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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00277602
		Study Code:	RIL_DE1_201
Generic drug name:	Riluzole	**Date:**	24/Mar/2010

Title of the study: A Phase III multicentre, 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 – extension phase

Investigator(s): The multinational study was coordinated by a steering committee made up of six academic members (Prof. B. Dubois, Paris, France; Prof. J. Garcia de Yébenes, Madrid, Spain, Prof. W. Gaus, Ulm, Germany, Prof. H.P.H. Kremer, Nijmegen, The Netherlands, Dr. Bernhardt Landwehrmeyer, Ulm, Germany and Prof. A.C. Ludolph, Ulm, Germany) and representatives of Sanofi-Aventis. Operational management of the study was provided by Dr W. Fischer, Sanofi-Aventis GmbH Germany.

Study center(s): Multinational study conducted in 44 centres in eight European countries (Austria, France, Germany, Italy, Netherlands, Poland, Spain, Switzerland)

Publications (reference – main trial): Landwehrmeyer GB, Dubois B, de Yebenes JG, Kremer B, Gaus W, Kraus PH, Przuntek H, Dib M, Doble A, Fischer W, Ludolph AC. Riluzole in Huntington's disease: a 3-year, randomized controlled study. Ann Neurol 2007;62: 262-72.

Study period:

Main Trial:

Date first patient was enrolled:	29th November 1999
Date last patient completed main trial:	13th July 2004

Extension Phase:

Date first patient entered extension phase:	22nd January 2003
Date last patient completed extension phase:	20th June 2005

Phase of development: Phase III

Objectives: The objective of the study was to demonstrate that riluzole slows the progression of Huntington's disease.

Primary Objective of main trial: to investigate the efficacy of riluzole treatment on the rate of progression of Huntington's disease as measured by (1) the decrease in score on the Total Functional Capacity (TFC) subscale of the Unified Huntington's Disease Rating Scale (UHDRS), (2) the increase in the motor score of the UHDRS (Huntington Study Group 1999) and (3) the increase in a combined score of these.

Secondary Objectives of main trial: to assess effects of treatment on (1) changes in the other subscales of the UHDRS, (2) the number of patients who required antichoreic medication, (3) the time to initiation of antichoreic medication in those patients who required it, and (4) the safety and tolerability of riluzole in patients with Huntington's disease.

Primary Objective of extension phase: to describe the influence of riluzole on the progression of Huntington's disease after more than three years of intake. This description would focus on (1) motor score and total functional capacity subscores of the UHDRS, (2) compliance, (3) laboratory tests of liver function and (4) adverse events.

Methodology: This was a randomised, placebo-controlled, parallel-group, double-blind study in out-patients with Huntington's disease, with a treatment phase of 36 months. The extension phase continued the double-blind treatment period for an additional period of up to 24 months.

Number of patients: Planned: 450 (ratio 1:2 placebo:riluzole)

Randomised: 537 (main trial)

Treated: 537 (main trial)

Evaluated:

	Main Trial			Extension Phase		
	Placebo	Riluzole	TOTAL	Placebo	Riluzole	TOTAL
Efficacy	128	251	379	70	147	217
Safety	180	357	537	96	198	294

Diagnosis and criteria for inclusion: The study included patients of either sex aged between 25 to 65 years old with a diagnosis of Huntington's disease and a UHDRS motor score ≥ 5 and a UHDRS total functional capacity score of ≥ 8. All patients completing the main trial (36 months of treatment) were invited to enter the extension phase.

Investigational product: Riluzole

Dose: 50 mg *bid per os*

Administration: oral: one tablet in the morning, one tablet in the evening

Duration of treatment: Treatment phase of 36 months + extension phase for an additional period of up to 24 months

Duration of observation: As duration of treatment

Reference therapy: Placebo

Dose: Not applicable

Administration: *bid per os*, one tablet in the morning, one tablet in the evening

Criteria for evaluation:

Efficacy: Treatment efficacy was primarily assessed using the UHDRS. In particular, the motor score and the total functional capacity score were evaluated. The primary outcome measures were (1) the change from baseline of the total functional capacity score and (2) the change from baseline of the motor score of the UHDRS after 36 months treatment as well as (3) a combined score of (1) and (2). The only secondary outcome measure assessed in the extension phase was the time until need for antichoreic medication.

Safety: The safety evaluation performed in the extension phase was restricted to reporting of adverse events and monitoring of serum markers of liver function.

Statistical methods: For all three primary efficacy parameters (UHDRS motor score, total functional capacity score and combined score), the difference in change in score over the treatment period (baseline visit to last visit of the extension phase) between the two treatment groups was used to determine the treatment effect.

The efficacy analysis was conducted in a per-protocol population, covering all patients entering the extension phase who presented no major protocol deviations and treated for at least 150 days. The safety analysis was conducted on all patients with at least one intake of study medication during the extension phase.

Summary:

- In the main trial, 537 patients (placebo: 180; riluzole: 357) were randomised and treated with study medication.
- Of these, 294 entered the extension phase and were randomised (the placebo: 96; riluzole: 198), constituting the safety set for the extension phase.
- A patient set of 217 patients (placebo: 70; riluzole: 147), devoid of major protocol deviations in both the main trial and the extension phase was considered valid for efficacy analysis in the extension phase.
- The demographic and clinical features of the safety and efficacy populations were similar.
- In the safety population, the mean age of the included patients was 45.3 ± 9.4 years and 48.6% were male.
- The mean age at disease onset was 40.2 ± 9.7 years, the number of CAG repeats on allele 2 was 45.3 ± 4.1 and the time since diagnosis at inclusion was 5.2 ± 4.6 years.
- The distribution of baseline variables was comparable between the two treatment groups.
- Compliance was estimated to be >90% at each visit of the extension phase.

Efficacy results: The efficacy data collected in the extension phase of this study are consistent with the findings of the main trial. They provide no evidence for an effect of riluzole on the rate of progression of Huntington's disease, despite a treatment duration of up to five years. The suggestion of an effect of riluzole on delaying the time to recourse to antichoreic medication observed in the main trial was not confirmed during the extension phase.

	Placebo	Riluzole
	N = 70	N = 147
Combined UHDRS score	21.5 [16.2 – 25.9]	17.0 [15.6 – 19.4]
UHDRS Motor score	19.5 [11 – 26]	18.0 [15 – 20]
UHDRS Total Functional Capacity Score	-3.0 [-4.0 – -2.0]	-3.0 [-4.0 – -2.0]

Median change [*95% confidence interval*] *in UHDRS subscales between inclusion and last visit in the extension phase.*

Safety results: Safety data obtained in the extension phase of the study are consistent with those reported in the main trial. The overall frequency of the different classes of adverse events was lower in the extension phase than during the main trial, although the pattern of adverse events described was very comparable. The proportion of patients reporting at least one TEAE was 35.4% (n = 34) in the placebo group and 36.9% (n = 73) in the riluzole group. The most frequently reported treatment emergent adverse events were depression, diarrhoea and insomnia in both groups. Insomnia was more frequent in the riluzole group than in the placebo group. As in the main trial, the incidence of depression was lower in the riluzole group than in the placebo group. Serious treatment-emergent adverse events were reported in nine patients (9.4%) in the placebo group and in 27 patients (13.6%) in the riluzole group. The incidence of adverse events leading to treatment discontinuation and of medically significant laboratory abnormalities reported as adverse events was higher in the riluzole group than in the placebo group, although absolute numbers were low. The safety data reported here are consistent with the known safety profile of riluzole.

Date of report: 19th February 2010