These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi Drug substance(s): Aspirin/clopidogrel	Study Identifiers: NCT00814268 Study code: CLOPI_L_02452/COMPRESS
Title of the study: Combination of clopidogrel and aspirin for prevention of recurrence in acute atherothrombotic stroke study: prospective, randomized, double-blind, placebo-controlled, multicenter trial (CLOPI_L_02452/COMPRESS)	
Study centers: 20 centers in Korea	
Study period: Date first patient enrolled: 22/Dec/2008 Date last patient completed: 16/May/2012	
Phase of development: 4	
Objectives: Primary objective: To compare the preventive effect of the aspirin and clopidogrel combination therapy to aspirin monotherapy for the recurrent ischemic lesion in acute atherothrombotic stroke patients. Secondary objectives: - Comparison of a Modified Rankin Scale (mRS) score, - Incidence of the composite endpoint for non-lethal strokes, myocardial infarctions and cardiovascular deaths within 30 days, - Incidence of all types of strokes within 30 days, - Safety: comparison of the incidence of hemorrhages (life-threatening, major and minor) and symptomatic cerebral hemorrhages.	
Methodology: prospective, randomized, double-blind, placebo-controlled, single-country, multicenter study.	
Number of patients: Planned: 180 (per group) Randomized: 358 Treated: 349 Evaluated: Efficacy: 349 Safety: 352	
Diagnosis and criteria for inclusion: Male or female patients aged 30 years or older with ischemic stroke diagnosed in 48 hours following the onset of the symptom and who could receive the study drug in 48 hours following the onset of the symptom, with ischemic brain lesion observed in diffusion-weighted magnetic resonance imaging (DWI MRI), and with atherothrombotic lesions in the large vessel corresponding to magnetic resonance angiography (MRA) or computed tomography angiography (CTA) (intracranial or extracranial large vessel): in case of extracranial internal carotid artery, only 30% or more of stenosis as per the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria was accepted. Besides, any cases those were judged as a significant stenosis at the Investigator's discretion were also accepted.	

Study treatments

Investigational medicinal products:

Aspirin (Aspirin Protect®) Formulation: White, circle-shaped tablet, aspirin 100mg contained per Aspirin Protect tablet Route of administration: Oral Dose regimen: - 300mg as a loading dose immediately after visiting the center, regardless of previous administration of aspirin, and after randomization, maintenance dose of 100mg with clopidogrel or placebo (any types of formulation of aspirin available at center could be used when loading dose of aspirin was given to subject before randomization and dose of aspirin could be changed at the discretion of Investigator). - Following randomization, a unified formulation supplied to the center as an investigational product study drug was administered. - From the next day of randomization, the maintenance dose of 100mg was used over 30 days (a total of 30±5 days of treatment period) with the same dose at the same time in every morning with or without food. - If there was dysphagia, it was injected through an L-tube.	Clopidogrel (Plavix® or placebo) Formulation: Pink, circle-shaped film-coated tablet, without identification mark on the tablet for double blinding, clopidogrel 75mg contained per Plavix tablet (same appearance for placebo but not containing clopidogrel). Route of administration: Oral Dose regimen: - 1 tablet (75mg) of clopidogrel or placebo used with aspirin once daily at the same time in every morning with or without food following initial use. - Both the start dose and maintenance dose of clopidogrel were identical as 75mg. - If there was dysphagia, it was injected through an L-tube.

Duration of treatment: 30 ± 5 days

Duration of observation: 30 ± 5 days

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint

Proportion of patients with a newly developing symptomatic or non-symptomatic cerebral infarction within 30 days following the onset of acute atherothrombotic stroke, as confirmed with MRI (or unavoidably confirmed on CT in case of a symptomatic cerebral infarction).

Secondary efficacy endpoints

- Distribution of Modified Rankin Scale (mRS) scores at 30 days following the stroke onset,
- Proportion of the occurrence of the composite endpoint of non-lethal strokes, myocardial infarctions and cardiovascular deaths within 30 days,
- Incidence of all types of strokes within 30 days.

