5 day period was the baseline from Day 1 for the entire 5 days in the period without analysis of the pre-dosing values from Days 2-5.

In these cross-over clinical pharmacology studies, only data from subjects who completed all treatments as per protocol were analyzed (i.e. completer analyses). Therefore 4 of the 5 studies would have had data excluded. Below is a brief discussion of the subjects which would have had their ECG data excluded from analyses. Interestingly, Subject #1 from study C93-070 had an isolated PR prolongation (PR=236msec) at 4hrs after 2.5mg but was not withdrawn and would have been <u>included</u> in the ECG analysis.

1) <u>Study 91-023</u>: no subject's data would have been excluded from analyses since all 6 subjects completed all treatments.

2) <u>Study C92-055</u>: only the 8 subjects who were randomized to and received 5mg, 10mg and 15mg were included in the ECG analyses and comparison to placebo was not analyzed although they all had placebo control. The other 10 subjects, who were randomized to treatment sequence with 2 or 3 doses, ranging from 0.5mg to 25mg and placebo, were not included in the analyses since they were not treated with all 3 doses. 5mg, 10mg, 15mg. Among these 10 other subjects are the 4 listed below who were reported in the clinical study report as having ECG changes but were not withdrawn from the study. Prolonged QTc for this trial was defined as >460msec.

Subject #1 - QTc of 469msec 2 hours after placebo;
Subject #2 - QTc of 471msec 3 hrs after placebo, 470msec 6 hrs after 0.5mg, and 490msec 6 hrs after 2.5mg;
Subject #3 - QTc of 487msec 2 hrs after 5mg;
Subject #7 - QTc of 473msec 1 hr after placebo, 462msec 1 hr after 20mg.

3) Study 93-060:

Subject #4 - withdrawn due to adverse events and did not complete all treatments and therefore would not have been included in the analysis; the subject was withdrawn after the first study day following 5mg+5mg and replaced because his anxious personality caused erratic blood pressure measurements; there was no mention in the clinical study report of ECG changes for any subject in this study including subject #4.

4) Study 93-070: The following 3 subjects were withdrawn from trial for the following reasons and therefore would not have been included in the ECG analyses:

Subject #6 - withdrawn due to adverse events and did not complete all treatments; experienced nausea and lightheadedness during Period I (following 5mg) and lightheadedness and other adverse events during Period II (following 7.5mg); there is no mention of ECG changes for this subject in the clinical study report; subject was not replaced;

Subject #7 - PR prolongation - according to the clinical study report and ECGs submitted with the CRF, the subject had 5 of 5 baseline ECGs for Period I (2.5mg) which showed PR increases (PR range= and increases for all post-treatment time-points (PR range=) except at 7hr (PR=198msec); for Period II (5mg) all 3 of 3 baseline ECGs showed PR increases (PR range= and all post-treatment ECGs showed increase (PR range=. this subject was replaced.

Subject #22 - PR prolongation - according to the clinical study report and ECGs submitted with the CRF, the subject had 2 sets of 3 baseline ECGs prior to Period I (7.5mg) - one set all showed PR prolongation (PR=233, 249, 271msec) and the second set also showed prolongation in 2 ECGs (PR=203, 210msec); following dosing with 7.5mg during Period 1 she developed PR prolongation (PR=248, 247, 214, 208, 202, 208, 204msec at 15min, 30min, 1hr, 2hr, 4hr, 5hr, 8hr, respectively) with remaining ECGs normal (PR range 173-187msec); upon return for Period II she again had PR prolongation for the 3 baseline ECGs (PR range) and was not given treatment but followed with serial ECGs which showed prolongation at 5 time-points (PR range= the remainder normal (PR range); this subject was replaced.

5) Study 94-071:

Subject #7 - withdrawn due to adverse events and did not complete all treatments and therefore would not have been included in the analysis; subject was withdrawn after the second dosing period (5mg daily X 5 days) because of increased blood pressure to 158/84 ten hours after dosing 5mg on Day 4; the clinical study report states there were no ECG changes or arrhythmia for this patient; the subject was not replaced.

In addition to the statistical analyses for each clinical pharmacology study, graphs were made displaying mean change from baseline in interval lengths across the observation period and for each individual subject.

Findings: Although intent-to-treat analyses were not conducted, valuable information is provided from examination of the results from study W91-023, which did not exclude data, and the 4 studies (C92-055, C93-070, C93-060, C94-071) on which completer analyses were conducted. Of the patients who were randomized but excluded from analysis, those that did not complete all treatments because they withdrew due to adverse events, were not reported to have ECG changes. Of the 2 subjects withdrawn who had PR prolongation post-dosing both also had PR prolongation at baseline. Of the 4 subjects that had QTc prolongation 2 had prolongations after placebo of similar magnitude to that after dosing with active drug and one other had prolongation only on placebo. The remaining subject had a single QTc prolongation of 487msec at 2 hrs after a 5mg dose. Exclusion of these data from the analyses would not be expected to effect the results materially or with a magnitude of clinical concern.

Below is a table displaying the direction and my count of the number of statistically significant differences between means of **each active treatment compared to placebo** across the post-dosing time-points for changes from baseline in interval length.

