Odds Ratio

The results of this analysis are shown in the next table. There was no difference between the results of the "survival" analysis and the Cox model analysis.

TABLE 9.3.5: 1. ODDS RATIO OF TREATMENT WITH ASA, DP OR DP-ASA
Source data: appendix 15.9.2.StAn.4: Efficacy / Pharmacodynamic Data

Endpoint	ASA			DP			DP-ASA		
	Odds Ratio	95 % Confidence Interval		Odds Ratio	95 % Confidence Interval		Odds Ratio	95 % Confidence Interval	
Stroke	0.79	0.65	0.97	0.81	0.67	0.99	0.59	0.48	0.73
Stroke : Non-fatal	0.78	0.64	0.96	0.77	0.63	0.95	0.56	0.45	0.70
Death	0.88	0.71	1.09	0.92	0.74	1.13	0.90	0.73	1.12
Stroke and/or Death	0.84	0.71	0.99	0.81	0.68	0.96	0.71	0.59	0.84
Myocardial Infarction	0.87	0.56	1.34	1.07	0.71	1.63	0.77	0.49	1.22
Ischaemic Event (I.E.)	0.84	0.70	1.00	0.86	0.71	1.02	0.63	0.52	0.76
I.E. : Non-fatal	0.78	0.64	0.95	0.83	0.68	1.01	0.57	0.46	0.71
Other Vascular Event	0.68	0.44	1.03	0.63	0.41	0.96	0.38	0.23	0.63
Vascular Death	0.93	0.71	1.21	1.01	0.78	1.30	0.94	0.73	1.23
Vascular Event	0.84	0.71	0.99	0.87	0.73	1.03	0.63	0.52	0.75

ASA alone and DP alone were effective at the $p<0.05$ level in preventing the following endpoints: all stroke, non-fatal stroke, stroke and/or death.

Additional and Post-Hoc Analyses

These analyses were not part of the initial protocol or the clinical trial report.

First-Stroke Handicap Based on Modified Rankin Scale Classification of First (Fatal or Non-Fatal)
Nonparametric analyses of patient handicap scores were performed on 804 patients with clinical stabilization, MMAG confirmed-strokes, and modified Rankin criteria available. Twenty patients did not have modified Rankin criteria available. The sponsor adjusted the modified Rankin criteria to include a score of 6 to represent fatal strokes. Neither ASA nor DP significantly affected the distribution of recurrent stroke according to the adjusted and modified Rankin criteria.

Non-Fatal First-Stroke Handicap Scores Based on Modified Rankin Scale Classification
Factorial analysis demonstrated that neither DP nor ASA significantly reduced the proportion with major handicap (i.e. modified Rankin score 3-5) following a non-fatal first stroke. However pairwise comparisons demonstrated that the DP+ASA group had a lower proportion of patients with major stroke handicap than did DP alone, ASA alone, and placebo.

Proportion of Patients with First Stroke (Fatal or Non-Fatal) by Type of First Stroke
An analysis of patients with first stroke by type (hemorrhage or infarction) was performed. This analysis did not include all patients. Type of stroke information was available for 604 patients and not available for 220 patients. Pairwise comparison demonstrated fewer patients had infarctions on the DP+ASA than on DP alone, ASA

alone, or placebo. These results must be interpreted with caution as there was no information available for nearly one-quarter of the patients with this event.

Proportion of Patients with First Stroke (Fatal or Non-Fatal), by Location of First Stroke
There were 630 hemispheric and 118 brain stem lesions. The sponsor comments *IT is clear from PANEL 8.8.2.7.4.13 that DP and ASA produced consistent, additive reductions in both hemispheric and brain stem strokes.* No other information to corroborate that statement is provided, clearly the ESPS2 data did support the statistically significant reduction in the primary endpoint of stroke.

Death By Cause of Death
The most frequent cause of death in each treatment group was fatal stroke, infection, sudden death, neoplasm, and myocardial infarction in descending order. There were no significant differences between treatment groups for the subcategories of death.

Proportion of Patients with First Stroke or Death By Category of Stroke and/or Death
The most frequent category in this analysis was non-fatal first stroke and never died (558 of 1319 endpoints) followed by death due to other causes with no previous non-fatal stroke (495 of 1319 endpoints). In the table below data for non-fatal first stroke are displayed.

Proportion of Patients with First Stroke By Category of Stroke and/or Death (modified ITT)

Treatment Group	Non-Fatal First Stroke and Never Died
DP 200mg/ASA 25 mg	101
DP 200 mg	133
ASA 25 mg	148
Placebo	176

Reviewer's table from sponsor's data

- Patients who suffer a non-fatal stroke are the major contributors to the combined endpoint of stroke and death. This subcategory drives the results seen for the combined endpoint.

Gender Analysis

No significant interaction was observed between gender and treatment (i.e. ASA alone, DP alone, and DP+ASA) for the primary endpoints of stroke and death.

Age Analysis

Subgroup analyses performed between patients less than 60 years of age and greater than or equal to 60 years of age did not demonstrate a significant interaction with treatment for the primary endpoints.

Race Analysis

This analysis was not performed. Only geographic analyses were performed which did not demonstrate a statistically significant interaction between geographic region and treatment.

Safety Assessment

Below is an overall listing of the common adverse events that occurred during ESPS2 trial.

PANEL 8.9.2.6.2:1 Overall Incidence of On-Treatment Adverse Events
Safety Population[1]

Body System/Preferred Term	Individual Treatment Group			
	DP+ASA	DP Alone	ASA Alone	Placebo
Total Number of Patients	1650	1654	1649	1649
Total Number of Patients With at Least One On-Treatment AE	1319 (79.9%)	1305 (78.9%)	1323 (80.2%)	1304 (79.1%)
Central & Peripheral Nervous System Disorders	909 (55.1%)	892 (53.9%)	834 (50.6%)	822 (49.8%)
Headache	647 (39.2%)	634 (38.3%)	558 (33.8%)	543 (32.9%)
Dizziness	501 (30.4%)	515 (31.1%)	503 (30.5%)	522 (31.7%)
Vertigo	61 (3.7%)	73 (4.4%)	55 (3.3%)	77 (4.7%)
Paraesthesia	27 (1.6%)	28 (1.7%)	27 (1.6%)	29 (1.8%)
Convulsions	28 (1.7%)	15 (0.9%)	28 (1.7%)	26 (1.6%)
Gastro-Intestinal System Disorders	721 (43.7%)	692 (41.8%)	621 (37.7%)	600 (36.4%)
Dyspepsia	303 (18.4%)	288 (17.4%)	299 (18.1%)	275 (16.7%)
Abdominal Pain	289 (17.5%)	255 (15.4%)	262 (15.9%)	239 (14.5%)
Nausea	264 (16.0%)	254 (15.4%)	210 (12.7%)	232 (14.1%)
Diarrhoea	210 (12.7%)	257 (15.5%)	112 (6.8%)	161 (9.8%)
Vomiting	138 (8.4%)	129 (7.8%)	101 (6.1%)	118 (7.2%)
Constipation	44 (2.7%)	22 (1.3%)	67 (4.1%)	54 (3.3%)
Dysphagia	23 (1.4%)	25 (1.5%)	23 (1.4%)	25 (1.5%)
Gastro-Intestinal Disorder NOS	15 (0.9%)	21 (1.3%)	24 (1.5%)	21 (1.3%)

[1] Reported by ≥ 1% of patients in any treatment group.
Note: DP = Dipyridamole; ASA = Acetylsalicylic acid.
Note: Adverse events were tabulated according to body system and preferred term based on the Boehringer Ingelheim WHOART dictionary.
Reference: Table 2.1.0.

ANEL 8.9.2.6.2:1 Overall Incidence of On-Treatment Adverse Events
Safety Population[1] (Page 2 of 6)

	Individual Treatment Group			
Body System/Preferred Term	DP+ASA	DP Alone	ASA Alone	Placebo
Gastro-Intestinal System Disorders (Cont'd)	721 (43.7%)	692 (41.8%)	621 (37.7%)	600 (36.4%)
Haemorrhage Rectum	26 (1.6%)	22 (1.3%)	16 (1.0%)	13 (0.8%)
Melaena	31 (1.9%)	10 (0.6%)	20 (1.2%)	13 (0.8%)
Haemorrhoids	16 (1.0%)	13 (0.8%)	10 (0.6%)	10 (0.6%)
GI Haemorrhage	20 (1.2%)	5 (0.3%)	15 (0.9%)	7 (0.4%)
Body as a Whole – General Disorders	472 (28.6%)	448 (27.1%)	483 (29.3%)	490 (29.7%)
Pain	105 (6.4%)	88 (5.3%)	103 (6.2%)	99 (6.0%)
Fatigue	95 (5.8%)	93 (5.6%)	97 (5.9%)	90 (5.5%)
Back Pain	76 (4.6%)	77 (4.7%)	74 (4.5%)	65 (3.9%)
Surgical Procedure	69 (4.2%)	59 (3.6%)	84 (5.1%)	75 (4.5%)
Leg Pain	34 (2.1%)	47 (2.8%)	38 (2.3%)	53 (3.2%)
Accidental Injury	42 (2.5%)	24 (1.5%)	51 (3.1%)	37 (2.2%)
Reaction Unevaluable	27 (1.6%)	42 (2.5%)	34 (2.1%)	37 (2.2%)
Fall	33 (2.0%)	21 (1.3%)	36 (2.2%)	33 (2.0%)
Chest Pain	18 (1.1%)	34 (2.1%)	27 (1.6%)	35 (2.1%)
Influenza-Like Symptoms	24 (1.5%)	23 (1.4%)	27 (1.6%)	30 (1.8%)
Malaise	27 (1.6%)	23 (1.4%)	26 (1.6%)	22 (1.3%)
Asthenia	29 (1.8%)	19 (1.1%)	17 (1.0%)	18 (1.1%)
Sudden Death	18 (1.1%)	14 (0.8%)	20 (1.2%)	25 (1.5%)
Syncope	17 (1.0%)	13 (0.8%)	16 (1.0%)	8 (0.5%)

PANEL 8.9.2.6.2:1 (continued) Overall Incidence of On-Treatment Adverse Events
Safety Population[1] (Page 3 of 6)

	Individual Treatment Group			
Body System/Preferred Term	DP+ASA	DP Alone	ASA Alone	Placebo
Vascular (Extracardiac) Disorders	303 (18.4%)	382 (23.1%)	390 (23.7%)	508 (30.8%)
Transient Ischaemic Attack	154 (9.3%)	176 (10.6%)	188 (11.4%)	253 (15.3%)
Stroke	123 (7.5%)	175 (10.6%)	187 (11.3%)	232 (14.1%)
Vascular Disorder	18 (1.1%)	28 (1.7%)	23 (1.4%)	23 (1.4%)
Thrombophlebitis Deep	4 (0.2%)	12 (0.7%)	13 (0.8%)	17 (1.0%)
Psychiatric Disorders	207 (12.5%)	199 (12.0%)	218 (13.2%)	225 (13.6%)
Depression	63 (3.8%)	54 (3.3%)	69 (4.2%)	79 (4.8%)
Amnesia	39 (2.4%)	40 (2.4%)	57 (3.5%)	34 (2.1%)
Insomnia	32 (1.9%)	28 (1.7%)	24 (1.5%)	41 (2.5%)
Anxiety	29 (1.8%)	34 (2.1%)	22 (1.3%)	38 (2.3%)
Confusion	18 (1.1%)	9 (0.5%)	22 (1.3%)	15 (0.9%)
Anorexia	19 (1.2%)	17 (1.0%)	10 (0.6%)	15 (0.9%)
Somnolence	20 (1.2%)	13 (0.8%)	18 (1.1%)	9 (0.5%)
Myo Endo Pericardial & Valve Disorders	145 (8.8%)	146 (8.8%)	133 (8.1%)	162 (9.8%)
Angina Pectoris	123 (7.5%)	120 (7.3%)	112 (6.8%)	126 (7.6%)
Myocardial Infarction	28 (1.7%)	41 (2.5%)	30 (1.8%)	41 (2.5%)

ANEL 8.9.2.6.2:1 (continued) Overall Incidence of On-Treatment Adverse Events
Safety Population (Page 4 of 6)

	Individual Treatment Group			
Body System/Preferred Term	DP+ASA	DP Alone	ASA Alone	Placebo
Musculo-Skeletal System Disorders	164 (9.9%)	144 (8.7%)	135 (8.2%)	139 (8.4%)
Arthralgia	91 (5.5%)	75 (4.5%)	91 (5.5%)	76 (4.6%)
Arthritis	34 (2.1%)	25 (1.5%)	17 (1.0%)	19 (1.2%)
Arthrosis	18 (1.1%)	22 (1.3%)	13 (0.8%)	14 (0.8%)
Myalgia	20 (1.2%)	16 (1.0%)	11 (0.7%)	11 (0.7%)
Respiratory System Disorders	120 (7.3%)	109 (6.6%)	154 (9.3%)	123 (7.5%)
Dyspnoea	28 (1.7%)	25 (1.5%)	39 (2.4%)	31 (1.9%)
Coughing	25 (1.5%)	18 (1.1%)	32 (1.9%)	21 (1.3%)
Pneumonia	18 (1.1%)	19 (1.1%)	21 (1.3%)	21 (1.3%)
Bronchitis	11 (0.7%)	16 (1.0%)	16 (1.0%)	16 (1.0%)
Upper Resp Tract Infection	16 (1.0%)	9 (0.5%)	16 (1.0%)	14 (0.8%)
Cardiovascular Disorders, General	97 (5.9%)	92 (5.6%)	142 (8.6%)	123 (7.5%)
Hypertension	42 (2.5%)	49 (3.0%)	79 (4.8%)	72 (4.4%)
Cardiac Failure	26 (1.6%)	17 (1.0%)	30 (1.8%)	25 (1.5%)
Oedema Dependent	14 (0.8%)	13 (0.8%)	20 (1.2%)	8 (0.5%)

ANEL 8.9.2.6.2:1 (continued) Overall Incidence of On-Treatment Adverse Events
Safety Population (Page 5 of 6)

