CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020884

STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION

NDA #: NDA 20-884

Drug: Aggrenox (extended release Dipyridamole 200 mg/Aspirin 25 mg) Capsule

Drug Class: 4P

Indication: [redacted]

Sponsor: Boehringer Ingelheim, Inc.

Clinical Reviewer: Ann Farrell, M.D.

APR 30 1999

Statistical Reviewer: Mushfiqur Rashid, Ph.D.

Documents Reviewed: Volumes 1-147, Dated December 15, 1998

User Fee Due Date: June 15, 1999

1.0 INTRODUCTION

Stroke is the third leading cause of death in the United States. Long term disability is significant among survivors of stroke. According to the American Heart Association, approximately 731,000 people in the United States usually have a new or recurrent stroke in every year. Out of these 731,000 people, 160,000 people die from stroke each year. Surgical intervention and anticoagulant therapy for prevention of secondary stroke have not been shown to be beneficial for most patients. However, in addition to risk management, antiplatelet therapy has been shown to be beneficial for prevention of secondary stroke and /or death.

Aggrenox Extended Release is a combination drug consisted of 200 mg dipyrdamole (DP) in a modified-release formulation and 25 mg acetylsalicyclic acid (ASA) in an immediate-release formulation. According to the protocol, the new combination of two previously known active ingredients is intended for use in the indication of prevention of (1) stroke and (2) death (all causes) in patients with transient ischemic attack (TIA) or documented ischemic stroke. The recommended dose is one capsule twice daily (b.i.d.) by oral administration. Note that DP is an antiplatelet drug, and ASA (50 mg daily dose according to a published FDA rule for professional labeling of ASA) has been used for the prevention of death and non-fatal stroke in patients who have had an ischemic stroke or TIA. In a previous clinical trial study, DP alone did not appear to have a role in secondary stroke prevention (Acheson, et al. 1969; Controlled

trial of dipyriamole in cerebral vascular disease, British Medical Journal, volume 1, 614-5). However, there is a wide acceptance of antiplatelet therapy as an effective therapy for the prevention of secondary thromboembolic cerebrovascular diseases including both ischemic stroke and TIA.

This submission presents the efficacy and safety data in support of the use of Aggrenox Extended Release Capsules for the prevention of death and stroke in patients who have had a prior stroke or transient ischemic attack. The principal clinical study presented in support of Aggrenox Extended Release Capsules for this indication is the European Stroke Prevention Study 2 (ESPS2).

The sponsor claims that the proposed indication for Aggrenox Extended Release is supported by the efficacy results from two additional studies 1) European Stroke Prevention Study 1 (ESPS1) and 2) U88-0473 which were conducted with Asasantine Immediate Release. Studies ESPS-1 and U88-0473 were submitted with this NDA for supportive purpose. It must be emphasized that the clinical trial materials utilized in ESPS2 were significantly different from those in ESPS1 and U88-0473. It is important to note the dose formulation for Asasantine Immediate Release differs markedly from Aggrenox Extended release both in dose of component compounds:

Asasantine Immediate Release: dipyridamole 75 mg + ASA 330 mg t.i.d.

Aggrenox Extended Release: dipyridamole 200 mg + ASA 25 mg b.i.d.

The ESPS1 study was based on 2500 patients with primary endpoints stroke and/or death. The trial was designed to compare the Asasantine Immediate Release with placebo. Although, the study showed that Asasantine Immediate Release was significantly more effective in preventing stroke or death (stroke and/or death) than that of placebo, it was not designed to compare the combination drug with the components.

Study U88-0473 was an active controlled study with 137 patients. The primary endpoints were TIA, RIND (reversible ischemic neurological deficit), and stroke. The patient population consisted of those who suffered from a previous TIA or RIND. This trial was designed to compare Asasantine Immediate Release with an active control. The active control was an anti-coagulant Apekumarol.

In light of above discussions, the efficacy data from ESPS1 and U88-0473 is not considered supportive. Thus, studies ESPS1 and U88-0473 will not further addressed in this review.

The rest of this review is organized as follows. Subsection 1.1 discusses study protocol of ESPS2 including the sponsor's analysis plan. Section 2

discusses the analyses of stroke, death, stroke and/or death, category of stroke or death , and subgroups. Section 3 summarizes the safety parameters. Section 4 summarizes the reviewer's conclusions and concerns of the study.

1.1 STUDY PROTOCOL ESPS2

The objective of ESPS2 is to evaluate the efficacy and safety of dipyridamole and aspirin alone and in combination (Aggrenox extended release capsules) in the prevention of stroke (fatal or non-fatal) or death in patients who had a transient ischemic attack (TIA) or ischemic stroke. The sponsor conducted a large multi-center trial to support the proposed indication and dosing regimen. A total of 6602 intent-to-treat patients were evaluated for efficacy in ESPS2. ESPS2 was a randomized, double blind, multi-center, factorial group, parallel design with four equal-sized (approximately) treatment groups: (1) DP 200 mg/ASA 25 mg b.i.d. (combination drug), (2) DP 200 mg b.i.d, (3) ASA 25 mg b.i.d., and (4) placebo. Patients received one capsule twice daily (morning and evening), with a total daily dosage of 400 mg DP+50 mg ASA for DP+ASA-treated patients, 400 mg DP for patients treated with DP alone and 50 mg ASA for patients with ASA alone. The treatment period was 24 months. This study was conducted between 1989 and 1995.

The target sample size planned in protocol was 5000 patients. The sample size was increased to 7000 patients following the interim analysis, however sample re-estimation was not mentioned in the protocol. A total of 7054 patients were enrolled in 60 centers in 13 European countries. Of these 7054 patients, fourteen patients were excluded afterwards, because of erroneous randomization entries (not corresponding to existing patients). Also, all the patients (438 patients) from center 2013 were excluded from the ITT population due to scientific misconduct at that center. The decision to exclude center 2013 was made while the study was ongoing and blinded. Thus, 6602 patients were included in the ITT population. The patient disposition is given in the following table.

Table 1.1: Patient Disposition in ESPS2

Study ESPS2	DP 200 mg /ASA 25 mg b.i.d.	DP 200 mg b.i.d.	ASA 25 mg b.i.d.	Placebo	Total
Randomized	1763	1765	1762	1764	7054
Excluded	113	111	113	115	452
Included (ITT)	1650	1654	1649	1649	6602

Note: DP: Dipyridamole; ASA: Acetylsalicyclic Acid; DP+ASA: Aggrenox

Because the randomization was programmed to balance the four treatment groups with respect to initial diagnosis (TIA or stroke), sex, age, and study center, the blinded exclusion of all

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members from center 2013 did not disturb the balanced size of the four treatment groups in the remaining 6602 patients.

Demographic characteristics are summarized in Table A.1 in the Appendix. Study patients were predominantly female (58%). The treatment groups did differ significantly in gender distribution (42% male versus 58% female). There were no significant differences (p-value .917) in the mean age (67 years) across the treatment groups were evident. The proportions of patients in four geographical regions (Scandinavia, Northwestern Europe, Southern Europe, and United Kingdom and Ireland) across the four treatment groups are homogeneous (p-value .999)

Discussion of Center 2013:

During the conduct of the study, several issues of concern were noted by the study monitor for center 2013. These issues included:

1) Recruitment of patients was very rapid (>300 patients/year) despite the fact that there was only one investigator in the center;
2) Study visits were perfectly regular, took place during weekends and holidays, and occurred when the investigator was not in the country;
3) The incidence of adverse events was lower in this center than at other centers;
4) Compliance was reported to be better at this center compared with other centers;
5) Variability of data (e.g. pill counts, blood pressures) was too low for a clinical study; and
6) The investigator declined open collaboration with Steering committee and the clinical monitor.

Patient Selection:

Inclusion Criteria

Male and female patients who are at least 18 years of age were eligible to be randomized into the study if they had an ischemic cerebrovascular accident (CVA) which is TIA or stroke within three months prior to randomization. The neurological and general clinical condition of the patient was to be established before entry into the study. Baseline evaluations were recorded before study entry, with nine efficacy evaluations scheduled at months 1, 2, 6, 9, 12, 15, 18, 21, and 24.

Study Endpoints:

The protocol identified two primary and four secondary efficacy parameters.

Efficacy:

Primary Endpoints:

The two (specified in the protocol, page 199, volume 116)) primary efficacy parameters were (1) first stroke (fatal or non-fatal) as confirmed by the Morbidity and Mortality assessment group (MMAG), and (2) all cause mortality with MMAG review of the cause of the death.

However, it was mentioned in the clinical trial report (page 19, volume 116) that a third primary endpoint stroke and/or death would be used. This represents a composite endpoint in which the first event was either stroke or death (for any cause). In order to avoid that the same patient was counted twice, only the first event that occurred was taken into consideration for the survival curve analysis.

It is to be noted here that the sample size was estimated using the composite endpoint, although it was not explicitly mentioned in the protocol. According to a teleconference with the sponsor on April 13, 1999, it was revealed that the trial statistician identified the composite endpoint as the primary endpoint although the trial clinicians identified the first two as the primary endpoints.
In addition, it was revealed in the teleconference that the third endpoint (composite endpoint) had come into primary consideration in the NDA submission after Aspirin (50 mg once a day) was included in FDA guidelines for prevention of non-fatal stroke and death.

The MMAG was responsible for insuring consistency of the primary and secondary endpoints with the exception of TIA. The MMAG reviewed endpoints on a blinded basis, and formulated guidelines in order to enhance the consistency in reporting.

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Secondary Endpoints:

The MMAG also reviewed the secondary efficacy endpoints of (1) myocardial infarction (MI) (2) other vascular events (which consists of pulmonary embolism, deep venous thrombosis, periphoral arterial occlision, or retinal vascular accident), (3) TIA (which was not reviewed by the MMAG), and (4) ischemic events (which comprised MMAG-reviewed stroke, MI, or sudden death).

The sponsor defined and analyzed many additional composite and cause-specific efficacy parameters have been defined and analyzed. These include. for example, fatal stroke, stroke or death, non-fatal stroke, and vascular death.

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Safety:

The safety assessments of ESPS2 consisted of the following events:
1) Adverse events;
2) Laboratory Assessments;
3) Blood Pressure Assessments.

The components of adverse events were described in the Appendix (Table A.1.1).

The laboratory examinations were performed at Baseline, months 12. and 24.
The following laboratory parameters were measured: leucicytes, erythrocytes, platelets, hematocrit, hemoglabin, erthrocyte sedimentation rate, BUN, creatinine, Uric Acid, Fasting glucose, cholesterol LDL, and liver function test. Laboratory data summarized by presenting the change from baseline values at Months 12 and 24.

Blood pressure measurements were recorded at Baseline, Months 1, 3, 6, 9, 12, 15, 18, 21, and 24. The change from baseline values at each visit and incidence of clinically notable values were presented.

Randomization and Sample Size Determination:

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Randomization:

Study patients were centrally randomized (see Table 1.1) by the EORTC (European Organization from Research and Treatment of Cancer) Data Center. The approach for treatment allocation was based on minimizing treatment imbalance in age group, gender,

center, and type of qualifying event (stroke or TIA). Patients were randomized to one of four parallel treatment arms – dipyridamole extended release 200 mg b.i.d., aspirin 25 mg b.i.d., the combination (Aggrenox Extended Release b.i.d.), and placebo, according to a minimization algorithm (Pocock and Simon, 1975) that simultaneously balanced the treatment assignments across type of qualifying event (stroke or TIA), gender, age group (<60, >=60 and <70, >= 70 years) and study center.

Sample Size Determination:

Initially a total of 5000 patients were planned. The sample size was estimated by computer simulation to detect an overall difference between treatment groups with 80% power at the two-sided 5% significance level. It was assumed that the best treatment would reduce the hazard rate of first stroke or death by 30-35% compared with placebo (reduction in hazard is defined as 1 - hazard ratio, see Subsection 2.1 for the definition), and the intermediate treatments would reduce the hazard by half that amount. A single planned interim analysis was planned to consider early termination for efficacy and to recalculate (sample size recalculation was not specified in the protocol) the sample size. Treatment group labels were randomly permuted in the interim tables and figures to preserve blindness.

The statistical methodology enclosure to the ESPS2 protocol shows that the sample size of 1250 patients per treatment group was based on simulation of the following conditions: generalized Mantel - Haenszel test across the four treatment groups evaluated at three-month intervals; 90% survival on placebo at one year and 83% at two years, piece-wise exponential failure rates in each year; 33% lower hazard on the best treatment than on placebo, with hazards on the other two treatments half-way between; and a 34% drop-out rate over two years. One hundred replications of each configuration over a range of assumptions yielded approximately 4% standard error for the estimated 80% power at the two-sided 5% significance level for 1250 patients per treatment group. Note that the planned final analysis was the generalized Wilcoxon-Gehan test, not the generalized Mantel-Haenszel test: the simulation utilized the latter for computational simplicity.

