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-aventis	**ClinicalTrials.gov Identifier:**	NCT00785811
		Study Code:	LARAS_L_02921
Generic drug name:	L-arginine aspartate	**Date:**	14 March 2011

Title of the study:	A national, phase IV, unicentric, double-blind, randomized, parallel, with two treatment arms, placebo-controlled study of the influence of chronic supplementation of L-arginine aspartate in muscle performance of non-athlete subjects (LARAS_L_02921).	
Investigator(s):	Dr. Renato Fraga Lotufo Rua Alvarenga, 1700. Butantã, São Paulo – SP - Brazil	
Study center(s):	01	
Publications (reference):	NA	
Study period: Date first **subject** enrolled: 20-Oct-2008 Date last **subject** completed: 19-Dec-2008		**Phase of development:** Phase IV
Objectives:	Primary: - To evaluate the effect of oral administration of L-arginine in the muscular fatigue of the *Quadriceps Femoris* Muscle, expressed in terms of the Fatigue Resistance Factor (FRF). Secondaries: - To evaluate the effect of oral administration of L-arginine in the muscular force of the *Quadriceps Femoris* Muscle. - To evaluate the effect of oral administration of L-arginine in the muscular fatigue and in the muscular force of the *Biceps Brachii* Muscle.	

Methodology:	Randomized (1:1) clinical trial, double-blind, placebo-controlled of parallel groups; It was planned 8 visits for the study: -Visit V1 (Baseline): presential. -Visits V2 to V7: weekly visits (presential, phone or email contact) to verify the treatment administration and daily physical activity practicing. - Visit V8 (60 days after V1): presential		
Number of subjects:	Planned: 152 (76 per treatment arm)	Randomized: 36 15 for active L-arginine aspartate Group and 21 for the Placebo Group)	Treated: 36
	The study was stopped early by a decision of the investigator, who reported no more interested in conducting the study. The imbalance of the sample observed between groups occurred as the investigator did not follow the randomization list: once there were screened patients who had received the number of randomization, without actually having been randomized. That is, a treatment was "allocated" to volunteers who never were randomized, generating the imbalance of those who actually were enrolled and treated. During the monitoring visit, it was observed by the MT that the process of treatment allocation to the subjects was not well understood by the site study staff. So, before the randomization of a new subject, the site staff was retrained by the MT about the details of that process. Of the volunteers included, all of them signed the consent form in the day of the initial study visit and met all criteria for inclusion/exclusion.		
Evaluated:	Efficacy : - Quadriceps Fatigue Resistance Factor (FRF). - Biceps Fatigue Resistance Factor (FRF). - Quadriceps and biceps muscular force.	Safety: Adverse events reported by the subject or observed by the investigator.	Pharmacokinetics: NA
Diagnosis and criteria for inclusion:	Healthy volunteers, aged between 20 and 55 years who practiced mild to moderate muscle physical activity in a regularly manner, considered as at least 90 minutes per week.		
Investigational product: Dose: Administration:	L-arginine aspartate (Effervescent tablets of 1,5g) 3g by day Oral: 2 tablets in a single administration		
Duration of treatment: 60 days		**Duration of observation:** 60 days	
Reference therapy: Dose: Administration:	Placebo 3g by day Oral: 2 tablets in a single administration		

