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Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00296218
		Study Code:	PM_C_0024
Generic drug name:	irbesartan	**Date:**	18 Jun 2008

Title of the study:	ARCHIPELAGO - Randomized comparison of a two-month regimen of irbesartan versus enalapril on cardiovascular markers in patients with acute coronary syndrome without ST segment elevation (PM – C – 0024, CV131- 244 ST)		
Investigator(s):	Coordinating Investigator: Professor G. Montalescot, Institut de Cardiologie, Hôpital La Pitié Salpêtrière, Paris, France		
Study center(s):	63 centers in 11 countries (Belgium: 6, Netherlands: 12, Germany: 8, Italy: 6, Switzerland: 3, Spain: 7, Hungary: 8, United Kingdom: 5, France: 4, USA: 3, Canada: 1)		
Publications (reference):	none		
Study period: Date first patient enrolled: 09-Feb-2006 Date last patient completed: 23-Mar-2007		Phase of development: IIIb	
Objectives:	The primary objective of this study was to assess if a two-month regimen of irbesartan in patients hospitalized for acute coronary syndrome without ST segment elevation can reduce inflammatory markers (i.e. high-sensitive C-reactive protein [hsCRP]) in comparison to a similar regimen of enalapril. The secondary objective of this study were: To compare both regimens on several other biological parameters which had demonstrated their relevance and their predictive clinical value (ie B-type natriuretic peptide [BNP], microalbuminuria, troponin I …) in this patient population. To compare on the above parameters the early initiation of treatment versus the initiation of treatment at hospital discharge.		
Methodology:	International, multicenter, double blind, double dummy , 2x2 factorial design, Phase IIIb study		
Number of patients:	Planned: 440 patients (irbesartan: 220, enalapril: 220),	Randomized: 440 patients (irbesartan: 219, enalapril: 221)	Treated: 429 patients (irbesartan: 212, enalapril: 217)
Evaluated:	Safety/Intent-to-treat (ITT): 429 (irbesartan: 212, enalapril: 217) patients Pure Per-Protocol: 238 (irbesartan: 115, enalapril: 123) patients Second Per-Protocol: 254 (irbesartan: 126, enalapril: 128) patients		Pharmacokinetics: Not applicable

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Diagnosis and criteria for inclusion:	Patients (men and women, ≥ 18 years of age) who were hospitalized with ischemic symptoms (last episode within the last 48 hours before randomization) and who had at least one of the following characteristics of non-ST-segment-elevation acute coronary syndrome (NSTEACS): electrocardiogram (ECG) ST or T changes (ST depression or transient elevation of at least 1 mm or T wave changes in at least 2 leads) and/or positive troponin (according to local threshold).
Investigational product:	Irbesartan
Dose:	Irbesartan 150mg tablets and matching placebo once daily (OD) (150mg started either on Day 1 [admission] or at hospital discharge (or Day 7 if patient not discharged) and followed by 300mg once daily from Day 15 ± 5 on.
Administration:	For all phases of this study, patients were asked to take their dose in the morning, once daily.

Duration of treatment: 2 months	Duration of observation: 2 months

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Reference therapy:	Enalapril
Dose:	Enalapril 10mg tablets (European countries, Switzerland, and Canada) or Enalapril 20mg capsules and matching placebo (US) (10mg) started either on Day 1 [admission] or at hospital discharge (or Day 7 if patient not discharged) and titrated up to 20mg once daily from Day 15 ± 5 on.
Administration:	For all phases of this study, patients were asked to take their dose in the morning, once daily.
Criteria for evaluation:	
Efficacy:	Primary efficacy variable comparison of the absolute (and relative) change from baseline in hsCRP at Day 60 ± 7 between the two treatment groups. Secondary efficacy variables • relative change from baseline of hsCRP at discharge (or Day 7 if the patient not discharged) between the two treatment groups • changes from baseline in BNP and Microalbuminuria (MAU) at discharge (or Day 7 if the patient not discharged) and Day 60 between the two treatment groups • change of Troponin I from baseline at discharge (or Day 7 if the patient not discharged) between the two treatment groups • blood pressure changes from baseline at discharge (or Day 7 if the patient not discharged), Day 15 and Day 60 between the two treatments groups • In addition, at baseline, discharge (or Day 7 if the patient not discharged) and Day 60 the following parameters were evaluated and their evolution compared in the two treatment groups: Interleukin- 6 (IL6), Cluster of differentiation 40Ligand (CD 40L), secretory phospholipase A2 ($sPLA_2$), Ischemic Modified Albumin (IMA), Matrixmetalloproteïnase-9 (MMP-9), myeloperoxidase (MPO), aldosterone.
Safety:	• Physical examination including blood pressure and heart rate. • All causes of death • Incidence of Major Adverse Cardiac Event (MACE) confirmed by adjudication: cardiovascular death, myocardial infarction, stroke, hospitalization for recurrent ischemia or urgent revascularisation • Incidence of adverse events (AEs) in each group • Drop-out rate from treatment due to systolic blood pressure (SBP) < 100 mm Hg
Pharmacokinetics:	Not applicable.