Total sample size was re-estimated (which was not explicitly planned in the protocol) at the interim analysis in November 1991 and required 7000 patients. The interim analysis was planned in the protocol, but was conducted earlier than planned due to rapid recruitment. The computer simulation method used to derive the original estimate was applied to the interim event rate 20 to 25% risk reduction from 3994 patients followed for an average of 12 months; and the Steering Committee decided in May 1994 to exclude Center #2013 from further participation in the study and from the primary analysis due to scientific misconduct by that investigator.

Interim Analysis:

The protocol specified that a single interim analysis was foreseen (1) three years after the beginning of study or (2) when 1600 patients reach two years of follow up (whichever occurred earlier). The protocol also mentioned that the results of this interim analysis would be communicated to the Ethics Committee and might be the basis for a new assessment of rationale of the trial by the Steering Committee. However, the sponsor reported in Statistics Section of the NDA submission (page 306, volume 87) that one of purposes of the interim analysis was to re-evaluate the sample size assumptions in the protocol. However, the sponsor did not mention explicitly in the protocol that the sample size would be re-estimated after the interim analysis.

Due to rapid recruitment, the interim analysis was carried out in November 1991, a few months earlier than planned. It included data on 3,994 patients followed for an average of 12 months. This analysis preserved the "A-B-C-D" blinding of treatment by randomly assigning treatment labels in each figure and table. The sponsor claimed that the independent assignment with interim displays made it impossible to decode the efficacy results by comparing one display with other.

The interim results did not reach the protocol-specified stopping guideline of p-value $<=$ .001. The final analysis of the primary efficacy parameters was adjusted for this stopping guideline by testing alpha= .049 (= .050 - .001) significance level. This reviewer could not locate in the submission the results (p-value, etc) of the interim analysis and the exact method used to obtain alpha for the final analysis. Note that the proposed alpha (.049)for the final analysis is not what is proposed in the literature for adjustment for interim analysis yet it is close to correct p-value. However, the sponsor was requested on a teleconference (April 13, 1999) to submit the results of interim analysis.

The sample size was recalculated based on the interim event and treatment cessation rates. At their meeting on December 7, 1991, The Steering Committee approved the study statistician's proposal to increase the sample size from 5000 to 7000 patients.

Sponsor's Statistical Analyses Plans

As mentioned earlier, the ITT population consisted of all 6602 randomized patients after excluding the 438 patients from Center #2013 due to scientific misconduct at that center. All efficacy analyses were based on the ITT population. The primary efficacy parameters were also analyzed for all 7040 randomized patents, including those from Center #2013.

The study has two primary endpoints, namely stroke and death. A significant reduction in either (or both) would have counted as a successful conclusion, and therefore it is necessary to adjust for multiplicity. The adjustment for two primary efficacy endpoints was carried out

using the conservative Bonferroni-Holm multiple test procedure. This requires the statistical significance of both main effects at each stage of the step down procedure.

Because ESPS2 used a balanced 2 by 2 factorial design, the results could be adequately characterized by the main effects of DP and ASA provided that the DP by ASA interaction was non-significant. Significant interaction would indicate the effect of one treatment differed in the presence or absence of the other. In accordance with the protocol, the primary conclusions were based on the main effects of DP and ASA supplemented by pair-wise treatment comparisons. To demonstrate the efficacy of Aggrenox Extended Release, it was necessary to show the statistical significance for both the ASA and DP main effects.

For each primary efficacy parameter, the sponsor's (per protocol) primary comparisons are the factorial analysis comparisons, as planned in the protocol. That is, testing was carried out for the factorial analysis comparisons DP versus no DP (the DP main effect). ASA versus no ASA (the ASA main effect), and DP by ASA interaction.

In addition to factorial analyses (main effects and interaction), the sponsored performed the following five pair-wise treatment group comparisons :

DP +ASA versus DP alone;

DP+ ASA versus ASA alone;

DP + ASA versus placebo;

DP alone versus placebo; and

ASA alone versus placebo.

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All pair-wise treatment group comparison are considered supportive, with the comparisons between the combination and its components (DP+ASA versus DP alone and DP+ASA versus ASA alone) of greatest relevance to this application.

The sponsor originally wanted to apply multiplicity adjustments to the analyses of the primary efficacy parameters to maintain the experiment-wise Type 1 error rate at alpha=0.05 in view of two data analyses (interim and final) and two primary efficacy endpoints (stroke and death). To adjust for the interim analysis, in which the null hypothesis was tested using the protocol specified stopping guideline of the p-value < =0.001, the final analysis was tested at the alpha= .049 significance level. To adjust for two primary endpoints, the Bonferroni-Holm multiple test procedure (Mendenhall, 1981) was applied. This requires that both the DP and ASA main effects reach the alpha/2= .0245 significance level in order to demonstrate the efficacy of the combination on the more significant endpoint, after which the less significant endpoint can be tested at the alpha=.049 significance level. However, because re-estimation of

the sample size estimation the type I error may be inflated.

It is to be mentioned here that for the approval of a combination drug, it is required to show that the combination drug is significantly more effective than the components. Therefore, adjustments for multiple endpoints required for combination versus each component comparison separately. Furthermore, testing for the main effects of each drug is not required for the approval of a combination drug even in the absence of interaction. The significant main effects of two components when there is no interaction between two drugs do not always imply that the combination drug is significantly more effective than either components.

Summary of Sponsor's Analysis:

The following are the summaries of the sponsor's analysis:

(1) Factorial analysis of treatment main effects and interaction, supplemented by pair-wise treatment comparisons;

(2) Generalized Gehan-Wilcoxon survival analysis and Kaplan-Meier survival curves and risk reductions at two years as descriptive statistics (primary analysis);

(3) Interim efficacy tested at the planned 0.001 significance level, with no adjustment of the significance level for the final analysis (however, the sponsor mentioned that .049 error rate for final analysis would be used for original 5000 patients).

(4) Two primary endpoints with no adjustment of multiplicity for the final analysis using 6602 patients.

(5) The composite endpoint 'stroke and /or death' with no penalty of interim analysis for the final analysis using 6602 patients.

(6) Exploratory Cox analysis of prognostic factors;

and

(7) Descriptive Kaplan-Meier estimates (and corresponding risk reductions) at two years within relevant subgroups.

The primary analyses of the primary efficacy parameters and the composite endpoint are time to event analyses i.e. survival analyses. The time period for all survival analyses was 730 days after randomization, unless otherwise specified. All results are based on the ITT population of 6602 patients, unless otherwise specified. As planned in the protocol, the sponsor performed

the primary statistical test using the unstratified Gehan –Wilcoxon test. For supporting purpose, the sponsor also performed log-rank test. It should, however, be noted that the sample size for this study was determined using somewhat less powerful generalized Mantel-Haenszel test.

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2. Sponsor's and Reviewer's Analyses

The results of analyses of stroke, death, stroke or death, and subgroups have been reported in this section. These results do not reflect any type I error rate adjustment due to multiple endpoints and the increase in sample size at the interim look.

Section 2.1 presents the results of the analyses of the stroke data. Section 2.2 presents the results of analyses of the death data. Section 2.3 presents the results of the analyses stroke and/or death data. Section 2.4 presents the analyses with respect to category of stroke or death. Section 5 presents subgroup analyses for stroke and death data.

It is to be noted here that the analyses of main effects and interaction effects are not of primary interest for the approval of the combination drug. However, it is required to show that the combination drug is significantly more effective than both components.

2.1 Analysis of Stroke (reviewer's and sponsor's)

Analysis of Main and Interaction Effects:

This reviewer performed Gehan-Wilcoxon test (time to events), Log-rank test (time to events) and Fisher exact test for number of events for the stroke endpoint. The reviewer's time to event analyses was similar to those of the sponsor's. The reviewer's Fisher's exact test and Log-rank test was for supportive purpose only.

The sponsor's hazard reduction rates for factorial analysis were based on a proportional hazard model that included terms for all significant prognostic factors. A stepwise model selection (see 6) procedure was carried out in which terms for prognostic factors were added to an initial model containing the main effects of DP and ASA until no further significant improvement in fit was obtained.

Table 2.1 summarizes the time to events and number of events analyses for stroke. We see first whether there was DP X ASA interaction.

Table 2.1: First Strokes (fatal or no-fatal) as Confirmed by the MMAG for ESPS2 (Intent to Treat Population) for Main Effects

Treatment comparisons	Risk/hazard reduction at 730 days (sponsor's)	p-value (reviewer's)		K-M estimate of survival rate at 730 days (sponsor's)	Number (%) of Patients with Stroke				p-value (reviewer's)
		G-W	Log-rank		DP (n=3304)	no DP (n=3298)	ASA (n=3299)	no ASA (n=3303)	Fisher's exact
DP Vs no DP	19.3% / 22%	.0010	.0011	88.3% vs. 85.6%	368 (11.1%)	456 (13.8%)	363 (11.0%)	461 (14.0%)	.001
ASA Vs no ASA	21.0 % / 25%	.0001	.0001	88.5% vs. 85.4%					.0003
DP X ASA Interaction	-	.8501	.8606						

Note: G-W: Gehan-Wilcoxon test for detecting a difference in the survival experience of the two groups; Log-rank: Log-rank test for detecting a difference in the survival experience of the two groups;
K-M: Kaplan-Meier

It can be seen from the p-value column that there was non-significant DP by ASA interaction. Therefore, the components are additive. Note that the non-significant interaction is not a requirement for the study of combination of drugs. Both DP and ASA were significantly effective in reducing secondary stroke as evidenced by p-values of both G-W and Log-rank tests. The Fisher's exact test (based on the number of events) agrees with those from G-W and Log-rank tests.

Descriptive measures such as risk reduction (RR), hazard reduction (HR) and percentage of strokes showed that both DP and ASA were beneficial in strokes.

(Note that the risk reduction (%) at the end of time interval (t) for treatment 1 versus treatment 2 is defined as follows:

$$RR\%(t) = 100 \times [S_1(t) - S_2(t)]/[1 - S_2(t)]$$

where $S_1(t)$ and $S_2(t)$ represent "survival" at time (t) for patients under treatment 1 and 2 respectively.

The hazard reduction at the end of the time interval for treatment 1 versus treatment 2 is defined as:

$$HR\%(t) = 100 \times [1 - h_1(t) / h_2(t)].)$$

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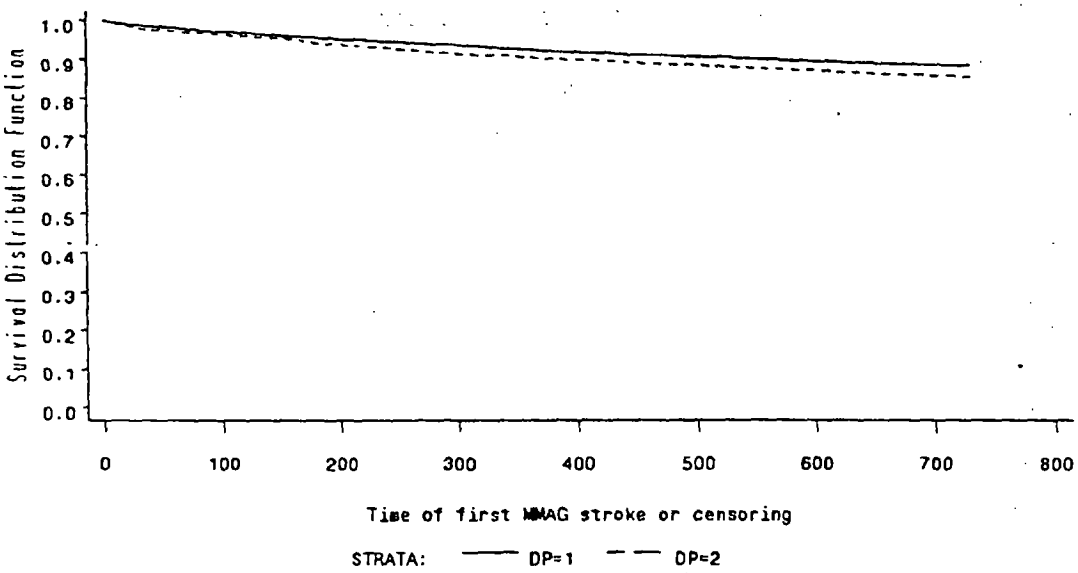
Both risk reduction and hazard reduction are relative measures. One may also consider an alternative measure to RR%(t) which is the survival rate increase (SRI) for treatment 1 relative to treatment 2 as follows:

$$SRI\%(t) = 100 \times [S_1(t) - S_2(t)] / [S_2(t)].$$

Note that the survival rate increase for DP relative to No DP at 730 days is 3.15% where as the survival rate increase for ASA relative to no ASA is 3.62%.

