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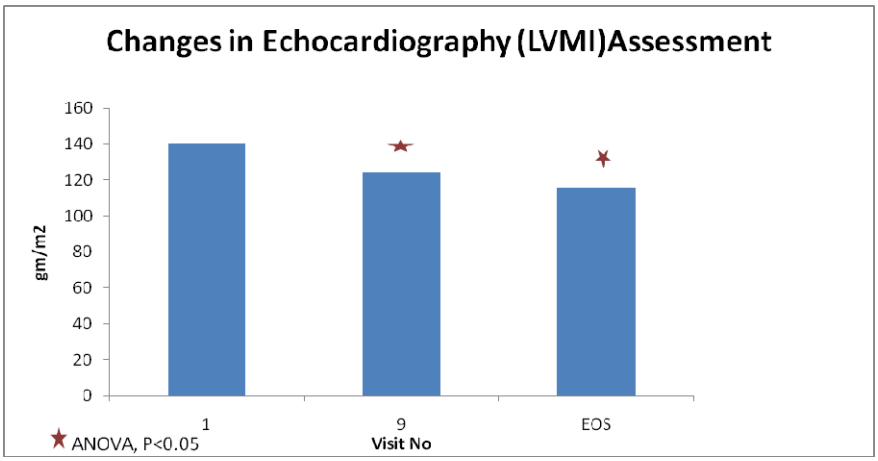
Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00362037
		Study Code:	PM_L_0255
Generic drug name:	irbesartan irbesartan/hydrochlorothiazide	**Date:**	27 May 2011

Title of the study:	"I SELECT" – Irbesartan in hypertensive patients with left ventricular hypertrophy		
Investigator(s):	34 investigators participated actively in the study.		
Study center(s):	The study was conducted in 34 centers. 34 centers were active out of 50 centers opened.		
Publications (reference):	NA		
Study period: Date first **Subject** enrolled: 07 Mar 2006 Date last **Subject** completed: 19 Jun 2008 Actual timelines of the study were extended from the planned to accommodate for the lack of enrollment.		**Phase of development:** Phase IV	
Objectives:	**Primary** a) Evaluation of blood pressure reduction to the targeted values (blood pressure (BP) ≤ 140/90 mm Hg in non-diabetic patients, and ≤ 130/80 mm Hg in diabetic patients). b) To evaluate the efficacy of Irbesartan in the reduction of left ventricular mass index in hypertensive patients with left ventricular hypertrophy (> 130g/m2 in men and > 100g/m2 in women) measured by echocardiography. **Secondary** To evaluate Irbesartan safety in studied population.		
Methodology:	This study was a multicenter, prospective, open, non-randomized, non-comparative, 36 weeks treatment phase trial . All eligible patients were assigned a treatment scheduled as follows: irbesartan (Aprovel) 150 mg once daily, assessed after 3 weeks (Week 3) for achievement of target BP (<140/90 mmHg) followed by dose titration. If target BP was not achieved then the dose of Aprovel was doubled to 300 mg once daily and assessed after 3 additional weeks (Week 6). If target BP was still not achieved, irbesartan+hydrochlorothiazide (CoAprovel) 300/12.5 mg once daily was started and assessment performed at follow-up visits. Whenever the BP target was achieved at a particular dose, that dose was maintained for the rest of the treatment period. The starting dose and the dose titration schedule were allowed to be modified according to the Investigator's judgment and based on patients' BP variability.		
Number of Subjects:	Planned: 418	Randomized: NA	Treated: 281

