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

		ClinialTrials.gov Identifier:	NA
Sponsor/company:	sanofi-aventis		
		Study Code:	**RIL_CA1_401**
Generic drug name:	Riluzole		
		Date:	06/Aug/2007

Title

A Canadian multicenter Phase IV comparative study of the effect of riluzole 50-mg bid on the survival of ALS subjects compared to historical controls.

Investigator(s), study site(s)

Multicenter: 13 sites across Canada

Study duration and dates	23 January 2001 to 20 December 2004	**Phase**	IV

Objectives

The objective of this study was to evaluate the efficacy of riluzole 50-mg bid defined by comparing the percentage of riluzole-treated subjects who experienced death, permanently assisted ventilation (PAV) or tracheostomy, to a group of recent historical controls for the treatment of amyotrophic lateral sclerosis (ALS).

Study design

The trial included two study arms: a prospective treatment arm in which subjects received open-label riluzole and a historical control arm in which an equal number of historical control subjects who had not received riluzole were matched 1:1 with the prospective treatment subjects. The prospective treatment arm included a screening visit, a baseline visit, and up to 11 additional study visits at 6-month intervals. Subjects were also contacted by telephone at Months 1, 2 and 3, and subsequently at 6-month intervals; so that after Month 3, subjects had alternating visits and telephone contacts every 3 months. The study duration was expected to be a minimum of 39 months and a maximum of 66 months, or until 200 riluzole-treated subjects reached a primary endpoint.

Number of subjects planned

A total of 414 subjects were to be enrolled into the prospective treatment arm of the study and matched with an equal number of historical control subjects after database finalization.

Inclusion criteria

The study included males or females between 18 to 75 years of age (inclusive) with a probable or definite diagnosis of Amyotrophic Lateral Sclerosis (ALS) and a duration of = 5 years. Subjects were also to have a Forced Vital Capacity (FVC) of = 60% at study entry.

Treatments

Each of the 414 prospective subjects received riluzole 50 mg oral tablets twice daily. The matching historical controls were not to have been treated with riluzole.

Efficacy data

The following data were collected for both prospective treatment subjects and historical controls: date of onset of symptoms; date of Permanently Assisted Ventilation (PAV) and/or tracheostomy; date of death.

Safety data

The following safety data were collected for the prospective subjects: serious adverse events and adverse events leading to discontinuation of the study drug reported by the subject or noted by the investigator, including serum transaminase laboratory values defined as alert terms.

Statistical procedures

The treated population and the safety population included all subjects who received at least one dose of study medication (riluzole). The efficacy analysis population included the treated subjects and matching historical controls. Descriptive statistics were used to summarize demographic and background data. Kaplan-Meier methods were applied to estimate the percentage of subjects who reached the endpoint of death, PAV or tracheostomy over time and the median time to the occurrence of death, PAV or tracheostomy. Log-rank statistics were used to compare the Kaplan-Meier curves for the prospective treatment subjects and the matching historical controls. In addition, matched analysis for the cases and controls was performed to obtain the stratified log-rank test result and hazard ratio estimates.

Interim analysis

No interim analysis was performed.

Results - Study subjects and conduct

A total of 421 subjects signed informed consent forms and 414 subjects received at least one dose of study medication in the prospective treatment arm; 32.1% (133/414) were alive at end of the study, 9.9% (41/414) were withdrawn, and 58.0% (240/414) reached an endpoint. The main reasons for study withdrawal were withdrawal of consent (24/41, 58.5%) and lost to follow-up (8/41, 19.5%), while 99.2% (238/240) reached an endpoint of death. A total of 1,066 historical controls who had not been treated with riluzole were used to find 414 matching controls.

Because the historical controls were matched to the treatment subjects based on four factors (age at onset of symptoms, gender, site of disease onset, and diagnosis of ALS) the two populations were well matched for baseline demographics and disease. Subjects in both groups had a mean age of 59.7 years, 60.4% were male; 66.4% had a peripheral onset, and 94.4% had a diagnosis of sporadic ALS.

At least 80% compliance with study treatment was reported for 92% of treated subjects.

Results – Efficacy

The primary efficacy endpoint was the time to the occurrence of an ALS-related event (PAV, tracheostomy or ALS-related death). The riluzole-treated subjects demonstrated a positive treatment effect. The event-free rate at 3 years was estimated to be 50.5% for the riluzole-treated subjects versus 42.8% for the historical controls. Compared with riluzole-naïve matched controls, a significant delay in the time to occurrence of an ALS related event was found by both the log-rank test ($p = 0.0005$) and stratified log-rank test ($p = 0.0131$); the median ALS event-free survival time was significantly increased by approximately 5.4 months (1,109 days in the treated subject compared with 946 days in the historical controls).

A sensitivity analysis including deaths from all causes also demonstrated a beneficial treatment effect with riluzole, with a significant increase in the time to PAV, tracheostomy or death (median difference 4.9 months; log-rank $p < 0.0002$; stratified log-rank $p = 0.0088$).

Secondary analyses were performed to examine the survival time to ALS related death and the time to any death (regardless of the occurrence of PAV and/or tracheostomy). Subjects treated with riluzole survived significantly longer than the historical controls.

Results – Safety

Treatment-emergent adverse events (TEAEs) were reported by 263 of 414 treated subjects (63.5%). TEAEs were considered possibly related to study medication in 91 of 414 subjects (22.0%). The most common TEAEs considered possibly related to study medication were nausea (24/414 subjects, 5.8%), fatigue (16/414 subjects, 3.9%), dizziness (15/414 subjects, 3.6%), and stomach discomfort (11/414 subjects, 2.7%).

Serious TEAEs were reported in 52 of 414 treated subjects (12.6%) and death was the outcome in 13 of these subjects. The 13 subjects with TEAEs resulting in death included 4 subjects with respiratory failure, 3 subjects with pneumonia, 2 subjects with pneumonia aspiration, and one subject each with pulmonary embolism, congestive heart failure, gastrointestinal hemorrhage, and circulatory collapse. None of these deaths were considered possibly related to study medication. There were only 2 subjects with serious adverse events considered possibly related to study medication. Serious possibly-related TEAEs were reported by one subject (0012001) with vomiting and diarrhea of moderate intensity that resulted in study drug discontinuation, and by another subject (0001001) with increased alanine aminotransferase (ALT) rated as severe in intensity, also resulting in study drug discontinuation. A total of 13 subjects with serious TEAEs permanently discontinued study medication; 6 of these subjects also died.

Altogether, study medication was permanently discontinued in response to a TEAE in 58 of 414 treated subjects (14.0%); 35 of these subjects had TEAEs that were considered possibly related to

study medication. Again, the most common possibly-related TEAEs that resulted in study drug discontinuation were nausea (13/414 subjects, 3.1%), dizziness (6/414 subjects, 1.4%), and fatigue (5/414 subjects, 1.2%).

Date of report: 31 July 2006 [FINAL]