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A Phase IIa trial assessing the effects of AZD1446 on two cohorts of adult Attention Deficit Hyperactivity Disorder (ADHD) patients: Users and non-users of nicotine-containing products

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Stimulation of nicotinic cholinergic neuronal systems may alleviate symptoms of Attention Deficit Hyperactivity Disorder (ADHD) and have a measurable effect on core cognitive deficits. AZD1446, a highly selective agonist of $\alpha4\beta2$ neuronal nicotinic receptors, has demonstrated efficacy in preclinical cognitive models. In this randomized, double blind, placebo-controlled, 3-period crossover study, the efficacy, pharmacokinetics (PK), safety and tolerability of AZD1446 was examined in adult ADHD patients (NCT01012375). Two cohorts were investigated: users and non-users of nicotine-containing products. The primary objective, to assess by cohort the effect of 2 weeks' AZD1446 treatment vs. placebo on ADHD core symptoms, was measured using the Connor's Adult ADHD Rating Scale - Investigator Rated (CAARS-INV) Total ADHD Symptoms score (18-item). Secondary objectives included evaluating the effects of AZD1446 vs. placebo on the 30-item CAARS-INV subscales, selected tests from the CogState computerized battery, the Clinical Global Impression (CGI) of ADHD, and the 30-item CAARS-Self-Report Screening Version (CAARS-S:SV). The PK of AZD1446 was also evaluated, and safety/tolerability monitored throughout. Seventy-nine ADHD patients were randomized (52 non-users and 27 users of nicotine) and received treatment. In each treatment period AZD1446 or placebo was given 3 times daily for 2 weeks. Each period was separated by a 21-day washout. Three dose regimens of AZD1446 were investigated: 80 mg tid, 80 mg qd, and (in non-nicotine users only) 10 mg tid. As measured by CAARS-INV Total ADHD Score, AZD1446 did not significantly improve ($p > 0.10$) ADHD core symptoms relative to placebo in any treatment group of either cohort after 2 weeks' treatment. Likewise, no significant effects of AZD1446 treatment were observed relative to placebo when assessed by CAARS-INV sub-scales, CGI, or CAARS-S. In non-nicotine users, significant improvement was observed for AZD1446 80 mg qd compared with placebo in one cognitive test of the CogState computerized battery (the Groton Maze Learning Task; $p = 0.019$). All other tests were non-significant across both cohorts. Daily doses of AZD1446 up to 80 mg tid for 2 weeks had acceptable safety and tolerability in adult patients with ADHD (whether users or non-users of nicotine): most adverse events were of mild or moderate intensity. The PK profile of AZD1446 in this population was similar to that observed previously in healthy volunteers. No difference in exposure could be seen between users and non-users of nicotine. Within the dose range tested, AZD1446 did not meet the primary endpoint in this study of adult ADHD.

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A cembranoid protects the brain against transient middle cerebral artery occlusion

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Ischemic brain stroke is the third leading cause of death in the United States and it is the major cause of long-term disability. Americans paid about $57.9 billion in 2006 for stroke-related medical costs including those related to disability. The majority of strokes are caused by occlusion of a blood vessel in the brain. Within minutes after the beginning of ischemic stroke, an early-onset neuronal death begins in the area most affected called the infarct core that has either low blood flow or no blood flow at all. The energy failure stops causes the collapse of the neuronal transmembrane ionic gradient, intracellular Ca^{2+} influx, and release of glutamate, which causing excitotoxicity. Tissue plasminogen activator (tPA) is the only FDA approved drug for stroke is highly successful one but only 3–6% of patients qualify to receive it. To be effective, tPA must be administered within a 3-h window from the onset of symptoms. The ischemic injury increases the synthesis of inflammatory cytokines which spread the inflammation into the surrounding area called the penumbra. Neurons in the penumbra area can be rescued by neuroprotective drugs when administered several hours after the onset of ischemic stroke. The period during which the penumbra neurons can be salvaged is called "the therapeutic window of opportunity". Therefore, the neuroprotective interventions that target delayed processes like apoptosis and inflammation in the penumbra have a potential for clinical treatment in acute stroke. However, the problem is not easy since almost 2000 drugs that proved to be effective in rodents were found to be harmful or ineffective in patients because they aimed at clinically irrelevant targets. On the other hand neuroprotective drugs, with antiinflammatory and antiapoptotic properties hold much promise since the delayed damage after stroke results from inflammatory and apoptotic processes which develop for days or weeks. Our group discovered a cyclic terpenoid with such properties the 4R-cembratrienol (4R) that shows robust neuroprotective activity in vivo and in vitro. 4R rapidly crosses the BBB, is not toxic in vivo or in vitro to cultured neurons and steam cells. Adult Sprague–Dawley rats subjected to middle cerebral artery occlusion (MCAO) for 60 min were injected with 6 mg/kg 4R in a vehicle of DMSO 2 h after reperfusion. Controls were injected with the same volume of vehicle. 24 h later the brains were sliced and incubated in triphenyl tetrazolium chloride (TTC) to determine the necrotic area. The subjects injected with 4R had a 50% reduction of the necrotic area in comparison with controls.

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