Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Aggrenox ®		**EudraCT No.:** 2006-004870-28	
Name of active ingredient: Dipyridamole + acetylsalicylic acid		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 29 JAN 2010	**Trial No. / U No.:** 9.182 / U10-1162-02	**Date of trial:** 13.07.2007 – 05.02.2009	**Date of revision:** 16 FEB 2010

Title of trial:	Prospective, randomised, national, multi-centre, open label, blinded endpoint study to compare Aggrenox® b.i.d. (200 mg dipyridamole MR + 25 mg acetylsalicylic acid) when started within 24 hours of stroke onset on an acute stroke unit, and Aggrenox® b.i.d. when started after a 7-day therapy with ASA 100 mg once daily outside of an acute stroke unit, in symptomatic ischaemic stroke patients over a three months treatment period (EARLY) - An exploratory study
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial, 46 active sites (in Germany)
Publication (reference):	P09-11781
Clinical phase:	IV
Objectives:	The objective of the trial was to investigate the tolerability and efficacy of a secondary stroke prevention treatment with Aggrenox® when initiated within 24 hours of stroke onset in a stroke unit compared to initiation after a 7-day acetylsalicylic acid (ASA) treatment outside of an acute stroke unit. Endpoints: • Telephone modified Rankin Scale (tele-mRS) on days 8 and 90 – centralised, blinded assessment by a specialised stroke centre • Modified Rankin Scale (mRS), (National Institute of Health Stroke Scale) (NIHSS) at baseline and on days 8 and 90 –assessment by investigator • Time to first relevant event (vascular or non-vascular death, non-fatal stroke, non-fatal myocardial infarction, bleeding complications) – centralised, blinded assessment by an adjudicating committee

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	• Neuroanatomical and neurofunctional images of the brain at baseline and on day 8 and day 90 as assessed by Magnetic Resonance Imaging (MRI) parameters – centralised, blinded evaluation by a central radiology centre • Inflammatory laboratory values (Matrix metalloproteinase-9 [MMP-9], Monocyte chemoattractant protein-1 [MCP-1] and C-reactive protein [CRP]) at Baseline and on day 8 – centralised, blinded assessment by a specialised central clinical laboratory • Safety and tolerability assessment by adverse event (AE) evaluation • Premature treatment discontinuations due to AEs
Methodology:	Prospective, randomised, 3 months open-label treatments with Aggrenox b.i.d. when started on a stroke unit within 24 hours after an ischaemic stroke, and when started after an initial one week ASA 100 mg therapy outside of a stroke unit. Blinded endpoint evaluation (Prospective randomised open blinded end-point [PROBE]-design) with regard to tele-mRS on day 90. Time points of assessment were at baseline and on days 8, 9 and 90. Optional visits were possible.
No. of subjects:	
planned:	Enrol 502 patients to randomise 488 and have 468 evaluable patients (234 patients per treatment group)
actual:	enrolled: 550; randomised: 548; Treated: 543 Treatment starting with ASA 100 mg: entered: 260 treated: 254 analysed (for primary endpoint): Treatment starting with Aggrenox: entered: 283 treated: 273 analysed (for primary endpoint):
Diagnosis and main criteria for inclusion:	Clinical diagnosis of ischaemic stroke causing a measurable neurological deficit defined as impairment of language, motor function, cognition and/or gaze, vision or neglect. Symptoms were distinguishable from an episode of generalised ischaemia (i.e. syncope), seizure, or migraine disorder.

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Main criteria for inclusion:

- Adult inpatient
- Clinical diagnosis of ischaemic stroke causing a measurable neurological deficit defined as impairment of language, motor function, cognition and/or gaze, vision or neglect. Symptoms were distinguishable from an episode of generalised ischaemia (i.e. syncope), seizure, or migraine disorder.
- Time of stroke onset was known. Symptoms of ischaemic attack began at a time point what makes the start with study medication within 24 hours possible. When a stroke happened during sleep, bedtime was assumed as time of onset.
- NIHSS assessment equal to or below 20 points (at pre-screening).
- Treatment indication was given either to valid German Summary of Product Characteristics (SPC) of Aggrenox capsules or to ASS STADA 100 mg tablets.
- A contraindication for stroke lysis was given
- Patients were able to swallow either medication or administration of the substances via nasogastral tube was possible.
- Signed and witnessed written informed consent obtained prior to the first study intervention. Patients who were unable to sign but able to understand the meaning of participation in the study gave an oral, witnessed (preferably by relatives) informed consent. These patients made clear without doubt that they were willing to participate voluntarily and were able to understand an explanation of the contents of the information sheet.