Evaluated:	Efficacy: Per protocol: 134 Intent to Treat: 214	Safety: 281
Diagnosis and criteria for inclusion:	- hypertensive patients aged between 30 and 75 years with left ventricular hypertrophy; - newly diagnosed "naïve" hypertensive patients (no prior treatment for hypertension) or receiving antihypertensive agents (maximum two - one of them being a diuretic) and having his/her blood pressure target achieved, yet, in the investigator's opinion would benefit more from switching to the study medication.	
Investigational product: Dose: Administration:	Aprovel and Co-Aprovel Aprovel 150 mg, Aprovel 300 mg and CoAprovel 300/12.5 mg Oral route	
Duration of treatment: 36 weeks		**Duration of observation:** 36 weeks
Reference therapy:	None	
Criteria for evaluation:		
Efficacy:	**Primary Variable** The mean reduction and mean percent reduction in Left Ventricular Mass Index (LVMI) compared to baseline levels: From the data available at the end of the 9-month study period. The mean overall reduction and mean percent reduction in systolic and diastolic blood pressure levels compared to baseline levels: From the data available at the end of the 9-month study period. **Secondary Variable** The proportion of patients controlled on Aprovel – Co-Aprovel in each concentration (150mg and 300mg) Proportion of enrolled patients reaching a blood pressure target (< 140/90) at 9 months. The mean reduction and percent reduction in systolic / diastolic blood pressure in patient subgroups (Patients on Aprovel 150mg only, patients on Aprovel 300mg only and patients on Co-Aprovel 300/12.5mg + other agents) Physicians' overall assessment of efficacy from the data available at the end of the 9-month study period.	
Safety:	**Primary Variable:** Reporting of any adverse drug reactions. **Secondary variable:** Physicians' and patients' overall assessment of tolerability at the end of the 9-month study period.	

Statistical methods:	The study sample was described by demographic variables, background variables, and other variables with appropriate statistics. The study sample was divided into 3 groups: **Aprovel 150:** Subjects who had only Aprovel 150 throughout the study period. **Aprovel 300:** Subjects that were titrated up to Aprovel 300 anytime during the study, but they never received Co-Aprovel throughout the study. **Co-Aprovel:** Subjects that were titrated up to Co-Aprovel, these subjects may have received Aprovel 150 mg, Aprovel 300 mg, and Co- Aprovel at some point during the study. The results were analyzed using descriptive methods. The tests of significance between patient groups depended upon the distribution of data. ANOVA mean of LVMI and systolic/diastolic blood pressure to assess either changes from baseline to a post-baseline study time point in one group or difference among subgroups. Cross tabulation with Chi-square test was applied for the grade of Hypertension. Other test such as Kruskal-Wallis Test was applied to compare the grade of satisfaction across the levels of more than 2 groups of patients.
Summary:	281 subjects were enrolled into the study. 67 lost to follow up after visit 1. These subjects were excluded from the intent to treat and per protocol analysis. Per Protocol analysis consisted of 134 subjects that had completed all 9 visits and had no selection criteria violation. Females represented 54.67%, males 44.86% (missing data for 0.47% of the study population). The mean age was 54 years (+/-9 SD), the mean of height was 164.27 cm (+/-10.72 SD) and the mean of weight was 90.51 Kg (+/-16.82 SD). 21.03% of the subjects had DM. Regarding the Hematology laboratory values; the mean value of Haemoglobin was 13.5 g/dl (+/-1.8 SD), mean value of WBC 8.0 10^9/l (+/-7.0 SD), mean value of erythrocyte sedimentation rate (ESR) 25.3 mm (+/-18.3 SD) and mean value of Platelets 278.7 10^9/l (+/-79.7 SD). Regarding the blood chemistry lab values; the mean value of Creatinine was 1.0 mg/dl (+/-0.3 SD), mean value of aspartate aminotransferase (AST) 25.2 U/L (+/-12.6 SD), mean value of alanine aminotransferase (ALT) 28.5 U/l (+/-14.7 SD), mean value of serum potassium 4.3 mmol/l (+/-0.5 SD), mean value of HbA1c 6.7 % (+/-1.4 SD) and mean value of blood urea nitrogen (BUN) 16.0 mg/dl (+/-7.8 SD) Regarding the left ventricular hypertrophy evaluation; the mean left ventricular thickness was 10.16 mm (+/-4.82 SD) and the mean left ventricular mass index was 140.43 gm/m^2 (+/-33.07). The mean left ventricular ejection fraction was 70.82 % (+/-11.03SD).