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Generic drug name:	irbesartan	**Date:**	18 Jun 2008

Statistical methods:	For the statistical analyses of the primary end point: absolute (and relative) change from baseline of hsCRP variable at Day 60 ± 7, all the patients with at least baseline value of hsCRP were considered. If for a patient post baseline data on hsCRP was not available, these hsCRP values were imputed by the Last Observation Carried Forward (LOCF) concept and were included for the analyses of the primary end point for the ITT population. In the PP Population analysis no missing value imputation was adopted. It was planned to analyze the relative change from baseline of hsCRP variable at Day 60 ± 7 as primary endpoint, but due to the skewness and non-homoscedasticity of the relative change values it was decided to analyze the absolute change as primary endpoint instead. Analysis of covariance (ANCOVA) was carried out for the absolute (and relative) change from baseline of hsCRP variable at Day 60 with 2 main factors as the drug effect (two treatment regimen), the time treatment effect (early vs. delayed treatment), the interaction between drug effect and time to treatment effect and the baseline value as a covariate. The interaction term was tested at p=0.10 and if it was found to be not significant, then each main effect in the same model was tested at p=0.05, adjusted for baseline value (ANCOVA). The main analyses were based on the relative change from baseline (visit 1) to Day 60 (visit 4) in the hsCRP comparison. Secondary efficacy analysis was carried out with the same model but taking into account the new co-variable, whether the patient was diabetic or not using 3 factors ANCOVA. Secondary endpoints were analyzed using the same modalities as primary endpoint but no adjustments were made for multiple tests.

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Summary:

Baseline results:

Overall, both treatment groups were similar with regard to demographic and baseline data. The median age was 61.0 years and the majority of patients was male with 161 of 212 (75.9%) patients in the irbesartan group and 217 (72.4%) patients in the enalapril group.

As disease characteristics at baseline, cardiac disorders and the cardiac risk factors current smoking, hyperlipidaemia, hypertension and diabetes were most frequently mentioned. The rates of previous myocardial infarction (p = 0.0347), previous angina (p = 0.0115), previous cardiac intervention (p = 0.0403) and of other evidence of coronary artery disease (0.0113) were significantly higher in the irbesartan group than in the enalapril group.

Most of the patients had ischemic symptoms (99.8%) or increase of local troponin (74.5% of patients in the irbesartan group and 80.2% patients in the enalapril group) at study entry without a clinically relevant difference between the 2 groups.

A planned coronarography was reported in 175 (82.5%) patients in the irbesartan group and in 181 (83.4%) patients in the enalapril group.

Efficacy results:

Comparison of the change from baseline in hsCRP at Day 60 ± 7 between the two treatment groups

Primary efficacy variables

Absolute changes of hsCRP from baseline to Day 60 (ITT)

In the ITT population, hsCRP decreased from baseline to Day 60 in a similar manner in both treatment groups. In the irbesartan group, the mean hsCRP decreased from 15.2 mg/L at visit 1 to 6.5 mg/L at visit 4 and in the enalapril group from 12.6 mg/L at visit 1 to 5.5 mg/L at visit 4. The mean absolute decrease of hsCRP from baseline to Day 60 was -8.7 mg/L in the irbesartan group and -7.1 mg/L in the enalapril group (analysis of LOCF values). In the ANCOVA model for the absolute change of hsCRP from baseline to Day 60 with treatment*initiation of treatment interaction term this term was found not statistically significant at level p = 0.1 (p = 0.1559, analysis of LOCF values). In the ANCOVA model for the absolute change of hsCRP from baseline to Day 60 without treatment*initiation of treatment interaction term the test for difference between the treatment groups was found not statistically significant (p = 0.5767, analysis of LOCF values). For the treatment effect, the LS mean difference (irbesartan minus enalapril) [95% CI] was 0.79 [-1.990; 3.570] mg/L. In the ANCOVA model for the absolute change of hsCRP from baseline to Day 60 without treatment*initiation of treatment interaction term the test for difference between early and late initiation of study treatment was found not statistically significant (p = 0.6374, analysis of LOCF values).