	Individual Treatment Group			
Body System/Preferred Term	DP+ASA	DP Alone	ASA Alone	Placebo
Platelet, Bleeding & Clotting Disorders	130 (7.9%)	73 (4.4%)	127 (7.7%)	87 (5.3%)
Haemorrhage NOS	52 (3.2%)	24 (1.5%)	46 (2.8%)	24 (1.5%)
Epistaxis	39 (2.4%)	16 (1.0%)	45 (2.7%)	25 (1.5%)
Purpura	23 (1.4%)	8 (0.5%)	9 (0.5%)	7 (0.4%)
Thrombosis Arterial	6 (0.4%)	9 (0.5%)	10 (0.6%)	19 (1.2%)
Resistance Mechanism Disorders	87 (5.3%)	108 (6.5%)	107 (6.5%)	105 (6.4%)
Infection	67 (4.1%)	89 (5.4%)	87 (5.3%)	89 (5.4%)
Urinary System Disorders	81 (4.9%)	69 (4.2%)	98 (5.9%)	86 (5.2%)
Urinary Tract Infection	38 (2.3%)	34 (2.1%)	42 (2.5%)	40 (2.4%)
Haematuria	11 (0.7%)	13 (0.8%)	26 (1.6%)	8 (0.5%)
Metabolic and Nutritional Disorders	67 (4.1%)	75 (4.5%)	74 (4.5%)	92 (5.6%)
Diabetes Mellitus	11 (0.7%)	12 (0.7%)	14 (0.8%)	22 (1.3%)
Skin and Appendages Disorders	67 (4.1%)	74 (4.5%)	62 (3.8%)	70 (4.2%)
Rash	20 (1.2%)	21 (1.3%)	13 (0.8%)	19 (1.2%)
Pruritus	15 (0.9%)	15 (0.9%)	11 (0.7%)	18 (1.1%)

PANEL 8.9.2.6.2:1 (continued) Overall Incidence of On-Treatment Adverse Events
Safety Population[1] (Page 6 of 6)

	Individual Treatment Group			
Body System/Preferred Term	DP+ASA	DP Alone	ASA Alone	Placebo
Neoplasm	47 (2.8%)	48 (2.9%)	51 (3.1%)	49 (3.0%)
Neoplasm NOS	28 (1.7%)	16 (1.0%)	23 (1.4%)	20 (1.2%)
Vision Disorders	38 (2.3%)	52 (3.1%)	56 (3.4%)	49 (3.0%)
Vision Abnormal	13 (0.8%)	16 (1.0%)	10 (0.6%)	25 (1.5%)
Heart Rate and Rhythm Disorders	53 (3.2%)	36 (2.2%)	56 (3.4%)	47 (2.9%)
Fibrillation Atrial	20 (1.2%)	17 (1.0%)	24 (1.5%)	22 (1.3%)
Palpitation	10 (0.6%)	7 (0.4%)	18 (1.1%)	13 (0.8%)
Red Blood Cell Disorders	29 (1.8%)	17 (1.0%)	21 (1.3%)	11 (0.7%)
Anaemia	27 (1.6%)	16 (1.0%)	19 (1.2%)	9 (0.5%)

Sponsor's tables

Headache and dizziness were the most frequently reported adverse events. Headache was reported by 1281 patients in the DP treatment groups versus 1101 in treatment groups without DP. More patients in the placebo group reported dizziness than in the treatment groups. Gastrointestinal events were more common in those treated with ASA and DP+ASA but these differences were not significant. Bleeding from any site was more common in patients treated with ASA.

Ten adverse events had a greater than 1% higher incidence in the DP+ASA group than in the placebo. These events were:

1) headache
2) dyspepsia
3) abdominal pain
4) nausea
5) diarrhea
6) vomiting
7) melena
8) hemorrhage NOS
9) purpura
10) anemia.

Analysis of the tables above demonstrate that for some adverse events, there were a greater number of patients in the DP containing treatment groups reporting events compared to the non-DP containing groups. These events were :

1) headache
2) nausea
3) vomiting.

Analysis of the tables above demonstrate that for some adverse events, there were a greater number of patients in the ASA containing treatment groups reporting events compared to the non-ASA containing groups. These events were :

1) dyspepsia
2) hemorrhage NOS
3) melena
4) anemia.

Abdominal pain was more common in the DP+ASA treatment group than in all other groups.

Headache

The increased incidence of headache in the DP and DP+ASA groups was particularly evident in the first month of treatment. Differences between groups diminished over time and by the three month visit the difference was virtually gone. This change over time may partially be accounted for by the fact that treatment cessation occurred very early in the DP-treated groups. In the first month of the study treatment cessation occurred in 65% (86 patients) in the DP alone group and 66% (88 patients) in the DP+ASA group. These results contrasted with those seen in the placebo (45%, 18 patients) and ASA (41%, 13 patients) groups. Treatment cessation as a result of headache accounted for 8.9% of the DP and the DP+ASA groups, however only 2.8% of the placebo group and 2.1% of the ASA group discontinued treatment.

Gastrointestinal Event

At the first follow up visit the frequency of adverse gastrointestinal events was significantly higher in the DP-treated groups ($p<0.001$), however this difference declined rapidly. As mentioned above under headache, this rapid decline may be accounted for in part by the higher frequency of treatment cessation in the DP-treated groups. In the DP and DP+ASA groups, treatment cessation accounted for 7.2% (103 patients) and 8.1% (116 patients) respectively. These results contrast with the placebo (60 patients, 4.3%) and ASA groups (61 patients, 4.3%).

Bleeding

This adverse event was a less frequent but more serious adverse event.

TABLE 10.2.3: 4. BLEEDING AS AN ADVERSE EVENT
Source data: appendix 15.9.2.StAn_5 : Safety Data

Type of Adverse Event	Number of patients who reported at least once the indicated event				
	Group 1 Placebo	Group 2 ASA	Group 3 DP	Group 4 DP-ASA	Total
Any bleeding*:	74	135	77	144	430
Severity of bleeding**:					
Mild:	52	82	53	84	271
Moderate:	15	33	18	33	99
Severe or fatal:	7	20	6	27	60
Origin of bleeding:					
Haematuria:	7	20	11	10	48
Haematemesis:	9	10	2	9	30
Melaena:	10	15	4	26	55
Proctorrhagia:	12	16	21	24	73
Purpura:	2	5	6	10	23
Epistaxis:	24	44	15	37	120
Gynecological:	2	2	4	5	13
Internal:	2	6	3	3	14
Other site:	15	27	17	43	102

* Bleeding at any site, reported during follow-up and within 15 days after eventual stroke or treatment cessation.

** Severity of bleeding: mild = requiring no special treatment; moderate = requiring specific treatment but no blood transfusion; severe = requiring blood transfusion.

Sponsor's table from the clinical trial report

Bleeding events were not equivalent between the groups. The patients in the ASA containing groups reported a higher number of bleeding events. Patients in the ASA-treatment groups also had a higher frequency of severe/fatal bleeding.

Severity of Bleeding

	Placebo	ASA	DP	DP+ASA
Mild	52/74 (70.3%)	82/135 (60.7%)	53/77 (68.8%)	84/144 (58.3%)
Moderate	15/74 (20.3%)	33/135 (24.4%)	18/77 (23.4%)	33/144 (23%)
Severe/Fatal	7/74 (9.5%)	20/135 (14.8%)	6/77 (7.8%)	27/144 (18.8%)

Reviewer's table

The risk of bleeding with ASA and DP+ASA remained elevated over placebo and DP throughout the trial however this risk was not elevated over the use of ASA alone.

TABLE 10.2.3: 5. TIME DEPENDENCE OF BLEEDING EVENTS DURING FU
Source data: appendix 15.9.2.STAT.5 : Safety Data

Follow Up at Month:	Number of patients who reported bleeding events during FU visit: Placebo	ASA	DP	DP-ASA	Total
1	13	14	10	23	60
3	8	24	15	21	68
6	11	27	12	26	76
9	13	22	17	15	67
12	12	20	12	21	65
15	9	16	7	13	45
18	9	22	11	12	54
21	7	16	6	16	45
24	5	10	5	14	34
total	87	171	95	161	514

Overall significance of treatment effect was calculated by the chi-squared test: NS.

Sponsor's table from clinical trial report

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ON ORIGINAL

Ulcers
The incidence of ulcers was highest in the DP+ASA and ASA alone treatment groups.

Serious Adverse Events (SAE)

Overall Incidence of Serious Adverse Events (> 1% incidence)

Event	DP 200mg/ASA 25 mg number/percent	DP 200 mg number/percent	ASA 25 mg number/percent	Placebo number/percent
Total number of patients with at least one SAE	454 (28%)	467 (28%)	529 (32%)	560 (34%)
Vascular Disorder	150 (9%)	218 (13%)	222 (13%)	274 (17%)
Stroke	123 (7%)	175 (11%)	187 (11%)	232 (14%)
General Disorders	104 (6%)	78 (5%)	119 (7%)	112 (7%)
Surgery	46 (3%)	35 (2%)	53 (3%)	50 (3%)
Pain	21 (1%)	12 (<1%)	37 (2%)	26 (2%)
Sudden Death	18 (1%)	14 (<1%)	20 (1%)	25 (2%)
Myo Endo Pericardial & Valve Disorders	35 (2%)	47 (3%)	36 (2%)	47 (3%)
Myocardial Infarction	28 (2%)	41 (2%)	30 (2%)	41 (2%)
Neoplasm	35 (2%)	35 (2%)	42 (3%)	38 (2%)
Central & Peripheral Nervous System Disorders	46 (3%)	20 (1%)	37 (2%)	42 (3%)
Convulsions	25 (2%)	10 (<1%)	25 (2%)	20 (1%)
Gastrointestinal Disorders	51 (3%)	26 (2%)	37 (2%)	25 (2%)
Resistance Mechanism Disorders	29 (2%)	27 (2%)	27 (2%)	31 (2%)
Infection	25 (2%)	25 (2%)	21 (1%)	30 (2%)
Platelet, Bleeding, & Clotting Disorders	20 (1%)	21 (1%)	32 (2%)	32 (2%)

Reviewer's table

For serious adverse events, the combination treatment had the lowest number of patients reporting at least one SAE. There was no category where the combination drug product was worse than the comparators in terms of number of patients with serious adverse events.

Gastrointestinal Ulcers During Treatment Classified as Serious Adverse Events

PANEL 8.9.2.8.1:1 Patients with Gastro-Intestinal Ulcers During Treatment Classified as SAEs

Patient ID	Treatment Group	Sex/Age	SAE	Treatment Cessation Associated with SAE
14131216	DP+ASA	M/59	Duodenal Ulcer	No*
14131254	DP+ASA	F/72	Gastric Ulcer	No
17221219	DP+ASA	F/85	Duodenal Ulcer Perforated; Peptic Ulcer Perforated	No*
17231217	DP+ASA	F/80	Duodenal Ulcer	Yes
21111288	DP+ASA	F/68	Gastric Ulcer	No
21111293	DP+ASA	M/57	Duodenal Ulcer	Yes
24131384	DP+ASA	M/66	Duodenal Ulcer Perforated	Yes
12111359	DP alone	F/73	Gastric Ulcer	No
15131258	DP alone	M/49	Gastric Ulcer	No
20111570	DP alone	M/65	Peptic Ulcer	No
12141291	ASA alone	M/75	Duodenal Ulcer Perforated	Yes
17111383	ASA alone	M/81	Duodenal Ulcer	Yes
19121253	ASA alone	M/84	Duodenal Ulcer Haemorrhagic	No
20111397	ASA alone	M/75	Gastric Ulcer	Yes
22121334	ASA alone	M/60	Gastric Ulcer	No
17171204	Placebo	M/64	Duodenal Ulcer perforated	Yes
17181314	Placebo	F/80	Gastric Ulcer	No

* Patient Died. See Section 8.9.2.9.
Reference: Appendix 2.3.0 and comments from the CRF.
Sponsor's table

There were more gastrointestinal ulcers in the DP+ASA treatment group.

<u>Patients with Bleeds During Treatment Classified as SAEs excluding intracranial hemorrhage</u>

PANEL 8.9.2.8.1:2 Patients with Bleeds During Treatment Classified as SAEs

Patient ID	Treatment Groups	Sex/Age	SAE	D/C	Comments
12121210	DP+ASA	M/78	GI Haemorrhage	Yes	Hiatal hernia
12131220	DP+ASA	M/66	Melaena	Yes	Gastric hemorrhage from hemangioma
17101205	DP+ASA	M/58	Haemorrhage NOS	No	Gum margin bleed
17101290	DP+ASA	M/61	Haematuria	No	Cytoscopy - bladder abnormal
17111213	DP+ASA	F/86	Haemorrhage Rectum	No	Patient had Crohn's Disease
17111231	DP+ASA	F/88	GI Haemorrhage	Yes	Polyps
17151371	DP+ASA	F/85	Haemorrhage Rectum	No	Diverticulitis
			Haemorrhage NOS		
17161215	DP+ASA	M/73	Haematuria	Yes	Bladder cancer
17161323	DP+ASA	F/87	GI Haemorrhage	No	Also had folate deficiency anemia
			Melaena		
17191245	DP+ASA	F/87	Melaena	Yes	-
17201276	DP+ASA	F/85	Melaena	No*	Bleeding ulcer
17201298	DP+ASA	F/87	GI Haemorrhage	Yes	GI bleed
17221255	DP+ASA	F/84	Melaena	Yes	Fecal occult blood +3
20111385	DP+ASA	F/85	GI Haemorrhage	Yes	GI neoplasia (stomach)
20111559	DP+ASA	F/67	GI Haemorrhage	Yes	-
			Melaena		-
20111579	DP+ASA	M/75	Melaena	No	Carcinoma stomach
20181203	DP+ASA	F/68	Haematemesis	No	Died of infection
			Epistaxis		-
			Purpura		-
			Haematuria		-
20181204	DP+ASA	M/69	Melaena	No	Bleed attribute to hemorrhoids; also had colon cancer
22121205	DP+ASA	M/76	Melaena	No*	Peptic ulcer
22121271	DP+ASA	F/46	Haemorrhage NOS	No	Gynecologic bleed
23111261	DP+ASA	M/70	Haemorrhage Rectum	Yes	-
			Melaena		-
23111385	DP+ASA	M/68	Haematemesis	Yes	Peptic ulcer
23121204	DP+ASA	M/80	GI Haemorrhage	No*	Esophageal bleeding
24111487	DP+ASA	M/40	Haematemesis	No	-
			Melaena		-
24111799	DP+ASA	M/77	Haematoma	Yes	Traumatic - patient fell
17111218	DP alone	F/76	Haemorrhage Rectum	No	Diverticulitis
17161325	DP alone	F/73	Haematemesis	Yes	-
17211324	DP alone	F/70	Haematemesis	Yes	Lung cancer and gynacologic bleed
			Haemorrhage NOS		-
			Haematuria		-
17231305	DP alone	F/80	GI Haemorrhage	No	Gastric bleed
20201379	DP alone	M/72	Haematuria	No	Prostate disease
22121654	DP alone	M/73	Melaena	Yes	Peptic ulcer

*Patient died in association with this event. See Section 8.9.2.9.
Note: D/C = Temporally associated with treatment cessation.
Note: This panel does not include patients with intracranial bleeds.
Reference: Appendix 2.3.0 and comments from the CRF.