Test product:	Aggrenox Retardkapseln (200mg dipyridamole + 25mg acetylsalicylic acid)
dose:	2 capsules per day
mode of admin.:	Oral
batch no.:	Aggrenox: 702287

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Reference therapy:	ASS STADA 100 mg tablets (acetylsalicylic acid)
dose:	1 tablet per day
mode of admin.:	Oral
batch no.:	ASA Stada: 4671
Duration of treatment:	90 days
Criteria for evaluation:	
Efficacy / clinical pharmacology:	• tele-mRS (centralised, blinded assessment) • NIHSS, mRS (assessed by investigator) • Time to first relevant event (vascular or non-vascular death, non-fatal stroke, non-fatal myocardial infarction, bleeding complication) – centralised, blinded assessment • MRI – centralised, blinded assessment • Laboratory tests (MMP-9, MCP-1, CRP) – centralised, blinded assessment
Safety:	• Adverse events • Discontinuation rates due to adverse events • Physical examination • Vital signs
Statistical methods:	Both treatment groups were compared with regard to all endpoints, especially with regard to the blinded assessment of the mRS on day 90. Cochran-Mantel-Haenszel test, logistic regression and Analysis of covariance (ANCOVA) were to be used as appropriate. 234 evaluable patients per group would deliver a half-length for the 95% Confidence interval (CI) of treatment difference in proportions of favourable outcomes of roughly 9%-points. Thus, in case of no observed treatment difference, a disadvantage of early vs. late start of treatment of Aggrenox of 9% or more could be excluded. Adverse events and all other variables were analysed descriptively.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Baseline characteristics were typical for the patient group under study and did not reveal clinical relevant differences between both treatment arms. Mean age was 67.3 years, 342 of 543 patients (62.4%) were male, 542 patients were white (99.8%), the mean BMI was 27.3, 265 patients (48.8%) never smoked, 125 patients (23.0%) currently smoked, 402 patients (74.0%) had hypertension, 126 patients (23.2%) had diabetes mellitus, 182 patients (33.5%) had hyperlipidaemia, 77 patients (14.2%) had a previous stroke, and 223 patients (41.1%) were previously treated with ASA. Some more than a third of the patients had minor strokes as qualifying event (patients with mRS of 0 or 1 as assessed by the investigators at baseline; 205 of 527 patients [38.9%]).

The primary endpoint tele-mRS on day 90 was available in 527 of 543 treated patients (97.1%). The analysis of the primary endpoint revealed that starting secondary stroke prevention with Aggrenox b.i.d. was comparable to starting treatment with ASA 100 mg. In fact, the odds for improvements in the mRS on day 90 (integrated across all cut-points of the scale) were slightly increased by the early treatment with Aggrenox b.i.d. (OR [95% CI] was 1.067 (0.780, 1.461), p=0.68). In the Aggrenox starting group, 154 of 273 patients (56.4%) had no or slight disability in the tele-mRS on day 90 whereas in the ASA 100 mg starting group only 123 of 254 patients (52.4%) had a tele-mRS of 0 or 1 on day 90. The absolute difference in the frequency of patients with no or slight disability was 4·1 %, 95%-CI -4·5% , 12·6%.

The analysis of relevant outcomes (vascular or non-vascular death, non-fatal stroke, TIA, non-fatal myocardial infarction, or bleeding complication) showed a nominal advantage for the Aggrenox starting group (HR [CI 95%] 0.725; 0.442, 1.189; p=0.20), especially with less strokes and TIAs (20 [7.1%] vs. 32 [12.3%]).

Differences between both treatment arms were neither obvious in MRI parameters nor in inflammatory lab values.