Relative changes of hsCRP from baseline to Day 60 (ITT)

The mean relative change of hsCRP from baseline to Day 60 was 55.9% in the irbesartan group and 76.5% in the enalapril group. Due to skewed distribution of the values, some patients had high relative increases which were linked to small absolute changes. As a consequence, the relative changes were positive while the absolute changes were negative. In the ANCOVA model for the relative change of hsCRP from baseline to Day 60 with treatment*initiation of

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Generic drug name:	irbesartan	**Date:**	18 Jun 2008

Efficacy results:

treatment interaction term this term was found not statistically significant at level p = 0.1 (p = 0.5725, analysis of LOCF values). In the ANCOVA model for the relative change of hsCRP from baseline to Day 60 without treatment*initiation of treatment interaction term the test for difference between the treatment groups was found not statistically significant (p = 0.8687, analysis of LOCF values). For the treatment effect, the LS mean difference (irbesartan minus enalapril) [95% CI] was -15.23 [-196.238; 165.778]%. In the ANCOVA model for the relative change of hsCRP from baseline to Day 60 without treatment*initiation of treatment interaction term the test for difference between early and late initiation of study treatment was found not statistically significant (p = 0.3892, analysis of LOCF values).

Secondary efficacy variables

Absolute changes of hsCRP from baseline to Day 60 (ITT, including diabetes)
In the ANCOVA model for the absolute change of hsCRP from baseline to Day 60 including diabetes status without interaction terms the test for difference between the treatment groups was found not statistically significant (p = 0.5779 for the treatment effect, analysis of LOCF values).

Absolute change from baseline of hsCRP at discharge between the two treatment groups
In the ITT population, the ANCOVA model for the absolute change of hsCRP from baseline to discharge with treatment*initiation of treatment interaction term this term was found not statistically significant at level p = 0.1 (p = 0.6389, analysis of LOCF values). In the ANCOVA model for the absolute change of hsCRP from baseline to discharge without treatment*initiation of treatment interaction term the test for difference between the treatment groups was found not statistically significant (p = 0.9311, analysis of LOCF values). For the treatment effect, the LS mean difference (irbesartan minus enalapril) [95% CI] was 0.21 [-4.631, 5.058] mg/L.

Relative change from baseline of hsCRP at discharge between the two treatment groups
In the ANCOVA model for the relative change of hsCRP from baseline to discharge with treatment*initiation of treatment interaction term this term was found not statistically significant at level p = 0.1 (p = 0.9286, analysis of LOCF values). In the ANCOVA model for the relative change of hsCRP from baseline to discharge without treatment*initiation of treatment interaction term the test for difference between the treatment groups was found not statistically significant (p = 0.8150, analysis of LOCF values). For the treatment effect, the LS mean difference (irbesartan minus enalapril) [95% CI] was 21.84 [-205.206; 161.523]%.

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Efficacy results:

Comparison of the absolute change from baseline in hsCRP at Day 60 ± 7 between the two treatment groups [mg/L]

ITT population	Baseline (Day 1)		Visit 4 (Day 60)	
	Irbesartan	Enalapril	Irbesartan	Enalapril
n	210	216	212	217
Mean (SD)	15.2 (30.2)	12.6 (26.4)	6.5 (17.4)	5.5 (11.4)
Median	4.2	4.3	2.2	2.0
n			210	216
Mean absolute change	---	---	-8.7	-7.1
LS Mean difference for treatment				0.79
p-value for treatment difference				0.5767
p-value for interaction				0.1559

Early initiation (ITT)	Baseline(Day 1)		Visit 4 (Day 60)	
	Irbesartan	Enalapril	Irbesartan	Enalapril
n	104	107	105	107
Mean (SD)	17.1 (33.9)	13.5 (29.4)	5.3 (13.9)	6.3 (13.3)
Median	4.6	4.1	2.1	2.2
n	---	---	104	107
Mean absolute change	---	---	-11.7	-7.3

Initiation at hospital discharge (ITT)				
n	106	109	107	110
Mean (SD)	13.5 (26.1)	11.7 (23.2)	7.7 (20.2)	4.8 (9.2)
Median	3.9	4.6	2.3	1.8
n	---	---	106	109
Mean absolute change	---	---	-5.7	-6.9

Changes from baseline in BNP and Microalbuminuria (MAU) at discharge and Day 60 between the two treatment groups

BNP decreased over time in a similar manner in both treatment groups. In the irbesartan group, the mean BNP decreased from 144.5 pg/mL at visit 1 to 143.1 pg/mL at visit 2 and to 116.3 pg/mL at visit 4 and in the enalapril group from 140.3 pg/mL at visit 1 to 125.8 pg/mL at visit 2 and to 91.9 pg/mL at visit 4. There were no statistically significant differences for absolute change of BNP from baseline to discharge and Day 60 with and without treatment*initiation of treatment interaction term and with regard to difference between early and late initiation of study treatment.