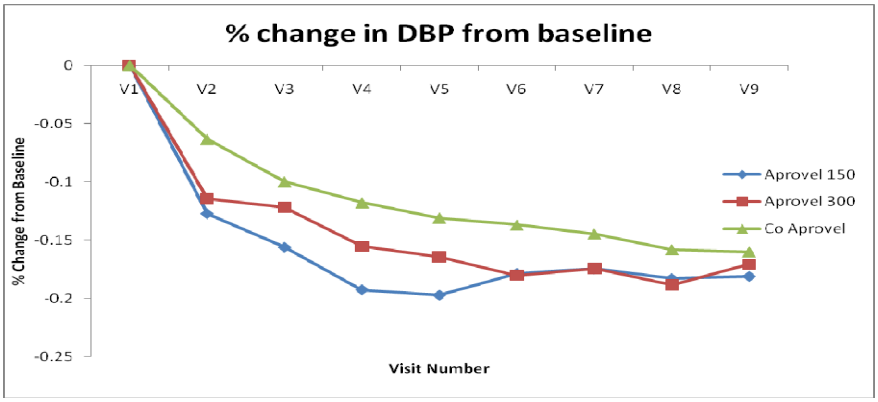
Efficacy results:	**<u>ITT</u>:** **LVMI:** Mean reduction in LVMI compared to baseline levels was statistically significant (p <0.05) using ANOVA test, a mean of 18% decrease was observed. . 

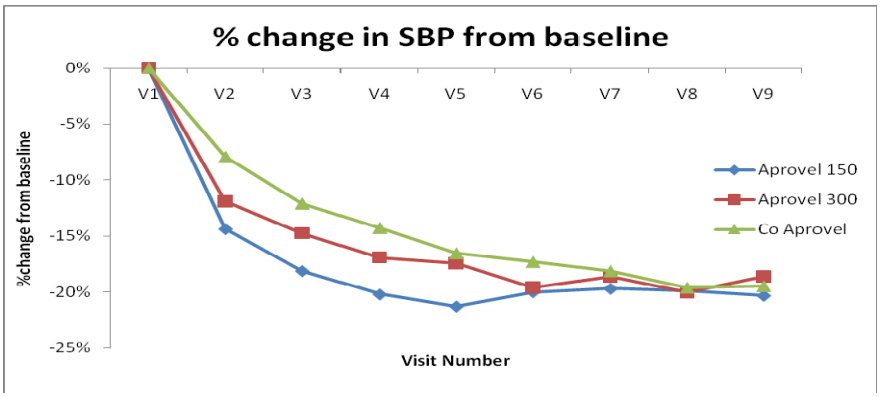
Systolic/diastolic blood pressure:
ANOVA statistical test was applied to the absolute and percentage reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP); It had revealed a statistically significant (P<0.05) reduction in both values and across all three study treatment groups compared to baseline values.

Aprovel 150 (p<0.0001ANOVA):
The mean SBP was reduced to 122.7 mmHg (+/- 9.3SD) at visit 9 compared to 153 mmHg (+/- 8.6 SD) at baseline.
The mean DBP was reduced to 78.1 mmHg (+/-5.0 SD) at visit 9 compared to 95.7 mmHg (5.3 SD) at baseline.

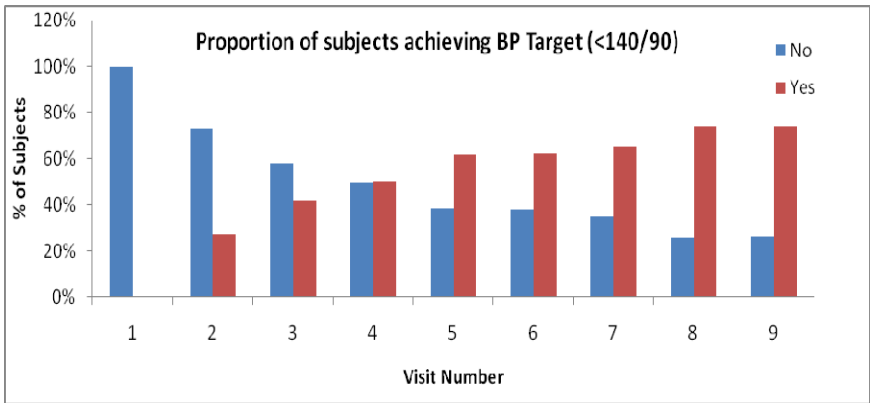
Aprovel 300 (P<0.0001 ANOVA):
The mean SBP was reduced to 129.0 mmHg (+/- 8.7 SD) at visit 9 compared to 157.5 mmHg (+/- 12.3 SD) at baseline.
The mean DBP was reduced to 80.9 mmHg (+/-5.4 SD) at visit 9 compared to 97.8 mmHg (7.3 SD) at baseline.