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Safety results:	A total of 212 of 283 patients (74.9%) in the Aggrenox starting group and 176 of 260 patients (67.7%) in the ASA 100 mg starting group experienced at least one AE. AE were of mild to moderate intensity in most cases. Nervous system disorders (44.6%) and gastrointestinal disorders (19.3%) were most common, with headache, cerebrovascular accident, nausea and vomiting as most frequently reported AEs. Headache were reported by 105 patients (37.1%) in the Aggrenox starting group and by 53 patients (20.4%) in the ASA 100 mg starting group, cerebrovascular accident by 10 patients (3.5%) and 23 patients (8.8%), nausea by 29 patients (10.2%) and 14 patients (5.4%), and vomiting by 26 patients (9.2%) and 10 patients (3.8%), respectively.
Conclusions:	Starting with Aggrenox b.i.d. within 24 hours after an ischemic stroke or TIA and continuing therapy for 90 days appeared to be at least as effective as starting with ASA 100 mg for 7 days and continuing therapy with Aggrenox until day 90. Regarding the primary endpoint tele-mRS and the combined relevant outcome (vascular or non-vascular death, non-fatal stroke, TIA, non-fatal myocardial infarction, or bleeding complication) slight nominal advantages were shown for an early start with Aggrenox. Although not statistically significant, more patients had no or only slight disability in the tele-mRS on day 90 (score 0 or 1) when starting with Aggrenox b.i.d., and less patients experienced a re-stroke or TIA compared with patients starting with ASA 100 mg therapy. Early start with Aggrenox b.i.d. was at least as safe as early start with ASA 100 mg with regard to number and type of, serious adverse events and premature discontinuations from therapy. Most common complaints were headache and gastrointestinal disorders which were more often reported after early start with Aggrenox.

Trial Synopsis - Appendix

The results tables on the following pages supplement the trial results presented in the Trial Synopsis. The tables complement the results for patient disposition, primary endpoints, secondary endpoints, and safety data.

Results for	**presented in**
Patient Disposition	Table 15.1.1: 1
Tele-mRS Day 8 (primary endpoint)	Table 15.2.1: 4
Investigator mRS, Day 8 and 90 (secondary endpoint)	Table 15.2.1: 6
National Institute of Health Stroke Scale (NIHSS), Day 8 and 90 (secondary endpoint)	Table 15.2.2: 1
Relevant Outcomes (secondary endpoint)	Table 15.2.3: 1
MRI-FLAIR, Day 8 and 90 (secondary endpoint)	Table 15.2.4: 1
MRI-DWI, Day 8 and 90 (secondary endpoint)	Table 15.2.4: 2
Inflammatory markers-CRP, MMP-9, MCP-1 (Day 8) (secondary endpoint)	Table 15.2.5: 1 Table 15.2.5: 2 Table 15.2.5: 3
Summary AEs	Table 15.3.2: 1

Table 15.1.1: 1 Disposition of Patients - Enrolled Set
Actual Treatment

	ASPIRIN	AGGRENOX	Total
Number of patients enrolled			550 (100.0)
Number of patients not randomised			2 (0.4)
Number of patients randomised	260 (100.0)	283 (100.0)	548 (100.0)
Number of patients not treated	0	0	5 (0.9)
Number of patients treated	260 (100.0)	283 (100.0)	543 (100.0)
Number of patients who did not prematurely stop medication	168 (64.6)	184 (65.0)	352 (64.8)
Number of patients who did prematurely stop medication	92 (35.4)	99 (35.0)	191 (35.2)
Reason for premature discontinuation			
Adverse Event	40 (43.5)	58 (58.6)	98 (51.3)
Unexpected worsening of disease/condition under study	10 (10.9)	6 (6.1)	16 (8.4)
Unexpected worsening of other pre-existing disease/condition	1 (1.1)	5 (5.1)	6 (3.1)
Other adverse event	29 (31.5)	47 (47.5)	76 (39.8)
Non compliant with protocol	30 (32.6)	26 (26.3)	56 (29.3)
Lost to follow-up	12 (13.0)	4 (4.0)	16 (8.4)
Consent withdrawn for further participation (not due to an adverse event)	10 (10.9)	9 (9.1)	19 (9.9)
Other	0	2 (2.0)	2 (1.0)