Study Number	Number of Post Treatment Observation Time-Points and Duration of Observation	Treatment Comparison and Number of Subjects in the Comparison (Number)	Statistically Significant Post-Treatment Time-Points for PR Interval		Statistically Significant Post-Treatment Time-Points for QRS Interval		Statistically Significant Post-Treatment Time-Points for QTc Interval	
			No.	Range Of Statistically Significant Differences (msec.)	No.	Range Of Statistically Significant Differences (msec.)	No.	Range Of Statistically Significant Differences (msec.)
W91-023	23 over 5 Hours	5mg - Placebo (6)	0 ↑ 0 ↓		0 ↑ 2 ↓		0 ↑ 2 ↓	
		10mg - Placebo (6)	3 ↑ 0 ↓		0 ↑ 0 ↓		0 ↑ 0 ↓	
C93-060	29 over 12 Hours	5mg+5mg - Placebo+Placebo (8)	0 ↑ 1 ↓		0 ↑ 0 ↓		0 ↑ 2 ↓	
		7.5mg+7.5mg - Placebo+Placebo (8)	1 ↑ 0 ↓		1 ↑ 0 ↓		2 ↑ 1 ↓	
		10mg+10mg - Placebo+Placebo (8)	2 ↑ 1 ↓		1 ↑ 1 ↓		1 ↑ 2 ↓	
C94-071	54 over 12 Hours each day X 5 days	5mg - Placebo (10)	1 ↑ 0 ↓		0 ↑ 2 ↓		2 ↑ 0 ↓	
		10mg - Placebo (11)	6 ↑ 0 ↓		6 ↑ 0 ↓		0 ↑ 1 ↓	

↑ - increase
↓ - decrease
* 95% C.I. : 8.3 - 31.0 msec
** 95% C.I.: 7.1 - 18.3 msec
*** 95% C.I. : 3.7 - 20.3 msec

Below is a table displaying the direction and my count of the number of statistically significant differences between means of the **highest compared to the lowest dose** across the post-dosing time-points for changes from baseline in interval length.

Study Number	Number of Post Treatment Observation Time-Points and Duration of Observation	Treatment Comparison and Number of Subjects in the Comparison (Number)	Statistically Significant Post-Treatment Time-Points for PR Interval		Statistically Significant Post-Treatment Time-Points for QRS Interval		Statistically Significant Post-Treatment Time-Points for QTc Interval	
			No.	Range Of Statistically Significant Differences (msec.)	No.	Range Of Statistically Significant Differences (msec.)	No.	Range Of Statistically Significant Differences (msec.)
C92-055	16 over 8 Hours	15mg - 5mg (8)	0 ↑ 1 ↓		3 ↑ 0 ↓		0 ↑ 0 ↓	
C93-070	10 over 8 Hours	10mg - 2.5mg (23)	1 ↑ 0 ↓		0 ↑ 1 ↓		0 ↑ 1 ↓	

↑ - increase
↓ - decrease

The numbers of statistically significant differences in the tables above displaying my counts from Tables 1-5 of the submission are, in general, slightly larger than the numbers reported by the sponsor in the discussion section of the submission.

From the summary tables above for these crossover trials, there appear to be relatively few statistically significant differences between active treatments and placebo or between high dose and low dose for the multiple comparisons made. These differences were both increases and decreases in interval lengths. From the placebo comparisons above there may be a slight suggestion of an increase in frequency of PR interval length for the 10mg-placebo comparisons; but there appears to be no clear trend for an increase in PR, QRS, or QTc interval length with increasing dose from 2.5mg to 10mg following single exposures or over time following repetitive administration of 5mg-10mg for 5 days.

With regard to the graphs, some graphs were incomplete; for study C93-060, only 5 hours of data were plotted instead of 12 hours. Nonetheless, in general, no obvious increase in interval length was detected, although a few subjects showed clinically insignificant separations from placebo. The graphs of PR interval changes from study C94-071 showed that several subjects (#1, 2, 3, 5, 6, and 9) appeared to have increases in PR interval compared to placebo (with separations from placebo generally below approximately 15-20msec in magnitude) during the first 12 hours of each day following the 10mg dose and that other subjects (#10, and 12) had a similar separation for QTc (with separations from placebo generally below approximately 35msec) also following the 10mg dose. These apparent separations from placebo were due in part to the general negative changes from baseline for the placebo treatment and appear at 10mg which is in substantial excess of the dose proposed for marketing.

According to the sponsor's tabulations for the number of patients in clinical study S2WB2001 with an abnormal ECG at anytime, there appears to be no increase in the number of patients with an abnormal ECG with increasing dose of naratriptan up to 10mg compared to placebo.

Summary: Although intent-to-treat analyses were not conducted. but would have been preferable, for ECG interval analysis for 4 of the 5 clinical pharmacology studies, valuable information can be obtained since subjects excluded for the completer analyses would not be expected to effect the results materially or with a magnitude of clinical significance.

The sponsor's discussion of the data is inaccurate regarding the numbers of statistically significant post treatment comparisons; but from examination of the statistical analyses presented in this submission, there appears to be no clear signal for an increase in PR, QRS, or QTc interval length with increasing dose from 2.5mg to 10mg+10mg following single exposures or over time following repetitive administration of 5mg or 10mg for 5 days, particularly since these doses are in excess of the 2.5mg dose proposed for marketing.

Michael J. Sevka, M.D. 11/7/97

Agree 11/10/97

RIC 11/10/97