FINAL REPORT 2011 - GALALZ4041

STUDY TITLE

Phase IV study for the assessment of the modulating effect of Galantamine (REMINYL PRC®) on circadian rhythm in patients with moderate Alzheimer's disease.

Protocol number: GALALZ4041; Phase IV

EudraCT Number: 2009-013689-18

Sponsor: Janssen-Cilag S.A.

IEC Approval Date: 29th March 2010

Hospital Board Approval Notification to Spanish Health Authority (AEMPS): 7th May 2010

AEMPS Approval Date: 11st May 2010

First Site Opened in Spain: 25th January 2011

Last Subject Enrolled: 28th June 2011

Site Closed: 19th September 2011

PARTICIPATING COUNTRIES / SITES

Participating countries: Spain

Participating Site in Spain:

Hospital del Mar, Barcelona.

Principal Investigator: Dr. R. A. Rocamora Zúñiga.

IEC:

IEC Parc de Salut Mar

STUDY OBJECTIVES

The primary objective is:

The primary objective is to assess the modulating effect of galantamine on circadian rhythm in patients with moderate Alzheimer's disease.

The secondary objectives are:

The secondary objective is to assess the perception of physicians and patients themselves on sleep-wake disorders in patients with moderate Alzheimer's disease before and following treatment with galantamine.

Overall safety will be assessed.

STUDY DESIGN

This is a pilot, interventional, multicenter, non-randomised, prospective study including 27 male and female patients with moderate Alzheimer's disease, treated with galantamine.

The patients participating in the study will receive a standard dose escalation regimen. The starting dose of treatment with galantamine will be 8 mg/day for 4 weeks. Subsequently, the initial maintenance dose will be 16 mg/day and patients should be maintained with 16 mg/day for 4 weeks. Then, an increase to the maintenance dose of 24 mg/day should be considered on an individual basis after appropriate assessment including evaluation of clinical benefit and tolerability.

In individual patients not showing an increased response or not tolerating 24 mg/day, a dose reduction to 16 mg/day should be considered.

Patients will be treated for a total of 13 weeks.

The sequence of visits will be:

- **Screening visit** (Day -10 ± 3 days from the baseline visit).
- **Visit 1 or Baseline visit** (Day 0, 7 days before the start of therapy with galantamine).
- **Visit 2** (Day 7 ± 2 days).
- **Visit 3** (Day 35 ± 2 days).
- **Visit 4** (Day 63 ± 2 days).
- **Visit 5** (Day 91 ± 2 days).
- **Visit 6** (Day 98 ± 2 days).

METHODS TO ASSESS EFFICACY PARAMETERS

The measure of the **primary study endpoint**, the actigraphy, is a technique which uses a small instrument called an actigraph worn on the wrist of the non-dominant arm to measure body movement. It creates a pattern based on activity that is useful in assessing sleep-wake cycles across many consecutive days and nights. It is useful for assessing sleep phase disorders.

The recorded data obtained by the actigraph is later read to a computer where it can be analyzed and create a day/night patient motor activity ratio. Actigraphic charts provide a global view of the rest and activity times.

The differences between pre and post-treatment values of the **secondary parametric variables** obtained in the actigraphy records will be evaluated as defined below:

- Sleep latency, defined as the time from bedtime to getting asleep expressed in minutes. The default criterion for the actigraphy program is the number of 1-minute epochs from the time of lights off to the first 10 successive sleep epochs (reflected in 10 minutes of immobility).
- Total wake time (TWT) defined as the time awake at night.
- Night total sleep time (NTST).
- Total time in bed (TIB) evaluated as difference between bedtime and wake time.
- Percentage of time awake and sleep
- Sleep efficiency (SE) defined as the percentage time the patient is asleep while in bed.
- Daytime Total Sleep Time (DTST)
- DTST/NTST ratio defined as the ratio of day to night sleep.
- Time immobile expressed in minutes.
- Time in movement expressed in minutes.
- Movement and fragmentation index defining the sleep agitation rate.
- Mean activity
- Variance of activity.
- Maximum activity time (Cosine peak)
- Daytime activity average (Light average)
- Night activity average (Dark average)

STUDY DOCUMENTS

1.- PROTOCOL:

Version: GALALZ4041/Protocolo/v 1.1/15 FEBRUARY2010

2.- INFORMED CONSENT

Version: GALALZ4041/Hoja Información al Paciente/v 1.0/3NOVIEMBRE2009

3.- STUDY DRUG SAFETY INFORMATION

For this study, the Summary of Product Characteristics of Galantamine has been considered as study drug safety information. Current version of Summary of Product Characteristics is dated on August 2010.

SERIOUS ADVERSE EVENTS

Unexpected and Serious Adverse Events associated with the use of the study drug (Galantamine) have been periodically reported to the site, IEC and the Spanish Health Authority (AEMPS).

The following Safety Reports were sent to the AEMPS:

- **Six-monthly Galantamine Safety Report** (SLL Galantamine) covering the period from 1st March 2010 to 28th August 2010, which was issued on 12th October 2010 and was sent to AEMPS on 26th October 2010.
- **Six-monthly Galantamine Safety Report** (SLL Galantamine) covering the period from 29th August 2010 to 28th February 2011, which was issued on 14th April 2011 and was sent to AEMPS on 25th April 2011.
- **Annual Galantamine Safety Report** (SLL Galantamine) covering the period from 1st March 2010 to 28th February 2011, which was issued on 14th April 2011 and was sent to AEMPS on 25th April 2011
- **Six-monthly Galantamine Safety Report** (SLL Galantamine) covering the period from 1st March 2011 to 28th August 2011, which was issued on 11st October 2011 and was sent to AEMPS on 13th October 2011.

None Serious Adverse Events were reported in Spain during the trial conduct.

EXCEPTIONS AND DEVIATIONS FROM PROTOCOL

1. EXCEPTIONS APPROVED BY SPONSOR

None exceptions occurred during the trial conduct.

2. DEVIATIONS

The deviations that occurred during the study were the following ones:

Patient	Deviation	Actions
[redacted]	The patient and the caregiver were informed of the trial by the investigator. The patient was a screening failure and was not provided the informed consent form in order to sign it.	Site staff was re-trained in informed consent form procedures. The investigator contacted with the patient and the caregiver, and they signed the informed consent form. An explanatory note was added in order to clarify when they were informed at the first time and when they accepted to participate. That deviation was reported to the IEC and to the AEMPS.
[redacted]	Vital signs were not measured during baseline visit.	Site staff was re-trained in protocol procedures.
[redacted]	The electrocardiogram (ECG) at the screening visit was performed out of the window visit (13 days before the baseline visit).	Site staff was re-trained in protocol procedures.
[redacted]	Vital signs were not measured during final study visit.	Site staff was re-trained in protocol procedures.

CURRENT STATUS OF THE STUDY

During the recruitment period established by the protocol, the following patients were included in the study:

- Patient [redacted], screening failure.
- Patient [redacted], early withdrawal on [redacted].

Site was closed last 19th September 2011 and all site closure procedures were conducted properly.

Collected data are not sufficient to perform a statistical analysis; therefore, it has not been done.

LOCAL CONTACTS

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