Note: Percentages for patients enrolled and patients not randomised based on the number of patients enrolled. Percentages for patients randomised and patients not treated based on the number of patients randomised in each treatment group. Percentages for patients treated, patients who did not prematurely stop medication and patients who did prematurely stop medication based on the number of patients treated in each treatment group. Percentages for reasons for premature discontinuation based on the number of patients who did prematurely stop medication in each treatment group.
Source data: Appendix 16.2, Listings 1.1, 5.3
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Table 15.2.1: 4 tele-mRS on Day 8 - Full Analysis Set
Actual Treatment

	ASPIRIN	AGGRENOX
Number of patients	254	273
tele-mRS score [N (%)]		
0	46 (18.1)	47 (17.2)
1	59 (23.2)	74 (27.1)
2	42 (16.5)	52 (19.0)
3	39 (15.4)	38 (13.9)
4	51 (20.1)	44 (16.1)
5	12 (4.7)	8 (2.9)
6	0	2 (0.7)
Missing	5 (2.0)	8 (2.9)
p-value[1] from CMH test	0.636	
p-value[2] from logistic regression	0.776	
Odds ratio (95% CI)	0.953 (0.685, 1.326)	
p-value[3] from responder analysis (mRS=0)	0.481	
p-value[3] from responder analysis (mRS=0 or 1)	0.801	

Note: For patients who drop-out from the study but are still alive, missing values have been imputed using the last available post-baseline score. For patients who die within the 90-day interval of the study, missing values have been imputed using the worst category (6).
[1] p-value comparing treatment groups from Cochran-Mantel-Haenszel test with adjustment for baseline investigator-assessed mRS.
[2] p-value comparing treatment groups from logistic regression model with factors for treatment and baseline investigator-assessed mRS, age, weight, baseline SBP, diabetes, previous stroke (complete results in Appendix 16.1.9.2, StatDoc 4).
[3] Responder analysis performed using the Cochran-Mantel-Haenszel statistic on the number of patients with mRS=0 or mRS=0 or 1 adjusting for baseline NIHSS category (0, 1-5, >5).
Source data: Appendix 16.2, Listings 6.2, 6.3
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Table 15.2.1: 6 Investigator Assessed mRS - Full Analysis Set
Actual Treatment

	ASPIRIN	AGGRENOX
Number of patients	254	273
Visit 1 (Screening/Baseline)		
0	38 (15.0)	39 (14.3)
1	56 (22.0)	72 (26.4)
2	43 (16.9)	56 (20.5)
3	58 (22.8)	51 (18.7)
4	49 (19.3)	43 (15.8)
5	10 (3.9)	12 (4.4)
6	0	0
Visit 2 (Day 8)		
0	59 (23.2)	81 (29.7)
1	67 (26.4)	67 (24.5)
2	40 (15.7)	36 (13.2)
3	33 (13.0)	30 (11.0)
4	28 (11.0)	32 (11.7)
5	8 (3.1)	6 (2.2)
6	1 (0.4)	2 (0.7)
Missing	18 (7.1)	19 (7.0)
p-value from responder analysis (mRS=0)	0.163	
p-value from responder analysis (mRS=0 or 1)	0.488	

Note: For patients who drop-out from the study but are still alive, missing values have been imputed using the last available post-baseline score. For patients who die within the 90-day interval of the study, missing values have been imputed using the worst category (6).
Responder analysis performed using the Cochran-Mantel-Haenszel statistic on the number of patients with mRS=0 or mRS=0 or 1 at Day 8 and Day 90 adjusting for baseline NIHSS category (0, 1-5, >5).
Source data: Appendix 16.2, Listing 6.2
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Table 15.2.1: 6 Investigator Assessed mRS - Full Analysis Set
Actual Treatment