PANEL 8.9.2.8.1:2 (continued) Patients with Bleeds During Treatment Classified as SAEs (Page 2 of 2)

Patient ID	Treatment Groups	Sex/Age	SAE	D/C	Comments
12141212	ASA alone	M/67	Melaena	Yes	Peptic ulcer
17101223	ASA alone	M/75	Haemoptysis	No	Lung cancer
17111273	ASA alone	F/87	GI Haemorrhage	No	Cause unknown
			Melaena		-
17121246	ASA alone	F/88	Haemorrhage Rectum	No	Diverticulitis
17201205	ASA alone	F/82	GI Haemorrhage	Yes	GI neoplasia, anemia, bleeding, rectal polyps, and gastritis
17201250	ASA alone	M/73	Melaena	Yes	Gastric ulcer
	ASA alone	M/73	Haematemesis	No	-
17211205	ASA alone	F/74	Haematemesis	Yes	Gastric bleed hiatal hernia
17231283	ASA alone	F/80	Melaena	Yes	Diverticulitis
17231313	ASA alone	M/79	Haemorrhage NOS	No	Prostate disease, bleeding after surgery; also epistaxis
19121253	ASA alone	M/84	Duodenal Ulcer Haemorrhagic	No	-
20111361	ASA alone	M/77	Haemorrhage NOS	Yes	Bladder carcinoma and surgery
			Haematuria		-
20111440	ASA alone	F/60	Haematemesis	Yes	Peptic ulcer
20171259	ASA alone	M/70	Haematemesis	No	Gastric carcinoma
			Melaena		-
20191205	ASA alone	M/65	Retinal Haemorrhage	No	-
20201345	ASA alone	M/61	Haematuria	Yes	Post-surgical prostate operation
23121216	ASA alone	M/50	Haematoma	No	Post-surgical
24131379	ASA alone	M/66	Haematuria	Yes	Prostate cancer
12111424	Placebo	M/71	Haematemesis	No	Gastric ulcer
			Melaena		-
15131254	Placebo	M/79	Haematemesis	No	Peptic ulcer and neoplasm
			Melaena		-
17101212	Placebo	F/73	Diarrhea Bloody	Yes	-
17121314	Placebo	F/85	Haemorrhage Rectum	No	Diverticulitis
17191274	Placebo	M/69	Melaena	Yes	-
20111313	Placebo	F/63	GI Haemorrhage	No	-
20111333	Placebo	F/75	Haematemesis	Yes	Gastric ulcer
			Melaena		-
20141278	Placebo	F/77	Uterine Haemorrhage	No	Uterine carcinoma
20201295	Placebo	M/52	Haematemesis	No	Gastric bleeding
22121289	Placebo	M/72	Haematemesis	No	Peptic ulcer
23111286	Placebo	F/52	Uterine Haemorrhage	No	Uterine carcinoma

*Patient died in association with this event. See Section 8.9.2.9.
Note: D/C = Temporally associated with treatment cessation.
Note: This panel does not include patients with intracranial bleeds.
Reference: Appendix 2.3.0 and comments from the CRF.

Sponsor's table

The incidence of serious bleeds (other than intracranial) during treatment is numerically highest in the DP+ASA treatment group followed by ASA alone.

Patients with Intracranial Hemorrhage During Treatment Classified as a SAE

PANEL 8.9.2.8.1:3 Patients with Intracranial Haemorrhage During Treatment Classified as SAEs

Patient ID	*Treatment Group*	*Sex/ Age*	*SAE*	*D/C*	*Comment*
17101232	*DP+ASA*	*55/M*	*Subarachnoid haemorrhage*	*No*	-
17101327	*DP+ASA*	*71/F*	*Cerebral haemorrhage and subarachnoid haemorrhage*	*No*	*due to aneurysm*
17181301	*DP+ASA*	*85/F*	*Haematoma, haemorrhage*	*Yes*	*subdural haematoma*
19121210	*DP+ASA*	*75/M*	*Intracranial haemorrhage*	*Yes*	*subdural haematoma*
22121469	*DP alone*	*65/M*	*Subarachnoid haemorrhage*	*No*	-
24111861	*DP alone*	*73/F*	*Cerebral haemorrhage*	*Yes*	*haemorrhagic stroke*
24131217	*DP alone*	*67/F*	*Intracranial haemorrhage*	*No*	*chronic subdural haematoma*
24131238	*DP alone*	*82/M*	*Intracranial haemorrhage*	*No*	*chronic subdural haematoma*
12111340	*ASA alone*	*77/M*	*Cerebral haemorrhage*	*No*	*intracranial haematoma and stroke*
15111231	*ASA alone*	*73/M*	*Cerebral haemorrhage*	*No*	*cerebral haematoma and stroke*
19121252	*ASA alone*	*76/F*	*Cerebral haemorrhage*	*Yes*	*stroke*
20201504	*ASA alone*	*82/F*	*Intracranial haemorrhage*	*No*	*intracranial bleeding*
20121219	*Placebo*	*75/F*	*Intracranial haemorrhage*	*Yes*	*haemorrhagic infarction*
24111387	*Placebo*	*67/F*	*Haematoma, haemorrhage*	*Yes*	*due to aneurysm*
24111543	*Placebo*	*69/M*	*Intracranial haemorrhage*	*No*	*subdural haematoma*
24111610	*Placebo*	*46/M*	*Subarachnoid haemorrhage*	*No*	
24131235	*Placebo*	*76/M*	*Intracranial haemorrhage*	*No*	*chronic subdural haematoma*

Note: D/C = Temporally associated with treatment cessation.
Reference: Appendix 2.3.0 and comments from the CRF.
Sponsor's table

The incidence of intracranial hemorrhage did not differ among treatment groups.

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Deaths

Overall Incidence of On-Treatment Deaths

System	DP+ASA	DP	ASA	Placebo
Total number who died	107	124	125	135
Vascular Disorder	30	53	43	46
General disorders	20	19	26	28
Sudden Death	18	14	20	24
Infection	23	23	19	25
Myocardial Infarction	13	11	15	16
Neoplasm	10	9	9	9
Cardiovascular Disorders, general	3	5	9	6
GI disorders	5	0	0	1
Respiratory system	0	1	3	1
Metabolic/nutritional	1	1	1	1
Urinary Disorders	1	1	1	1
Psychiatric disorders	1	0	0	2
Liver/biliary disorders	0	1	1	0
Red cell disorder	1	0	0	0
Skin disorder	0	1	0	0

Reviewer's table

The greatest incidence of deaths occurring on treatment is in the vascular disorder category. The greatest incidence in this subcategory is due to stroke.

Number of deaths occurring more than 30 days after cessation of treatment

	DP+ASA	DP	ASA	Placebo
Total number died	97	79	65	81

Reviewer's table

Vascular disorders contributed the most to this category. Within the category of vascular disorders, stroke contributed the most deaths but not more than 2% for any group.

Patients who died of Ulcers or Bleeds During Treatment

PANEL 8.9.2.10:1 Patients Who Died of Ulcers or Bleeds During Treatment

Patient ID	Treatment	Sex/Age	Cause of Death	Treatment Duration	Day of Death	Comments
14131216	DP+ASA	M/59	Duodenal ulcer	82	94	Death attributed to bleeding ulcer
17201276	DP+ASA	F/85	Melaena	22	24	Death attributed to left ventricular failure, also reported gastro-intestinal bleed and melaena
17221219	DP+ASA	F/85	Peptic Ulcer Perforated	2	19	Died of perforated peptic ulcer
22121205	DP+ASA	M/76	Melaena	591	591	Patient had severe acute anemia. Peptic ulcer diagnosed by endoscopic exam on day of death
23121204	DP+ASA	M/80	GI Haemorrhage	489	489	Patient had esophageal bleeding
22121469	DP alone	M/65	Subarachnoid haemorrhage	685	685	TIA and subarachnoid haemorrhage
20111313	Placebo	F/63	GI haemorrhage and stroke	201	201	Death attributed to stroke
24111610	Placebo	M/46	Subarachnoid haemorrhage	390	390	Aneurysm and subarachnoid bleed

Reference: Table 2.5.2 and comments from the CRF.
Sponsor's table

The DP+ASA treatment group had the highest incidence.

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Treatment Interruptions

TABLE 10.2.5: 2. TREATMENT INTERRUPTION (TEMPORARY OR NOT): SUMMARY OF DATA
Source data: appendix 15.9.2.StAn.5 : Safety Data

Treatment Group	Cessations				No Cessations	Loss to FU or EP	Total
	Adverse Events	Other Medical Reason	Non-Medical Reason	Unknown Reason			
Placebo	127	148	81	4	931	358	1649
ASA	141	149	72	4	981	302	1649
DP	249	136	95	5	890	279	1654
DP-ASA	262	136	79	2	923	248	1650
Total	779	569	327	15	3725	1187	6602

Sponsor's table from clinical trial report

EP means Endpoint reached in above table. The number of patients who stopped taking treatment for non-medical reasons was not influenced by treatment. More patients in the DP containing treatment regimens

experienced a treatment cessation. As mentioned previously, these individuals discontinued treatment earlier than those patients in the non-DP containing treatment groups.

I was not able to locate information regarding the number of patients who had to decrease their dose of medicine during the trial.

Incidence of Adverse Events associated with a treatment cessation

PANEL 8.9.2.7.1:1 Incidence of AEs Associated With Treatment Cessation: AEs With an Incidence ≥1% in Any Treatment Group

	Treatment Groups			
	DP+ASA	DP	ASA	Placebo
Total Number of Patients	1650	1654	1649	1649
Patients with at least one AE associated with Treatment Cessation	417 (25%)	419 (25%)	318 (19%)	352 (21%)
Headache	165 (10%)	166 (10%)	57 (3%)	69 (4%)
Dizziness	85 (5%)	97 (6%)	69 (4%)	68 (4%)
Nausea	91 (6%)	95 (6%)	51 (3%)	53 (3%)
Abdominal Pain	74 (4%)	64 (4%)	56 (3%)	52 (3%)
Dyspepsia	59 (4%)	61 (4%)	49 (3%)	46 (3%)
Vomiting	53 (3%)	52 (3%)	28 (2%)	24 (1%)
Diarrhoea	35 (2%)	41 (2%)	9 (<1%)	16 (<1%)
Stroke	39 (2%)	48 (3%)	57 (3%)	73 (4%)
Transient Ischemic Attack	35 (2%)	40 (2%)	26 (2%)	48 (3%)
Angina Pectoris	23 (1%)	20 (1%)	16 (<1%)	26 (2%)
Myocardial Infarction	3 (<1%)	12 (<1%)	8 (<1%)	18 (1%)

Note: DP+ASA = dipyridamole 200 mg+aspirin 25 mg b.i.d; DP = dipyridamole 200 mg b.i.d.; ASA = acetylsalicylic acid (aspirin) 25 mg b.i.d.
Reference: Table 2.3.0.
Sponsor's table

Central Nervous System and Gastrointestinal adverse events accounted for the greater number of treatment cessations in the DP+ASA treatment group.

Laboratory Parameters

Comparing the mean values for hemoglobin, there was a less than 1 gm/dl difference in mean hemoglobin for patients in the ASA, DP, or DP+ASA treatment groups compared to placebo.

No clinically significant treatment effect was noted for the following laboratory tests:
1) Blood urea nitrogen
2) Creatinine
3) Uric acid
4) Fasting glucose
5) Total cholesterol
6) LDL cholesterol
7) White blood cell counts

8) Platelet counts
9) Sedimentation rate
10) Fibrinogen.

Caution must be added to this interpretation because the number of patients participating in the laboratory evaluation in for certain parameters was quite small.

Number of patients participating (i. e. having values at three time points)

Laboratory value sampled	Placebo	ASA	DP	DP+ASA
Fibrinogen	44	54	63	60
LDL cholesterol	441	449	426	432
Sedimentation rate	953	978	931	952

Reviewer's table

All other parameters had greater than 1000 per group.

Controlled Clinical Supportive Studies:

The sponsor proposes the following two trials in support of the pivotal trial. There are major obstacles to using these two trials to support Aggrenox™.
The trials listed below are presented chronologically.

U88-0473

The trial was designed to compare the efficacy of anticoagulant and antiplatelet treatments in the prevention of secondary stroke and/or death from any cause in patients who suffered a previous TIA or RIND. Patients in the two treatment arms were given heparin if they presented within 24 hours of the onset of symptoms. Patients in the antiplatelet treatment group were given heparin for the first 24 hours only, while the anticoagulant group received heparin until the thrombin time was less than 20%. No difference was demonstrated in stroke recurrence between the groups. See Clinical Studies Summary section for further information.

Problems with this study for support include:

1) Formulation of the combined product is not the final product in ESPS2
2) No placebo group
3) Patients who could not tolerate the combination of drugs were continued on in the trial with a single agent
4) Anticoagulant therapy has not been proven to be efficacious in this setting
5) Both treatment arms received anticoagulation
6) Not all patients reached the endpoint of 24 months
7) Negative final results in a trial of uncertain merit.

The safety data is presented in more detail as any potential toxicity seen may have more clinical relevance.

ESPS1

ESPS1 compared efficacy of Asasantin® Immediate Release (DP 75 mg/ASA 330 mg) with placebo. ESPS1 did demonstrate a benefit of the use of a combination product when the primary efficacy endpoint is analysed. Secondary endpoints of stroke (fatal and non-fatal), stroke (non-fatal), death (any cause), myocardial infarction, and ischemic death were improved in the patients treated with the combination compared to patients treated with placebo. Statistical significance was reached in the secondary endpoints of stroke (fatal and non-fatal).

Problems with this study for support include:

1) Formulation of the combined product is not the final product in ESPS2

2) The trial was not designed to look at the effect of the individual components and the additive benefit of the combined product
3) Not all patients were followed for 24 months – some because of late entry had only a few months follow up
4) ESPS1 arose out of two slightly different trials conducted at two different centers. Both trials had poor accrual so the trials combined and more centers were permitted to join.
5) Single center in Finland contributed more patients to the study than all other sites in Europe combined.
6) Some inequities in stratification and randomization occurred.
7) Sites in the Netherlands had their own randomization scheme, which was separate from the rest of the trial.

The safety data is presented in more detail as any potential toxicity seen may have more clinical relevance.

