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INTRINSIC ACTIVITY

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MEETING ABSTRACT

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Montelukast in mouse and man – preclinical and clinical (BUENA study) data of leukotriene inhibition in Alzheimer's disease

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Background: Expression of 5-lipoxygenase, the rate-limiting enzyme in the leukotriene pathway, is elevated in the brain of Alzheimer's disease (AD) mouse models and in the hippocampus of AD patients. Leukotrienes are involved in a number of pathological hallmarks of AD such as neuroinflammation, blood–brain barrier disruption, and reduced neurogenesis via signaling through leukotriene receptors. Leukotriene receptors are therefore recognized as potential drug targets in AD. A novel pharmaceutical formulation of the leukotriene receptor antagonist montelukast (MTK) (VersaFilm™, IntelgenX), *i.e.* a buccal mucoadhesive film containing the active drug has shown improved bioavailability compared to the standard MTK tablet and has demonstrated a CNS pharmacokinetic profile suggesting a pharmacological active concentration.
Methods: For the preclinical experiment 45 five-months-old 5xFAD mice, a commonly used transgenic mouse model of AD, were orally treated with two different doses of MTK VersaFilm™ or placebo for 13 weeks. Effects on cognition were assessed with behavioural tests. Immunohistochemistry was performed on brain slices to analyze brain-resident immune cells and plaque pathology. RNA sequencing was done using hippocampal tissue. Furthermore we present the design of a phase IIA clinical trial testing safety and efficacy of this novel MTK formulation in patients with mild to moderate AD (NCT03402503): The primary study objective is to evaluate whether 26 weeks of treatment with 10 mg MTK administered once a day is safe as well as superior to placebo, assessed at week 26 using the global neuropsychological test battery (NTB) composite score. This composite score is based on an equally-weighted average of standardized change from baseline scores on the ISLT, ISLT-Delay, One Back Test, One Card Learning Test, Verbal Fluency Test, Category Fluency Test, Identification Test and Detection Test.
Results: In our preclinical *in vivo* study we demonstrate that inhibition of leukotriene signaling with prolonged oral treatment MTK VersaFilm did show improvements in cognitive tests compared to placebo. Furthermore, treatment significantly increased the number of microglia primarily located in plaque-free areas, whereas numbers of microglia surrounding plaques did not change significantly. However, mRNA levels of various genes related to neuroinflammation (*e.g.* CST7, Tyrobp) were significantly downregulated in the high-dose treatment group compared to placebo.
Discussion: The results from the preclinical study indicate that MTK improves cognitive function and influences neuroinflammation. Given the inherent attributes of montelukast VersaFilm™, this might be a novel effective therapeutic and treatment modality as part of the armamentarium against AD.

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Keywords: neurobiology – Alzheimer's disease – leukotrienes – neuroinflammation

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