First in Human study with ALZ-101, a unique and highly specific therapeutic vaccine against the neurotoxic oligomeric form of Aβ 1-42

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Background

Alzinova AB is developing a new unique active immunotherapy to treat Alzheimer's disease (AD). ALZ-101 is a synthetic peptide immunogen based on the human amyloid-β 42 (Aβ42) sequence. The immunogen is composed of stable Aβ42 oligomer mimics that stimulate the production of antibodies targeting endogenous oligomers only. These oligomers are overproduced in AD and thought to be involved in its pathogenesis. Inert forms of Aβ, including plaques, are not targeted by these antibodies, thereby increasing the likelihood of target engagement across the blood-brain-barrier.

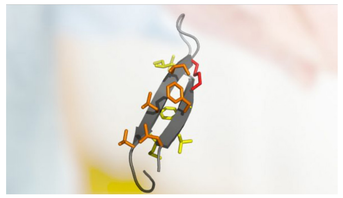


Figure 1: The AβCC peptide in hairpin conformation. Picture courtesy of Prof. T. Härd, SLU, Sweden.

Dosing with ALZ-101 in mice and rabbits drives a strong oligomer-specific humoral immune response. Studies in mice have also highlighted a positive effect of ALZ-101 on several biochemical parameters of AD, including serum Aβ levels and synapse density. Moreover, studies conducted in zebrafish embryos evaluating the toxic effect of brain extracts from deceased AD patients confirm the capacity of ALZ-101 antisera to specifically target the form of human Aβ that causes cognition deficits in this zebrafish model. Finally, studies in rabbits have allowed the identification of the optimal immunogenic doses of ALZ-101 and Alhydrogel®, its adjuvant, to be administered in the FIH study.

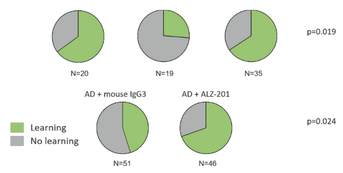
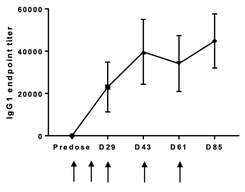


Figure 2: Distribution of learners and non-learners in the five zebrafish experimental groups

The safety and immunogenicity of ALZ-101 was assessed in a GLP-compliant toxicology study in the cynomolgus monkey. The primary aim was to evaluate the potential toxicity of five administrations of ALZ-101, given as a two-week treatment cycle, followed by a four-week, treatment-free observation period. Both cellular and humoral immune responses to the test item were monitored. ALZ-101 was well tolerated as there were no signs of toxicity related to the treatment. A humoral immune response to ALZ-101 was measured in all dosed animals, which increased over time. No significant cytotoxic T-cell response was detected.



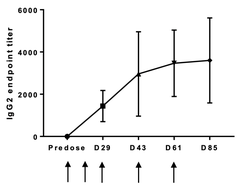


Figure 3: Graph showing the endpoint titres of IgG1 and IgG2 (n=10) in sera collected on Day 29, 43, 61, and 85 after the priming dose. Data are from the GLP compliant toxicology study, and are shown as mean titres ± SD. Arrows indicate the administration of study drug.

Study Objectives

Objectives:
To investigate the safety, tolerability and immunogenicity of ALZ-101. The study is not designed to evaluate the clinical efficacy of ALZ-101 in the treatment of AD.

Primary objective:
- Evaluate the safety and tolerability of ALZ-101 in subjects with early AD

Secondary objectives:
- Evaluate the ability of ALZ-101 to induce an Aβ-specific antibody response following multiple immunizations with ALZ-101
- Characterize the time course and magnitude of the Aβ-specific antibody response following multiple immunizations with ALZ-101

Study Design

This is a phase I, First-In-Human, placebo-controlled, randomized and double-blinded parallel group multiple dose immunization study of ALZ-101 in subjects diagnosed with mild AD or Mild Cognitive Impairment (MCI) due to AD. Two doses of ALZ-101 will be compared to placebo. The study will be performed at a single site in Finland.

The total duration of the study for a single subject will be up to 80 weeks. The treatment period will last up to 20 weeks and the follow-up period may last up to 48 weeks. During the treatment period, the study subjects will receive four doses of study drug (ALZ-101/placebo) at Weeks 0, 4, 8 and 16.

Patient Population

Study Population
Subjects participating in this study will be diagnosed with mild AD or MCI due to AD. 26 subjects will be enrolled into the study.

Main inclusion criteria:
1. Male and female between 50 and 80 years (inclusive)
2. MCI due to AD or mild AD, according to National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria:
   a. CDR global score (GS) of 0.5 or 1
   b. CDR memory score of ≥0.5
   c. MMSE score of ≥20 points
3. Screening CSF results showing a pattern consistent with amyloid plaque load and indicative of AD pathology.

Clinical Safety

Safety and tolerability will be evaluated using the following assessments:
Solicited and non-solicited AEs (including SAEs and AESIs); Clinical laboratory tests from blood, urine and CSF; Vital signs (including body temperature and weight); 12-lead ECG; Physical and neurological examinations; MRI (3T); Suicidality assessment with C-SSRS

In addition, the ADCS-CGIC scale will be reviewed at each immunization visit for detection of clinically significant cognitive or functional worsening of AD (scores 6 and 7).

Safety MRI scans of the brain will be performed once during the screening period, 3 times during the treatment period and once during the follow-up period. The results of each MRI evaluation must be available and reviewed before each subsequent dosing.

Possible clinical signs of inflammation (e.g. fever, increases in inflammatory markers in laboratory tests) will be followed carefully throughout the study.

After the first dosing, subjects will be hospitalized for 24 h for observation of possible acute adverse reactions. There will be minimum intervals of 48 h between the first doses of each of the first 8 subjects.

An independent DSMB will convene periodically to review the collected safety data.

Immunogenicity

Immunogenicity Evaluation
Aβ-specific antibodies (Abs) be analysed in both serum and in CSF. Blood samples for immunogenicity assessment will be drawn at screening, 4 weeks after each immunization and 3 times during follow-up. CSF samples will be drawn at screening and 4 weeks after the last immunization.

Endpoints related to immunogenicity:
- Aβ-specific Ab titre of post-baseline samples (if baseline sample is negative) OR titre fold increase defined as the ratio of any post-baseline Aβ-specific Ab titre to baseline antibody titre in serum and CSF
- Number of titre-based responders
- Area under serum Aβ-specific Ab titre curve (AUC) from Week 0 to Week 20, maximum titre level (Cmax), and time to Cmax (tmax)
- Relative abundance of Aβ-specific Ab subclasses (IgG, IgM and IgA) in blood and CSF
- Oligomer-specificity of Aβ-specific Abs in blood and CSF
- Affinity maturation of Aβ-specific Abs

In addition, patterns of possible T-cell activation induced by ALZ-101 in PBMCs will be evaluated.

Conclusions

In a FiH study, safety and tolerability are the most important parameters to evaluate for further clinical product development. Risks for subjects included in a FiH study must be minimal. Alzinova and CRST have designed a study with adequate safety precautions. At the same time, the strength and duration of the immunologic response to multiple doses of ALZ-101 will be evaluated in participants representing the target population of the novel agent.

This project is a collaboration between:

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