In Figure 1 we compare the survival curves of DP and No DP treated groups.

Figure 1 (reviewer's): Survival Curve of stroke for DP and No DP



Note: DP=1: Dipyridamole; DP=2: No Dipyridamole

The survival curve of the DP treated group is superior (statistically significantly) than that of No DP treated group which indicates that DP is superior to No DP in reducing stroke.

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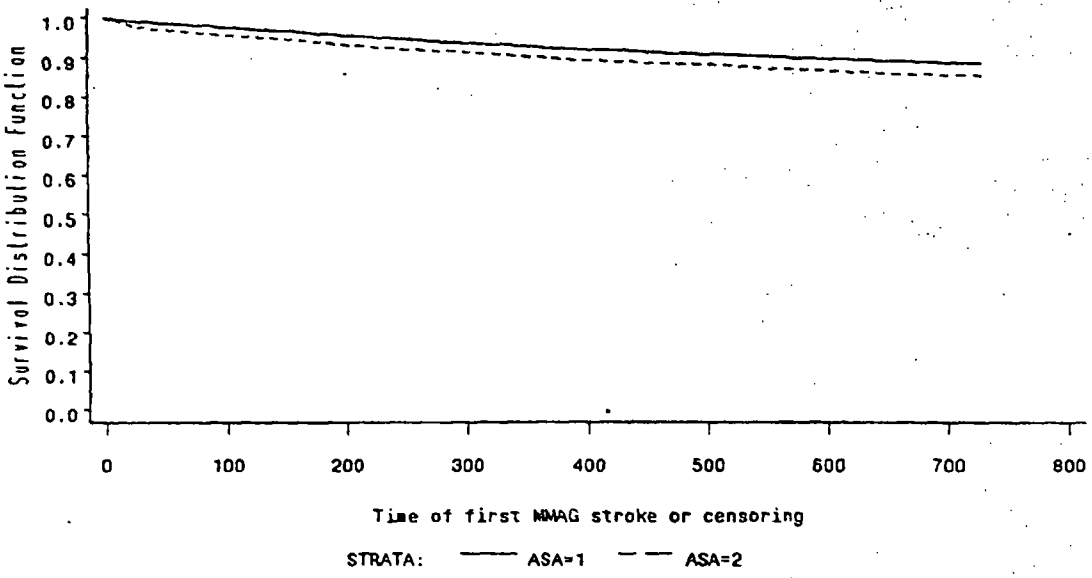
In Figure 2 we compare the survival curves of ASA and No ASA treated groups.

Figure 2 (reviewer's): Survival Curve of stroke for ASA and No ASA



Note: ASA=1: Acetylsalicyclic Acid; ASA=2: No Acetylsalicyclic Acid

The survival curve of the ASA treated group is significantly higher than that of No ASA treated group which indicates that ASA is more effective in reducing stroke.

Randomized Patient Population

The results of the analyses (DP vs. No DP comparison of G-W test's p-value=.0009; ASA vs. No ASA comparison of G-W test's p-value=.0001) of first stroke for the randomized patient population were consistent with the results of the primary analysis of first stroke for the ITT population.

Worst Case Analysis (ITT Population)

This reviewer also performed worst case analyses of stroke. The 860 strokes included in the worst case analyses of first stroke comprised the 824 first MMAG confirmed strokes included

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in the primary analyses of strokes, 28 strokes imputed at the time of lost to follow up and eight investigator diagnosed stroked not reviewed by MMAG. The results of the analyses (DP vs. No DP comparison of G-W test's p-value=.0015, ASA vs. no ASA comparison of G-W test's p-value=.0003) of first stroke were consistent with the results of the primary analysis of first stroke for the ITT population and the randomized population.

First 5002 Patients

Table A.2 (Appendix) summarizes the results of the analyses of first 5002 patients. DP (ASA) was significantly more effective than No DP (No ASA) in reducing strokes in the first 5002 enrolled patients. Note that the patients from center # 2013 were excluded from these 5002 patients.

Individual Treatment Combination

This reviewer performed Gehan-Wilcoxon test (time to events), log-rank test (time to events) and Fisher exact test (using number of events). The reviewer's time to event analyses were similar to those of the sponsor's. The reviewer's Fisher's exact test was for supportive purpose only.

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Table 2.2 summarizes time to event and number of events analyses for stroke corresponding to individual treatment combination.

Table 2.2: First Strokes (fatal or Non-fatal) as Confirmed by the MMAG for ESPS - 2 for Individual Treatment Combination (ITT Population)

Treatment Comparisons	Risk/hazard Reduction at 730 days (sponsor's)	p-value (reviewer's)		K-M Estimate of survival rate at 730 days (%)	Number (%) of Patients with the Event				p-value (reviewer's)
		G-H	Log-rank		DP/ASA (n=1650)	DP (n=1654)	ASA (n=1649)	Placebo (n=1649)	Fisher's
DP/ASA Vs DP	24.7 % / 27 %	.0019	.0029	89.9 vs. 86.7	157 (9.5%)	211 (12.8%)	206 (12.5%)	250 (15.2%)	.003
DP/ASA Vs ASA	23.1 % / 25 %	.0081	.0096	89.9 vs. 87.1					.006
DP/ASA Vs Placebo	37.0 % / 42%	.0001	.0001	89.9 vs. 84.1					< .0001
ASA Vs Placebo	18.86 % / 23%	.0093	.0124	87.1 vs. 84.1					.030
DP Vs Placebo	16.35/19	.0363	.0369	86.7 vs. 84.1					.050

Note: G-W: Gehan-Wilcoxon test for detecting a difference in the survival experience of the two groups; Log-rank: Log-rank test for detecting a difference in the survival experience of the two groups;
K-M: Kaplan-Meier

It can be seen from the above table that Aggrenox was significantly more effective than placebo in reducing the number of strokes. In addition, Aggrenox was significanly more effective than either component in reducing strokes. Even we perform multiplicity adjustments for the primary (two or three) endpoints within each comparison, the conclusions do not change.

Note that the survival rate increase for Aggrenox relative to DP alone at 730 days is 3.69% where as the survival rate for Aggrenox relative to ASA alone is 3.21%. However. survival rate increase for Aggrenox relative to placebo alone at 730 days is 6.89%.

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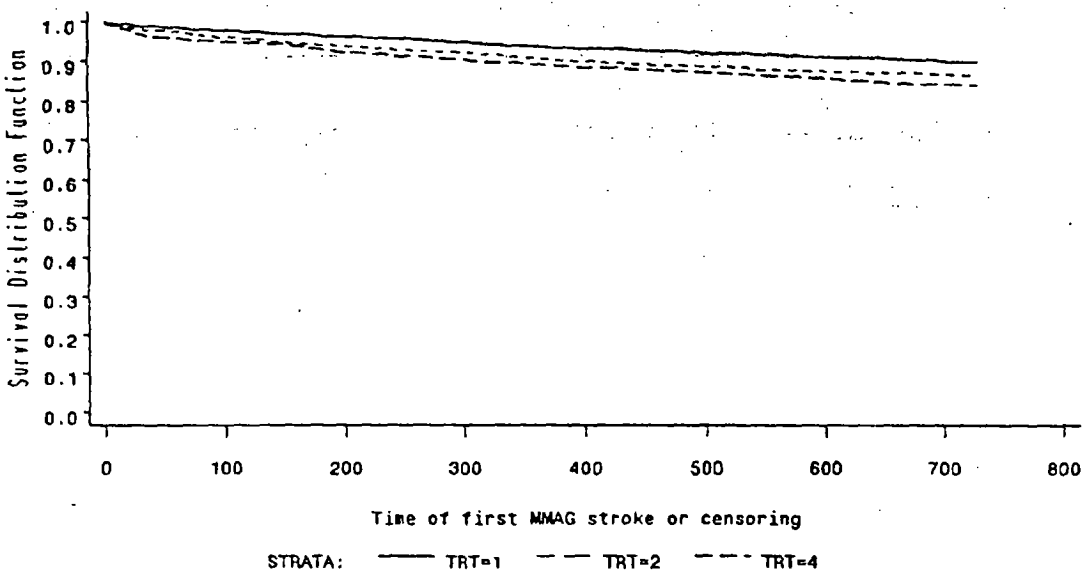
In Figure 3 we compare the survival curves of DP +ASA, DP and placebo treated groups for stroke.

Figure 3 (reviewer's): Survival Curves of stroke for DP+ASA, DP and Placebo



Note: TRT=1:DP+ASA (top); TRT=2: Dipyridamole (middle); TRT=3: Placebo (bottom)

The survival curve for DP+ASA is superior (statistically significant) to those of placebo and DP which indicating that Aggrenox is superior to both DP and placebo in reducing stroke (p-value=.0001 for homogeneity of all three survival curves).

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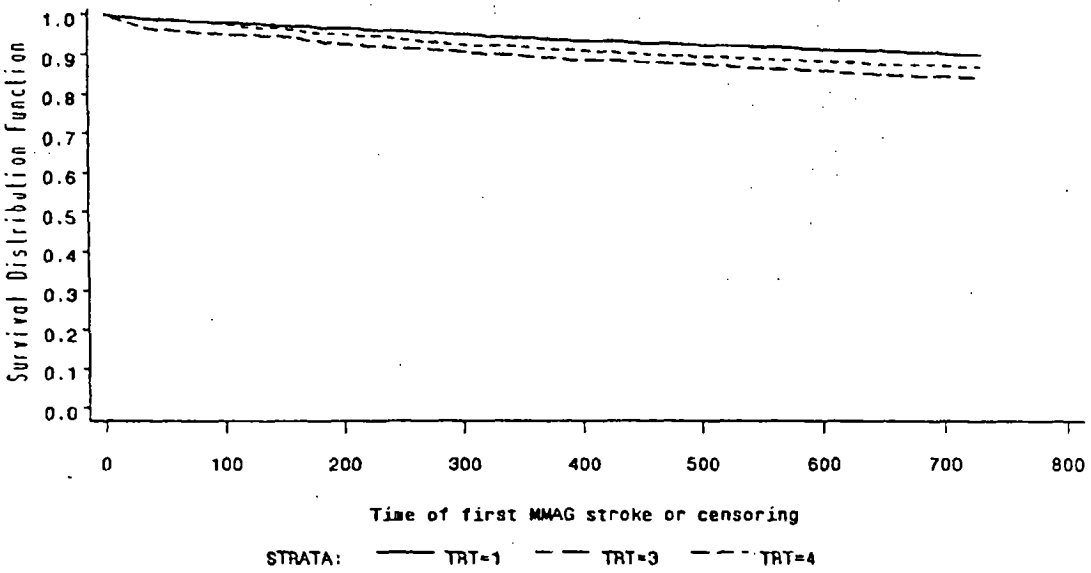
In Figure 4 we compare the survival curves of DP +ASA, DP and placebo treated groups for stroke.

Figure 4 (reviewer's): Survival Curves of stroke for DP+ASA, ASA and Placebo



Note: TRT=1:DP+ASA (top); TRT=3: ASA (middle); TRT=4: Placebo (bottom)

The survival curve for DP+ASA treated group is superior (statistically significant) than those of placebo and ASA indicating that Aggrenox is superior to both ASA and placebo (p-value=.0001 for the homogeneity of all three curves).

Randomized Population

This reviewer performed the analysis of stroke for the randomized patient population. The results of the analyses (DP/ASA vs. DP comparison of G-W test's p-value = .0018. DP/ASA vs. ASA comparison of G-W test's p-value=.0077, DP/ASA vs. Placebo comparison of G-W test's p-value=.0001, DP vs. Placebo comparison of G-W test's p-value=.0352. and ASA vs. Placebo comparison of G-W test's p-value=.0093) of first stroke for the randomized patient population were consistent with the results of the primary analysis of first stroke for the ITT population.

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Worst Case Analysis (ITT Population):

This reviewer also performed the worst case analyses of first for individual treatment combination. The 860 strokes included in the worst case analyses of first stroke comprised the 824 first MMAG confirmed strokes included in the primary analyses of strokes, 28 strokes imputed at the time of lost to follow up and eight investigator diagnosed stroked not reviewed by MMAG. The results of the analyses (DP/ASA vs. DP comparison of G-W test's p-value=.0062, DP/ASA vs. ASA comparison of G-W test's p-value=.0159, DP/ASA vs. Placebo comparison of G-W test's p-value=.0001, DP vs. Placebo comparison of G-W test's p-value=.0344, and ASA vs. Placebo comparison of G-W test's p-value=.0152) of first stroke were consistent with the results of the primary analysis of first stroke for the ITT population and the randomized population.

