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ALZ-801 – Phase 3-Ready Oral Small Molecule Program Designed to Inhibit Formation of Neurotoxic Soluble Amyloid Oligomers Represents Optimized and Differentiated Treatment Paradigm for Alzheimer's Disease

Precision Medicine Therapeutic Approach with ALZ-801 Focusing on Patients Homozygous for Apolipoprotein E4 Gene, Delivering Highly Brain-Penetrant Therapy to Inhibit Formation of Neurotoxic Soluble Amyloid Oligomers, with Favorable Safety Profile and Long-Term Clinical Data from over 1,600 Alzheimer's Patients

Central Role of Beta Amyloid in Pathogenesis of Both Early and Late Onset Alzheimer's Disease is Supported by Genetic and Biomarker Data

Multiple amyloid immunotherapies have failed to show efficacy in Phase 3 trials of patients with Alzheimer's disease (AD), likely related to targeting the wrong amyloid species and very limited brain penetration. These multiple failures have led to a generalized criticism of all amyloid-related approaches to AD, despite the specificity of the reasons for the failures of these monoclonal antibody programs and the strength of the science that underpins the amyloid hypothesis in pathogenesis of AD.

The central role of beta amyloid (Aβ) in AD pathogenesis has been extensively confirmed by genetic and biomarker studies in both familial (early onset) and sporadic (late onset) AD. Dominant mutations related to processing of the amyloid precursor protein (APP), which lead to increased amyloid production, are the cause of early-onset familial AD. Individuals with Down syndrome who have three copies of the APP gene, show excess amyloid production and develop early onset dementia. In contrast, the Icelandic mutation, an APP genetic variant leading to decreased amyloid production is associated with a lower risk of AD. Large genome-wide association studies also show that genetic variants affecting APP and Aβ processing are associated with high risk for late onset sporadic AD.[1,2] Finally, longitudinal biomarker studies in the elderly demonstrate that the appearance of brain amyloid deposits precedes tau pathology and neurodegeneration,[3] and are now the basis for the new biomarker-based definition of AD that has been accepted by both U.S. FDA and European EMA regulators.

Focus on Neurotoxic Soluble Aβ Oligomers is Critical for Success

The brain amyloid forms consistently shown to be associated with acute neuronal toxicity and neurodegeneration are the soluble amyloid oligomers, which are formed by aggregation of

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misfolded Aβ monomers.[4,5] In contrast, insoluble amyloid fibrils and plaques are non-toxic and even complete removal of insoluble plaques from the brains of AD patients has not been correlated with clinical efficacy. Aβ oligomers have been isolated from the brains of AD patients and their levels correlate with the onset and severity of clinical symptoms.[6,7]

In contrast, oligomers derived from post-mortem brains of AD patients cause acute synaptic neurotoxicity, inhibition of long-term potentiation (an established model of memory formation), dysregulation of neurotransmitter receptors (in particular NMDA), and dystrophy of synapses in nonclinical models.[8,9] Therefore, clearing or inhibiting the formation of Aβ oligomers is a logical and promising therapeutic approach to inhibit or prevent the neurotoxicity of soluble amyloid oligomers. None of the first generation of AD immunotherapies evaluated to date in Phase 3 trials (bapineuzumab, crenezumab, aducanumab) is selective for amyloid oligomers over insoluble fibrils or plaques, and none has shown efficacy in large Phase 3 trials.[10-12] This lack of selectivity may also lead to a preferential binding of antibodies to insoluble fibrils or plaques over neurotoxic oligomers.[13]

Eisai/Biogen presented Phase 2 clinical data with their monoclonal antibody BAN2401 in 2018. BAN2401, which demonstrates selectivity to protofibrils (large oligomers) over monomers, and some selectivity for oligomers over insoluble plaque, showed promising clinical efficacy in AD patients, with much more pronounced improvements in patients who are APOE4 carriers in a recently completed Phase 2b trial. [14,15] This efficacy pattern is similar to the ALZ-801/tramiprosate clinical data, where APOE4 carriers, and especially APOE4/4 homozygotes, show the largest efficacy signal with clinically meaningful benefit on both cognitive (ADAS-cog) and functional outcomes (CDR-SB and DAD, a disability assessment for dementia).[16,17] This preferential efficacy from two distinct drug programs that target oligomers, is consistent with the fact that APOE4 carriers, and especially homozygotes, have three-fold higher brain levels of soluble amyloid oligomers compared to noncarriers[18] and, therefore, are expected to respond well to anti-oligomer agents.

Limitations of Amyloid Immunotherapies for AD

BAN2401 and other monoclonal immunotherapies for AD patients have substantial limitations:

- Immunotherapies are administered as intravenous infusions, which are inconvenient for patients and may be associated with infusion-related adverse reactions.
- As a class, antibody therapies have limited blood-brain barrier penetration: it is estimated that only <1.5% of an administered dose enters the brain.
- Antibodies have a propensity to cause brain vasogenic edema (ARIA-E), or small bleeds (microhemorrhage, ARIA-H), particularly in APOE4 carriers who have a higher burden of

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vascular amyloid.[19] ARIA is likely related to antibody-mediated removal of vascular amyloid, resulting in inflammation and leakage from small vessels.