Safety Information for Supportive Studies

Safety information for U88-0473

Scant information was provided. Not all patients had 24 months of follow up. From the unpublished text provided the following table was generated:

Adverse Events Trial U88-0473 for the combination of ASA 990mg + DP 150mg

Total n=68	Number of patients with event reported
Myocardial infarction	3
Hemorrhage (unknown type/severity)	6
Gastrointestinal Distress	15
Allergy	1
Flushing reaction	1
Drop in hemoglobin	Unknown
Increased Uric Acid	5
Decreased platelet aggregation	68

Reviewer's table

There was no placebo arm in this trial to compare the incidence of adverse events. The dose of aspirin was markedly higher than the planned product. No unexpected new adverse events were reported with the combination product. Scant information was provided on these events making further comment impossible.

Safety Information for ESPS1

Serious Adverse Events for the DP-ASA treatment group in ESPS1 trial

Total n=1250	
Total number of patients with at least one serious adverse event	158
Stroke	115
Myocardial infarction	24
Neoplasm NOS	31
Surgical Procedure	25
Death NOS	22
Sudden Death	13
Cardiac Failure	9
Vascular Disorder	8
Infection	3
Embolism Pulmonary	3

Reviewer's table

The number of serious adverse events was lower for all categories in the Asasantin® Immediate Release group compared to the placebo group.
Other Adverse Events for the DP-ASA treatment group in ESPS1 trial

Total n=1250	Number of patients with event reported
Stomach pains/abdominal pain/cramp	228
Nausea	76
Vomiting	33
Dyspepsia	305
Diarrhea	31
Constipation	19
Ulcus/Ulcer	21
Heaviness in legs	3
Headache	144
Headache-Migraine	3
Vertigo/Dizziness	42
Meteroism-flatulence tenesmus	17
Paresthesia	12
Bleeding Events	107
Hemorrhage NOS	53
Epistaxis	23
Rectal	13
GI	11
Hematuria	6
Hemoptysis	1
Redness/sweat	13
Esophagus/throat	10
Tiredness/sleepiness/drowsiness	43
Skin/hyperemia	12
Others	52

Reviewer's table

The total number of patients reporting at least one adverse event was higher in the Asasantin® Immediate Release group. The incidence of all events was higher in the Asasantin® Immediate Release group except for the category of diarrhea. There were 4 cases of vaginal hemorrhage and 1 case of oral hemorrhage in the placebo group. No new unexpected adverse events were reported in the Asasantin® Immediate Release group.

Post-Marketing Spontaneous Adverse Events

Persantin® Retard (extended release dipyridamole) has been manufactured and distributed throughout Europe since May 1984. Persantin® Retard contains 150 to 200 mg of dipyridamole per capsule. Asasantin® Immediate Release (immediate release aspirin and dipyridamole) has been manufactured and distributed in Germany, Spain, and Argentina since December 1987.

Persantin® Retard

Sixty-four adverse events have been reported since the marketing of Persantin® Retard until December 31, 1997. This drug is not approved in the United States.

Post-Marketing Spontaneous Adverse Events for Persantin® Retard

Spontaneous Adverse Event	Number of times reported	Reported in US label for Persantine tablets (immediate release)
Headache	8	Yes
Diarrhea	6	Yes
Pruritis	4	Yes
Rash	2	Yes
Urticara	2	No
Angina	2	Yes
Chest Pain	2	Yes
Flushing	2	Yes
Myeloproliferative Disorder	2	No
Purpura	2	No
Hepatic Dysfunction	1	Yes
Cerebral Hemorrhage	1	No

Table complied by reviewer.

Post-Marketing Serious Spontaneous Adverse Events for Persantin® Retard

Case #	Drug formulation	Organ System	Mitigating Factors Other factors	Outcome
95-NB-00085	Persantine-L 150 mg BID x 4 weeks	Cerebral Hemorrhage	Chronic renal disease Hypertension (well-controlled for 5 years) All other medication taken for a long time	Unknown
97-NB-00119	Persantine 150 mg BID started on admission to hospital	Hepatic dysfunction	Renal insufficency Multiple other serious medical problems, one week after start of Persantine abnormal liver function tests Persantine discontinued	Died in hepatic failure 3 weeks after admission to hospital
BZ-86-5B031	Persantine 75 mg x 10 years switched to Persantin® Retard for several months	Aplastic Anemia	Unknown	Unknown
BZ-88-5C195	Persantin® 200 mg BID	Myeloproliferative Disorder (Essential Thrombocythemia)	Seizures, hypertension Concomitant meds-phenobarbital, amphetamine sulfate	Unknown
BZ-88-5C196	Persantin® SR 200 mg BID	Myeloproliferative Disorder (Essential Thrombocythemia)	Unknown	Unknown

Reviewer's table

Asasantin® Immediate Release

One hundred and twenty-eight adverse events were reported after the marketing of Asasantin® Immediate Release until December 31,1997.

Post-Marketing Spontaneous Adverse Events for Asasantin® Immediate Release

Events	Number of Patients
Gastrointestinal Bleeds	N=32
Gastrointestinal Symptoms	N=17
Gastrointestinal Ulcers	N=13
Allergic-type reactions	N=13
Other Bleeding Events	N=8

Reviewer's table

Serious Spontaneous Adverse Events for Asasantin® Immediate Release

Case #	Organ System	Mitigating Factors	Outcome
92-TH-00333	Skin-Stevens-Johnson Syndrome	Taking Asasantin for 3 years	Discontinued Asasantin rash resolved
95-DE-06054	Paraplaegia Venous Thrombosis Pulmonary Embolism	Multiple medical problems, admitted to hospital for cervical spine surgery, within a few hours post-op developed numbness of legs, discharged from hospital, readmitted with acute paraplegic symptoms, five days later had DVT and PE diagnosed	Unknown
BZ-88-5A371	Hematology-Thrombocytopenia	Other medication including Prednisone, Bronchocetord, Dymerck	Unknown
BZ-86-5C748	Hematology-Thrombocytopenia	Unknown	Unknown
BZ-87-5A155	Cardiac-Arrhythmia	Arrhythmia started 4 days after starting Asasantin	Stopped after Asasantin was discontinued
BZ-88-5C217	Hematology-Anemia, Purpura	Multiple medications including heparin, colfarit	Unknown
BZ-88-5c297	Allergic-Vasculitis	Developed vasculitis 1 day after starting medication	Unknown

Reviewer's table

Four Month Post-NDA Safety Update

The submission included all known events until December 31, 1997. The firm submitted a safety update for the time period of January 1, 1998 through August 31,1998 for Asasantin® Extended Release which is the same formulation as Aggrenox™ Extended Release capsules. Twenty-one cases involved either Asasantin® Extended Release or Persantin® Retard.

<u>Serious Adverse Events</u>

Five of the twenty-one cases were serious adverse events.

Asasantin® Extended Release
One case of femoral artery thrombosis of a vascular shunt was not related to Asasantin® Extended Release use according to the reporting physician.
Two cases of headache required hospitalization. No other information is provided about these cases requiring hospitalization.

Persantin® Retard
One of the cases of headache occurred in an asthmatic patient who had an allergic reaction with bronchospasm and headache. Another patient complaining of headache also reported sweating and anxiety. No further information is provided about the severity and possible other confounding causes.

One case of pancytopenia developed in a 67-year-old female patient started on 300 mg daily of Persantin® Retard for nephrotic syndrome. Her other medications included temocapril and brotizolam. After two weeks of initial therapy she developed a progressive decline in her platelet count and white blood cell count. Her platelet count on admission to the hospital was 148,000 and reached its nadir at 72,000 on February 27, three days after all her medication was stopped. Similarly her white blood cell count was 5200 on admission and declined to 2400 on February 27. March 10 her laboratory parameters demonstrated an improvement. By March 25 her platelet count had risen to 118000 and her white blood cell count had risen to 4100.

Non-serious Adverse Events for both Asasantin® Extended Release and Persantin® Retard
Six patients out of the 21 reported headache with one of the patients reporting a migraine.
Three patients experienced chest pain. One patient had a prior history of angina pectoris. A second patient had a history of coronary artery disease. A third patient with known cerebrovascular disease and diabetes developed chest pain.
Gastrointestinal symptoms including epigastric pain (1), nausea (1), diarrhea (2), and vomiting with hypokalemia (1) were reported.
Two patients reported confusion and malaise reported by 1 patient on Persantin® Retard. One patient who experienced confusion had improvement after the dose was lowered.
Generalized muscle aches and pain were reported by two patients.
One case of postural hypotension was reported.

Other Cases Reported
One case of cerebral hemorrhage was reported in a 57 year old hypertensive patient on Persantine and warfarin. This event is likely related to warfarin use although an additive effect of Persantine cannot be completely discounted.

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Approved Marketing

Listed below are tables highlighting the current marketing status.

PANEL 8.8.1.2.4:1 Approved Marketing Applications for Asasantine™ Extended Release Capsules by Country

Country	Date of Submission	Date of Approval	Date of Launch
France	29 August 1996	9 July 1997	8 June 1998
Switzerland	26 November 1996	28 August 1997	1 July 1998
Sweden	29 November 1996	12 December 1997	6 April 1998
South Africa	27 November 1996	10 February 1998	4 May 1998
Finland	16 December 1996	9 March 1998	Pending
United Kingdom	28 November 1996	12 May 1998	15 July 1998
Belgium	8 October 1996	8 June 1998	Pending
New Zealand	17 March 1997	11 June 1998	Pending
Netherlands	21 November 1996	13 July 1998	2 November 1998

PANEL 8.8.1.2.4:2 Pending Marketing Applications for Asasantine™ Extended Release Capsules by Country

Country	Date of Submission
Austria*	12 September 1996
Denmark	20 September 1996
Norway*	25 September 1996
Greece	15 October 1996
Portugal	16 October 1996
Italy*	8 November 1996
Ireland*	27 November 1996
Spain	29 November 1996
Germany	12 December 1996
Australia*	16 December 1997

* Approvable letter received.

Sponsor's tables

The product has not been withdrawn from investigation or marketing in any country for issues related to safety or efficacy.

Uncontrolled Clinical Trials:

There were no uncontrolled clinical trials performed in support of the Aggrenox™ NDA.

Reviewer's Discussion

The sponsor has submitted this NDA with one pivotal efficacy study (ESPS2) to obtain marketing approval for Aggrenox™, a combination product containing extended release dipyridamole 200 mg and immediate release aspirin 25 mg to be taken orally twice a day. The indication the sponsor is requesting is "to reduce the combined risk of death and non-fatal stroke in patients who have had transient ischemia of the brain or completed stroke". This is a single trial submission for efficacy and safety. The sponsor has submitted two additional studies (U88-0473 and ESPS1) to provide efficacy and safety support for the pivotal trial.

Assessment of ESPS2

The ESPS2 trial is an adequate and well-controlled trial. Despite some irregularities that occurred during the trial particularly with center 2013, the trial appeared to be conducted appropriately. The sponsor conducted

audits of several of the largest centers involved in the study. The audit provided the basis for the exclusion of center 2013.

The patients were allocated with respect to baseline characteristics (sex, age, qualifying event, and center).

The inclusion and exclusion criteria were reasonable for this trial however there were several exceptions.
1) The study did consider individuals with transient global amnesia to have experienced a TIA. Transient global amnesia is not considered a form of TIA in this country. Merritt's textbook of Neurology does not suggest that patients with Transient Global Amnesia have a higher risk for subsequent TIAs or CVAs. *The frequency of both seizures and subsequent stroke, including TIAs is probably no different from that in a comparable age-matched population... Theoretic considerations support treatment with antiplatelet agents, but the benign natural history makes uncertain what benefit "preventative" treatment.* [1] Usually patients with transient global amnesia are not treated with medication in the United States. It is not known the number of patients with transient global amnesia who participated in this study.
2) The study did have an imbalance in those patients who underwent carotid endarterectomies in favor of the combined drug arm. Continuing those who underwent carotid endarterectomies in the trial influenced the primary efficacy outcome.
3) The study also had an imbalance with respect to the Bamford classification. The sponsor analyzed the data for the primary endpoints by the Bamford classification system and found no effect. However there were more than two thousand patients who did not have a Bamford classification who could not be part of that subgroup analysis. Additionally there was an imbalance in the percentage of patients in the subgroups of the Bamford classification scheme in this trial compared to the original paper. Thirty-nine percent of patients in this trial had a lacunar infarct compared to the original paper where 25% had a lacunar infarct. Lacunar infarcts in the Bamford classification scheme are associated with a better prognosis in terms of recurrence risk and mortality.

In the study, the combination was compared to placebo and to each of the components. Aspirin is approved to *reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli.* The dose of aspirin approved for this indication is 50 – 325 mg once a day. The comparison with dipyridamole is limited by the fact that dipyridamole is not approved by itself for the treatment of stroke. Dipyridamole is approved as an adjunct to coumarin anticoagulants in the prevention of postoperative thromboembolic complications of cardiac value replacement. The FDA approved dipyridamole in 1961 on the basis of safety.

The follow up visits and information assessed were reasonable. Two methods were used to assess compliance namely patient recall and plasma sampling, however plasma sampling was only performed in approximately twenty percent of patients.

There are some discrepancies in regard to interim analyses and endpoints in this study. The original study protocol provides scant information regarding the interim analyses. The original study protocol states that yearly interim analyses will be performed with results given to the Steering Committee. The clinical trial report makes reference to only one interim analysis, which was used to increase the sample size.
The original study report had only two primary endpoints stroke or death. The clinical trial report mentions three endpoints. The original trial report was never amended to include the combined endpoint.

The safety information collected was appropriate however details of liver function tests were not collected or provided. The labeling on dipyridamole tablets includes *rare reports of liver dysfunction.* The Post Marketing information provided on Persantin® Retard described one case of liver dysfunction. This patient later died from hepatic failure. The trial should have provided a more complete safety database with a more detailed assessment of liver function tests.

Approximately 25% of patients were discontinued due to an adverse event.

I could not locate information on the number of patients who had to reduce their dose of medication and for how long.

EFFICACY ASSESSMENT-ENDPOINTS

This review will consider all three endpoints and the secondary endpoint of TIA. Below is a table for the pairwise analysis of the endpoints of the trial using the evaluable patient population only. The intention-to-treat analysis was not performed for all endpoints, applying the "worst case" scenario and including patients from center 2013.