The mean level of microalbuminuria changed from 33.4 mg/L at visit 1 to 39.3 mg/L at visit 2 and to 38.2 mg/L at visit 4 in the irbesartan group and from 23.0 mg/L at visit 1 to 16.3 mg/L at visit 2 and to 19.3 mg/L at visit 4 in the enalapril group. There were no statistically significant differences for absolute change of microalbuminuria from baseline to discharge and Day 60 with and without treatment*initiation of treatment interaction term and with regard to difference between early and late initiation of study treatment.

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Efficacy results:

Change of Troponin I from baseline at discharge between the two treatment groups

In the irbesartan group, the mean troponin I level decreased from 3.1 ng/mL at visit 1 to 0.1 ng/mL at visit 2 and in the enalapril group from 3.4 pg/mL at visit 1 to 0.8 pg/mL at visit 2. There were no statistically significant differences for absolute change of troponin I from baseline to discharge with and without treatment*initiation of treatment interaction term and with regard to difference between early and late initiation of study treatment.

Analysis of cardiovascular markers IL6, CD40 L, $sPLA_2$, IMA, MMP-9, MPO, aldosterone

The markers of myocardial damage, ischemia and dysfunction as well as those of endothelial dysfunction decreased over time, in a similar manner in both treatment groups. The difference in the time to initiation of treatment had no detectable effect on these CV markers. In the ITT population, the ANCOVA models for the absolute changes from baseline to discharge with treatment*initiation of treatment interaction terms these terms were found not statistically significant at level p = 0.1. In the ANCOVA models for the absolute changes from baseline to discharge without treatment*initiation of treatment interaction terms the tests for difference between the treatment groups were found not statistically significant.

For aldosterone, an early treatment initiation was associated with a clear decrease of aldosterone levels between baseline and visit 2 and the least squares means (LSMEANS) (early — late) of change from baseline was -19.15 pg/mL (p <0.0001). The change from baseline and D60 was not statistically significant.

	p-values (LOCF analysis)		
	Interaction treatment*initiation	treatment effect	initiation of treatment
IL-6	0.2275	0.1218	0.9966
CD40 L	0.8044	0.6479	0.7036
s-PLA2	0.3406	0.2796	0.1099
IMA	0.8666	0.3818	0.2358
MMP-9	0.9922	0.2234	0.9624
MPO	0.9581	0.3894	0.5555
Aldosterone	0.4964	0.8517	<0.0001

Drop-out due to systolic blood pressure < 100 mmHg

Overall, 22 (10.4%) patients in the irbesartan group and 11 (5.1%) patients in the enalapril group discontinued the study due to a systolic blood pressure < 100 mmHg. Both treatment groups were similar with regard to blood pressure.

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Safety results:	Overall, 286 treatment-emergent AEs (TEAEs) were reported in 132 (62.3%) patients in the irbesartan group and 295 TEAEs in 143 (65.9%) patients in the enalapril group. Under early initiation of treatment, 146 TEAEs in 62 (59.0%) patients in the irbesartan group and 141 TEAEs in 68 (63.6%) patients in the enalapril group were reported and 140 TEAEs in 70 (65.4%) patients in the irbesartan group and 154 TEAEs in 75 (68.3%) patients in the enalapril group when treatment was initiated as discharge. There were no clinically relevant differences between the treatment groups with regard to timepoint of treatment initiation. Treatment groups were also clinically similar with regard to frequency and distribution, severity and relationship to study drug of TEAEs, TEAEs leading to discontinuation and MACE. In total, 20 TEAEs in 16 (7.5%) patients in the irbesartan group and 15 TEAEs in 13 (6.0%) patients in the enalapril group were adjudicated as MACE, thereof myocardial infarction in 9 (4.2%) patients in the irbesartan group and in 5 (2.3%) patients in the enalapril group, hospitalization for recurrent angina in 4 (1.9%) patients in the irbesartan and in 5 (2.3%) patients in the enalapril group, hospitalization for urgent revascularization in 4 (1.9%) patients in the irbesartan and in 2 (0.9%) patients in the enalapril group and cardiovascular death in 2 (0.9%) patients in the irbesartan and 3 (1.4%) patients in the enalapril group. Severe or very severe related TEAEs were reported in 14 (6.6%) patients in the irbesartan group and in 8 (3.7%) patients in the enalapril group. Overall, 49 serious TEAEs were reported in 39 (18.4%) patients in the irbesartan group and 43 serious TEAEs in 36 (16.6%) patients in the enalapril group. Six deaths were reported, thereof 4 deaths as TEAEs with fatal outcome in 3 (1.4%) patients in the irbesartan group and in 1 (0.5%) patient in the enalapril group, the 2 other deaths occurred in post-treatment period. None of the deaths was related to the study drugs. Treatment groups were similar with regard to laboratory parameters and vital signs. In summary, both treatments were safe and well tolerated and showed a good safety profile.
Pharmacokinetic results	Not applicable.
Date of report:	09 June-2008