- In APOE4 carriers, BAN-2401 showed the largest clinical benefit at the highest administered dose of 10mg/kg/bi-monthly, where ARIA-E side effects occurred in ~15% of subjects and included some serious adverse events.[15] This led EU regulators to prohibit the highest dose in APOE4 carriers. Nevertheless, this is the dose that will be evaluated in the recently initiated confirmatory Phase 3 CLARITY AD trial.
- ARIA may be asymptomatic in most patients, however, ~30% present with clinical symptoms including seizures and other serious adverse effects.[12,15] As a result, the U.S. FDA and EMA regulatory agencies have required quarterly magnetic resonance imaging (MRI) monitoring in clinical trials of monoclonal antibodies, which adds to the patient burden of these trials.
- A consistent challenge with antibodies has been the narrow therapeutic window, since doses that show clinical benefit in Phase 2 trials are also associated with ARIA side effects, especially in APOE4 carriers, limiting the use of higher, potentially more efficacious doses.

Selective Inhibition of Formation of Neurotoxic Soluble Aβ Oligomers with Small Molecule Drug ALZ-801/Tramiprosate Provides Advantages

1. Convenience of an oral, easy to swallow tablet.
2. High brain penetration: ~40% of drug in plasma enters the brain, which is important to achieve full inhibition of oligomer formation and clinical efficacy.[20, 21]
3. The new ALZ-801 formulation also shows consistent absorption from the gut and sustained plasma levels.[21]
4. No observed cases of vasogenic edema: there were no events of ARIA-E in 426 patients evaluated by serial MRIs in the tramiprosate Phase 3 studies,[16] an expected benefit since tramiprosate does not bind to insoluble amyloid plaques or engage the immune system.
5. No requirement for quarterly MRI monitoring due to the low risk of ARIA.
6. Favorable long-term safety profile: tramiprosate safety profile has been confirmed in over 1,600 AD patients treated with the active drug for up to 1.5 years, and with 400 treated up to 2.5 years. The main adverse events were nausea and vomiting that were mostly mild or moderate.[16,17]
7. Improved tolerability with ALZ-801 formulation: based on completed Phase 1b studies with the optimized formulation ALZ-801, the incidence and severity of nausea and vomiting was decreased by ~50%.[21]

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Rationale for Initial Confirmation of ALZ-801 Efficacy and Approval in Homogeneous Patient Population of APOE4/4 AD Homozygotes

The ALZ-801 Phase 3-ready program addresses the key issues faced by other amyloid-targeted drug development programs by selectively inhibiting the formation of neurotoxic soluble amyloid oligomers with an oral therapy, which achieves high brain levels sufficient for full inhibition of oligomer formation. Furthermore, the registration program will initially focus on homozygous APOE4/4 AD patients, who carry the burden of high levels of amyloid oligomers,[18] and are at the highest risk of developing vasogenic edema with immunotherapies.[19]

Key Features of ALZ-801 Development Program

- ALZ-801 oral tablet formulation shows good oral bioavailability with an excellent brain penetration of ~40%[4] (versus <1.5% for antibodies).[21]
- ALZ-801/tramiprosate selectively and dose-dependently inhibits the formation of neurotoxic soluble amyloid oligomers, without affecting insoluble amyloid plaques or fibrils.[20,22]
- Several molecules of tramiprosate and its active metabolite, 3-SPA, interact reversibly with the Aβ42 monomer at specific sites, preventing its misfolding and stabilizing monomer in a conformation that inhibits aggregation to oligomers.[20]
- The active metabolite of ALZ-801/tramiprosate, 3-SPA, has also shown potent anti-oligomer activity *in vitro* and was found to be endogenously expressed in the human brain.[23] The endogenous nature of ALZ-801 metabolite may provide the basis for the clinical efficacy, favorable drug properties and long-term safety profile of ALZ-801. The metabolite, 3-SPA, may act as a physiological inhibitor of amyloid aggregation and ALZ-801 administration amplifies this endogenous anti-aggregation mechanism.[23]
- ALZ-801/tramiprosate treatment has *not* been associated with vasogenic edema side effects in AD patients, even in APOE4 carriers,[16] who have a high burden of vascular amyloid.
- ALZ-801/tramiprosate achieves sustained brain concentrations in AD patients that are above the levels required for full inhibition of amyloid monomer aggregation into neurotoxic oligomers.[20,22]
- ALZ-801 showed meaningful clinical benefits in APOE4 AD carriers, especially APOE4/4 homozygotes, who are known to have high levels of amyloid oligomers.[16,17,18]
- The planned Phase 3 study of ALZ-801 will focus on the homogeneous population of APOE4/4 homozygotes with Early AD, treated with a dose that achieves consistently high cerebrospinal fluid drug levels required for full inhibition of amyloid oligomer formation. This dose has shown clinical efficacy in the APOE4 carrier subgroup in prior trials.[17,21]

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- The planned Phase 3 study in APOE4/4 patients with Early AD will be powered to detect ~3.0 points benefit on ADAS-cog compared to placebo. In the APOE4/4 Mild AD subgroup in the prior tramiprosate Phase 3 study, the high dose showed nominally significant benefit of 5.4 points on ADAS-cog.[17]
- Tramiprosate, the active agent in ALZ-801, showed an acceptable safety profile in over 1,600 AD patients treated up to 1.5 years, with no cases of vasogenic edema even in APOE4 carriers. Therefore, ALZ-801 has no limitation on the use of the clinically efficacious dose.[16]

The emerging data from BAN2401 and other amyloid immunotherapy programs further increases our confidence in the ALZ-801 development program and Alzheon remains committed to initiating the Phase 3 with ALZ-801 in the near future. The first confirmatory study with ALZ-801 will be conducted in APOE4/4 homozygous patients with Early AD, and will evaluate drug effects on cognition and function, as well as preservation of brain hippocampus volume during 78 weeks of treatment.

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