Statistical Analysis using the Evaluable Population Only

Pairwise analysis	Stroke P-value	Death P-value	Death and non-fatal stroke P-value
DP 200mg/ASA 25mg vs. DP 200 mg	0.002	0.791	0.079
DP 200mg/ASA 25 mg vs. ASA 25 mg	0.008	0.744	0.084
DP 200 mg/ASA 25 mg vs. Placebo	0.001	0.285	0.001
DP 200 mg vs. Placebo	0.036	0.421	0.012
ASA 25 mg. vs. Placebo	0.009	0.162	0.009

Reviewer's table

Stroke

The ESPS2 study does demonstrate the efficacy of the combined product to prevent the recurrence of stroke in those individuals who have experienced either a TIA or stroke. The robustness of this endpoint was demonstrated in all analyses: the evaluable population, the inclusion of data from center 2013, and in the sponsor's "worst case" analysis. For all three populations, the combination product was statistically significantly better when compared to either of its components. The combined product was also statistically significantly better when compared to placebo for all three populations. The demonstration of the statistically significant benefit of the combination product over its component drugs provides proof of the effectiveness of the combination product. The subgroup analysis of patients with the qualifying event of TIA did not demonstrate statistically significant superiority over ASA, but demonstrated some benefit.

Death

The ESPS2 study failed to demonstrate any benefit of the combination product over placebo, similarly there was no benefit demonstrated by any of the component arms (i.e. aspirin or dipyridamole).

Death and Non-fatal Stroke

The ESPS2 study failed to demonstrate a statistically significant benefit of the combination product over its components. This demonstration is necessary for the approval of a combination drug product. The combination drug product did demonstrate a benefit over placebo. The endpoint of stroke was responsible for observed benefit in the above table for the combination and the component arms.

TIA

This was an important secondary endpoint for the ESPS2 trial. The pairwise analysis failed to demonstrate a statistically significant benefit for the combination product over aspirin. However the data collected is subject to bias.

SAFETY

No unexpected adverse events were seen with the combination of DP+ASA in ESPS2. The relevant safety data the combination should be compared to is that of aspirin which is approved for this indication. Below is a table of non-serious adverse events from the ESPS2 trial where the combination drug product was worse than aspirin by greater than 1% or more. There were no serious adverse events that were seen with a greater than 1% incidence in the DP+ASA group compared to ASA.

Selected Adverse Events

Event	DP+ASA number/percent	ASA number/percent
Central & Peripheral Nervous System Disorders	909 (55.1%)	834 (50.6%)
Headache	647 (39.2%)	558 (33.8%)
Gastro-Intestinal Disorders	721 (43.7%)	621 (37.7%)
Abdominal Pain	289 (17.5%)	262 (15.9%)
Nausea	264 (16%)	210 (12.7%)
Diarrhea	210 (12.7%)	112 (6.8%)
Vomiting	138 (8.4%)	101 (6.1%)
Musculo-Skeletal Disorders	164 (9.9%)	135 (8.2%)
Arthritis	34 (2.1%)	17 (1%)

Reviewer's table

In the combination product, serious adverse events did not occur at a greater rate than with ASA. No new unexpected side effects are demonstrated in the combination.

Supporting Trials

Both trials (U88-0473 and ESPS1) used different combinations of dipyridamole and aspirin. The dose of aspirin in those trials 19.8 times the dose used in ESPS2 and the dose of dipyridamole was 0.5625 times that used in ESPS2. The trials had significant flaws in the design and conduct. The ESPS1 compared a combination product with a dipyridamole:aspirin ratio of 1:4.4 with placebo and the U88-0473 trial had a different comparator other than placebo. The safety data from these two supportive trials did not demonstrate any new unexpected adverse events.

Overall Significance of Aggrenox™

The submission of this application without dose ranging studies properly conducted for both components begs many questions. Aspirin is approved for the prevention of the combined risk of death and non-fatal stroke at doses from 50 mg to 325 mg per day. Dipyridamole is not currently approved for stroke therefore its use and the proper dose as a single agent in the treatment of stroke have not been established. Should this combination drug product be first line therapy to reduce the risk of recurrence of stroke?

Drug Development

Very few studies were conducted with the 8:1 dipyridamole:aspirin ratio of Aggrenox™. Only one single dose toxicology study was submitted. The data from the ESPS2 trial was not designed to collect pharmacokinetic data yet. The formulation appears to have been changed during the conduct of the trial. The reviews from chemistry, pharmacology, and biopharmaceutics are pending.

Conclusion

The submitted ESPS2 trial does provide evidence that the combination product, Aggrenox™, does significantly reduce the risk of stroke over its components, aspirin and dipyridamole. There is no benefit of the combination product or its components for the endpoint of death. The positive trend seen in the composite endpoint of stroke and death results from the statistically significant result on the endpoint of stroke outweighing the nonsignificant result on the endpoint of death.

Recommendations

From a clinical perspective, I recommend that Aggrenox™ be approved for the indication "to reduce the risk of stroke for patients who have had transient ischemia of the brain or completed stroke due to thrombosis." Further recommendations are pending review of FDA biopharmaceutics, chemistry, and pharmacology reviews as well as the findings of DSI.

Labeling Review

The chemistry, clinical pharmacology, and biopharmaceutics sections of the labeling will be addressed by those reviews.
Sponsor's draft labeling with my recommended modifications is attached to this review as Appendix 3.

/S/

Ann T. Farrell, M.D.
5-13-99

Concur with above recommendation
/S/
5-13-99

cc:
NDA 20-884
HFD-180
HFD-180/LTalarico
HFD-180/KRobie-Suh
HFD-180/AFarrell
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 5/13/99 jgw
N/20884905.0AF

Appendix 1

- Modified Rankin (R96-0263) scale classifies all patients according to the severity of the residual/stable clinical handicap.

Score 0: no residual symptoms at all
Score 1: no significant disability, despite symptoms; able to carry out all usual duties and activities
Score 2: slight disability; unable to carry out all previous activities, but able to take care of own affairs without assistance
Score 3: moderate disability; requiring some help, but able to walk without assistance
Score 4: moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
Score 5: severe disability: bedridden, incontinent, and requiring constant nursing care and attention

Bamford classification
Total Anterior Circulation Infarcts (TACI) have both cortical and subcortical involvement. These infarcts are associated with a negligible chance of good functional outcome and a high mortality.
Partial Anterior Circulation Infarcts (PACI) have a more restricted and predominantly cortical location. These infarcts are associated with a high risk of stroke recurrence early after a neurological event.
Lacunar Infarcts (LACI) are ischemic lesions confined to the territory of the deep perforating arteries. These infarcts are usually associated with a substantial residual handicap.
Posterior Circulation Infarcts (POCI) result from ischemia in a territory perfused by the great vertebrobasilar artery. These infarcts are associated with a greater risk of stroke recurrence later in the first year following a neurological event but have the best chance of a functionally good outcome.

24 pages
Redacted
DRAFT
LABELING

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 14, 1999

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, HFD-180

Subject: NDA 20-884
Aggrenox (extended release dipyridamole 200mg/aspirin 25mg)
[submitted: December 15, 1998]

To: Director, Division of Gastrointestinal and Coagulation Drug Products
(HFD-180) /S/

The sponsor is seeking approval of Aggrenox, a fixed dose combination product consisting of extended-release dipyridamole 200mg plus aspirin 25mg, given twice daily for use in preventing death and non-fatal stroke in patients with transient ischemic attack (TIA) or documented ischemic stroke.

To support effectiveness of the drug product for the proposed indication the sponsor has submitted report of ESPS2 (European Stroke Prevention Study 2), a multinational, randomized, double-blind, placebo-controlled trial.

Background:
Current professional labeling for aspirin with regard to vascular indications and revascularization procedures is summarized in the following table:

Professional Labeling Indications for Aspirin

Indication	Dose
Ischemic Stroke and TIA*	50-325 mg once a day. Continue therapy indefinitely.
Prevention of recurrent MI	75-325 mg once a day. Continue therapy indefinitely.
Unstable angina pectoris	75-325 mg once a day. Continue therapy indefinitely.
Chronic stable angina pectoris	75-325 mg once a day. Continue therapy indefinitely.
Carotid endarterectomy	80 mg once daily to 650 mg twice daily beginning before surgery and continuing indefinitely
CABG	325 mg daily for starting post-procedure and continuing for 1 year post-procedure.
PTCA	325 mg 2 hours pre-surgery. Maintenance dose of 160-325 mg daily. Continue therapy indefinitely.

* Aspirin is indicated to "reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli". The **CLINICAL STUDIES** section of the labeling states: "In clinical trial of subjects with TIA's due to fibrin platelet emboli or ischemic stroke, aspirin has been shown to significantly reduce the risk of the combined endpoint of stroke or death and the combined endpoint of TIA, Stroke, or death by about 13-18 percent."

reviewer's original table based on 21 CFR 343

Dipyridamole currently is approved only for use "as an adjunct to coumarin anticoagulants in the prevention of postoperative thromboembolic complications of cardiac valve replacement". The recommended dose is 75-100 mg four times daily as an adjunct to the usual warfarin therapy. The approved product (Persantin) is an immediate release formulation.

Information to support approval of aspirin for ischemic stroke and TIA consisted of the accumulated published literature on aspirin, including particularly reports of 7 major clinical trials. Features and outcomes of these major studies are summarized in the table below. These studies were presented and discussed at a joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee on January 23, 1997.

Studies Evaluated for Effect of Aspirin on Cerebrovascular Events

Study	EntryCriteria	n	Aspirin (mg/day)	Months followup	Outcomes assessed	Number of Events (%)		Odds Ratio (95% CI)	FDA comments
						Aspirin	Placebo		
SALT	TIA, retinal artery occlusion, or minor stroke	1360	75	32	all strokes	93/676 (13.8%)	112/684 (16.4%)	0.82 (0.61, 1.10)	Risk of stroke and death reduced by 18%.
AICLA	Cerebral or retinal ischemic event	402	990	36	strokes and deaths	27/198 (13.6%)	36/204 (17.6%)	0.74 (0.43, 1.26)	Only study providing stat sig result for endpoint of stroke alone
					all strokes	17/198 (8.6%)	31/204 (15.2%)	0.53 (0.29, 0.98)	
Canadian	TIA or partial nonprogressing stroke	283	1300	26	strokes and deaths	26/144 (18.0%)	30/139 (21.6%)	0.80 (0.45, 1.44)	
					all strokes	22/144 (15.2%)	20/139 (14.4%)	1.07 (0.56, 2.06)	
Fields	TIA	178	1300	6 to 24	strokes and deaths	13/88 (14.8%)	19/90 (21.1%)	0.65 (0.30, 1.40)	
					all strokes	11/88 (12.5%)	14/90 (15.6%)	0.78 (0.33, 1.81)	
UK-TIA	TIA or minor ischemic stroke	2435	1200 or 300	48 (mean)	strokes and deaths	382/1621 (23.6%)	220/814 (27.0%)	0.83 (0.68, 1.01)	No difference in effectiveness between 300mg and 1200mg daily dose, but higher incidence of side effects, particularly GI with higher dose. Stat sig benefit on combined endpoint all death, nonfatal major stroke, and nonfatal MI. Trend toward benefit on major stroke alone and on combined disabling stroke or vascular death.
					all strokes	163/1621 (10.1%)	98/814 (12.0%)	0.81 (0.62, 1.07)	
Danish	Reversible cerebral ischemic attack	203	1000	43 (mean 24)	strokes and deaths	21/101 (20.8%)	17/102 (16.7%)	1.04 (0.65, 2.65)	
					all strokes	17/101 (16.8%)	11/102 (10.8%)	1.66 (0.75, 3.68)	
Swedish	Minor or major stroke due to cerebral infarction	505	1500	24	strokes and deaths	57/253 (22.5%)	55/252 (21.8%)	1.04 (0.68, 1.58)	No effect of aspirin overall.
					all strokes	32/253 (12.6%)	32/252 (12.7%)	1.00 (0.59, 1.68)	
All Studies					strokes and deaths	526/2405 (21.9%)	377/1601 (23.5%)	0.86 (0.73, 0.999	
					all strokes	355/3081 (9.3%)	318/2285 (13.9%)	0.84 (0.71, 0.99)	

table based on data from Federal Register, Vol 63, No. 205/Friday, October 23, 1998/Rules and Regulations, pages 56807-56808.

Support for use of aspirin in completed stroke and for the 50 mg daily dose came from subsequent FDA review of the aspirin and placebo arms of ESPS-2 which observed with regard to efficacy that: "The treatment group randomized to aspirin 25 mg twice daily experienced 16% fewer deaths and strokes than did the placebo group." and "The effects of aspirin on death and stroke individually were comparable. Both effects appear to contribute to the observed effect of the combined end point." (Consultative Joint Clinical Review, NDA 12-836, N. Stockbridge and J. Hung, Division of Cardio-Renal Drug Products, July 21, 1998). The following analysis was presented:

Table 4. Pair-wise end point analyses (ESPS2)

	Trialists			Reviewers			
	Placebo N=1649	ASA N=1649	Odds ratio 95% CI	Placebo N=1649	ASA N=1649	Odds ratio 95% CI	p*
Death or stroke	378	330	0.84 0.71-0.99	380	330	0.84 0.71-0.99	0.009
Stroke	250	206	0.79 0.65-0.97	250	206	0.80 0.66-0.97	0.009
Death	202	182	0.88 0.71-1.09	204	182	0.88 0.71-1.09	0.16

*p value from Gehan test

from Consultative Joint Clinical Review, NDA 12-836, N. Stockbridge and J. Hung, Division of Cardio-Renal Drug Products, July 21, 1998

It should be noted that the review advised caution in interpreting the results presented, in part because the analyses evaluated were not prospectively planned and because the sample size of the study was increased at interim analysis without protocol provision specifically for that.