	ASPIRIN	AGGRENOX
Visit 4 (Day 90)		
0	86 (33.9)	106 (38.8)
1	64 (25.2)	69 (25.3)
2	38 (15.0)	36 (13.2)
3	20 (7.9)	23 (8.4)
4	22 (8.7)	19 (7.0)
5	4 (1.6)	4 (1.5)
6	4 (1.6)	5 (1.8)
Missing	16 (6.3)	11 (4.0)
p-value from responder analysis (mRS=0)	0.595	
p-value from responder analysis (mRS=0 or 1)	0.650	

Note: For patients who drop-out from the study but are still alive, missing values have been imputed using the last available post-baseline score. For patients who die within the 90-day interval of the study, missing values have been imputed using the worst category (6).
Responder analysis performed using the Cochran-Mantel-Haenszel statistic on the number of patients with mRS=0 or mRS=0 or 1 at Day 8 and Day 90 adjusting for baseline NIHSS category (0, 1-5, >5).
Source data: Appendix 16.2, Listing 6.2
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Table 15.2.2: 1 Investigator Assessed NIHSS - Full Analysis Set
Actual Treatment

	ASPIRIN		AGGRENOX	
	Actual	Change	Actual	Change
Number of patients	254		273	
Visit 1 (Screening/Baseline)				
N	254		273	
Mean	3.8		3.5	
SD	3.3		3.3	
Min	0		0	
Q1	1.0		1.0	
Median	3.0		3.0	
Q3	6.0		5.0	
Max	20		15	
Visit 2 (Day 8)				
N	236	236	255	255
Mean	2.6	-1.2	2.5	-1.1
SD	3.5	3.0	4.8	4.0
Min	0	-11	0	-10
Q1	0.0	-3.0	0.0	-3.0
Median	1.0	-1.0	1.0	-1.0
Q3	4.0	0.0	3.0	0.0
Max	22	19	42	38
pvalue[1]		0.772		

[1] p-value comparing treatment groups from repeated measures ANCOVA model with factors for treatment, day, age, weight, baseline SBP, diabetes and previous stroke and baseline NIHSS as a covariate and unstructured covariance structure.
Source data: Appendix 16.2, Listing 6.1
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Table 15.2.2: 1 Investigator Assessed NIHSS - Full Analysis Set
Actual Treatment

	ASPIRIN		AGGRENOX	
	Actual	Change	Actual	Change
Visit 4 (Day 90)				
N	238	238	262	262
Mean	2.3	-1.5	2.2	-1.3
SD	6.0	5.0	6.1	5.8
Min	0	-12	0	-11
Q1	0.0	-4.0	0.0	-3.0
Median	1.0	-2.0	0.0	-2.0
Q3	2.0	0.0	2.0	0.0
Max	42	39	42	42
pvalue[1]		0.607		

[1] p-value comparing treatment groups from repeated measures ANCOVA model with factors for treatment, day, age, weight, baseline SBP, diabetes and previous stroke and baseline NIHSS as a covariate and unstructured covariance structure.

Source data: Appendix 16.2, Listing 6.1

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Table 15.2.3: 1 Time to First Relevant Event - Full Analysis Set
Actual Treatment

	ASPIRIN	AGGRENOX
Number of patients	260	283
Number of patients with any relevant AE	38 (14.6)	28 (9.9)
Death - vascular	3 (1.2)	4 (1.4)
Death - nonvascular	1 (0.4)	1 (0.4)
Stroke - non-fatal	26 (10.0)	16 (5.7)
MI - non-fatal	1 (0.4)	2 (0.7)
Bleeding complications	1 (0.4)	1 (0.4)
TIA	6 (2.3)	4 (1.4)
Hazard ratio[1]	0.725	
95% confidence interval	0.442, 1.189	
p-value	0.202	

Note: The first relevant event is defined as vascular or non-vascular death, non-fatal stroke or TIA, non-fatal myocardial infarction or bleeding complications. These events will be assessed by a centralised, blinded adjudicating committee. Complete results in Appendix 16.1.9.3, StatDoc 6

[1] Hazard ratio, 95% confidence interval and p-value from Cox proportional hazards model.