Co-Aprovel (p<0.0001 ANOVA):
The mean SBP was reduced to 132.2 mmHg (+/- 14.6 SD) at visit 9 compared to 164.5 mmHg (+/- 9.9 SD) at baseline.
The mean DBP was reduced to 82.0 mmHg (+/-7.4 SD) at visit 9 compared to 98.6 mmHg (6.4 SD) at baseline.





Proportion of enrolled patients reaching blood pressure target (< 140/90):
The % of subject reaching the blood pressure target (<140/90 mmHg) increased gradually till visit 5 then reached a plateau phase.

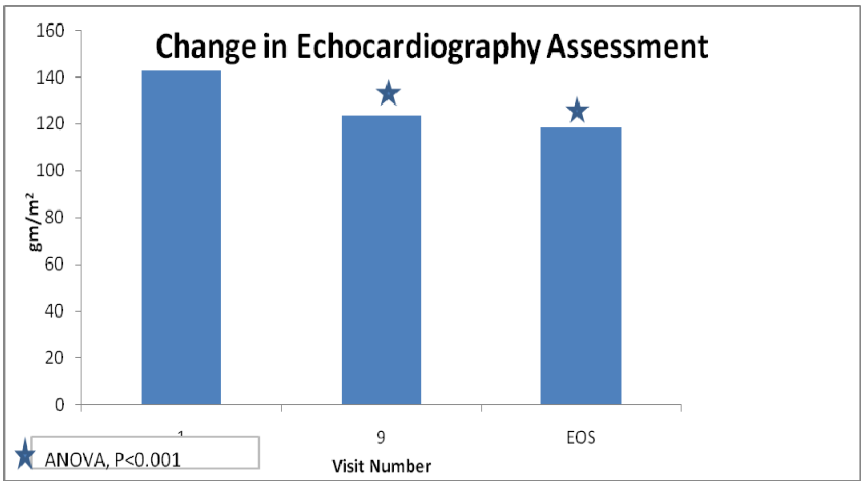


Overall efficacy evaluation by physicians:
At visit 9, 153 (86.44%) physicians evaluated the overall efficacy as being improved, 21 (11.86%) as being unchanged and 3 (1.69%) as having failed.

Per Protocol

LVMI:

Mean reduction in LVMI compared to baseline levels was statistically significant ($p < 0.05$) using ANOVA test, a mean of 15% decrease was observed.



Systolic/diastolic blood pressure:

ANOVA statistical test was applied to the absolute and percentage reduction in SBP and DBP; had revealed a high statistical significance (P<0.05) reduction in both values and across all three study treatment groups compared to baseline values.

Aprovel 150(p<0.0001ANOVA):

The mean SBP was reduced to 122.9 mmHg (+/- 8.2 SD) at visit 9 compared to 154.7 mmHg (+/- 7.2 SD) at baseline.

The mean DBP was reduced to 78.5 mmHg (+/-3.0 SD) at visit 9 compared to 95.8 mmHg (4.5 SD) at baseline.

Aprovel 300(P<0.0001 ANOVA):

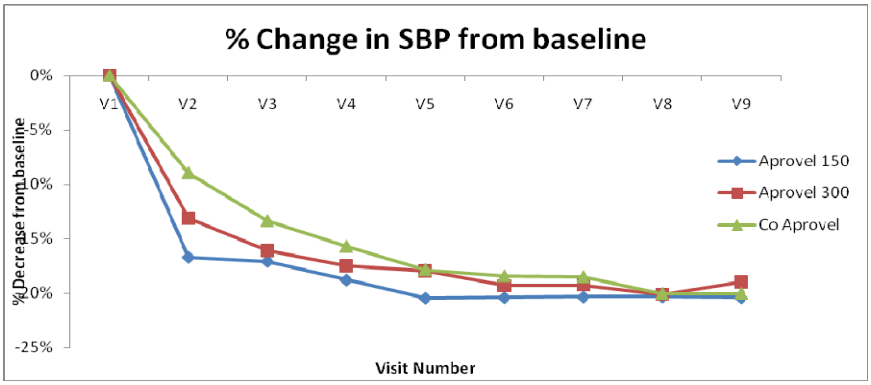
The mean SBP was reduced to 129.2 mmHg (+/- 9.0 SD) at visit 9 compared to 160.2 mmHg (+/- 9.1 SD) at baseline.

