

## The intermediate results from the Grifols AMBAR study support its continuation

- ***AMBAR (Alzheimer Management By Albumin Replacement) is a phase III clinical trial that explores the combination of plasma extraction and replacement with albumin (the most abundant protein in blood plasma) to stabilize Alzheimer's disease.***
- ***The intermediate results show the tolerability and safety of the treatment, meeting the necessary conditions for patients to undertake it and for the continuation of the AMBAR study.***
- ***AMBAR is a blind study in which it is unknown which patients have been treated and which have not. Therefore, treatment efficacy will not be evaluated until the end of the study.***
- ***At this point of time, 250 patients with mild to moderate Alzheimer's disease have been recruited, of a total target of 365 participants at 40 hospitals in Spain and the United States.***
- ***The recruitment process is expected to be completed in 2016, with preliminary results to be presented in 2017, once all patients have completed the study.***
- ***Grifols presents its intermediate results at the 8th International Congress of Clinical Trials on Alzheimer's Disease (CTAD), held in Barcelona.***

**Barcelona, November 6, 2015:** Grifols (MCE: GRF, MCE: GRF.P and NASDAQ: GRFS), one of the world's leading manufacturers of plasma-derived biological medicines and a pioneer in the research and development of therapeutic alternatives designed to contribute to both scientific and social development, has presented the intermediate results of its AMBAR study ("Alzheimer Management By Albumin Replacement") which explores the combination of plasma extraction (plasma exchange) and replacement with albumin (the most abundant protein in blood plasma) to stabilize Alzheimer's disease (AD).

Following analysis of the tolerability and safety of the treatment, intermediate results from the AMBAR study support its continuation. The results show that the profile of adverse events is as expected and that mild to moderate Alzheimer's disease patients who participate can be treated in a routine manner. In other words, the treatment is feasible according to the study conditions.

Investigators have not analyzed the efficacy of treatment because it is a blind study in which it will not be known until the end which patients have received the treatment and which have not. To date, 250 patients have been recruited, and Grifols plans to present the preliminary results of AMBAR in 2017.

As planned, the intermediate results of the phase III clinical trial have been presented at the 8th International Congress "Clinical Trials on Alzheimer's Disease" (CTAD), held in Barcelona.

AMBAR is an international multi-center study that will include a total of 365 participants with Alzheimer's disease at the mild to moderate stage, randomly assigned to three treatment groups plus a fourth control group, at 40 hospitals in Spain and the United States.

### **The treatment of Alzheimer's with plasma proteins, a novel therapeutic approach**

It is over a decade since Grifols began to explore the potential therapeutic applications of plasma proteins in the treatment of Alzheimer's disease. The company has focused in particular on human albumin, the most abundant protein in plasma, whose most important function is to transport substances through the bloodstream including not only nutrients to the cells, but also the toxic elements which are rejected to be subsequently excreted from the organism.

Grifols' approach starts from the hypothesis that AD is related to the presence of senile plaques or neurofibrillary tangles in the brain. These plaques consist primarily of amyloid beta peptide (A $\beta$ ) and it is known that a significant part of A $\beta$  peptide circulating in the blood is bound to albumin.

The AMBAR study therefore started from the hypothesis that extracting plasma with A $\beta$  peptide using plasmapheresis and replacing it with Grifols Albumin (plasma exchange), could mobilize A $\beta$  peptide from the brain to the plasma that would limit the impact of the disease over the patient's cognitive functions. In addition, the AMBAR study tests a special type of low-volume plasma exchange called apheresis. In the event that other substances in plasma were involved in the development of AD, this technique could also withdraw them from the circulatory system.

The 365 patients with AD at the mild to moderate stage who will be included in the AMBAR study will be randomly allocated between the three treatment groups and the control group. In the three treatment groups, patients undergo two types of plasma extraction:

- An initial joint phase, consisting of a complete weekly plasma exchange for six weeks and replacement with albumin 5%. A complete plasma exchange involves the extraction of 2.5/3 liters of plasma.
- A second treatment phase, with different doses of albumin for each group, involving one apheresis session per month during one year. Apheresis involves extracting 800 ml of plasma from the patient, which is very similar of a plasma donation.
- In the control group, plasma exchanges are simulated.

## **AMBAR: the continuation of two clinical trials that suggest stabilization of the disease**

Before AMBAR, Grifols conducted two clinical trials based on a similar approach: the treatment of Alzheimer's disease with plasma exchange with albumin. The phase II study suggested positive effects for patients that pointed towards stabilization of the disease.

During the treatment period, levels of A $\beta$ 42 peptide in patients who underwent plasma exchange pointed towards a tendency to increase the cerebrospinal fluid, while levels of A $\beta$ 42 in plasma were significantly lower in the treatment group.

In addition, the group that underwent plasma exchange presented improvements in cognition, and recorded better performance in language and memory tests, improvements that persisted after the treatment had been completed. 42 patients took part in this study.

After the results of these two previous clinical trials, Grifols investigators decided to perform a larger clinical trial, the AMBAR study with 365 patients, a larger sample, which will make possible to obtain more conclusive results.

### **About Alzheimer's disease**

Alzheimer's disease is a neurodegenerative pathology characterized by the death of neurones in the brain. It is currently incurable and has been described as a 21st-century epidemic, destined to have an increasing impact on the elderly population in the developed world.

According to the *Alzheimer's Association* in the USA, the disease affects 10% of those aged over 65, and up to 50% of people aged over 85, although only between 2% and 7% of cases are diagnosed at the early stages.

The WHO estimates that 24.3 million people currently suffer from Alzheimer's disease, with 4.6 million new cases each year. Experts predict that by 2030 there could be over 65 million sufferers across the globe, and that this figure could exceed 115 million in 2050. Of these, between 9 and 11 million would be in the United States. In Spain, the situation is similar to that of other developed countries. In 2010, the prevalence of the illness in Spain was 500,000 diagnosed cases, according to estimates by the country's *National Epidemiology Center*, although the progressive ageing of society means that the number of sufferers could rise by as much as 75% by 2030.

### **About Grifols:75 years of serving people's health**

Grifols is a global company that has been committed to serving people's health since 1940. In 2015 the company celebrates 75 years of improving people's health and well-being through the development of life-saving plasma medicines, hospital pharmacy products and diagnostic technology for clinical use.

The company is present in more than 100 countries worldwide and its headquarters are located in Barcelona, Spain. Grifols is a leader in plasma collection with a network of 150 plasma donation centers in the U.S., and is a leading producer of plasma-derived biological medicines. Within the field of in vitro diagnostics it is a world leader in transfusion medicine, and has a very strong position in immunology and hemostasis, enabling it to offer integrated solutions to clinical analysis laboratories, blood banks and transfusion centers.

Its revenue in 2014 exceeded 3,350 million euros, and it employs approximately 14,000 members of staff. Grifols allocates a share of its income to R&D, an investment that demonstrates the company's commitment to scientific progress.

The company's class A shares are listed on the Spanish Stock Exchange, where they are part of the Ibex-35 (MCE:GRF). Its non-voting class B shares are listed on the Mercado Continuo (MCE:GRF.P) and on the U.S. NASDAQ via ADRs (NASDAQ: GRFS). For more information, visit [www.grifols.com](http://www.grifols.com)