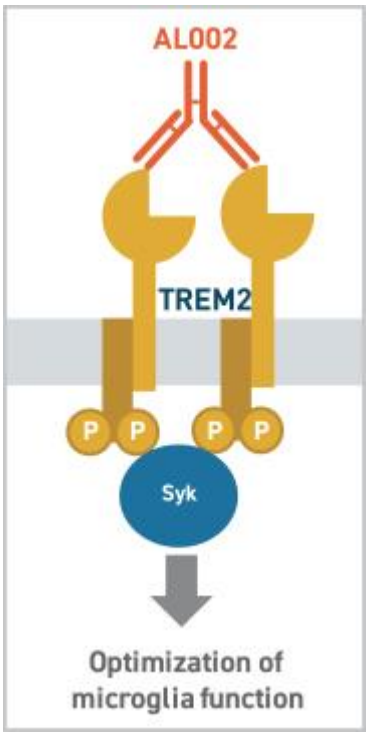
AL002

Name: AL002
Synonyms: AL 002
Indication: Alzheimer's disease
Company: Alector

AL002, an antibody targeting TREM2 (Triggering Receptor Expressed on Myeloid Cells 2) expressed on microglia is being developed by Alector in collaboration with AbbVie for the treatment of Alzheimer's disease and other neurodegenerative disorders.

AL002, is a humanized, TREM2 activating, monoclonal antibody that is intended to be delivered by intravenous, peripheral infusion into the blood stream (Figure 14). AL002 is a microglia cell regulator that modulates the TREM2 receptor and is being developed for the treatment of Alzheimer's disease in collaboration with AbbVie.



Mechanism of action our TREM2 activating product candidate AL002.

There are currently no cures or disease-modifying therapies for Alzheimer's disease and there are only two classes of approved therapies for symptomatic treatment: acetylcholinesterase inhibitors and glutamatergic modulators. These drugs are designed to help preserve neuronal communication, but only provide temporary benefit and do not slow or halt neuronal death. In addition, antidepressants and antipsychotics are often prescribed off-label to treat the symptoms of severe Alzheimer's disease in patients suffering from agitation, aggressive behaviors, psychosis, and depression.

Recent drug candidates under development for Alzheimer's disease include those focused on blocking synthesis, enhancing clearance or disaggregating misfolded amyloid-beta or TAU proteins in the brain, reversing chronic inflammation, and repairing vascular dysfunction, metabolic dysregulation, as well as

neurotoxicity. Almost all of these candidates were designed to target just one of the multiple Alzheimer's disease pathologies, and most of these drug candidates have so far failed to demonstrate any significant benefit.

Although amyloid-beta plaques and TAU protein in the brain represent physical pathologies of the disease and are believed to cause a loss of neuronal connectivity in the brain and neuronal death, recent scientific data paints a more complex picture. Therapeutic approaches that address only one of the multiple pathologies observed in Alzheimer's disease, for example, pathology-directed therapies that clear amyloid-beta or TAU proteins, have had limited efficacy. More efficacious therapies will require addressing additional pathologies which we believe are associated with microglial failure.

AL002 binds to TREM2 on the surface of microglia and is designed to optimize microglial activity through the phosphorylation of Spleen Associated Tyrosine Kinase (Syk). We have demonstrated that AL002s, an antibody that is functionally similar to AL002 but cross-reacts to the mouse TREM2, can normalize gene expression signature associated with Alzheimer's disease, induce microglial proliferation, increase microglial survival, increase the number of microglia surrounding amyloid-beta plaques, and increase the compaction, insulation, and phagocytosis of these pathological proteins (Figure 15). Moreover, AL002s following intraperitoneal injection increases migration of microglia to sites of neurodegenerative damage, and restores

AL002 is currently being tested in a randomized, double-blind, placebo-controlled, dose-escalating Phase 1 study that is ongoing in Australia. Up to 48 healthy volunteers and 12 Alzheimer's patients will be randomized and receive four doses of AL002 or placebo. The primary endpoints of the study are safety and tolerability. The secondary endpoints include pharmacokinetic measurements, including serum and CSF concentrations of AL002 at specific time points. In all five dose cohorts enrolled to date, no dose-limiting adverse events or serious adverse events have been reported.