First 5002 patient population

Table A.3 (Appendix) summarizes the results for the first 5002 patient population.
It can be seen that Aggrenox was significantly more effective than DP, ASA and placebo in reducing strokes. However, Both DP and ASA were not significantly effective in reducing strokes.

2.2 Analysis of Death (reviewer's /sponsor's):

Main and Interaction Effects

Table 2.3 summarizes time to events and number of events analyses for death. It is required to know first whether there was DP X ASA interaction.

Table 2.3: Deaths as Confirmed by the MMAG for ESPS - 2 (Intent to Treat Population) for Main Effects

Treatment Comparisons	Risk /hazard reduction at 730 days (sponsor's)	p-value (reviewer's)		K-M estimate of survival rate at 730 days	Number (%) of Patients with the Event				p-value (reviewer's)
		G-W	Log-rank		DP (n=3304)	No DP (n=3298)	ASA (n=3299)	No ASA (n=3303)	Fisher's
DP Vs no DP	3.1% / 6%	.7252	.6849	88.7% vs. 88.3%	375 (11.3%)	386 (11.7%)	368 (11.2%)	393 (11.9%)	.672
ASA Vs no ASA	5.8%/ 12%	.2390	.2796	88.8% vs. 88.2%					.355
DP X ASA Interaction		.4201	.4380						

Note: G-W: Gehan-Wilcoxon test for detecting a difference in the survival experience of the two groups;
Log-rank: Log-rank test for detecting a difference in the survival experience of the two groups:
K-M: Kaplan-Meier

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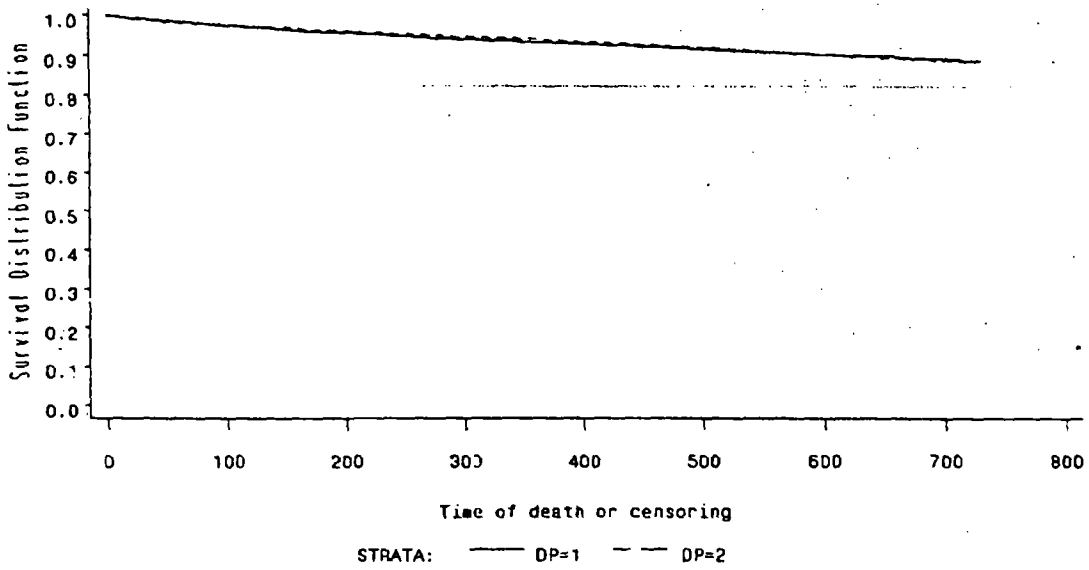
It can be seen that there was no DP by ASA interaction. Both DP and ASA were not significantly effective in reducing death.

Note that the survival rate increase for DP relative to no DP at 730 days is .453% where as the survival rate for ASA relative to no ASA alone is .58%.

In Figure 5 we compare the survival curves of DP and No DP treated groups for death.

Figure 5 (reviewer's): Survival Curves of death for DP and No DP



Note: DP=1: Dipyridamole ; DP=2: No Dipyridamole

It can be seen that the survival curve of the DP treated group and No DP treated group were not distinguishable. Thus there is no significant difference between the DP treated group and No DP treated group with respect to the prevention of death.

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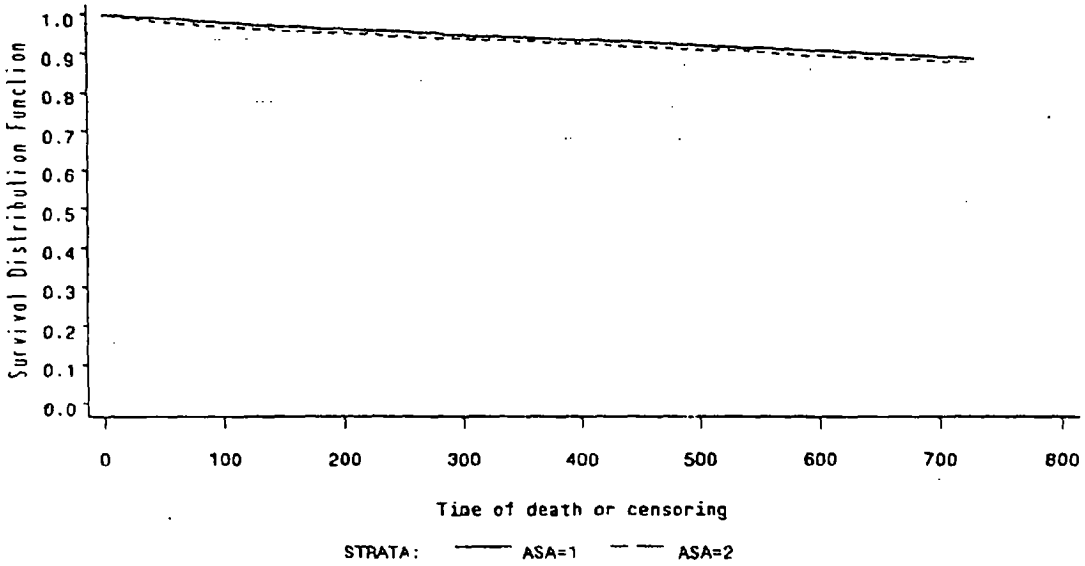
In Figure 6 we compare the survival curves of DP and No DP treated groups for death.

Figure 6 (reviewer's): Survival Curves of death for ASA and No ASA



Note: ASA=1: Acetylsalicyclic Acid; ASA=2: No Acetylsalicyclic Acid

It can be seen that the survival curve of the ASA treated group and No ASA treated group were almost coincident . There is no significant difference between the ASA treated group and No ASA treated group with respect to the prevention of death.

Randomized patient Population

The results of the analyses (DP vs. No DP comparison of G-W test's p-value=.7271; ASA vs. No ASA comparison of G-W test's p-value=.1056) of death for the randomized patient population are consistent with the results of the primary analysis of death for the ITT population.

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Worst Case Analysis

This reviewer also performed worst case analyses of death. The 782 deaths included in the worst case analyses of first stroke comprise the 761 deaths included in the primary analyses of patient survival, 15 deaths imputed at the time of lost to follow up and six deaths within two years discovered during the special investigation. The results of the analyses (DP vs. No DP comparison of G-W test's p-value=.6280, ASA vs. no ASA comparison of G-W test's p-value=.2012) of death were consistent with the results of the primary analysis of first stroke for the ITT population and the randomized population.

First 5002 Patient Population:

Table A.4 (Appendix) describes the results for the first 5002 enrolled patients.
It can be seen that DP (ASA) was not significantly more effective than No DP (No ASA) in reducing deaths in first 5002 patients.

Individual Treatment Combinations:

In the following table we summarize time to event and number of events analyses for death corresponding to individual treatment combination.

Table 2.4: Deaths as Confirmed by the MMAG for ESPS2 for Individual Treatment Combination (ITT Population)

Treatment Comparisons	Risk /hazard reduction At 730 days (sponsor's)	p-value (reviewer's)		K-M Estimate of survival rate at 730 days (%) (sponsor's)	Number (%) of Patients with the Event				p-value (reviewer's)
		G-W	Log-rank		DP/ASA (n=1650)	DP (n=1654)	ASA (n=1649)	Placebo (n=1649)	Fisher's
DP/ASA Vs DP	1.3% / 4%	.7911	.8280	88.7 vs. 88.5	186 (11.3%)	189 (11.4%)	182 11.0%)	204 (12.4%)	.913
DP/ASA Vs ASA	-2.7% / -2%	.7438	.7903	88.7 vs. 88.9					.868
DP/ASA Vs Placebo	8.5% / 17%	.2849	.2979	88.7 vs. 87.6					.352
ASA Vs Placebo	10.9% /17%	.1617	.1907	88.9 vs. 87.6					.255
DP Vs Placebo	7.3% / 12%	.4212	.4102	88.5 vs. 87.6					.420

Note: G-W: Gehan-Wilcoxon test for detecting a difference in the survival experience of the two groups;
Log-rank: Log-rank test for detecting a difference in the survival experience of the two groups;
K-M: Kaplan-Meier

It can be seen from the above table that Aggrenox was not significantly more effective than placebo in reducing the number of secondary strokes. In addition, Aggrenox was not significantly more effective than either component in reducing number of secondary strokes. Even we perform multiplicity adjustments for primary (two or three) endpoints within each

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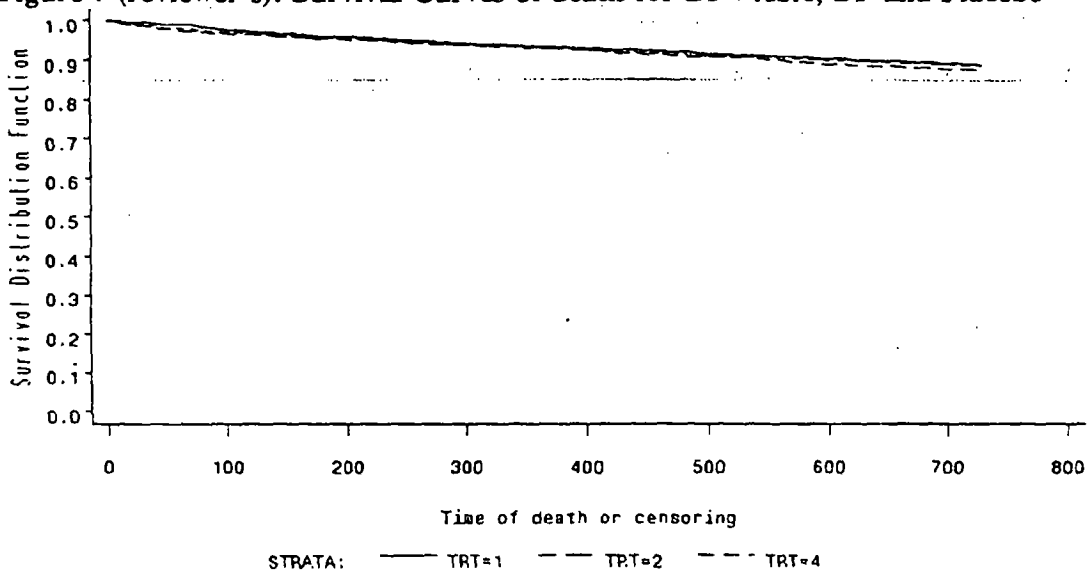
comparison, the conclusions do not change.

Note that the survival rate increase for Aggrenox relative to DP alone at 730 days is .226 % where as the survival rate for Aggrenox relative to ASA alone is -.225%. However, survival rate increase for Aggrenox relative to placebo alone at 730 days is 1.25%.

In Figure 7, we compare the survival curves for Aggrenox, DP and placebo.

Figure 7 (reviewer's): Survival Curves of death for DP+ASA, DP and Placebo



Note: TRT=1:DP+ASA (top); TRT=2: DP (middle); TRT=4: Placebo (bottom)

It can be seen that all three survival curves are almost coincident which shows also that Aggrenox was not different from both placebo and DP (p-value=.5340 for the homogeneity of all three curves) in prevention of death.