Criteria for evaluation:	
Efficacy:	- Fatigue Resistance Factor (FRF) for *Quadriceps Femoris and Biceps Brachii* Muscles. FRF= {(Fatigue index before treatment - Fatigue index after treatment)/ Fatigue index before treatment] *100 - *Quadriceps Femoris* and *Biceps Brachii* Muscles maximum and minimum force in Newton (N) and fast or explosive force at time 30%, 50% and 90% of the maximum isometric force. These time points were chosen to evaluate the force development or how fast the muscles were recruited to generate movement - *Quadriceps Femoris* and *Biceps Brachii* Muscles Force Resistance: Time (in seconds) required for the individual reaches 50% of maximal isometric force. For force evaluation it was used a cell - strain gauge - Globus Ergo System (Treviso, Italy). For *Quadriceps Femoris* Muscle the volunteers were positioned sitting in an equipment of leg extension with the hip position of 85° of flexion and knees in position angle of 60°, with a resistance pad attached just above the lateral malleolus of the fibula. It should be performed three sets of 10 seconds of maximal isometric contractions of the Quadriceps with an interval of 90 seconds between each set to quantify the values For *Biceps Brachii* Muscle the volunteers were positioned sitting in the equipment biceps scott with arms and elbows on a support to stabilize and maintain the elbow flexed at 90º. To perform the contraction, the subjects should held a handle that was attached to the load cell. The physician used a goniometry to ensure the correct angle of elbow flexion during force evaluation. It should be performed three sets of 10 seconds of maximal isometric contractions of the Biceps with an interval of 90 seconds between each set to quantify the values The values reported for isometric muscle strength were obtained from the peak torque and other data generated from the average muscle torque measured by the load cell (strain gauge). The fatigue index was calculated using the time in seconds that the volunteer could keep at least 50% of the maximum force.
Safety:	Adverse events reported by subject or noted by the investigator.
Statistical methods:	The treatment groups were compared using Chi-square test for categorical variables (or Fisher's exact test in tables of type 2x2, when the expected frequency of one or more cells was less than 5) and t-test for numeric variables under the assumption of normality. In some situations, it was not possible to assume the normal distribution of data and thus the groups were compared using the Wilcoxon nonparametric test for two samples. These situations refer specifically to the variables that measure the explosive force of 30%, 50% and 90% of maximal isometric force. Statistical significance was defined for p-values ≤ 5%. All tests were performed on the Intent to Treat (ITT) Population and no interim analysis was performed. It was used the SAS statistical software (version 8.01) and Minitab (version 15.1) for statistical analysis.

Summary:	Demographic Data: Between 20-Oct-2008 and 27-Oct-2008, all 36 subjects were enrolled to the study. The most of subjects were male (87% in the active group and 71% in the placebo group) and Caucasians (93% in the active group and 95% in the placebo group). The patient's age ranged from 20 to 47 years in the active group and from 20 to 41 years in the placebo group. Weight and height ranged from 59 to 104 kg and 159 to 190 cm in the active group and 54 to 56 kg and 159 to 197 cm in the placebo group. It was no detected statistically significant difference between groups regarding to gender, ethnicity, age, weight and height. Physical activity: All the volunteers who were enrolled to the study have reported at Visit V1 practicing of physical activity regularly and none of them, who continued to be evaluated throughout the study, interrupted the activities. From the total of patients enrolled, seven (19%) did resistance training for strength, 6 (17%) were quick strength training and 28 (78%) were training for hypertrophy. There was no statistically significant difference in the type of the training conducted. The mean time for the practicing of physical activity was 8.5 (s.d: 3,8) hours per week in the active group and 7.6 (s.d: 2,9) hours per week in the placebo group with no statistically significant difference between groups (p = 0.420). One volunteer in the active group did not report the time devoted to the physical activity. Study completion: From the 36 volunteers enrolled, 24 (67%) were followed until the end of the study (visit V8): 10 (67%) in the active group and 14 (67%) in the placebo group. For the remaining 12 volunteers, the premature interruption was reported as "lost to follow-up" and occurred at visit 4 (day 21) or visit 7 (day 42). From the 14 volunteers in the placebo group that attended the last visit, one of them refused to perform the Final Force Evaluation. Treatment adherence: Only 12 volunteers, 5 in the active group and 7 in the placebo group, were evaluated in the Final visit (V8) regarding to the treatment adherence: in all cases it was reported at least 80% of treatment intake.

Efficacy results:

The Tables 1 and 2 below show the comparison between the active group and placebo for the difference observed between the evaluations performed at the Baseline (V1) and Final (V8) visits, for *Quadriceps Femoris* and *Biceps Brachii* Muscles, respectively.