Other orally administered drugs that are approved to prevent stroke in patients who have experienced stroke include clopidogrel bisulfate (PLAVIX), ticlopidine hydrochloride (TICLID). Studies supporting approval of these products are summarized in the following table:

Studies Evaluated for Effect of Ticlopidine and Clopidogrel on Cerebrovascular Events

Study	EntryCriteria	n	Drug	Months followup	Outcomes assessed	Number of Events		FDA comments
						Drug	Comparator	
TASS	TIA, amarosis fugax, minor stroke	3069	ticlopidine 250mg BID vs. aspirin 650mg BID	24-60	all strokes	13.8%	18.1%	over course of study risk reduced by 24% (p=0.011) from 18.1 to 13.8 per 100 patients followed for 5 yrs, compared to aspirin arm; during first year risk reduced by 48% as compared to aspirin arm.
CATS	previous atherothrombotic stroke	1073	ticlopidine 250mg BID vs. placebo	36	all strokes	18.6%	24.6%	over course of study risk reduced by 24% (p=0.017) from 24.6 to 18.6 per 100 patients followed for 3 yrs, compared to placebo; during first year risk reduced by 33% as compared to placebo.
CAPRIE	recent history of MI (within 35 days); recent history of ischemic stroke (within 6 months) with at least a week of residual neurological signs; or objectively established peripheral vascular disease	19185	clopidogrel 75mg daily vs. aspirin 325mg daily	up to 36 (mean 19)	ischemic stroke, MI other vascular death	438/9599 (4.56%) 275/9599 (2.86%) 226/9599 (2.35)	461/9586 (4.81%) 333/9586 (3.47%) 226/9586 (2.36%)	Overall risk reduction of 8.7% (9.78% vs. 10.64%) (p=0.045) in time to event for combined events; risk reduction was similar for each component of the combined endpoint. For fatal or nonfatal stroke the risk reduction was about 5.5% (4.56% vs. 4.81%).

reviewer's original table based on data from approved labeling for TICLID and PLAVIX

A few other drugs are labeled for reducing the risk of stroke. PRAVACHOL (pravastatin), an HMG-Co A reductase inhibitor which reduces cholesterol biosynthesis, is indicated to reduce the risk of stroke and TIA in patients who have previously suffered MI and who have normal serum cholesterol. ZOCOR (simvastatin), another HMG-CoA reductase inhibitor is indicated to reduce the risk of stroke and TIA in patients who have coronary artery disease and hypercholesterolemia. Coumadin is indicated "to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction."

PIVOTAL EFFICACY TRIAL:

ESPS 2 - Second European Stroke Prevention Study 2 – A double-blind, randomized, placebo controlled, multicentre study of four parallel groups organized in a 2 x 2 factorial design

Description: ESPS2 was a multinational, randomized, double-blind, parallel groups, placebo-controlled study having a factorial design with patients allocated in a 1:1:1:1 ratio to either extended release dipyridamole 200mg/apirin 25mg BID, extended release dipyridamole 200mg BID, aspirin 25mg BID, or placebo BID. General features of the trial are summarized in the following table:

ESPS2: Trial Description and Reviewer Comments

Feature	Protocol
Objectives	To investigate the effect of low dose aspirin and dipyridamole alone and in combination "in the prevention of stroke and death" in patients who have suffered a recent minor or major CVA of ischemic origin
Design	R,DB,MC,PG,factorial ***Reviewer comment:*** *The process for randomization is not clear. The study report indicates that randomization was performed centrally by the European Organisation for Research and Treatment of Cancer (EORTC) using a "minimisation technique which took into account the initial diagnosis (TIA or stroke), sex, age and study center."*
Subjects	Incl: M or F; age ≥18 yrs; CVA in prior 3 mos (CVA = completed stroke ["major stroke"] or TIA ["minor stroke"]; clinically stable; Excl: cerebral hemorrhage, brain tumor; cerebral disorders related to congenital vascular malf. stroke – focal disturbance of the cerebral circulation resulting in a clin neurol deficit lasting >24hrs. TIA – focal disturbance of the cerebral circulation that resulted in a clinical neurological deficit recovering within 24 hrs without functional impairment at std clin neurol exam ***Reviewer comment:*** *Study was initially planned for 5000 patients (1250 per treatment) but was increased to 7000 after interim analysis. (See "Statistical plan" section below).*
Drugs	aspirin(ASA), 25mg capsule BID dipyridamole (DP), 200mg slow release capsule BID aspirin/dipyridamole (ASA/DP), 25mg ASA capsule + 400mg DP slow release capsule BID placebo, 1 capsule BID In the combination product the dipyridamole is contained as modified release granules along with immediate release aspirin in a capsule. plasma levels are about 2-5uM after dipyridamole 200mg BID ***Reviewer comment:*** *The slow release dipyridamole product is not marketed in the U.S.*
Plan	Screen pts with clinical symptoms of stroke (CT recommended but not required); stroke classified on Rankin scale (0-5, none to severe functional handicap; note: 0-2=minor stroke; 3-5=major stroke); note: Bamford classification for "first-ever stroke" was added during study (may be unreliable,[retrospectively applied in 93% of pts, CTs may miss 50% of strokes in acute phase]; F/U at end of 1,3,6,9,12,15,18,21 and 24 mos; MMAG composed of 3 neurologists and a geriatrician;
Compliance	pill counts: blood levels at 2 times randomly during the study
Endpoints	*Primary*: stroke-first stroke occurring within 2 yrs of entry; total mortality-death due to any cause occurring within 2 yrs of entry. *Secondary*: other "relevant events": TIAs; first acute MI; ischemic events (combo of stroke, acute MI, sudden death); other vascular events (pulm embolus, DVT, obstruction of peripheral arteries, retinal vascular accidents). ***Reviewer comment:*** *Protocol is not clear as to whether individual primary endpoints of "stroke" and "death" were intended or whether the primary endpoint was to be combined first stroke or death. The 1996 study report for this trial indicates three primary endpoints: stroke (fatal or not), death from any cause, and stroke and/or death from any cause*
Statistical plan	Interim analysis planned at 3 yrs after study start or 1600 patients with 2 yrs F/U for unclear purpose: "The results of this interim analysis will be communicated to the Ethics Committee and might be the basis for a new assessment of the rationale of the trial by the Steering Committee." The Statistical Methods section indicates: "Yearly interim analysis." ***Reviewer comment:*** *Interim analysis was done in 11/91 after 3795 patients had been enrolled. Results of the interim analysis are not provided. The study sample size was increased from 5000 to 7000 patients based on that analysis. Study appears not specifically designed to demonstrate superiority of DP/ASA over ASA alone and DP alone, but rather to demonstrate (via the factorial design) that DP alone and ASA alone are both effective (see NDA Vol. 1.116, p.230, last paragraph); 50% power for combo]*
Safety	Patients were followed specifically with regard to bleeding events (type of bleeding, date, severity) and any unusual events. Checklists were provided for some expected events such as nausea, dyspepsia, vomiting, gastric pain, diarrhea, headache and dizziness.
Amendments	(Summarized in sponsor's narrative). After recruitment had been completed the protocol was modified at the recommendation of the Ethics Committee (6/11/94) to direct that in patients with non-rheumatic atrial fibrillation who developed stroke or TIA, the clinical trialists were allowed to decide, at their own discretion, whether or not the patients should be kept in the trial treatment regimen, or switch to anticoagulation therapy with vitamin K antagonists. There were some unspecified "minor modifications" to the case report form in 12/89 to improve the clarity of the form

Results: ESPS2 was carried out from 1989-1995. The trial involved a total of 7040 patients who were randomized at 60 centers in 13 countries. Most patients were from sites in The Netherlands (22.9%), United Kingdom (20,7%) or Finland (14.3%). No other individual country contributed more than 10% of patients. All 438 patients from one investigational site (#2013) were excluded from the efficacy analysis because of scientific misconduct at that site. A total of 6602 patients were included in the efficacy analyses.

Some characteristics of the efficacy population are summarized in the sponsor's table attached to this review as Appendix A. Fifty-eight percent of the patients were males. Mean age was about 67 years. Seventy-six percent of patients had stroke as their qualifying event for study entry.

Treatment groups were somewhat imbalanced with regard to location of qualifying event (Bamford classification) though in all groups most were lacunar infarcts or partial anterior circulation infarcts. Treatment groups were well-balanced with regard to severity of baseline handicap, alcohol consumption, coffee consumption, smoking, and medical history conditions. The most frequent medical conditions by history were hypertension (60% of patients), ischemic heart disease (35%), peripheral vascular disease (22%), hypercholesterolemia (23%), and diabetes mellitus (15%). About 8% of patients had history of cardiac failure and 6.5% had history of atrial fibrillation. About 76% of patients were current nonsmokers. Most frequent medical history conditions are summarized in Appendix B.

Compliance with study drug treatment for the duration of study participation was about 96% in all treatment groups.

Duration of study drug treatment is summarized in the following table:

ESPS2: Duration of Study Treatment

Duration of Treatment (days)	Treatment Group			
	DP 20mg/ASA 25mg BID (n=1650)	DP 200mg BID (n=1654)	ASA 25mg BID (n=1649)	Placebo BID (n=1649)
Mean ±S.E.	507±8	502±7	559±7	540±7
0-91	343 (20.8%)	345 (20.9%)	187 (11.3%)	249 (15.1%)
92-365	209 (12.7%)	208 (12.6%)	237 (14.4%)	215 (13.0%)
366-730	164 (9.9%)	184 (11.1%)	211 (12.8%)	216 (13.1%)
>730 days	934 (56.6%)	917 (55.4%)	1014 (61.5%)	969 (58.8%)

based on sponsor's table Panel 8.8.2.4:1

Most patients continued on study treatment for the protocol defined 730 days. Early discontinuations tended to be greater in the DP/ASA and DP groups as compared to the ASA and placebo groups, with about 20% of patients DP/ASA and DP patients discontinuing in the first 3 months while only 11% of ASA patients and 15% of placebo patients discontinued during this time. In all treatment groups the major reason for study treatment discontinuation was adverse events with about 25% of patients discontinuing

for this reason. Most common adverse events leading to study withdrawal were headache (particularly in the DP/ASA and DP groups), dizziness, nausea, abdominal pain, dyspepsia and vomiting.

Dsiposition of patients is shown in the sponsor's table below:

PANEL 8.8.2.2.1:1 Summary of Patient Disposition
ESPS2 – Randomized Population

	Treatment Group				
	DP 200 mg/ ASA 25 mg. b.i.d. n (%)	DP 200 mg b.i.d. n (%)	ASA 25 mg b.i.d. n (%)	Placebo n (%)	Overall n (%)
Total Number of Patients Randomized[1]	1650	1654	1649	1649	6602
Intent-to-Treat Population	1650 (100.0%)	1654 (100.0%)	1649 (100.0%)	1649 (100.0%)	6602 (100.0%)
Completed Study[2]	1027 (62.2%)	1023 (61.9%)	1125 (68.2%)	1088 (66.0%)	4263 (64.6%)
Treated Until Month 24	945 (57.3%)	923 (55.8%)	1023 (62.0%)	980 (59.4%)	3871 (58.6%)
Treated Until Death	82 (5.0%)	100 (6.0%)	102 (6.2%)	108 (6.5%)	392 (5.9%)
Ceased Treatment	623 (37.8%)	631 (38.1%)	524 (31.8%)	561 (34.0%)	2339 (35.4%)
Reason for Treatment Cessation:					
Adverse Event	459 (27.8%)	467 (28.2%)	382 (23.2%)	390 (23.7%)	1698 (25.7%)
Non-Medical	86 (5.2%)	107 (6.5%)	79 (4.8%)	98 (5.9%)	370 (5.6%)
Other	70 (4.2%)	48 (2.9%)	50 (3.0%)	64 (3.9%)	232 (3.5%)
Unknown	8 (0.5%)	9 (0.5%)	13 (0.8%)	9 (0.5%)	39 (0.6%)
Lost to Follow-Up for Stroke					
Before Special Investigation	38 (2.3%)	28 (1.7%)	11 (0.7%)	31 (1.9%)	108 (1.6%)
After Special Investigation	6 (0.4%)	6 (0.4%)	6 (0.4%)	10 (0.6%)	28 (0.4%)
Lost to Follow-Up for Death					
Before Special Investigation	6 (0.4%)	16 (1.0%)	8 (0.5%)	14 (0.8%)	44 (0.7%)
After Special Investigation	2 (0.1%)	2 (0.1%)	4 (0.2%)	7 (0.4%)	15 (0.2%)

1 Excluding 438 patients at Center 2013 due to scientific misconduct at that center. Patient disposition, demographic variables, background characteristics, and medical history conditions for Center 2013 are presented in Appendices 1.1.0, 1.2.0, and 1.2.2, respectively. The primary efficacy parameters (stroke and death) for all centers including Center 2013 are presented in Appendices 1.3.0 and 1.3.1.

2 Completed study is defined as treated until Month 24 or treated until death.

Note: DP = Dipyridamole; ASA = Acetylsalicylic acid; DP+ASA = AGGRENOX™

Note: Percentages for the Intent-to-Treat population are based on the number of patients randomized. Percentages for remaining rows are based on the number of patients in the Intent-to-Treat population.

Note: See Section 8.8.9, (Efficacy Data Handling Rules for ESPS2) for the complete definition of treatment cessation, reason for treatment cessation, and lost to follow-up.

Reference: Table 1.1.0.

sponsor's table

Fewer patients in the DP/ASA group died while on study treatment as compared to the other groups (5.0% vs. 6.0-6.5%). Causes of all deaths occurring during treatment and follow-up are summarized in Appendix C. About 45% of patient deaths in this study resulted from events judged related to stroke or other cardiovascular events.