Source data: Appendix 16.2, Listing 7.1

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Table 15.2.4: 1 MRI Examination: Flair - Full Analysis Set

	ASPIRIN		AGGRENOX	
	Actual	Change	Actual	Change
Number of patients with MRI examination	164		156	
Flair - volume of lesion (mL)				
Visit 1 (Screening/Baseline)				
N	139		134	
Mean	3.2427		2.0037	
SD	12.6518		6.5482	
Min	0.000		0.000	
Q1	0.0000		0.0000	
Median	0.1700		0.0400	
Q3	0.8700		0.6000	
Max	125.190		45.840	
Visit 2 (Day 8)				
N	122	116	120	111
Mean	5.5980	2.5159	5.1768	4.1379
SD	17.5774	7.5412	28.5340	29.1163
Min	0.000	-13.390	0.000	-5.860
Q1	0.2900	0.1050	0.2500	0.0200
Median	0.9850	0.4100	0.8600	0.3300
Q3	3.1400	2.0450	2.3200	1.3500
Max	172.860	47.670	308.930	304.870
p-value[1]		0.358		

[1] p-value comparing treatment groups from Wilcoxon rank-sum test.
Source data: Appendix 16.2, Listings 6.6, 6.7. 6.8
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Table 15.2.4: 1 MRI Examination: Flair - Full Analysis Set

	ASPIRIN		AGGRENOX	
	Actual	Change	Actual	Change
Visit 4 (Day 90)				
N	110	101	98	90
Mean	2.8655	0.9774	1.8230	0.3569
SD	8.1785	4.1256	4.2384	2.0355
Min	0.000	-12.300	0.000	-9.390
Q1	0.2100	0.0000	0.1400	0.0000
Median	0.5650	0.1900	0.6000	0.1150
Q3	1.9500	1.1400	1.4300	0.9000
Max	58.790	27.170	24.960	9.550
p-value[1]		0.537		

[1] p-value comparing treatment groups from Wilcoxon rank-sum test.
Source data: Appendix 16.2, Listings 6.6, 6.7. 6.8
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Table 15.2.4: 2 MRI Examination: DWI - Full Analysis Set

	ASPIRIN		AGGRENOX	
	Actual	Change	Actual	Change
Number of patients with MRI examination	164		156	
DWI - volume of lesion (mL)				
Visit 1 (Screening/Baseline)				
N	148		138	
Mean	5.4654		4.5693	
SD	16.9620		15.4800	
Min	0.000		0.000	
Q1	0.4350		0.3500	
Median	1.0450		0.9050	
Q3	2.8100		2.9400	
Max	177.890		163.560	
Visit 2 (Day 8)				
N	123	120	123	117
Mean	5.5009	-0.2728	4.9242	0.5856
SD	17.7627	5.2544	21.2036	6.7573
Min	0.000	-30.040	0.000	-22.090
Q1	0.2800	-0.7050	0.2800	-0.5000
Median	1.0300	-0.0600	1.0300	0.0000
Q3	3.5200	0.5650	2.7200	0.3000
Max	183.850	16.510	220.730	57.170
p-value[1]		0.816		

[1] p-value comparing treatment groups from Wilcoxon rank-sum test.
Source data: Appendix 16.2, Listings 6.6, 6.7. 6.8
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Table 15.2.4: 2 MRI Examination: DWI - Full Analysis Set

	ASPIRIN		AGGRENOX	
	Actual	Change	Actual	Change
Visit 4 (Day 90)				
N	82	80	77	70
Mean	0.3157	-2.2202	0.2673	-2.4327
SD	1.9593	3.8189	1.1115	6.2489
Min	0.000	-22.920	0.000	-45.480
Q1	0.0000	-2.0850	0.0000	-1.9300
Median	0.0000	-0.8400	0.0000	-0.7100
Q3	0.0000	-0.3550	0.0000	-0.2600
Max	17.520	1.160	7.830	5.170
p-value[1]		0.444		

[1] p-value comparing treatment groups from Wilcoxon rank-sum test.
Source data: Appendix 16.2, Listings 6.6, 6.7. 6.8
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Table 15.2.5: 1 Special Biochemistry Laboratory Values: CRP - Full Analysis Set