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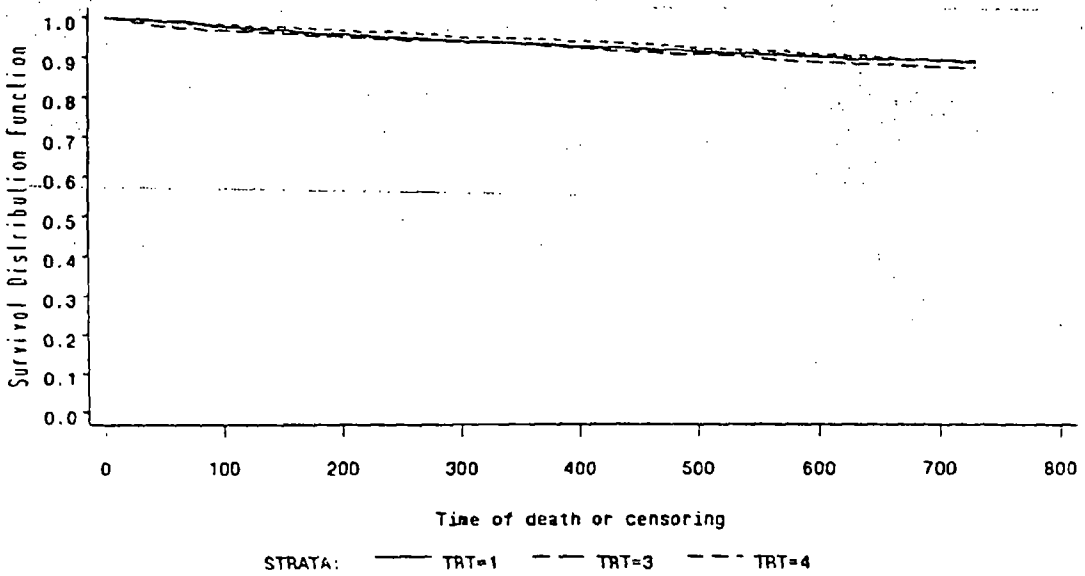
In Figure 8, we compare the survival curves for Aggrenox, ASA and placebo.

Figure 8 (reviewer's): Survival Curves of Death for DP+ASA, ASA and Placebo



Note: TRT=1:DP+ASA (top); TRT=3: ASA (middle) ; TRT=4: Placebo (bottom)

The survival curve of Aggrenox is not much higher than those of ASA and placebo indicating also that Aggrenox was not different from both ASA and placebo (p-value=.3375 for the homogeneity of all three curves) in prevention of death.

Randomized Patient Population:

The results of the analyses (DP/ASA vs. DP comparison of G-W test's p-value=.6281, DP/ASA vs. ASA comparison of G-W test's p-value=.6697, DP/ASA vs. Placebo comparison of G-W test's p-value=.1694, DP vs. Placebo comparison of G-W test's p-value=.3743, and ASA vs. Placebo comparison of G-W test's p-value=.0716) of death for the randomized patient population were consistent with the results of the primary analysis of death for the ITT population.

Worst Case Analysis (ITT Population):

This reviewer also performed the worst case analyses of death for individual treatment combination. The results of the analyses (DP/ASA vs. DP comparison of G-W test's p-value= .6826, DP/ASA vs. ASA comparison of G-W test's p-value= .8739, DP/ASA vs. Placebo comparison of G-W test's p-value=.2171, DP vs. Placebo comparison of G-W test's p-value=.4085, and ASA vs. Placebo comparison of G-W test's p-value=.1637) of death were

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consistent with the results of the primary analysis of death for the ITT population and the randomized population.

First 5002 Population:

Table A.5 (Appendix) summarizes the results from first 5002 patients. It can be seen that none of the drugs was significantly effective in reducing deaths in first 5002 enrolled patients.

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2.3 Analysis Based on the Composite Endpoint 'First Strokes (fatal or non-fatal) and /or Deaths' (reviewer's and sponsor's)

The composite endpoint 'First Strokes (fatal or non-fatal) and /or Deaths' is defined as stroke or death. Table 2.5 summarizes p-values of the factorial analysis comparisons and pair-wise independent group comparison for the composite endpoint stroke and/or death.

Table 2.5: First Strokes (fatal or non-fatal) and /or Deaths as Confirmed by the MMAG for ESPS2 for Main Effects, Interaction Effect and Individual Treatment Comparison (ITT Population)

Comparisons	Gehan-Wilcoxon Test p-value (reviewer's)	Log-rank Test p-value (reviewer's)	Fisher's Exact Test (for # of events) p-value (reviewer's)	Risk reduction at 730 days (sponsor's)	K-M estimate of Survival rate at 730 days(sponsor's)	Event Rate (reviewer's)
Factorial Comparison:						
DP vs. No DP	.0026	.0023	.0017	14.0%	81.4 vs. 78.3	18.4 vs. 21.5
ASA vs. No ASA	.0019	.0040	.0097	12.2%	81.1 vs. 78.5	18.7 vs. 21.3
DP X ASA Interaction	.5044	.5230				
Pair-wise Treatment Comparison:						
DP/ASA vs. DP	.0785	.104	.127	10.3%	82.4 vs. 80.3	17.4% vs. 19.5%
DP/ASA vs. ASA	.0837	.078	.055	12.1%	82.4 vs. 79.9	17.4% vs. 19.5%
DP/ASA vs. Placebo	< .001	< .001	< .001	24.4%	82.4 vs. 76.7	17.4% vs 23.0 %
DP vs. Placebo	.0119	.0112	.038	15.7%	80.3 vs. 76.7	19.5% vs. 23%
ASA vs. Placebo	.0089	.0147	.038	13.9%	79.9 vs. 76.7	20% vs 23%

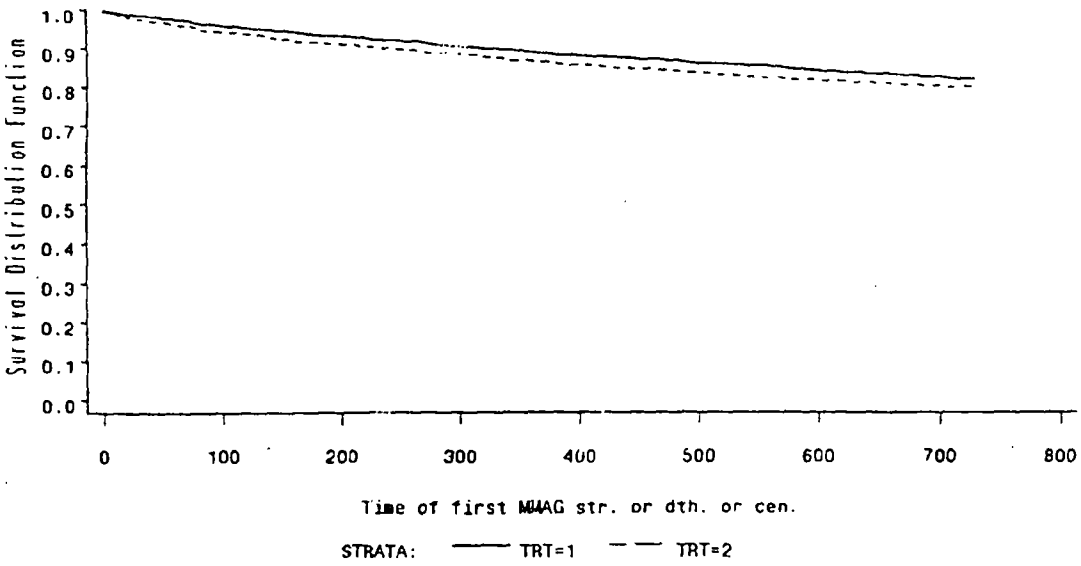
Note: G-W: Gehan-Wilcoxon test for detecting a difference in the survival experience of the two groups; Log-rank: Log-rank test for detecting a difference in the survival experience of the two groups; K-M: Kaplan-Meier

There are significant differences between a) ASA and no ASA treated groups and b) DP and no DP treated groups when the two primary endpoints (stroke and death) are combined. Also there is no interaction between DP and ASA. Therefore both DP and ASA were significantly more effective than placebo.

Note that the survival rate increase for Aggrenox relative to DP alone at 730 days is 2.615% where as the survival rate for Aggrenox relative to ASA alone is 3.13%. However, survival rate increase for Aggrenox relative to placebo alone at 730 days is 7.43%.

Although DP/ASA is significantly more effective than placebo, it is not significantly (see Figures 9 and 10) better than either components when the two primary endpoints (stroke and/or death) are combined. It is to be noted that in order to a combination drug to be effective, it must be significantly more effective than either component. Even we perform multiplicity adjustments for primary (three) endpoints within each comparison, the conclusions do not change; however, it should be noted here that the adjusted p-values for both comparisons (Aggrenox vs. DP and Aggrenox vs. ASA) would be doubled.

Figure 9 (reviewer's): Survival Curves of Stroke or Death for DP/ASA vs. DP



Note: TRT 1: DP/ASA; TRT=2: DP

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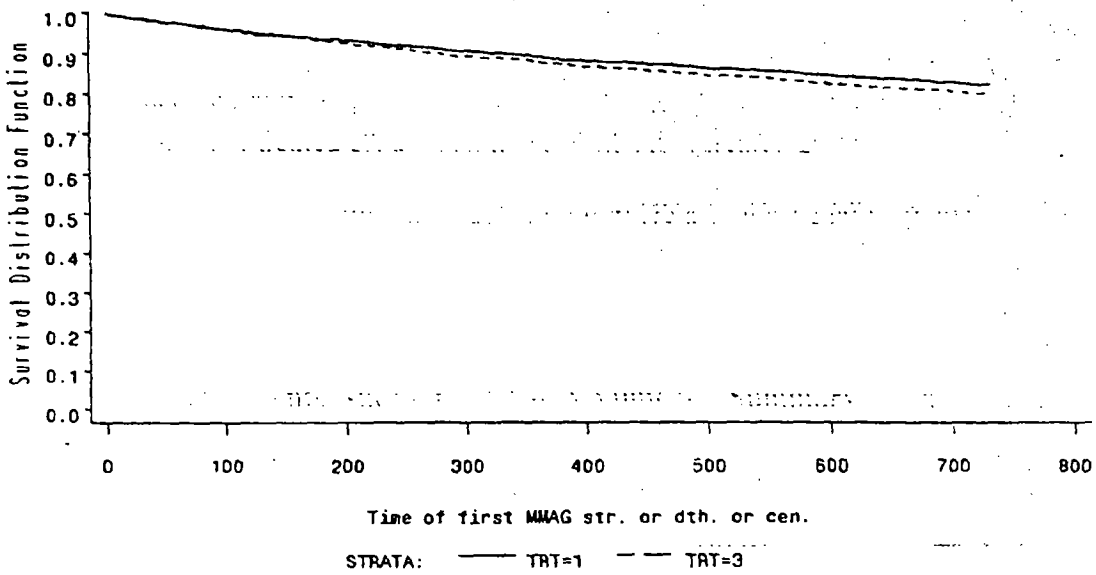
Figure 10 (reviewer's): Survival Curves of Stroke or Death for DP/ASA vs. ASA



Note: TRT 1: DP/ASA; TRT=2: ASA

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2.4 Catregory of Stroke or Death (reviewer's)

Table 2.6 describes the p-values of the factorial analysis comparisons by category of stroke or death.

Table 2.6: Summary of Category of Stroke or Death as Confirmed by the MMAG for ESPS2 for Main Effects (Intent to Treat Population)

Category of Stroke or Death:	Events (%) for Factorial Analysis (reviewer's)				p-value (reviewer's) (Fisher's exact)	
	DP (n=3304)	No DP (n=3298)	ASA (n=3299)	No ASA (n=3303)	DP vs. No DP	ASA vs. No ASA
Fatal First Stroke	74 (2.2%)	73 (2.2%)	67 (2.0%)	80 (2.4%)	1.0	.317
Non-fatal First Stroke and later died due to fatal stroke	20 (.6%)	9 (.3%)	10 (.3%)	19 (.6%)	.061	.135
Non-fatal First Stroke and later died due to cause other than stroke	40 (1.2%)	50 (1.5%)	37 (1.1%)	53 (1.6%)	.291	.111
Death due to cause other than stroke and previous nonfatal stroke	241 (7.3%)	254 (7.7%)	254 (7.7%)	241 (7.3%)	.544	.544
Non-fatal first stroke and never died	234 (7.1%)	324 (9.8%)	249 (7.5%)	309 (9.4%)	<.0001	<.0001
Total	609 (18.4%)	710 (21.5%)	617 (18.7%)	702 (21.3%)		

It can be seen that neither DP nor ASA are significantly effective in reducing fatal strike.

Table 2.7 describes the p-values of the pair-wise independent group comparison by category of stroke or death.