It is not totally clear whether the sponsor intended the primary endpoints to be only stroke and death evaluated separately or whether the combined endpoint of stroke and/or death was to be considered a primary endpoint. The sponsor's efficacy analyses looking at the data for stroke and death separately and combined are summarized in the following table:

ESPS2: Summary of Sponsor's Efficacy Analyses

Number of Patients With Event Within 730 Days/ n (%)		Kaplan-Meier Estimate of Survival at 730 Days (95% C.I.)	Gehan-Wilcoxon Test P-value*	Risk Reduction at 730 Days	Odds Ratio (95% C.I.)
First Stroke (Fatal or Non-Fatal):					
DP 200 mg/ASA 25 mg b.i.d.	157/1650 (9.5%)	89.9% (88.4%, 91.4%)			
DP 200 mg b.i.d.	211/1654 (12.8%)	86.7% (85.0%, 88.4%)	0.002**	24.4%	0.72 (0.58, 0.90)
ASA 25 mg b.i.d.	206/1649 (12.5%)	87.1% (85.4%, 88.7%)	0.008**	22.1%	0.74 (0.59, 0.92)
Placebo	250/1649 (15.2%)	84.1% (82.2%, 85.9%)	<0.001**	36.8%-	0.59 (0.48, 0.73)
DP 200 mg vs. Placebo	-	-	0.036*	16.5%	0.82 (0.67, 1.00)
ASA 25 mg vs. Placebo			0.009**	18.9%	0.80 (0.66, 0.97)
Death (Any Cause):					
DP 200 mg/ASA 25 mg b.i.d.	186/1650 (11.3%)	88.7% (87.2%, 90.2%)			
DP 200 mg b.i.d.	189/1654 (11.4%)	88.5% (87.0%, 90.1%)	0.791	1.6%	0.99 (0.79, 1.22)
ASA 25 mg b.i.d.	182/1649 (11.0%)	88.9% (87.4%, 90.4%)	0.744	-2.0%	1.02 (0.82, 1.27)
Placebo	204/1649 (12.4%)	87.6% (86.0%, 89.2%)-	0.285	9.2%	0.90 (0.73, 1.11)
DP 200 mg vs. Placebo			0.421	7.7%	0.91 (0.74, 1.13)
ASA 25 mg vs. Placebo			0.162	11.0%	0.88 (0.71, 1.09)
Non-Fatal First Stroke:					
DP 200 mg/ASA 25 mg b.i.d.	126/1650 (7.6%)	91.8 (90.5%, 93.2%)			
DP 200 mg b.i.d.	168/1654 (10.2%)	89.2 (87.6%, 90.7%)	0.008**	24.5%	0.73 (0.57, 0.93)
ASA 25 mg b.i.d.	170/1649 (10.3%)	89.2 (87.6%, 90.7%).	0.009**	24.5%	0.72 (0.57, 0.92)
Placebo	213/1649 (12.9%)	86.2 (84.5%, 87.9%)	<0.001**	40.8%	0.56 (0.44, 0.70)
DP 200 mg vs. Placebo			0.010**	21.6%	0.76 (0.62, 0.95)
ASA 25 mg vs. Placebo			0.008**	21.7%	0.78 (0.63, 0.96)
Fatal First Stroke					
DP 200 mg/ASA 25 mg b.i.d.	31/1650 (1.9%)	97.9 (97.2%, 98.7%)			
DP 200 mg b.i.d.	43/1654 (2.6%)	97.2 (96.4%, 98.0%)	0.109	26.2%	0.72 (0.45, 1.14)
ASA 25 mg b.i.d.	36/1649 (2.2%)	97.6 (96.9%, 98.4%)	0.507	12.8%	0.86 (0.53, 1.39)
Placebo	37/1649 (2.2%)	97.5 (96.7%, 98.3%)	0.298	16.4%	0.83 (0.52, 1.35)
DP 200 mg vs. Placebo			0.569	-13.2%	1.16 (0.75, 1.81)
ASA 25 mg vs. Placebo			0.700	4.1%	0.97 (0.61, 1.55)
Any Fatal Stroke:					
DP 200 mg/ASA 25 mg b.i.d.	38/1650 (2.3%)	97.6 (96.8%, 98.3%)			
DP 200 mg b.i.d.	56/1654 (3.4%)	96.5 (95.6%, 97.4%)	0.051	31.2%	0.67 (0.44, 1.02)
ASA 25 mg b.i.d.	39/1649 (2.4%)	97.6 (96.8%, 98.3%)	0.901	1.2%	0.97 (0.62, 1.53)
Placebo	43/1649 (2.6%)	97.3 (96.5%, 98.1%)	0.480	10.8%	0.88 (0.57, 1.37)
DP 200 mg vs. Placebo			0.213	-29.5%	1.31 (0.87, 1.96)
ASA 25 mg vs. Placebo			0.571	9.8%	0.91 (0.58, 1.40)
First Stroke and/or Death:					
DP 200 mg/ASA 25 mg b.i.d.	287/1650 (17.4%)	82.4 (80.5%, 84.2%)			
DP 200 mg b.i.d.	322/1654 (19.5%)	80.3 (78.4%, 82.3%)	0.079	10.3%	0.87 (0.73, 1.04)
ASA 25 mg b.i.d.	330/1649 (20.0%)	79.9 (78.0%, 81.9%)	0.084	12.1%	0.84 (0.71, 1.00)
Placebo	380/1649 (23.0%)	76.7 (74.6%, 78.7%)	<0.001**	24.4%	0.70 (0.59, 0.84)
DP 200 mg vs. Placebo			0.012*	15.7%	0.81 (0.68, 0.95)
ASA 25 mg vs. Placebo			0.009**	13.9%	0.84 (0.71, 0.99)

* Except where indicated, comparison is between DP 200mg/ASA 25mg b.i.d. and comparator treatment in column at left.

from sponsor's tables NDA Vol. 1.87, pp. 98, 103, 141, 147, 152, and 174.

The sponsor's analyses show DP/ASA to be superior to each of the individual components only for first stroke ($p<0.01$ for all comparisons). This result is driven mainly by effect on non-fatal strokes (which accounted for about 82% of strokes in this study). There was no significant treatment by geographic location interaction with regard to this result. In this study DP/ASA clearly was not superior to the individual components with regard to all cause death.

The benefit of DP/ASA appeared to apply irrespective of risk factors such as previous CVA, baseline handicap, smoking, previous MI, male gender, older age, diabetes, atrial fibrillation, cardiovascular disease. Efficacy result did not appear to be affected by location of qualifying event (Bamford classification).

There was some concurrent use of disallowed medications during the study. However, this use was reasonably well-balanced across treatment groups. These medications included: non-study aspirin (18.3% of patients), antiplatelet drugs (4.2% of patients), NSAIDs (7.8% of subjects, and anticoagulants (4.9% of patients). Efficacy analysis with this drug use as covariate was not shown.

There was a trend toward a benefit of DP/ASA over DP alone ($p=0.042$) and over ASA alone ($p=0.076$) for category of non-fatal first stroke handicap (minor stroke vs. major stroke); however, neither DP alone or ASA alone was superior to placebo for this comparison (p-values = 0.961 and 0.608, respectively).

No benefit of DP/ASA or of DP alone or ASA alone over placebo was seen with regard to time to first myocardial infarction (fatal or non-fatal).

It is not clear how many interim analyses were done during the study. No results of interim analyses are included in the submission. The sponsor has performed some supportive efficacy analyses for the first 5002 patients enrolled (excluding center #2013). The results appeared similar for these first 5002 patients as compared to the total 6602 patients in the efficacy analysis. However, for the patients enrolled after this time (i.e., for the last 1600 patients enrolled) the ASA group had a lower rate of stroke than the first 5002 patients (10.0% vs. 13.3%), resulting in a slightly weaker p-value ($p= 0.008$ for the first 5002 vs. $p= 0.001$ overall).

Safety:
The safety database for this application is still under review.

About 80% of patients suffered an adverse event while on study treatment. The most frequent events were: headache (35%), dizziness (31%), dyspepsia (17%), abdominal pain (16%), nausea (14%), diarrhea (10%). Gastrointestinal adverse events (particularly diarrhea, nausea, and vomiting) tended to be more prevalent in the treatment groups receiving dipyridamole alone or in combination with aspirin. Headache also tended to be more common in patients receiving dipyridamole. Platelet, bleeding and clotting disorders were reported in 7.0% of DP/ASA patients, 4.4% of DP alone patients, 7.7% of ASA alone patients, and 5.3% of placebo alone patients. Overall incidence of on-treatment adverse events of special interest is summarized in the Appendix D.

Four patients each on DP/ASA, on DP alone, and on ASA alone and 5 patients on placebo suffered serious intracranial hemorrhage during treatment. Twenty-five patients on DP/ASA, 6 patients on DP

alone, 17 patients on ASA alone, and 11 patients on placebo suffered other serious bleeding adverse events.

Discussion:

Efficacy: With regard to combination drug products the FDA regulations state: "Two or more drugs may be combined in a single dosage form when "each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling." (21CFR 300.50(a)). In ESPS2 Aggrenox (DP/ASA) was shown to be superior to each of the individual components only for first stroke ($p<0.01$ for all comparisons by sponsor's analysis). This result is driven mainly by effect on non-fatal stroke. There was no benefit of the combination product on death. There was no convincing evidence of lessening of severity of stroke by the combination product as compared to the component drugs for strokes experienced in this study.

The May 1998 **Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products** identifies the following as characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim:

- large multicenter study - No single study site should contribute an unusually large fraction of the patients and no single investigator or site should be disproportionately responsible for the favorable effect seen.
- demonstration of consistency across study subsets – Analysis of the results of the trial for consistency across key patient subsets should address concerns about generalizability of findings to various populations.
- multiple studies in a single study – Properly designed factorial studies may be analyzed as a series of pairwise comparisons, representing, within a single study, separate demonstrations of activity of a drug as monotherapy and in combination with another drug.
- multiple endpoints involving different events – Statistically persuasive evidence of an effect on two or more prospectively identified, distinct, but logically related, endpoints.
- statistically very persuasive finding – In a multicenter study, a very low p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect.

In addition, to the clinical issues discussed here, there are statistical issues with regard to the evaluation of ESPS2, including interim analysis and lack of clear designation, *a priori*, of primary endpoints. (See FDA Statistical Review).

Safety: Preliminary review of the safety database does not suggest any unusual or unexpected adverse effects of either the component drugs (aspirin and dipyridamole) or the combination product. The safety profile appears to be consistent with the known adverse effects of these drugs. The major complaints with the dipryidamole-containing drugs are headache and gastrointestinal disturbances while the aspirin-containing drugs had more bleeding events and ulcers. These results suggest that combining a low dose of aspirin with dipyridamole does not eliminate the adverse events known to be associated with aspirin. The combination product does not appear to be safer than aspirin taken alone for this indication.

Conclusions and Recommendations:

The sponsor has demonstrated in a single large multicenter, European study a benefit of Aggrenox (combination of dipyridamole 200mg/aspirin 25mg) given twice daily in reducing stroke in patients having recent (within 3 months) completed stroke or TIA. However, the aspirin dose used as the comparator was low (at the bottom limit of the aspirin professional labeling dose recommendation) and

dipyridamole alone is not approved for this indication. No benefit of Aggrenox on mortality was demonstrated. There does not appear to be a clear benefit of DP/ASA as compared to ASA with regard to safety.

This application is to be presented to a combined session of the Neuropharmacologic Drugs Advisory Committee and Gastrointestinal and Coagulation Drugs Advisory Committee on April 28, 1999.

Clinical issues that might be considered by the Committee include:

1. appropriate endpoint for primary analysis - There is some uncertainty in the study protocol for ESPS 2 as to what the primary endpoints were to be: stroke, death and/or composite endpoint of stroke and/or death.

2. whether the product has met the efficacy requirements for a combination product - For a combination product to be approved each of the component drugs must be shown to contribute to the effectiveness of the combination product. The aspirin dose in the combination product is 25mg, which with the proposed BID dosing regimen would provide a daily dose of 50mg aspirin. This daily dose (50mg) is the lowest recommended dose of aspirin for the indication; and the 50mg aspirin dose was supported mainly based on the ESPS2 data. Dipyridamole is approved only for prevention of thromboembolism after heart valve replacement.

3. whether ESPS 2 meets the requirements for use of a single efficacy trial for approval - The effectiveness of Aggrenox, a fixed combination of dipyridamole 200mg and aspirin 25mg, is being supported by a single clinical trial (ESPS2). For a single study to convincingly support efficacy of a drug the trial must be multicenter and well-designed with regard to entry criteria, study endpoints, and conduct of the trial. The efficacy result must be statistically persuasive and must show consistency across sites/investigators and across study subsets. No single study site should contribute an unusually large fraction of the patients and the study population should be sufficiently diverse to address concerns about generalizability of the findings to various populations.

4. target population - ESPS2 was done in Europe. The study results must be generalizable to the U.S. target population with regard to disease and practice of medicine.

5. whether there are any particular safety concerns with regard to Aggrenox.

/S/

Kathy M. Robie-Suh, M.D., Ph.D.

cc:
NDA 20-884
HFD-180/Division File
HFD-180/JDuBeau
HFD-180/KRobie-Suh
HFD-180/AFarrell
HFD-180/MRashid
HFD-427/EDuffy

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APPENDIX A

PANEL 8.8.2.2.3:1 Summary of Demographic Variables and Background Characteristics ESPS2 – Intent-to-Treat Population

	Treatment Group					
	DP 200 mg/ ASA 25 mg b.i.d.	DP 200 mg b.i.d.	ASA 25 mg b.i.d.	Placebo	Overall	Comparison P-value
Total Number of Patients	1650	1654	1649	1649	6602	
Age (years)[1]	66.8 ± 0.3	66.7 ± 0.3	66.8 ± 0.3	66.6 ± 0.3	66.7 ± 0.1	0.917
Weight (kg)[1]	71.5 ± 0.3	72.1 ± 0.3	71.8 ± 0.3	72.2 ± 0.3	71.9 ± 0.2	0.405
Gender n (%)						
Male	956 (57.9%)	965 (58.3%)	956 (58.0%)	951 (57.7%)	3828 (58.0%)	0.984
Female	694 (42.1%)	689 (41.7%)	693 (42.0%)	698 (42.3%)	2774 (42.0%)	
Geographical Region n (%)						
Scandinavia	412 (25.0%)	416 (25.2%)	420 (25.5%)	417 (25.3%)	1665 (25.2%)	0.999
Northwestern Europe	607 (36.8%)	608 (36.8%)	603 (36.6%)	607 (36.8%)	2425 (36.7%)	
Southern Europe	270 (16.4%)	272 (16.4%)	265 (16.1%)	268 (16.3%)	1075 (16.3%)	
United Kingdom	361 (21.9%)	358 (21.6%)	361 (21.9%)	357 (21.6%)	1437 (21.8%)	
Type of QE (%)						
Stroke	1246 (75.5%)	1265 (76.5%)	1257 (76.2%)	1270 (77.0%)	5038 (76.3%)	
TIA	403 (24.4%)	388 (23.5%)	392 (23.8%)	379 (23.0%)	1562 (23.7%)	0.798
Unknown	1 (<0.1%)	1 (<0.1%)	0	0	2 (<0.1%)	
Duration of Symptoms of QE[1]						
Stroke (days)	9.7 ± 0.4	10.9 ± 0.5	10.6 ± 0.5	9.8 ± 0.4	10.2 ± 0.2	0.913
TIA (hours)	5.0 ± 0.4	4.6 ± 0.3	4.8 ± 0.4	4.2 ± 0.3	4.7 ± 0.2	0.571
Time from QE to Randomization (days)[1]						
Stroke	30.4 ± 0.7	30.4 ± 0.7	29.7 ± 0.7	29.5 ± 0.7	30.0 ± 0.4	0.968
TIA	32.4 ± 1.3	31.6 ± 1.3	33.9 ± 1.4	32.9 ± 1.4	32.7 ± 0.7	0.851
Overall	30.9 ± 0.6	30.6 ± 0.6	30.7 ± 0.6	30.3 ± 0.6	30.6 ± 0.3	0.983

** p-value ≤ 0.010.
1Mean ± S.E.
2Percentages are based on patients with qualifying event of stroke.
3The Bamford classification was applied to patients with a qualifying event of stroke. Percentages are based on patients with a qualifying event of stroke.
Note: DP = Dipyridamole; ASA = Acetylsalicylic acid; DP+ASA = AGGRENOX™; QE = Qualifying event; TIA = Transient ischemic attack.
Note: TACI = Total anterior circulation infarct; PACI = Partial anterior circulation infarct; LACI = Lacunar infarct; POCI = Posterior circulation infarct.
Reference: Tables 1.3.0 and 1.3.1.

sponsor's table

APPENDIX B

ESPS2: Most Common Medical History Conditions

Condition	Treatment Group			
	DP 20mg/ASA 25mg BID (n=1650)	DP 200mg BID (n=1654)	ASA 25mg BID (n=1649)	Placebo BID (n=1649)
Cardiovascular disease[a]	1269 (76.9%)	1299 (78.5%)	1264 (76.7%)	1270 (77.0%)
Hypertension	979 (59.3%)	1012 (61.2%)	983 (59.6%)	1020 (61.9%)
Ischemic heart disease	573 (34.7%)	598 (36.2%)	571 (34.6%)	577 (35.0%)
Peripheral vascular disease[b]	358 (21.7%)	371 (22.4%)	362 (22.0%)	363 (22.0%)
Hyper cholesterolemia	410 (24.8%)	375 (22.7%)	377 (22.9%)	347 (21.0%)
Diabetes mellitus	254 (15.4%)	278 (16.8%)	240 (14.5%)	239 (14.5%)
Previous myocardial infarction	157 (9.5%)	138 (8.3%)	132 (8.0%)	136 (8.2%)
Cardiac failure	140 (8.5%)	143 (8.6%)	134 (8.1%)	138 (8.4%)
Atrial fibrillation	104 (6.3%)	114 (6.9%)	104 (6.3%)	107 (6.5%)

[a] Cardiovascular disease includes ischemic heart disease, peripheral vascular disease, cardiac failure or hypertension.