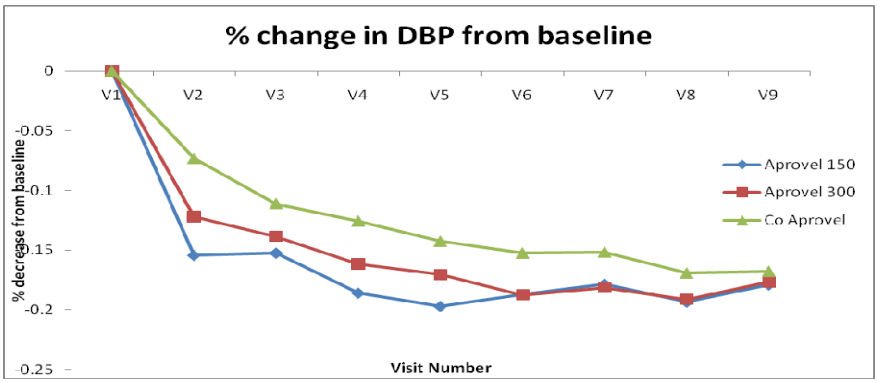
The mean DBP was reduced to 81.5 mmHg (+/-5.3 SD) at visit 9 compared to 99.1 mmHg (5.0 SD) at baseline.

Co-Aprovel(p<0.0001 ANOVA):

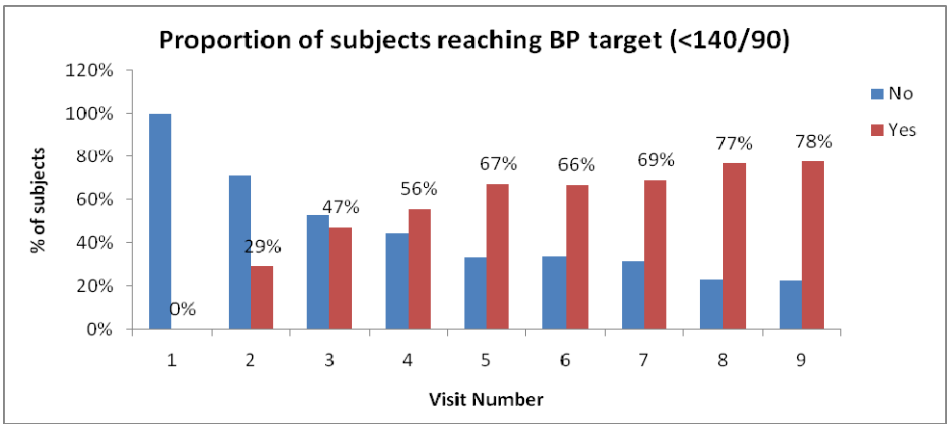
The mean SBP was reduced to 130.6 mmHg (+/- 11.1 SD) at visit 9 compared to 163.8 mmHg (+/- 8.9 SD) at baseline.

The mean DBP was reduced to 81.7 mmHg (+/-6.0 SD) at visit 9 compared to 98.5 mmHg (5.0 SD) at baseline.





Proportion of enrolled patients reaching a blood pressure target (< 140/90):
The % of subject reaching the blood pressure target (<140/90 mmHg) increased gradually till visit 5 then reached a plateau phase.



Overall efficacy evaluation by physicians:
At visit 9, 114 (87.02%) physicians evaluated the overall efficacy as being improved, 15 (11.45%) as being unchanged and 2 (1.53%) as having failed.

Safety results:

45 study subjects (21% of intent to treat pool) reported at least one adverse event. 60 adverse events were reported with headache, dizziness and nausea being the most common.