Safety:

Safety endpoint

Proportion of patients with a hemorrhage (classified as life-threatening, major, or minor) within 30 days.

Statistical methods:

Analysis set

- ITT set (Intention-To-Treat): Patients who used the study drug once at least following randomization were included and analyzed per randomized group. Patients who withdrew consent on data at the time of study drop-out were excluded from the analysis.

- Safety set: Patients who were randomized and used the study drug once at least were included, and analyzed per actually treated group.

Statistical analysis

All statistical tests were conducted at the 5% two-sided significance level.

When primary efficacy evaluation data of total 180 patients (90 patients per group) was prepared during the study period, interim analysis was planned. Interim analysis was conducted using the O'Brien and Fleming test method, and the initial design of this study specified that when there was statistically significant difference in the result between groups, the study was to be discontinued; otherwise, the study was to be continued until the final completion time to see if there was statistically significant difference in the incidence rate(%) of ischemic lesions newly a occurred 30-day treatment period following onset of acute atherothrombotic stroke of primary endpoint between combination therapy group and monotherapy group, frequency and percentage were obtained for each group, and comparison was made between groups on the difference of incidence rate using Chi-square test or Fisher's exact test.

Secondary endpoints were analyzed only in final analysis. Regarding mRS of secondary endpoint, distribution of 0~ 6 scales per group was summarized by frequency and percentage, and a Chi-square test was conducted to see if two groups had the same score distribution difference in the incidence rates of combined endpoints of non-fatal stroke, myocardial infarction and cardiovascular death over 30 days and incidence rates of stroke of all types was tested using Chi-square test (or Fisher's exact test) between groups

Summary:

Population characteristics

Among 358 subjects enrolled in this study, 349 subjects who were randomized and received at least 1 dose of study medication after randomization were included in ITT analysis population. Also, 303 subjects (151 in monotherapy group, 152 in combination therapy group) completed this study. Among 358 enrolled subject, 6 subjects (4 in monotherapy group, 2 in combination therapy group) were not exposed to study treatment and 3 subjects (1 in monotherapy, 2 in combination therapy) withdrew consent on data use among 46 drop-out cases (24 in monotherapy, 22 in combination therapy). (Table below)

Distribution of enrolled subjects

	Monotherapy group	Combination therapy group	Total
Enrolled cases, n	180	178	358
Randomized cases, n	180	178	358
ITT Analysis Set, n	175	174	349
Use of study drug, n	176	176	352
Withdrawal of consent for data use	1	2	3
Completion of study, n	151	152	303
Drop-out, n	24	22	46
Consent withdrawal	1	0	1
Protocol violation	2	1	3
Investigator's discretion	13	11	24
Loss of follow up	1	0	1
Adverse event	4	9	13
others	3	1	4

Demographic data and underlying status

The demographic characteristics and baseline data were summarized in the table below.

The mean age of subjects was 65.9±12.03 years in monotherapy group and 66.33±11.47 years in combination therapy group (p=0.6976). For gender, there were 108 male subjects (61.71%) and 67 female subjects (38.29%) in monotherapy group, while 114 male subjects (65.52%) and 60 female subjects (34.48%) in combination therapy group (p=0.4603). Mean BMI (kg/m2) was 23.79±3.55 kg/m2 and 23.81±3.19 kg/m2 in monotherapy group and combination therapy group, respectively (p=0.9666).

Among subject's relevant medical history and co-morbidities, hypertension was predominant in both groups: 19 subjects (68.00%) were in monotherapy group and 112 subjects (64.37%) were in combination therapy group (p=0.4733).

mRS (Modified Rankin Scale) was executed for 175 subjects in monotherapy group and 174 subjects in combination therapy group, and the difference of the execution of mRS was not statistically significant between 2 groups (p=0.9148).

Regarding subtype of stroke under TOAST classification, LAA (Large artery atherosclerosis) was most found in both group: 173 subjects (98.86%) were in monotherapy group and 168 subjects (96.55%) were in combination group (p=0.2014). For the location of territory corresponding to index stroke, MCA (Middle Cerebral Artery) was predominant part in both groups.