It was not observed statistically significant difference between groups for any of the parameters evaluated, for *Quadriceps Femoris* Muscle.

Table 1: *Quadriceps Femoris* Muscle– Comparative evaluation: Difference between V8 and V1

Quadriceps (V8 - V1)	Active Group N=10	Placebo group N=13	p-value
Minimum force (N)			0,374
Mean (s.d.)	55 (305)	151 (198)	
min. // max.	-602 // 465	-138 // 582	
Maximum force (N)			0,684
Mean (s.d.)	57 (123)	39 (93)	
min. // max.	-147 // 251	-98 // 175	
Explosive Force at 30% of the maximum isometric force (N/s)			0,799
Mean (s.d.)	3587 (21607)	36493 (106188)	
min. // max.	-24750 // 25980	-17719 // 298468	
Explosive Force at 50% of the maximum isometric force (N/s)			0,824
Mean (s.d.)	-3484 (23705)	9388 (23597)	
min. // max.	-42048 // 39605	-11413 // 72175	
Explosive Force at 90% of the maximum isometric force (N/s)			0,204
Mean (s.d.)	-2722 (8337)	44465 (136747)	
min. // max.	-26268 // 1082	-13275 // 495410	
Force Resistance (s)			0,670
Mean (s.d.)	3 (15)	0,1 (19)	
min. // max.	-18 // 35	-47 // 23	
Fatigue Resistance Factor (%)			0,675
Mean (s.d.)	-34 (111)	-19 (66)	
min. // max.	-340 // 44	-172 // 81	

Force Resistance: time to reach 50% of the maximum isometric force;
s.d. = standard deviation; N = Newton; s = seconds; min. = minimum; max = maximum;

	It was not observed statistically significant difference between groups for any of the parameters evaluated for *Biceps Brachii* Muscle, exception for Explosive Force at 50% of the maximum isometric force - in the active group it was observed a reduction of V1 to V8 Force and an increase in the placebo group. Table 2: *Biceps Brachii* Muscle – Comparative evaluation: Difference between V8 and V1

Biceps (V8 - V1)	Active Group N=10	Placebo group N=13	p-value
Minimum force (N)			0,747
Mean (s.d.)	-15 (160)	2 (35)	
min. // max.	-426 // 174	-65 // 59	
Maximum force (N)			0,484
Mean (s.d.)	-73 (82)	-51 (62)	
min. // max.	-223 // 38	-168 // 63	
Explosive Force at 30% of the maximum isometric force (N/s)			0,255
Mean (s.d.)	-4843 (10305)	-932 (9195)	
min. // max.	-25285 // 1967	-25347 // 7273	
Explosive Force at 50% of the maximum isometric force (N/s)			0,006
Mean (s.d.)	-1160 (1552)	2203 (3402)	
min. // max.	-4017 // 1065	-509 // 9972	
Explosive Force at 90% of the maximum isometric force (N/s)			0,598
Mean (s.d.)	1403 (4223)	138 (288)	
min. // max.	-236 // 13385	-109 // 861	
Force Resistance (s)			0,478
Mean (s.d.)	-0,1 (19)	-5 (9)	
min. // max.	-37 // 19	-20 // 7	
Fatigue Resistance Factor (%)			0,190
Mean (s.d.)	-23 (73)	11 (31)	
min. // max.	-144 // 92	-43 // 67	

Force Resistance: time to reach 50% of the maximum isometric force;
s.d. = standard deviation; N = Newton; s = seconds; min. = minimum; max = maximum;

Safety results:	It was reported the occurrence of adverse events during the study for two volunteers, one of each treatment group. The patient in the active group had flatulence and the patient in the placebo group had drowsiness. Both of them were reported as of mild intensity, not requiring treatment or corrective therapy and unrelated to the study treatment. The two events were assessed at visit 2, and in no other visit.
Date of report:	03-Mar-2011