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Table 2.7: Summary of Catregory of Stroke or Death as Confirmed by the MMAG for ESPS2 for Individual Treatment Comparison (Intent to Treat Population)

Category of Stroke or Death:	Events (%) for Individual Treatment (reviewer's's)				p-value (reviewer's) (Fisher's exact)				
	DP/ASA (n=1650)	DP (n=1654)	ASA (n=1649)	Placebo (1649)	DP/ASA vs. DP	DP/ASA vs. ASA	DP/ASA vs. Placebo	DP vs. Placebo	ASA vs. Placebo
Fatal First Stroke	31 (1.9%)	43 (2.6%)	36 (2.2%)	37 (2.2%)	.196	.540	.466	.572	1.0
Non-fatal First Stroke and later died due to fatal stroke	7 (.4%)	13 (.8%)	3 (.2%)	6 (.4%)	.262	.343	1.0	.166	.507
Non-fatal First Stroke and later died due to cause other than stroke	18 (1.1%)	22 (1.3%)	19 (1.2%)	31 1.9%)	.634	.871	.063	.216	.116
Death due to cause other than stroke and previous nonfatal stroke	130 (7.9%)	111 (6.7%)	124 (7.5%)	130 (7.9%)	.204	.744	1.0	.204	.744
Non-fatal first stroke and never died	101 (6.1%)	133 (8.0%)	148 (9.0%)	176 (10.7%)	.035	.0019	<.0001	.01	.114
Total	287 (17.4)	322 (19.5%)	330 (20.0%)	380 (23.0%)					

It can be seen that neither Aggrenox nor DP alone or ASA alone was significantly effective in preventing fatal stroke. .

2.5 Subgroup Analyses (sponsor's/reviewer's)

Main Effects

In the following we describe drug versus subgroup analyses for factorial analysis.

Note that the p-values (sponsor's) for subgroup by main effect interactions were based on a proportional hazard model with terms for the main effect, subgroup, and subgroup by main effect interactions. The categories in the subgroups were modeled as unordered categorical variables.

This reviewer performed Gehan-Wilcoxon test for each component of subgroups. The results were summarized in Tables A.6 - A.11 in the Appendix.

Gender:

The sponsor's analyses results indicated that there was no evidence of treatment-by-gender interaction for the primary endpoints indicating that the treatment effects were consistent for both males and females.

This reviewer's gender analysis (see Table A.6) showed that both DP and ASA are significantly effective in reducing secondary strokes in both male and female patients. However, only ASA is significantly effective in reducing death in the female patient population.

Age-group:

The sponsor's age-group analysis results showed no evidence of a treatment by age interaction for both primary endpoints when patients were classified into five age-groups (<= 54, 55 to 64 years, 65 to 74 years, 75 to 84 years, and greater than or equal to 85) indicating that the treatment effects were consistent across the age group.

This reviewer's age-group analyses (see Table A.7) showed that both DP and ASA were effective in reducing stroke for the patients who were between 65 to 85 years old. However, both DP and ASA were not significantly effective in reducing deaths in any age group.

Geographical Region:

The sponsor's analysis results showed no evidence of a treatment by age interaction for both primary endpoints when patients were classified into four geographical regions indicating that the treatment effects were consistent across the regions.

This reviewer's analysis results (see A.8) by geographical region showed that DP was effective in reducing stroke in patients who were from Northern Europe where as ASA was effective in reducing strokes in patients who were from Scandinavia and Southern Europe. However. both DP and ASA were not effective in reducing death in any region.

Smokers:

The sponsors analysis showed that there were no evidence of DP-by-smoking behavior interaction and ASA-by-smoking habit interaction for both secondary stroke and death suggesting that treatment effects were reasonably consistent across the three smoking habits.

This reviewer's analysis results (see Table A.9) by smoking behavior showed that ASA was effective in reducing strokes in all kinds of smoking habit patients whereas DP was effective in reducing deaths only currently smoking patient population. However, Both DP and ASA were not significantly effective in reducing deaths in any category.

Coffee Drinkers:

The sponsor's analysis showed that there were no evidence of DP-by-coffee consumption interaction and ASA-by-coffee consumption habits interaction for both secondary stroke and death suggesting that treatment effects were reasonably consistent between the two groups of coffee drinking patients.

This reviewer's analysis results (see Table A.10) showed that ASA was effective in reducing strokes in patients who drank at most 5 and more than cups a day whereas DP was effective in reducing deaths for only patients who drinks at most 5 cups a day. However, Both DP and ASA were not significantly effective in reducing deaths in any category.

Diabetes at Baseline:

The sponsor's analysis showed that there were no evidence of DP-by-diabetes (at baseline) interaction and ASA-by-diabetes (at baseline) interaction for both secondary stroke and death suggesting that treatment effects were reasonably consistent among the three groups of diabetes.

This reviewer's analysis results showed (see Table A.11) that ASA was significantly effective in reducing strokes in patients who were non-diabetic and non-insulin dependent diabetic whereas DP was effective only in non-diabetic patients. However, both DP and ASA were not significant in reducing deaths in any category.

Individual Treatment comparisons

The subgroup analyses for stroke and death corresponding to individual treatment combination (sponsor's and reviewer's) are summarized in the appendix (see Tables A.12–A.16).

Table A.18 summarizes the p-values of the G-W test for the treatment comparisons by region

3. Summary of Safety Analyses

Adverse Events:

Table 3.1 summarizes the patient's adverse events experiences for the factorial treatment groups.

Table 3.1: Safety Events (sponsor's Table 2.1.0, Volume 91) Summary by Main Effects (ITT Population)

Safety Parameter	DP (n=3304)	No DP (n=3298)	ASA (n=3299)	No ASA (n=3303)	p-value (reviewer's)	p-value (reviewer's)
					DP vs. No DP	ASA vs. No ASA
Total number of patients With at least one AE	2624 (79.4 %)	2627 (79.7%)	2642 (80.1%)	2609 (79.0%)	.831	.448
Gastro-Intestinal System Disorders	1413 (42.8%)	1221 (37.0%)	1342 (40.7%)	1292 (39.1%)	<.001	.200
Platelet, Bleeding and Clotting Disorders	203 (6.1%)	214 6.5%)	257 (7.8%)	160 (4.8%)	.578	<.001

Note: p-value (reviewer's) using the Fisher's exact test

There are no statistically significant differences between DP and No DP treated groups with respect to the number of patients with at least one adverse event, and platelet, bleeding and clotting disorders. However, there are significantly more (42.8% versus 37.0% with p-value < .001) gastrointestinal system disorder patients in DP treated group that that of no DP treated group.

There are no statistically significant differences between ASA and no ASA treated groups with respect to the number of patients with at least one adverse event, and gastrointestinal system disorders. There are more patients with at least one adverse events, gastrointestinal system disorders in the ASA treated group than those of no ASA treated groups.

In platelet, bleeding and clotting disorders group, there are significantly (statistically) more patients in the ASA treated group than those of no ASA treated groups.

In the following table we describe overall safety events summary by individual treatment groups.

Table 3.2 : Safety Events (sponsor's 2.1.0, Volume 91) Summary by Individual Treatment (ITT Population)

Safety Parameter	DP/ASA (n=1650)	DP (n=1654)	ASA (n=1649)	Placebo (n=1649)	p-value	p-value	p-value	p-value	p-value
					DP/ASA vs. DP	DP/ASA Vs. ASA	DP/ASA vs. Placebo	ASA vs. Placebo	DP vs. Placebo
Total number of patients With at least one AE	1319 (79.9%)	1305 (78.9%)	1323 (80.2%)	1304 (79.1%)	.465	.862	.546	.436	.932
Gastro-Intestinal System Disorders	721 (43.7%)	692 (41.8%)	621 (37.7%)	600 (36.4%)	.291	<.001	.<.001	.471	<.001
Platelet, Bleeding and Clotting Disorders	130 (7.9%)	73 (4.4%)	127 (7.7%)	87 (5.3%)	<.001	.897	.0031	.0057	.257

Note: p-value (reviewer's) using the Fisher's exact test

There are no significant differences between DP/ASA and DP, DP/ASA versus ASA, DP ASA and placebo, ASA and placebo, and DP and placebo with respect to number of patients with at least one adverse event and gastro-intestinal system disorders. However, there are more patients suffering from at least one adverse event and gastro-intestinal system disorders in DP/ASA treated group than those of the other groups.

Table A.19 in the Appendix summarizes the safety results by the remaining components of the adverse events.

Laboratory Assessments:

The sponsor reported that the results of the liver function test analyses suggested that exposure to dipyridomole and aspirin in combination or singularly had no significant or clinically meaningful effect on liver function tests.

The sponsor also reported that red blood cells indices for the main-effect composition of DP versus no DP underwent modest but statistically significant changes in mean values from baseline to study endpoint. Similarly, more patients in the DP+ASA and DP alone treatment group had shifted from high or normal values in red blood cell indices to low values at study endpoint. However, the incidence of clinically relevant and clinically notable values was comparable in the main effect comparison groups as was the incidence of anemia and bleeding level adverse events. Thus, the sponsor claimed that the statistically significant changes in red blood cell indices observed are unlikely to have clinically meaningful consequences.

Overall, the changes in kidney function tests from baseline to endpoint in all four analysis groups were small. Factorial analysis for mean from baseline to endpoint revealed the following:

a) A significant DP X ASA interaction with respect to BUN (blood urine nitrogen);
b) A significant effect of DP on creatinine;
c) A significant effect of DP on uric acid;

The sponsor reported that there were no significant mean changes from baseline for the main effect comparisons in fasting glucose, total cholesterol, and cholesterol LDL. Furthermore, for the analyses of shifts from baseline to endpoint, no statistically significant differences were observed for the main effect comparisons in any of the three parameters measured.

Blood Pressure Measurements:

The sponsor reported that no statistically significant differences for the main effect comparisons in either supine systolic or diastolic blood pressure results were observed. The sponsor also commented that these results suggest that exposure to dipyridamole and aspirin in combination or singularly has no effect on these two parameters.

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4. Conclusions:

4.1 Efficacy

4.1.1 Stroke (fatal and non-fatal):

Drug Components:

The analyses of efficacy data in study ESPS-2 showed that DP was significantly more effective than No DP (p-value =.001, Table 2.1) in reducing stroke (fatal or non-fatal). The analysis also showed that ASA was significantly more effective (p-value= .0001, Table 2.1) than no ASA in reducing stroke (fatal or non-fatal).

However, the analyses of efficacy data in study ESPS2 also showed that DP was not more effective (p-value 1.0, Table 2.6) than No DP in preventing first fatal stroke. The analysis also showed that ASA was not more effective (p-value = .317, Table 2.6) than No ASA in preventing first fatal stroke.

Therefore, the significance of both DP and ASA for preventing first stroke (fatal or non-fatal) appear to be due the contribution of non-fatal component of first stroke.

Drug Combination:

The analyses of efficacy data showed that Aggrenox was significantly more effective (p-value =.0019, see Table 2.2) than DP in reducing stroke (fatal or non-fatal). The data also showed that that Aggrenox was significantly more effective (p-value =.0081, see Table 2.2) than ASA in reducing stroke (fatal or non-fatal).

However, the analyses of efficacy data in study ESPS2 showed that Aggrenox was not more effective (see Table 2.7) than either component and placebo in preventing first fatal stroke. Therefore, the significant benefit of Aggrenox for preventing first stroke (fatal or non-fatal) appear to be due to contribution of the non-fatal component of first stroke.

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4.1.2 Death

Drug Components

The analyses of efficacy data in ESPS-2 showed that the components (DP and ASA) were not significantly more effective (p-value =.7252 for DP vs. No DP; p-value =.239 for ASA vs. No ASA ; see Table 2.3) in reducing deaths from all causes.

Drug Combination:

The analyses of efficacy data in study ESPS-2 showed that Aggrenox was not significantly more effective than either of the components and placebo in reducing deaths from all causes (p-value =.7911 for Aggrenox vs. DP; p-value =.7438 for Aggrenox vs ASA; p-value =.2849 for Aggrenox vs. placebo; see Table 2.4) in reducing deaths (all causes)

4.1.3 Composite Endpoint:

Because the composite endpoint "Stroke (fatal or non-fatal) and/ or Death " was not explicitly planned in the protocol, it is not clear to this reviewer that this outcome can be viewed as the primary outcome.

Drug Components

The efficacy data in study ESPS-2 showed that DP is significantly more effective (p-value =.0026, Table 2.5) than No DP in reducing stroke and/or death. The data also showed that ASA is significantly more effective (p-value .0019) than No ASA in reducing stroke and/or death.

Drug Combination:

The efficacy data in study ESPS-2 showed that Aggrenox was significantly more effective (p-value < .001, Table 2.5) than placebo in reducing stroke (fatal or non-fatal) and /or death. However, the data did not show that that Aggrenox was significantly more effective than DP alone (p-value = .0785) or ASA alone (p-value .0837) in reducing stroke (fatal or non-fatal) and or death. Therefore, Aggrenox (as a combination drug) cannot be considered effective for the composite parameter endpoint (stroke and/or death) because it was not statistically superior to either component.