At the time of enrollment, 153 subjects (87.43%) in monotherapy group received 279.61±75.33 mg of aspirin on average as a loading dose and 159 subjects (91.38%) in combination therapy group received 282.08±80.99 mg of aspirin on average as a loading dose, and there was no statistically significant difference between 2 groups (p=0.8234).

Demographic characteristics

		Monotherapy group (N=175)	Combination therapy group (N=174)	p-value
General	Age (year)			
	Mean ± S.D.	65.9±12.03	66.33±11.47	0.6976 [2)]
	Median [Min, Max]	67[36,89]	68[37,96]	
	Sex, n(%)			
	male	108(61.71)	114(65.52)	0.4603[3)]
	female	67(38.29)	60(34.48)	
	Height (cm)			
	Mean ± S.D.	162.27±8.47	162.28±8.65	0.9541[2)]
	Median [Min, Max]	162[140,181]	163[142,180]	
	Weight (kg)			
	Mean ± S.D.	62.68±11.46	62.82±10.45	0.9025[1)]
	Median [Min, Max]	63[34,105]	62[36,99]	
	BMI(kg/m^2)			
	Mean ± S.D.	23.79±3.55	23.81±3.19	0.9666[1)]
	Median [Min, Max]	23.73[15.52,36.33]	23.8[17.19,32.45]	

Demographic characteristics (cont't)

		Monotherapy group (N=175)	Combination therapy group (N=174)	p-value
Relevant medical history & co-morbidities	Hypertension, n(%)			
	Yes	119(68)	112(64.37)	0.4733[1)]
	No	56(32)	62(35.63)	
	Diabetes Mellitus, n(%)			
	Yes	55(31.43)	58(33.33)	0.7038[1)]
	No	120(68.57)	116(66.67)	
	Dyslipidemia, n(%)			
	Yes	50(28.57)	59(33.91)	0.2821[1)]
	No	125(71.43)	115(66.09)	
	Coronary artery disease, n(%)			
	Yes	8(4.57)	8(4.6)	0.9906[1)]
	No	167(95.43)	166(95.4)	
	Previous Ischemic Stroke, n(%)			
	Yes	16(9.14)	20(11.49)	0.4702[1)]
	No	159(90.86)	154(88.51)	
	Previous hemorrhagic Stroke, n(%)			
	Yes	0 (0.00)	0 (0.00)	NA
	No	175(100)	174(100)	
mRS score	Yes	175(100)	174(100)	-
	No	0(0)	0(0)	
	n(%)			
	0	151(86.29)	149(85.63)	0.9148[2)]
	1	16(9.14)	17(9.77)	
	2	5(2.86)	3(1.72)	
	3	2(1.14)	3(1.72)	
	4	1(0.57)	2(1.15)	
	5	0(0)	0(0)	
	6	0(0)	0(0)	
TOAST classification	LAA	173(98.86)	168(96.55)	0.2014[2)]
	SVO	0(0)	0(0)	
	CE	0(0)	0(0)	
	SOE	0(0)	1(0.57)	
	SUE	2(1.14)	5(2.87)	

LAA : Large artery atherosclerosis, SVO : Small vessel occlusion, CE : Cardioembolism, SOE : Stroke of other determined etiology, SUE : Stroke of undetermined etiology

Demographic characteristics (cont'd)

		Monotherapy group (N=175)	Combination therapy group (N=174)	p-value
Location of territory	ICA, n(%)	13 (7.43)	6 (3.45)	0.1013[1)]
	MCA, n(%)	121 (69.14)	108 (62.07)	0.1642[1)]
	ACA, n(%)	6 (3.43)	6 (3.45)	0.9919[1)]
	PCA, n(%)	14 (8)	22 (12.64)	0.1538[1)]
	VA, n(%)	4 (2.29)	11 (6.32)	0.0630[1)]
	SCA, n(%)	3 (1.71)	7 (4.02)	0.2191[2)]
	AICA, n(%)	0 (0.00)	1 (0.57)	0.4986[2)]
	PICA, n(%)	6 (3.43)	13 (7.47)	0.0960[1)]
	Border-zone, n(%)	10 (5.71)	7 (4.02)	0.4630[1)]
	BA, n(%)	15 (8.57)	22 (12.64)	0.2166[1)]