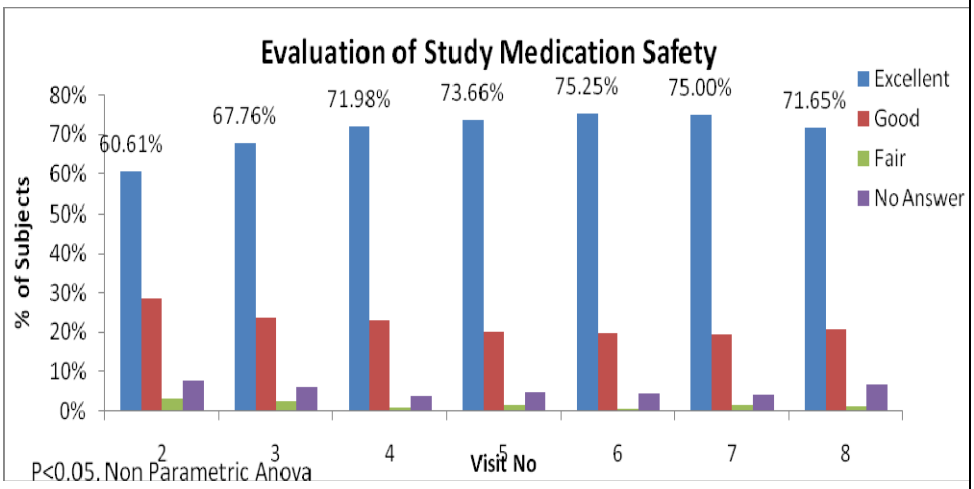
Adverse events grouped	Count	%
Headache, dizziness, nausea	39	65.0%
Pulmonary; chest pains; hypertension like symptoms	10	16.7%
Musculoskeletal symptoms	3	5.0%
Impotence	2	3.3%
Renal pains	1	1.7%
Allergy and itching	2	3.3%
Sweating	1	1.7%
Frequent urination	1	1.7%
Flatulence	1	1.7%

Six Serious Adverse Events were reported, 2 resulted in Hospitalisation, 2 in Death, 1 pregnancy followed by abortion and 1 sexual impotence (investigator judjement)

Clinical Adverse Experience	Grade	Action Taken Study Medication	Consequences	Relation to Study Medication
Left sided hemiplegia	Severe	Discontinued	Death	None
Pulmonary embolism	Severe	Discontinued	Hospitalized, recovery with sequelae	None
Sexual impotence	NA	None	Unknown-Patient lost to follow-up	Possible
Pregnancy/ abortion	NA	Discontinued	Recovery without sequelae	Possible
Sudden death	Severe	Discontinued	Death	None
Atrial fibrillation	Severe	Interrupted	Hospitalized, Recovery without sequelae	None

Hematology:

At the end of study, the mean value of hemoglobin was 13.4 g/dl (+/-1.6 SD) with -0.98% (+/-9.92 %SD) decrease from baseline, the mean value of White blood cells (WBC) was 8.3 109/l (+/-8.4 SD) with 7.13%(+/-73.01% SD) increase from baseline, the mean value of ESR was 23.0 mm (+/-18.2 SD) with -6.27% (+/- 59.50%SD) decrease from baseline and the mean value of Platelets was 275.3 109/l (+/-78.2 SD) with -2.02% (+/-21.66% SD) decrease from baseline.

	Blood chemistry: At the end of study, the mean value of Creatinine was 1.1 mg/dl (+/-1.0 SD) with 11.53 %(+/-95.67%SD) increase from baseline, the mean value of AST was 25.4 U/L (+/-13.5 SD) with 3.90% (+/- 40.62% SD) increase from baseline, the mean value of ALT was 30.9 U/l (+/-17.2 SD) with 11.28% (+/-46.72% SD) increase from baseline, the mean value of serum potassium was 4.4 mmol/l (+/-0.5 SD) with 2.82% (+/-13.06%SD) increase from baseline, the mean value of HbA1c was 6.7 % (+/-1.7 SD) with 2.53 %(+/- 14.67%SD) increase from baseline and the mean value of BUN was 16.3 mg/dl (+/-7.6 SD) with 1.87% (+/-144.62%SD) increase from baseline. **Mean overall tolerability** **Patients Assessment:** At visit 9,138 (77.97%) subjects evaluated the study medication as being excellent, 36 (20.34%) as being good and 3(1.69%) as being fair. **Physicians Assessment:** At visit 9, 142 (80.23%) physicians evaluated the study medication as being excellent, 31 (17.51%) as being good and 4 (2.26%) as being fair. 
Date of report:	18 Jan 2011