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4.2 Safety:

DP vs. No DP

There are no significant differences between DP and No DP with respect to number of patients with at least one adverse events.(see Table 3.2). DP is significantly less safe than no DP (p-value < .001 Table 3.1) with respect to Gastro-Intestinal System Disorders

ASA vs. No ASA

There are no significant differences between ASA and No ASA with respect to number of patients with at least one adverse events.(see Table 3.1). ASA is significantly less safe than no ASA (p-value < .001 Table 3.2) with respect to platelet, bleeding and clotting disorders.

Drug Components

ASA alone is not significantly safer than placebo (p-value = .0057, Table 3.2) with respect to platelet, bleeding and clotting disorders.

DP alone is not significantly safer than placebo (p-value < .001) with respect to Gastro-Intestinal System Disorders.

Drug Combination vs. components

There are no significant differences between Aggrenox and DP alone, Aggrenox and ASA Alone, and Agrrenox and Placebo with respect to number of patients with at least one adverse events. However, ASA has a numerical advantage over Aggrenox (see table 3.2).

Aggrenox is significantly worse (less safe) than ASA alone and placebo with respect to Gastro-Intestinal System Disorders (see Table 3.2). Aggrenox is also significantly less safe than DP alone and ASA alone with respect to Platelet, Bleeding and Clotting Disorders

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4.3 Pediatric:

Because the minimum age requirement for all three studies is 18 years, the implications of these findings on patients who are less than 18 years are unclear.

4.4 Summary of Reviewer's Issues:

1) Study ESPS2 is a single multi-center, European study intended to provide sole confirmatory evidence for drug approval. As such the integrity and conduct of the trial needs to be of high standard, and the demonstrated statistical and clinical benefit should be clearly demonstrated. In this reviewer's opinion, there remain questions about primary endpoint definition and the sample size increase after the interim look that need to be recognized in reviewing the results of this study. Moreover, statistical arguments can support the need for a p-value much smaller than the standard .05 level as a requirement for a single study confirmation of drug efficacy, although this further adjustment has not been argued for in this review.

2) Due to sample size re-estimation, the type I error rate for the final analysis should have been lower than the planned value of .049. However, such an adjustment would likely to have had little impact on study results.

3) An additional adjustment to the study's reported p-values is required due to the presence of three primary endpoints. Such an adjustment would not affect the significance of the results for stroke, however, the adjusted p-values (using Holm's procedure) are doubled for the composite endpoint, and these adjustments further weakens the results of each primary comparison.

5. Reviewer's Comments

From a statistical perspective, the sponsor has shown that the combination drug product is effective only in stroke (fatal and non-fatal). However, it is not clear that there is any added benefit for fatal stroke. The sponsor did not demonstrate clear and significant efficacy results for either the mortality or the composite endpoint.

/S/ 4/[illegible]

M. Mushfiqur Rashid, Ph.D.
Mathematical Statistician

Concur:
Dr. Al-Osh /S/ 4/30/99
Dr. Welch /S/ 4/30/99

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cc: Archival NDA # 20884
HFD - 180
HFD - 180/ Dr. Talarico
HFD - 180/ Mrs. DuBeau
HFD - 180/ Dr. Farrell
HFD -180/ Dr. Robie-Suh
HFD - 715/ Dr. Nevius
HFD - 715/ Dr. Welch
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APPENDIX

Table A.1 (reviewer's): Baseline Characteristics in ESPS2

	DP/ASA (n=1650)	DP (n=1654)	ASA (n=1649)	Placebo (n=1649)	Total (n=6602)
Age (year)					
Mean	66.8	66.7	66.8	66.6	66.7
# of patients <65	623(38%)	648(39%)	655(40%)	639(39%)	2565(39%)
# of patients >65	1027(63%)	1006(61%)	994(60%)	1010(61%)	4037(61%)
Gender					
Male	956(57.9%)	965(58.3%)	956(58.0%)	951(57.7%)	3828(58.0%)
Female	694(42.1%)	689(41.7%)	693(42.0%)	698(61.4%)	2274(42.0%)
Geographical Region					
Scandinavia	412(25.0%)	416 (25.2%)	420 (25.5%)	417 (25.3%)	1665(25.2%)
Northwestern Region	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 and Ireland	361(21.90%	358 (21.6%)	361 (21.9%)	357 (21.6%)	1437 (21.8%)

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Table A.1.1: Components of Adverse Events:

1) Central and Peripheral Nervous System Disorders;
2) Gastro-Intestinal System Disorders;
3) Body as a Whole-General Disdorders;
4) Vascular (Extracardiac) Disorders;
5) Psychiatric Disorders;
6) Myo Endo Pericardial and Valve Disorders;
7) Musculo-Skeletal System Disorders;
8) Respiratory Disorders;
9) Cardiovascular Disorders, General;
10) Platelet, Bleeding and Clotting Disorders;
11) Resistance Mechanism Disorders;
12) Urinary System Disorders;
13) Metabolic and Nutritional Disorders;
14) Skin and Appendages Disorders;
15) Neoplasm;
16) Vision Disorders;
17) Heart Rate and Rhythm Disorders;
18) Red blood cell disorders;
19) Hearing and Vestibular Disorders;
20) Reproductive Disorders;
21) Liver and Billary System Disorders;
22) Special Senses their Disorders;
23) Endocrine Disorders;
24) Collagen Disorders;
25) Applicatin Site Disorder;
26) White Cell and Res Disorders;
27) Foetal Disorders;
28) Poison Specific Terms.

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Table A.2: First Strokes (fatal or no-fatal) as Confirmed by the MMAG for ESPS2 (first 5002 Population) for Main Effects and Interaction (extracted from sponsor's Appendix 5.1.0, volume 89)

Treatment comparisons	Risk Reduction At 730 days (sponsor's)	p-value		K-M estimate of survival rate at 730 days (sponsor's)	Number (%) of Patients with the Event			
		G-W	Log-rank		DP (n=2504)	No DP (n=2498)	ASA (n=2497)	No ASA (n=2505)
DP Vs no DP	22.5	<001	<.001	88.5% vs. 85.0%	276 (11.0%)	358 (14.3%)	363 (11.3%)	461 (14.1%)
ASA Vs no ASA	20.1	.001	.002	88.2% vs. 85.2%				
DP X ASA Interaction	-	.456	.472					

Note: G-W: Gehan-Wilcoxon test for detecting a difference in the survival experience of the two groups;
Log-rank: Log-rank test (also known as the Mantel-Haenszel test) for detecting a difference in the survival experience of the two groups;
K-M: Kaplan-Meier

Table A.3: First Strokes (fatal or no-fatal) as Confirmed the MMAG for ESPS2 for Individual Treatment Combination (first 5002 patients)

Treatment Comparisons	Risk Reduction at 730 days (sponsor's)	p-value (sponsor's)		K-M Estimate of survival rate at 730 days (%)	Number (%) of Patients with the Event			
		G-H	Log-rank		DP/ASA (n=1250)	DP (n=1254)	ASA (n=1247)	Placebo (n=1251)
DP/ASA Vs DP	27.3%	.002	.004	90.2 vs. 86.6	115 (9.2%)	161 (12.8%)	166 (13.3%)	192 (15.3%)
DP/ASA Vs ASA	29.3%	.001	.002	90.2 vs. 86.2				
DP/ASA Vs Placebo	39.5%	<.001	< .001	90.2 vs. 83.9				
ASA Vs Placebo	14.4%	.085	.098	86.2 vs. 83.9				
DP Vs Placebo	16.8%	.064	.063	86.6 vs. 83.9				

Table A.4: Deaths as Confirmed the MMAG for ESPS 2 (first 5002 patients) for Factorial Analysis (extracted from sponsor's Appendix 5.1.1, volume 89)

Treatment comparisons	Risk Reduction At 730 days (sponsor's)	p-value (sponsor's)		K-M estimate of survival rate at 730 days (sponsor's)	Number (%) of Patients with the Event			
		G-W	Log-rank		DP (n=2504)	No DP (n=2498)	ASA (n=2497)	No ASA (n=2505)
DP Vs no DP	4.1	.690	.640	88.3% vs. 87.8%	291 (11.6%)	302 (12.1%)	292 (11.7%)	301 (12.0%)
ASA Vs no ASA	3.0	.602	.648	88.3% vs. 87.9%				
DP X ASA Interaction	-	.835	.866					

Note: G-W: Gehan-Wilcoxon test for detecting a difference in the survival experience of the two groups; Log-rank: Log-rank test (also known as the Mantel-Haenszel test) for detecting a difference in the survival experience of the two groups; K-M: Kaplan-Meier

Table A.5: Deaths as Confirmed the MMAG for ESPS2 for Individual Treatment Combination (first 5002 Population)

Treatment Comparisons	Risk Reduction at 730 days (sponsor's)	p-value (sponsor's)		K-M estimate at 730 days (%) (sponsor's)	Number (%) of Patients with the Event			
		G-H	Log-rank		DP/ASA (n=1250)	DP (n=1254)	ASA (n=1247)	Placebo (n=1251)
DP/ASA Vs DP	2.0%	.823	.838	88.5 vs. 88.2	144 (11.5%)	147 (11.7%)	148 (11.9%)	154 (12.3%)
DP/ASA Vs ASA	3.1%	.892	.831	88.5 vs. 88.1				
DP/ASA Vs Placebo	6.9%	.518	.515	88.5 vs. 87.6				
ASA Vs Placebo	3.9%	.607	.660	88.1 vs. 87.6				
DP Vs Placebo	4.9%	.669	.654	88.2 vs. 87.6				

Table A.6: Summary of Drug-Gender Interaction for Main Effects (ITT Population)

Gender	Primary Endpoint	Survival at 730 days (%)Factorial Analysis Group (sponsor's)				p-value			
		DP	No DP	ASA	No ASA	Subgroup X DP Main effect (sponsor's)	Subgroup X ASA main Effect (sponsor's)	DP vs. No DP (GW: reviewer's)	ASA vs. No ASA (G-W: reviewer's)
Male	Stroke	87.8	85.6	88.1	85.3	.382	.663	.0486	.0037
Female	Stroke	89.0	85.5	89.0	85.5			.0053	.0055
Male	Death	89.0	88.4	88.5	88.9	.675	.082	.6111	.7732
Female	Death	88.0	88.1	89.2	86.9			.9597	.0353

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Table A.7: Summary of Drug-Age Interaction for Main Effects (ITT Population)

Age in years	Survival rate at 730 days (%) Factorial Analysis Group (sponsor's)				p-value			
	DP	No DP	ASA	No ASA	Subgroup X DP Main effect (sponsor's)	Subgroup X ASA main Effect (sponsor's)	DP vs. No DP (G-W) (reviewer's)	ASA vs. No ASA (G-W) (reviewer's)
Stroke								
< =54	94.8	92.4	95.2	92.1	.736	.480	.1552	.0495
55 to 64 years	90.4	90.1	91.5	89.1			.7800	.0992
65 to 74 years	88.1	84.1	88.0	84.3			.0090	.0061
75 to 84 years	83.3	79.4	82.8	79.7			.0373	.0655
> =85 years	79.2	77.0	81.5	73.8			.6112	.1947
eath								
< =54	98.9	98.0	98.9	98.0	.260	.755	.2708	.2843
55 to 64 years	86.0	94.7	95.7	95.0			.2196	.4673
65 to 74 years	88.5	89.2	89.0	88.6			.5063	.7359
75 to 84 years	78.6	77.3	78.9	77.0			.5801	.2106
> =85 years	62.7	64.8	67.0	59.7			.8823	.3588

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Table A.8: Summary of Drug-Geographical Region Interaction for Main Effects (ITT Population)

Geographical Region	Survival rate at 730 days (%) Factorial Analysis Group				p-value			
	DP	No DP	ASA	No ASA	Subgroup X DP Main effect (sponsor's)	Subgroup X ASA main Effect (sponsor's)	DP vs. No DP (G-W) (reviewer's)	ASA vs. No ASA (G-W)
Stroke					.674	.757		
Scandinavia	89.1	86.7	89.6	86.1			.1221	.0406
Northern Europe	90.2	87.8	90.8	87.2			.0078	.0754
Southern Europe	90.2	89.8	90.9	89.1			.0610	.0030
United Kingdom and Ireland	82.5	77.0	81.2	78.4			.8942	.2509
Death					.675	.873		
Scandinavia	92.6	93.5	93.4	92.8			.4378	.5957
Northern Europe	90.6	90.6	90.9	90.2			.3233	.6641
Southern Europe	93.0	92.3	93.5	91.8			.8635	.4630
United Kingdom and Ireland	77.4	75.1	76.5	76.0			.6637	.2636

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Table A.9: Summary of Drug-Smoking Habit Interaction for Main Effects (ITT Population)

