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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00277602
		Study Code:	RIL_DE1_201
Generic drug name:	Riluzole	**Date:**	19/Sep/2007

Title of the study:	European Huntington's Disease Initiative: A phase III multicenter, double-blind, parallel-group, placebo-controlled study to measure the effect of riluzole 50 mg bid over a period of three years on the progression of Huntington's Disease. RIL.DE1.201)
Investigator(s):	B. Dubois, Dept. of Neurology, Hopital de la Salpetriere, Paris; J. Garcia de Yebenes, Dept. Of Neurology, Centro Ramon y Cajal, Madrid ; H.B.H. Kremer, Dept. of Neurology, UMC St. Radboud, Nijmegen, NL; G.B. Landwehrmeyer, A.C. Ludolph, Dept. Of Neurology, Ulm, Germany
Study center(s):	44 centers; Austria, France, Germany, Italy, Netherlands, Poland, Spain, Switzerland
Publications (reference):	J. Garcia de Yebenes et al. EHDI Study: Effect of riluzole on Huntington's Disease. Journal of neurology, neurosurgery & psychiatry (2005), 76, Suppl. IV: A23 G.B. Landwehrmeyer et al. Riluzole in Huntington's disease: a 3year, randomized controlled study. Annales of Neurology Epub 2007, 13 August

Study period: **Date first patient enrolled:** **29-11-1999** **Date last patient completed:** **13-07-2004**	**Phase of development:** III

Objectives:	**Primary**: To investigate the efficacy of riluzole treatment on the rate of progression of Huntington's disease by assessing the total functional capacitiy (TFC) and the motor scores of the Unified Huntington's Disease Rating Scale (UHDRS) as well as combined scores of these. **Secondary**: If the assessment of the primary endpoints (TFC-, motor and combined score) demonstrates a significant treatment effect these parameters are reassessed following a washout period of study medication (4 weeks) to identify persisting therapeutic effects of riluzole after withdrawal; these effects will be interpreted as neuron-protective. In addition the progression of clinical signs and symptoms are assessed by: the other subscales of the Unified Huntington's Disease Rating Scale, Beck's Depression Inventory (BDI) and Clinical Global Assessment (CGI), the number of patients who need anti-choreic treatment, the time until anti-choreic treatment has to be started, the safety/tolerability of riluzole in Huntington's Disease patients.
Methodology:	

Number of patients:	Planned: 450	Randomized: 537	Treated: 537
Evaluated:	Efficacy/Pharmacodynamics: 379	Safety: 537	Pharmacokinetics: 0
Diagnosis and criteria for inclusion:	Age range: 25 to 65 years old inclusive Male or female: Female require a negative blood pregnancy test at inclusion Diagnosis of Huntington's Disease with the aid of clinical features and the presence of more than 36 CAG repeats in the Huntington gene UHDRS motor score more than 5 and UHDRS TFC-score more than 8 (i.e. patients must be independently ambulatory and may not require nursing care		
Investigational product: Dose: Administration:	riluzole 50 mg bid oral		
Duration of treatment: 3 years	**Duration of observation:** 3 years		
Reference therapy: Dose: Administration:	placebo 1 tablet bid oral		
Criteria for evaluation:			
Efficacy:	Changes in the TFC-score of the UHDRS, changes in the motor score of the UHDRS, changes in the combined score of the TFC- and motor score		
Safety:	Adverse events reported by the patients, Laboratory data i.e. standard hematology and blood chemistry		
Pharmacokinetics:	Not done		
Pharmacokinetic sampling times and bio-analytical methods:	Not done		
Statistical methods:	To investigate the efficacy of riluzole a stepwise testing procedure was used which is based on the closure principle. A global hypothesis and two elementary hypotheses were formulated. All hypotheses are two-sided and tested at a multiple level of significance of alpha=0.005. Due the closure principle of hypothesis testing no adjustment of type I error probability was necessary for the 3 hypotheses. Each of the three hypotheses was tested with the Wilcoxon-test (Mann-Whitney rank test) for two parallel groups. In addition a descriptive analysis was performed. No interim analyses were done.		
Summary:	This large, placebo-controlled, double-blind study found no evidence for the efficacy of riluzole at a dose of 50 mg bid in Huntington's disease. No difference in outcome was observed on the primary efficacy outcome measures motor score and TFC of the UHDRS and a composite parameter combining both. Results using the ITT and PP population and from analysis of secondary outcome variables were quite consistent. No unexpected or serious safety issue associated with the use of riluzole was identified during the study.		

Efficacy results:	The protocol-specified primary efficacy analysis was the distribution of the individual changes from baseline in combined scores in the ITT population, compared between the two treatment groups with the Mann-Whitney U test. This yielded a p value of 0.66. According to the stepwise testing procedure established a priori, the MS and TFC score are therefore not significant either. No significant inter-group differences in change from baseline in the chorea items of the UHDRS, or in chorea scores at any time point during the study were observed. Moreover no difference was observed between treatment groups for changes in score on the cognitive, behavioral, independence and functional and chorea dimensions of the UHDRS. No influence of CAG repeat size could be demonstrated on rate of progression of MS, TFC or CS in the riluzole group, the placebo group or in both groups combined.
Safety results:	Treatment-emergent adverse events were reported in 149 patients (83%) in the placebo group and 286 patients (80%) in the riluzole group. Depression and diarrhea occurred in more than 10% of patients. Depression (p=0.008) and insomnia (p=0.02) were more frequent in the placebo group. The incidence of the other adverse events did not differ significantly between groups. Six deaths occurred during the treatment period, five of these were suicides (two in the placebo group and three in the riluzole group) and the sixth (in the placebo group) was a case of cardiac failure. Six other patients (two in the placebo group and four in the riluzole group) attempted to commit suicide but failed. Increase of serum markers of hepatic injury were observed in 13 riluzole-exposed patients and 1 patient in the placebo group. 13 patients (7%) in the placebo group and 45 patients (13%) in the riluzole group discontinued treatment because of an adverse event, most frequently a psychiatric event
Pharmacokinetic results:	Pharmacokinetic measurements were not done.
Date of report:	02-Aug-2007