[b] Peripheral vascular disease is defined as a history of peripheral vascular disease, the absence of one or more peripheral pulse (carotid, radial, femoral, or popliteal artery), or the presence of one or more vascular murmers (carotid or femoral artery).

based on sponsor's table Panel 8.8.2.2.3.3 and Study Report NDA Vol. 1.116, p. 55

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APPENDIX C

Summary of Causes of Death During First 730 Days of Study

Cause of Death	Treatment Group			
	DP 200 mg/ ASA 25 mg. b.i.d. n (%)	DP 200 mg b.i.d. n (%)	ASA 25 mg b.i.d. n (%)	Placebo n (%)
Total Number of Patients	1650	1654	1649	1649
Qualifying stroke	2 (0.1%)	2 (0.1%)	3 (0.2%)	1 (<0.1%)
Endpoint stroke	38 (2.3%)	56 (3.4%)	39 (2.4%)	43 (2.6%)
Myocardial infarction (MI)	17 (1.0%)	15 (0.9%)	21 (1.3%)	16 (1.0%)
Cardiac failure	7 (0.4%)	9 (0.5%)	11 (0.7%)	12 (0.7%)
Other vascular events[1]	7 (0.4%)	4 (0.2%)	3 (0.2%)	8 (0.5%)
Miscellaneous vascular events[2]	9 (0.5%)	8 (0.5%)	5 (0.3%)	6 (0.4%)
Bleeding events	4 (0.2%)	2 (0.1%)	1 (<0.1%)	2 (0.1%)
Neoplasm	27 (1.6%)	18 (1.1%)	20 (1.2%)	24 (1.5%)
Infection	29 (1.8%)	36 (2.2%)	35 (2.1%)	43 (2.6%)
Sudden death	25 (1.5%)	24 (1.5%)	27 (1.6%)	31 (1.9%)
Other	12 (9.7%)	9 (0.5%)	9 (0.5%)	11 (0.7%)
Unknown	9 (0.5%)	6 (0.4%)	8 (0.5%)	7 (0.4%)
Total deaths within 730 days of follow-up	186 (11.3%)	189 (11.4%)	182 (11.0%)	204 (12.4%)

[1] Other vascular events consist of pulmonary embolism, deep venous thrombosis, peripheral arterial occlusion, or retinal vascular accidents

[2] Miscellaneous vascular events consist of vascular events not included in the category of other vascular events, such as chronic arterial disease.

reviewer's table based on sponsor's table, NDA Vol. 1.87, p. 171 and 172

APPENDIX D

PANEL 8.9.2.6.3:1 Overall Incidence[1] of On-Treatment Adverse Events of Special Interest
ESPS2 - Safety Population

	Treatment Group			
Event of Special Interest/Preferred Term	DP+ASA	DP alone	ASA alone	Placebo
Total Number of Patients	1650	1654	1649	1649
Total Number of Patients With at Least One AE of Special Interest	1074 (65%)	1052 (64%)	1004 (61%)	950 (58%)
Headaches	648 (39%)	636 (38%)	559 (34%)	544 (33%)
Headache	647 (39%)	634 (38%)	558 (34%)	543 (33%)
Gastro-Intestinal Events	649 (39%)	644 (39%)	550 (33%)	537 (33%)
Dyspepsia	303 (18%)	288 (17%)	299 (18%)	275 (17%)
Abdominal Pain	289 (18%)	255 (15%)	262 (16%)	239 (14%)
Nausea	264 (16%)	254 (15%)	210 (13%)	232 (14%)
Diarrhoea	210 (13%)	257 (16%)	112 (7%)	161 (10%)
Vomiting	138 (8%)	129 (8%)	101 (6%)	118 (7%)
Dizziness	506 (31%)	521 (31%)	504 (31%)	528 (32%)
Dizziness	501 (30%)	515 (31%)	503 (31%)	522 (32%)
Vertigo	61 (4%)	73 (4%)	55 (3%)	77 (5%)
Bleeding Events	171 (10%)	94 (6%)	160 (10%)	92 (6%)
Haemorrhage NOS	52 (3%)	24 (1%)	46 (3%)	24 (1%)
Epistaxis	39 (2%)	16 (<1%)	45 (3%)	25 (2%)
Hemorrhage Rectum	26 (2%)	22 (1%)	16 (<1%)	13 (<1%)
Melaena	31 (2%)	10 (<1%)	20 (1%)	13 (<1%)
Haematuria	11 (<1%)	13 (<1%)	26 (2%)	8 (<1%)
GI Haemorrhage	20 (1%)	5 (<1%)	15 (<1%)	7 (<1%)
Purpura	23 (1%)	8 (<1%)	9 (<1%)	7 (<1%)
Ulcers[2]	19 (1%)	10 (<1%)	20 (1%)	14 (<1%)

[1] Reported by ≥ 1% of patients in any treatment group.
[2] None of the 10 preferred terms coding to ulcers occurred in ≥1% in any of the four treatment groups.
Note. DP = Dipyridamole; ASA = Acetylsalicylic acid.
Note: Adverse events were tabulated according to body system and preferred term based on the Boehringer Ingelheim WHOART dictionary.
Note: Adverse events of special interest are: bleedings/haemorrhages, ulcers, selected gastro-intestinal events (nausea, dyspepsia, vomiting, abdominal pain, and diarrhea), headaches/migraine, and dizziness/vertigo.
Reference: Table 2.2.0, Part 1.

sponsor's table

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: February 5, 1999 APR 14 1999

From: Acting Director /S/ 4/14/99
Division of Neuropharmacological Drug Products, HFD-120

Subject: Consult Request on European Stroke Prevention Trial

To: Director, Division of GI and Coagulation Drug Products; HFD-180

The enclosed review by Dr. John Feeney, dated February 5, 1999 represents the division's response to your request of January 29, 1999.

Consultative Review and Evaluation of Clinical Data

SUBJECT: European Stroke Prevention Trial

FROM: Director, Division of GI and Coagulation Drug Products; HFD-180

MATERIAL RECEIVED: Study Report

DATE RECEIVED: February 2, 1999

DATE REVIEWED: February 5, 1999

Overview of Second European Stroke Prevention Trial

This is a 7000 patient randomized, double-blind, placebo-controlled trial of the prevention of ischemic stroke and death in patients who have had at least one ischemic stroke or TIA. There were 4 treatment groups:

Placebo
ASA alone, 25mg bid
Persantin Retard alone, 200mg bid
Combination ASA and Persantin Retard

While the trial can be dissected on many levels, I would like to view the Second European Stroke Prevention Trial almost as a large, simple trial for the prevention of ischemic stroke *and/or* death. The Inclusion/Exclusion Criteria basically capture anyone over the age of 18 years of age who has had a clinically defined ischemic stroke or TIA within the last 3 months. Neuroimaging, to confirm the diagnosis and to rule out other etiologies such as tumor and intracranial bleed, was not required although it was encouraged. There were minimal stipulations about the severity of the stroke: patients with dementia, coma, or a poor life expectancy were excluded. Patients requiring anticoagulation (coumadin) were excluded.

The trial was conducted from 1989-1995. During that time, several other trials were completed and supported the use of coumadin in the prevention of stroke in the setting of non-rheumatic atrial fibrillation. Therefore, a protocol amendment was approved in 1994 allowing trialists to decide

whether or not to switch their patients from study medication to coumadin. I do not know how many patients were affected by this amendment, but Table 8.3.3: 2 on page 55 of the study report states that only 100/1650 patients per group had baseline atrial fibrillation.

Once entered, patients were all to be followed for a duration of 2 years. Patients returned for clinic visits every 3 months. It is not clear from the protocol or the study report how ascertainment of events was obtained. Most strokes and deaths would occur between the scheduled visits. Who was responsible for obtaining follow-up on the events in question ? What documentation was required for the events ?

The protocol states that the 2 primary endpoints were stroke and death. While the protocol does not clearly state that the primary outcome of the study would be a survival analysis with a *combined* endpoint of stroke or death, I believe that would be the appropriate primary outcome. (The Ticlopidine Aspirin Stroke Study is one example of a study that had death from any cause or nonfatal stroke as the primary outcome.)

With the ambiguity about the analysis of the two events, stroke and death, in the protocol, the study report implies that there should be 3 different primary outcomes: stroke (fatal or not), death from any cause, and stroke or death combined (page 19 of the study report).

The outcome of stroke, alone, is problematic. Under the umbrella of stroke are both nonfatal and fatal strokes. The classification "fatal stroke" implies the ability to classify all deaths by cause of death--an undertaking recognized to be near impossible in many cases. In fact, the current study had a committee charged with reviewing the classification of all important vascular events. Table 7.5: 3 on page 30 of the study report states the 208/782 deaths were classified differently by the committee and the investigator. The different views arose because of both lack of data and different views of available data regarding the deaths.

The outcome of all deaths is not relevant by itself where stroke prevention is proposed.

Therefore, even if not clearly stated in the protocol, I believe the logical outcome would be stroke or death, combined.

Data Integrity

While 7054 patients were randomized, the sponsor has included only 6602 patients in the final analysis. An entire center with 438 randomization numbers was excluded because of serious concern about investigator misconduct.

I also note on the cover page of the trial report the statement, "GCPs procedures were introduced after the study was designed and initiated." While I do not know what the regulatory ramifications of not having GCPs would be, I would want to clarify what facets of current GCPs were missing during the early conduct of this trial.

Overall, I think a case could be made that a trial that requires 450/7000 (6-7%) patients to be excluded because of concerns about fraud should not be taken in final form as the conclusive evidence of a drug's effectiveness.

Statistical Issues

The protocol called for a single interim analysis for effectiveness. I note that after the interim analysis, the sample size was increased from 5000 to 7000. It is my understanding that, in any trial, increasing the sample size is reasonable under certain conditions. I would want to discuss the change in sample size further with the statistician reviewing this trial to see if those conditions were met.

I have already discussed the primary *outcomes* (as opposed to *endpoints*) above. I believe the protocol is vague on this issue, but I believe that only a combined endpoint, stroke or death, is reasonable for the primary outcome. If the sponsor wishes to pursue 3 primary outcomes, as they have done in the study report, then some correction for multiple comparisons seems appropriate.

I also note that, for the outcome of combined stroke or death, the combination therapy is not statistically different from ASA alone or Persantine alone. ASA alone is statistically different from placebo; Persantine is statistically different from placebo. I have attached the Kaplan-Meier curves for the 4 groups to this review. [It appears that events were placed in 1 month bins for purposes of constructing the curves.]

Safety

It is worth commenting on the incidence of bleeding complications experienced by the ASA groups in the trial. I note from Table 10.2.3: 4 on page 144 of the study report that there were 20 severe (severe defined as requiring blood transfusion) or fatal bleeding events in the ASA alone group; the comparable number was only 6 for the Persantine alone group, but was 27 for the combination group. It is interesting to me that even this low a dose of ASA is associated with bleeding of this degree.

Inclusion/Exclusion Criteria

The consult asked for specific comments on inclusion/exclusion criteria. As I mentioned above, the protocol was designed to capture patients with the *clinical* diagnosis of ischemic stroke or TIA. Neuroimaging was encouraged, but not required. I assume this is in keeping with the usual standard of practice in the countries involved in the trial. In the United States, it would be unusual for a patient with stroke not to have imaging performed. The study report informs us that 80% of patients had CT or MRI scanning performed for the qualifying event, while 54% had doppler or angiography. These numbers are reassuring to me.

For those patients not imaged, other diagnostic categories, such as tumor or bleeds, may have occasionally been missed and the patients included in the trial. However, I think we can assume that the investigators participating in the trial were generally capable of recognizing a clinical stroke accurately. Additionally, an independent committee reviewed cases for misdiagnosis and misinclusion. That committee disagreed with the original diagnosis in only 44 cases, and these cases seem evenly distributed across treatment groups (10,11,8,and 15).

During the conduct of the study, the independent committee clarified that transient global amnesia (TGA) could be considered a rare type of TIA and could thus serve as a qualifying event. The exact nature of TGA is really unknown, but it may in fact be due to a transient ischemic event. It is rare enough that I do not think it would affect the interpretation of the results.

The committee also clarified that retinal artery events could be regarded as qualifying events. This seems reasonable to me.

I do not see information on carotid endarterectomies in the study report. I may have overlooked that data. I would want to see that the numbers of CEAs were balanced across treatment groups.

Conclusions

If concerns about data integrity could all be addressed, and pending statistical review of the sponsor's analyses, ESPS 2 appears to support the use of Persantin Retard alone in the prevention of stroke or death in patients clinically diagnosed with ischemic stroke or TIA. ESPS 2 also appears to support the use of ASA for the same indication. However, it is not clear that the combination is superior to either component.

/S/

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February 5, 1999

FIGURE 9.3.1.3: 1. "SURVIVAL" CURVES FOR STROKE AND/OR DEATH
Source data: appendix 15.9.2.StAn.4: Efficacy / Pharmacodynamic Data