Smoking Habit	Survival rate at 730 days (%) Factorial Analysis Group (sponsor's)				p-value			
	DP	No DP	ASA	No ASA	Subgroup X DP Main Effect (sponsor's)	Subgroup X ASA Main Effect (sponsor's)	DP vs. No DP (G-W) (reviewer's)	ASA vs. No ASA (G-W) (reviewer's)
Stroke					.640	.984		
Never Smoked	88.5	86.5	89.1	85.9			.1091	.0072
Stopped Smoking	87.9	85.3	88.1	85.1			.0756	.0232
Currently Smoking	88.5	84.2	87.9	84.9			.0144	.0531
Death					.092	.053		
Never Smoked	88.3	90.0	90.2	88.2			.1421	.0617
Stopped Smoking	87.5	85.6	85.6	87.4			.2479	.2149
Currently Smoking	90.6	88.9	90.9	88.7			.2522	.1171

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Table A.10: Summary of Drug-Coffee Drinkers Interaction for Main Effects (ITT Population)

Coffee Consumption	Survival rate at 730 days (%) Factorial Analysis Group (sponsor's)				p-value			
	DP	No DP	ASA	No ASA	Subgroup X DP Main effect (sponsor's)	Subgroup X ASA main Effect (sponsor's)	DP vs. No DP (G-W) (reviewer's)	ASA vs. No ASA (G-W) (reviewer's)
Stroke					.742	.650		
< = 5 Cups/Day	87.9	85.1	88.1	85.0			.0011	.0002
> 5 Cups/Day	90.8	89.2	91.8	88.4			.5604	.1042
Death					.079	.160		
< = 5 Cups/Day	88.2	87.5	88.1	87.6			.4444	.4177
> 5 Cups/Day	91.7	94.6	94.6	91.6			.1038	.0950

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Table A.11: Summary of Drug-Diabetes at Baseline for Main Effects (ITT Population)

Diabetes at Baseline	Survival at 730 days (%) Factorial Analysis Group (sponsor's)				p-value			
	DP	No DP	ASA	No ASA	Subgroup X DP Main effect (sponsor's)	Subgroup X ASA main Effect (sponsor's)	DP vs. No DP (G-W) (reviewer's)	ASA vs. No ASA (G-W) (reviewer's)
Stroke					.882	.432		
Diabetes Absent	89.0	86.4	89.1	86.3			.0037	.0004
Diabetes present (Non-insulin dependent diabetes mellitus)	84.6	81.3	86.2	80.1			.2015	.0319
Diabetes Present (Insulin dependent diabetes mellitus)	84.2	78.4	80.0	82.4			.1773	.8697
Death					.426	.809		
Diabetes Absent	89.5	88.7	89.3	88.8			.3680	.4386
Diabetes present (Non-insulin dependent mellitus)	85.9	87.7	87.8	85.7			.3843	.3493
Diabetes Present (Insulin dependent diabetes mellitus)	75.8	78.4	78.7	75.5			.5265	.5315

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Table A.12: Summary of Drug-Gender Interaction for Individual Treatment Group (ITT Population)

Gender	Primary endpoint	p-values (reviewer's) of Gehan-Wilcoxon test					Survival rate at 730 days (%) Factorial Analysis (sponsor's)			
		DP/ASA vs. DP	DP/ASA vs. ASA	DP/ASA vs. Placebo	DP vs. Placebo	ASA vs. Placebo	DP /ASA	DP	ASA	Placebo
Male	Stroke	.0163	.0634	.0007	.3093	.114	89.5	86.1	86.8	84.4
Female	Stroke	.0504	.0559	.0001	.0405	.031	90.5	87.5	87.5	83.5
Male	Death	.9504	.6207	.8715	.8299	.7303	89.0	89.1	88.0	88.7
Female	Death	.6438	.2625	.1563	.3527	.0120	88.3	87.8	90.2	86.0

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Table A.13: Summary of Drug-Age Group Interaction for Individual Treatment Group (ITT Population)

Age in years	DP/ASA Vs. DP (p-value: reviewer's)	DP/ASA Vs. ASA (p-value: reviewer's)	DP/ASA Vs. Placebo (p-value: reviewer's)	DP Vs. Placebo (p-value: reviewer's)	ASA Vs. Placebo (p-value: reviewer's)	Survival rate at 730 days (%) for Factorial Analysis (sponsor's)			
						DP /ASA	DP	ASA	Placebo
Stroke									
<=54	.1633	.3070	.0179	.3330	.1752	96.2	93.3	94.1	90.8
55 to 64 years	.3686	.9836	.1750	.6199	.1486	91.4	89.5	91.6	88.6
65 to 74 years	.0128	.0156	.0001	.1952	.1776	90.3	86.0	85.6	82.7
75 to 84 years	.1641	.1122	.0048	.1416	.1879	84.9	81.6	80.9	77.7
>=85 years	.3595	.7761	.2250	.7508	.3413	82.9	74.2	80.3	73.2
Death									
<=54	.1655	.1576	.0981	.7745	.7908	99.6	98.2	98.2	97.9
55 to 64 years	.6122	.3941	.1616	.3551	.5601	96.4	95.7	95.1	94.3
65 to 74 years	.7112	.2556	.8224	.8796	.5601	88.0	88.9	90.1	88.4
75 to 84 years	.5881	.9475	.1978	.4499	.2087	79.1	78.1	78.6	75.8
>=85 years	.6395	.6965	.6437	.9522	.3834	66.1	57.7	68.1	61.4

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Table A.14: Summary of Drug by Geographical Region for Individual Treatment Group Geographical Region (ITT Population)

Geographical Region	DP/ASA Vs. DP (p-value: reviewer's)	DP/ASA Vs. ASA (p-value: reviewer's)	DP/ASA Vs. Placebo (p-value: reviewer's)	DP vs. Placebo (p-value: reviewer's)	ASA vs. placebo	Survival rate at 730 days (%) Factorial Analysis Group (sponsor's)			
						DP /ASA	DP	ASA	Placebo
Stroke									
Scandinavia	.1368	.2524	.0103	.2752	.1519	90.6	87.6	88.6	84.7
Northern Europe	.2035	.0539	.0018	.0616	.1927	92.6	87.8	89.0	86.6
Southern Europe	.0035	.0287	.0004	.5488	.1761	90.2	90.2	91.6	88.0
United Kingdom and Ireland	.9074	.5235	.3746	.4546	.1280	84.2	80.8	78.2	75.9
Death									
Scandinavia	.7090	.5918	.8615	.5825	.7146	92.9	92.3	93.8	93.3
Northern Europe	.7105	.9777	.3219	.1713	.3325	91.4	89.7	90.5	90.7
Southern Europe	.2894	.6574	.6816	.5075	.9668	92.2	93.7	94.7	89.9
United Kingdom and Ireland	.5311	.2378	.3058	.1049	.0315	76.7	78.1	76.4	73.9

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Table A.15: Summary of Drug by Smoking Habits for Individual Treatment Group (ITT Population)

Smoking Habit	p-values(reviewer's)					Survival rate at 730 days (%) Factorial Analysis Group (sponsor's)			
	DP/ASA Vs. DP	DP/ASA Vs. ASA	DP/ASA Vs. Placebo	DP Vs. Placebo	ASA Vs. Placebo	DP/ASA	DP	ASA	Placebo
Stroke									
Never Smoked	.3173	.8007	.0028	.0441	.0057	89.2	87.8	88.9	83.9
Stopped Smoking	.0170	.0380	.0035	.5921	.3643	90.2	85.5	86.1	84.6
Currently Smoking	.0284	.0105	.0016	.3392	.5309	90.7	86.1	84.9	83.5
Death									
Never Smoked	.8264	.0263	.9516	.9599	.0134	88.4	88.3	91.8	88.1
Stopped Smoking	.5964	.2549	.0581	.629	.2283	86.9	88.1	84.3	86.8
Currently Smoking	.3114	.4844	.3173	.3776	.2341	91.7	89.5	90.1	87.8

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Table A.16: Summary of Drug by Coffee Drinkers for Individual Treatment Group (ITT Population)

Coffee Consumption	DP/ASA Vs.DP (p-value: reviewer's)	DP/ASA Vs. ASA (p-value: reviewer's)	DP/ASA Vs. Placebo (p-value: reviewer's)	DP vs. Placebo (p-value: reviewer's)	ASA vs. Placebo	Survival rate at 730 days (%) Factorial Analysis Group			
						DP /ASA	DP	ASA	Placebo
Stroke									
<= 5 Cups/Day	.0067	.0152	.0105	.0260	.0105	89.5	86.4	86.7	83.5
> 5 Cups/Day	.0792	.2633	.5632	.9005	.5632	93.5	88.5	90.1	88.4
Death									
<= 5 Cups/Day	.6960	.6716	.2738	.1398	.1293	87.9	88.5	88.3	86.6
> 5 Cups/Day	.0141	.6164	.9807	.0154	.6406	95.3	88.3	94.0	95.2

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Table A.17: Summary of Drug by Diabetes at Baseline for Individual Treatment Group (ITT Population)

Diabetes at Baseline	DP/ASA Vs. DP (p-value: reviewer's)	DP/ASA Vs. ASA (p-value: reviewer's)	DP/ASA Vs. Placebo (p-value: reviewer's)	DP Vs Placebo (p-value: reviewer's)	ASA Vs. Placebo (p-value: reviewer's)	Survival rate at 730 days (%) Factorial Analysis Group			
						DP /ASA	DP	ASA	Placebo
Stroke									
Diabetes Absent	.0067	.0202	.0001	.0672	.0204	90.5	87.5	87.8	85.0
Diabetes present (Non-insulin dependent diabetes mellitus)	.1435	.4563	.0142	.2507	.1037	7.5	82.1	84.8	77.7
Diabetes Present (Insulin dependent diabetes mellitus)	.7527	.1895	.3958	.5307	.6850	84.1	84.5	76.5	80.4
Death									
Diabetes Absent	.7138	.6416	2396	.4246	.4705	89.5	88.7	89.3	88.8
Diabetes present (Non-insulin dependent diabetes mellitus)	.7447	.0834	.9269	.6713	.0767	85.9	87.7	87.8	85.7
Diabetes Present (Insulin dependent diabetes mellitus)	.8890	.5183	.9790	.7899	.5013	75.8	78.4	78.7	75.5

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Table A.18: P-values (G-W) for the composite endpoint corresponding to Individual Treatment Group (ITT Population) copmparison

Region	DP/ASA Vs. DP	DP/ASA Vs. ASA	DP vs. PL	ASA vs. PL
Scandinavia (n=1665)	.51	.47	.32	.36
N. Europe (n=2425)	.88	.32	.02	.12
S. Europe (n=1075)	.02	.05	.51	.27
U. K. and Ireland (n=1437)	.81	.43	.22	.03

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Table A.19: Safety Events ((sponsor's 2.1.0, Volume 91) Summary by Individual Treatment (ITT Population)

Safety Parameter	DP/ASA (n=1650)	DP (n=1654)	ASA (n=1649)	Placebo (n=1649)
Cardiovascular Disorders, Genaral	97 (5.9%)	92 (5.6%)	142 (8.6%)	123 (7.5%)
Resistance Mechanism Disorders Infection	87 (5.3%)	108 (6.5%)	107 (6.5%)	105 (6.4%)
Urinary System Disorders	81 (4.9%)	69 (4.2%)	98 (5.9%)	86 (5.2%)
Metabolic and Nutritional Disorders	67 (4.1%)	75 (4.5%)	74 (4.5%)	92 (5.6%)
Central & Peripheral Nervous System Disorders	909 (55%)	892 (53.9%)	834 (50.6%)	822 (49.8%)
Skin and Appendages Disorders	67 (4.1%)	74 (4.5%)	62 (3.8%)	70 (4.2%)
Body as a Whole-General Disorders	472 (28.6%)	448 (27.1%)	483 (29.3%)	490 (29.7%)
Neroplasm	47 (2.8%)	48 (2.9%)	51 (3.1%)	49 (3.0%)
Vascular (Extracardiac) Disorders	303 (18.4%)	382 (23.1%)	390 (23.7%)	508 (30.8%)
Psychiatric Disorders	207 (12.5%)	199 (12.0%)	218 (13.2%)	225 (13.6%)
Myo Endo Pericardial and Valve Disorders	145 (8.8%)	146 (8.8%)	133 (8.1%)	162 (9.8%)
Heart Rate and Rhythm Disorders	53 (3.2%)	36 (2.2%)	56 (3.4%)	47 (2.9%)
Muscculo-Skelletal Disorders	145 (8.8%)	146 (8.8%)	133 (8.1%)	162 (9.8%)
Red Blood Cell Disorders	29 (1.8%)	17 (1.0%)	21 (1.3%)	11 (.7%)
Respiratory Disorders	120 (7.3%)	109 (6.6%)	154 (9.3%)	123 (7.5%)

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