ICA: Internal Carotid A, MCA: Middle Cerebral A, ACA: Anterior Cerebral A, PCA: Posterior Cerebral A, BA: Basilar A, SCA:Superior Cerebellar A, AICA: Anterior Inferior Cerebellar A, PCA: Posterior Inferior Cerebellar A, VA: Vertebral A, BG/IC: Basal Ganglia/Internal Capsule

1) p-value by Chi-square test 2) p-value by Fisher's exact test

Efficacy results

Primary endpoint

A total of 349 subjects were included in Intention-To-Treat (ITT) analysis. And this ITT population was defined as the people who met all of the inclusion criteria and none of the exclusion criteria, voluntarily consented to participate in the study, were randomized, and received at least one dose of the study treatment (aspirin, clopidogrel, clopidogrel placebo) after randomization.

Primary objective of this clinical study was to compare the preventive effect of the aspirin and clopidogrel combination therapy to aspirin monotherapy for the recurrent ischemic lesion in acute atherothrombotic stroke patients. The primary endpoint was to compare the proportion of patients with a newly developing symptomatic or non-symptomatic cerebral infarction within 30 days following the onset of acute atherothrombotic stroke, with confirmed by MRI (or unavoidably confirmed on CT in case of a symptomatic cerebral infarction) between monotherapy group and combination therapy group.

Adjudication committee reviewed baseline MRI (CT) to figure out whether there were atherothrombotic lesions in the large vessel or not. And IRC specialists reviewed follow-up MRI (CT) to evaluate newly occurred cerebral infarction within 30 days treatment period regardless of clinical symptoms. The definition of newly occurred cerebral infarction was separate lesion from the primary ischemic lesion on follow-up MRI (CT) regardless of vascular territory.

Interim analysis for 180 subjects (85 subjects in monotherapy group, 95 subjects in combination therapy group) revealed that the incidence rate of ischemic lesions was 15.79% (N=15) in combination therapy group (aspirin and clopidogrel), while it was 14.12% (N=12) in monotherapy group (aspirin), which indicates that there was no statistically significant difference between 2 groups as a result of the analysis using O'Brien and Feming test method on the adjusted significance level of 0.5% (p=0.7538).

ITT analysis revealed that the incidence rate of ischemic lesions was 35.93% in monotherapy group (aspirin), while it was 36.53% in combination therapy group (aspirin and clopidogrel) indicating that there was no statistically significant difference between groups at the 4.8% significance level through Chi-square test (p=0.9094). (Table below)

Comparison on incidence rates of ischemic lesions

	Monotherapy group (N=175)	Combination therapy group (N=174)	p-value
Occurrence of ischemic lesions, n(%)			
Not found	107(64.07)	106(63.47)	0.9094[1)]
found	60(35.93)	61(36.53)	

p-value by Chi-square test; * Missing: 15 (Monotherapy group: 8, Combination therapy group: 7)

Secondary endpoints

Distribution of mRS (Modified Rankin Scale) scores at last visit

Distribution of mRS (Modified Rankin Scale) scores measured at the last visit following onset of stroke, which was performed to see if there was any difference of the distribution of mRS score in ITT Analysis population between monotherapy group and combination therapy group, revealed that the difference between 2 groups was not statistically significant at the 5% significance level (p=0.2022). (Table below)

mRS scores measured at last visit

	Monotherapy group (N=175)	Combination therapy group (N=174)	p-value
mRS, n(%)			
0 point	43(27.92)	38(25.17)	0.2022[1)]
1 point	42(27.27)	50(33.11)	
2 points	30(19.48)	15(9.93)	
3 points	13(8.44)	15(9.93)	
4 points	18(11.69)	25(16.56)	
5 points	8(5.19)	8(5.3)	
6 points	0(0)	0(0)	

1) p-value by Chi-square test; *Missing : 44 (Monotherapy group : 21, Combination therapy group : 23)

mRS was categorized into 0-1 points versus 2-6 points, and 0-2 points versus 3-6 points between monotherapy group and combination therapy group, frequency and percentage were obtained for each cut-off point per group, comparison on distribution difference was made, and the difference between groups was not statistically significant (Table below).