	ASPIRIN		AGGRENOX	
	Actual	Change	Actual	Change
Number of patients	263		266	
Visit 1 (Screening/Baseline)				
N	250		247	
Geometric mean	2.517		2.612	
95% Confidence interval	2.161, 2.931		2.244, 3.040	
Visit 2 (Day 8)				
N	214	213	216	212
Geometric mean	3.234	1.271	3.009	1.174
95% Confidence interval	2.647, 3.950	1.060, 1.524	2.501, 3.620	0.999, 1.380
pvalue[1]		0.605		

Note: For change from baseline results, data is log-transformed prior to calculating change from baseline and calculating geometric mean and 95% confidence interval and then back-transformed.
[1] p-value comparing treatment groups from ANCOVA model with factor for treatment and baseline as a covariate.
Source data: Appendix 16.2, Listing 6.9
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Table 15.2.5: 2 Special Biochemistry Laboratory Values: MMP-9 - Full Analysis Set

	ASPIRIN		AGGRENOX	
	Actual	Change	Actual	Change
Number of patients	263		266	
Visit 1 (Screening/Baseline)				
N	251		247	
Geometric mean	85.0875		82.7808	
95% Confidence interval	77.8168, 93.0375		75.5046, 90.7582	
Visit 2 (Day 8)				
N	214	213	216	212
Geometric mean	78.8071	0.9738	80.4025	0.9831
95% Confidence interval	72.1688, 86.0560	0.8838, 1.0730	73.6078, 87.8244	0.8945, 1.0805
pvalue[1]		0.826		

Note: For change from baseline results, data is log-transformed prior to calculating change from baseline and calculating geometric mean and 95% confidence interval and then back-transformed.
[1] p-value comparing treatment groups from ANCOVA model with factor for treatment and baseline as a covariate.
Source data: Appendix 16.2, Listing 6.9
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Table 15.2.5: 3 Special Biochemistry Laboratory Values: MCP-1 - Full Analysis Set

	ASPIRIN		AGGRENOX	
	Actual	Change	Actual	Change
Number of patients	263		266	
Visit 1 (Screening/Baseline)				
N	250		247	
Geometric mean	184.4414		180.2533	
95% Confidence interval	176.6714, 192.5532		171.3105, 189.6630	
Visit 2 (Day 8)				
N	214	213	216	212
Geometric mean	190.4205	1.0559	192.6234	1.0816
95% Confidence interval	182.8894, 198.2617	1.0091, 1.1048	182.7196, 203.0641	1.0322, 1.1334
pvalue[1]		0.531		

Note: For change from baseline results, data is log-transformed prior to calculating change from baseline and calculating geometric mean and 95% confidence interval and then back-transformed.
[1] p-value comparing treatment groups from ANCOVA model with factor for treatment and baseline as a covariate.
Source data: Appendix 16.2, Listing 6.9
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Table 15.3.2: 1 Adverse Event Overall Summary - Treated Set

	ASPIRIN	AGGRENOX	Total
Number of patients	260	283	543
Number of patients with an adverse event	176 (67.7)	212 (74.9)	388 (71.5)
Number of patients with an adverse event of severe intensity	37 (14.2)	40 (14.1)	77 (14.2)
Number of patients with a drug-related adverse event	55 (21.2)	107 (37.8)	162 (29.8)
Number of patients with an adverse event leading to discontinuation	54 (20.8)	77 (27.2)	131 (24.1)
Number of patients with a serious adverse event	48 (18.5)	45 (15.9)	93 (17.1)
Results in death	4 (1.5)	5 (1.8)	9 (1.7)
Immediately life-threatening	3 (1.2)	1 (0.4)	4 (0.7)
Persistent or significant disability/incapacity	8 (3.1)	5 (1.8)	13 (2.4)
Requires patient hospitalisation	23 (8.8)	24 (8.5)	47 (8.7)
Prolongs patient hospitalisation	18 (6.9)	16 (5.7)	34 (6.3)
Congenital anomaly/birth defect	0	0	0
Other comparable medical criteria	0	1 (0.4)	1 (0.2)

Source data: Appendix 16.2, Listing 7.1
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