Distribution of mRS (Modified Rankin Scale) cut-off points measured at last visit

	Monotherapy group (N=175)	Combination therapy group (N=174)	p-value
mRS, n(%)			
0-1 points	85(55.19)	88(58.28)	0.5869[1)]
2-6 points	69(44.81)	63(41.72)	
missing	21	23	
0-2 points	115(74.68)	103(68.21)	0.2113[1)]
3-6 points	39(25.32)	48(31.79)	

1) p-value by Chi-square test; *Missing : 44 (Monotherapy group : 21, Combination therapy group : 23)

Regarding mRS per score of NIHSS, mRS was categorized into 0 point and 1-6 points if NIHSS is 0-7 point(s), 0-1 point(s) and 2-6 points if NIHSS was 8-14 points, and 0-2 point(s) and 3-6 points if NIHSS was ≥15 points, frequency and percentage were obtained per group, comparison on the difference of distribution was made, and the difference between 2 groups was not statistically significant (Table below).

Distribution of mRS scores under NIHSS measured at last visit

		Monotherapy group (N=175)	Combination therapy group (N=174)	p-value
Total NIHSS scores	mRS score, n(%)			
0-7 points	0 point	43(31.39)	38(28.57)	0.6138[1)]
	1-6 point(s)	94(68.61)	95(71.43)	
8-14 points	0-1 point(s)	0(0)	0(0)	NA
	2-6 points	15(100)	15(100)	
≥15 points	0-2 point(s)	0(0)	0(0)	NA
	3-6 points	2(100)	3(100)	

1) p-value by Chi-square test; *Missing : 44 (Monotherapy group : 21, Combination therapy group : 23)

Incidence rates of combined endpoints of non-fatal stroke, myocardial infarction and cardiovascular death over 30 days

Regarding combined cardiovascular outcomes, 6 subjects (2.61%) were found in monotherapy group and 3 subjects (1.8%) were found in combination therapy group (p=0.3363). (Table below)

Incidence rates of combined cardiovascular outcomes

	Monotherapy group (N=175)	Combination therapy (N=174)	p-value
Combined cardiovascular outcomes, n(%)			
No	160(96.39)	164(98.2)	0.3363[1)]
Yes	6(3.61)	3(1.8)	
Causes of combined CV outcomes, n(%)			
Ischemic stroke	5(83.33)	2(66.67)	
Hemorrhagic stroke	0(0)	1(33.33)	
Unknown cases of stroke	0(0)	0(0)	
Myocardial infarction	1(16.67)	0(0)	
Death by vascular disease	0(0)	0(0)	

1) p-value by Fisher's exact test; *Missing : 16 (Monotherapy group : 9, Combination therapy group : 7)

Incidence rates of stroke for all types over 30 days

The all types of stroke over 30 days were investigated by Investigators' judgment regardless of MRI results reviewed by IRC for primary endpoint. Regarding all types of stroke, there was no statistically significant difference between both groups (p=1.000). (Table below)

Incidence rates of stroke

	Monotherapy group (N=175)	Combination therapy group (N=174)	p-value
Stroke of all types n(%)			
No	161 (96.99)	164 (98.2)	0.5018[1)]
Yes	5 (3.01)	3 (1.8)	
Ischemic stroke	5(100)	2(66.67)	0.3750[1)]
Hemorrhagic stroke	0 (0.00)	1 (33.33)	
Unknown cause	0 (0.00)	0 (0.00)	

1) p-value by Fisher's exact test; *Missing : 16 (Monotherapy group : 9, Combination therapy group : 7)

Incidence rate of hemorrhage over 30 days

In interim analysis, incidence rate of hemorrhage of over 30 days was also reviewed for 180 subjects for primary endpoint. Incidence rate of hemorrhage over 30 days was 11.76% (N=10) in monotherapy group and 20.00% (N=19) in combination therapy group. These data was reviewed by IDMC and IDMC decided to continue this trial.

After interim analysis, clopidogrel safety issue was raised in the other previous IST. IDMC reviewed safety data and results for detecting safety issues in this study, and 295 subjects (147 in monotherapy and 148 in combination therapy) safety data were reviewed, including 180 subjects already reviewed in interim analysis. Incidence rate of hemorrhage over 30 days was 11.97% (N=17) in monotherapy group and 19.44% (N=28) in combination therapy group and there was no statistically significant difference (p=0.083). Based on this result, IDMC decided to continue this study.

Percentage of patients who had hemorrhage (life-threatening/major/minor) over 30 days was calculated between monotherapy group and combination therapy group and the most severe hemorrhage was counted in case patient experienced more than 2 categories of hemorrhage during study period. Regarding this endpoint, there was no statistically significant difference between both groups (p=0.0999). (Table below)

Incidence rates of hemorrhage over 30 days

	Monotherapy group (N=178)	Combination therapy group (N=174)	p-value
Hemorrhage, n(%)			
No	153(88.95)	139(82.74)	0.0999[1)]
Yes	19(11.05)	29(17.26)	
Life-threatening hemorrhage	2(10.53)	4(13.79)	
Major hemorrhage	0(0.00)	3(10.34)	
Minor hemorrhage	17(89.47)	22(75.86)	

Combined case : 4 (1 case of life-threatening hemorrhage and major hemorrhage in monotherapy group, 3 cases of major hemorrhage and minor hemorrhage in combination therapy group)

1)p-value by Chi-square test; *Missing : 12 (Monotherapy group : 6, Combination therapy group : 6)

Safety results

A total of 352 subjects were included in safety evaluation. And this population was defined as the people who consented to participate in this study, were randomized, and received the study drug once at least. The proportion of subjects who experienced at least 1 adverse event after investigational product administration was 73.03% (130/178 subjects, 394 events) in monotherapy group and 71.84% (125/174 subjects, 375 events) in combination therapy group (p=0.8020). There were 3 deaths in combination therapy group during study period, and there was no causality between study treatment and all deaths. The reasons of deaths were as follows: progression of cerebral infarction, suspicious aortic aneurysm rupture, unknown. Regarding adverse events and serious adverse events, there was no statistically significant difference between both groups.

The incidence rate of adverse drug reactions (ADR) for which the relationship with the investigational product (Plavix or placebo) could not be excluded was 10.11% (18/178 subjects, 19 event) in monotherapy group and 9.20% (16/174 subjects, 24 events) in combination therapy group (p=0.7709). (Table below)

In both groups, adverse events were classified by System Organ Class (SOC) and most commonly reported SOC was 'gastrointestinal disorders' and the 2nd was 'nervous system disorders'. The most frequently observed adverse event PT was 'constipation' in both groups.

Adverse event summary

	Total (N=352)		Monotherapy group (N=178)		Combination therapy group (N=174)		p-value
	N (%)	N of events	N (%)	N of events	N (%)	N of events	
Adverse event (AE)	255(72.44)	769	130(73.03)	394	125(71.84)	375	0.8020[1)]
Serious adverse event (SAE)	29(8.24)	39	10(5.62)	14	19(10.92)	25	0.0705[1)]
Adverse drug reaction (ADR)	34 (9.66%)	43	18 (10.11)	19	16 (9.2)	24	0.7709[1)]
Adverse event resulting in withdrawal	33 (9.38)	36	16 (8.99)	17	17 (9.77)	19	0.8015[1)]
Death	3(0.85)	3	0(0)	0	3(1.72)	3	0.1197[2)]

Issue date: 05-Sep-2013