# (*S*)-(+)-Mecamylamine (TC-5214): A Neuronal Nicotinic Receptor Modulator Enters Phase III Trials as an Adjunct Treatment for Major Depressive Disorder (MDD)

Major Depressive Disorder (MDD) is a common illness that affects >40 million people worldwide, and antidepressants are one of the top 5 leading classes of pharmaceuticals with annual sales in excess of $20 billion (*1*, *2*). The current standard of care focuses on serotonin−norepinephrine reuptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI); however, patients often respond poorly. In fact, the National Institute of Mental Health conducted a large-scale STAR*D study and found that 63% of patients did not achieve remission with the SSRI Citalopram (*1*, *3*−*5*). Citalopram was originally developed in Lundbeck in the late 1980s and sold as a racemate. Lundbeck, in collaboration with Forest Laboratories, has recently released an updated version called Escitalopram (also known as Lexapro), which is the single (*S*)-enantiomer of the racemic Citalopram, which provided new patent life. In 2009, Lexapro garnered ∼$2.7 billion in sales in the US (Figure 1) (*2*).

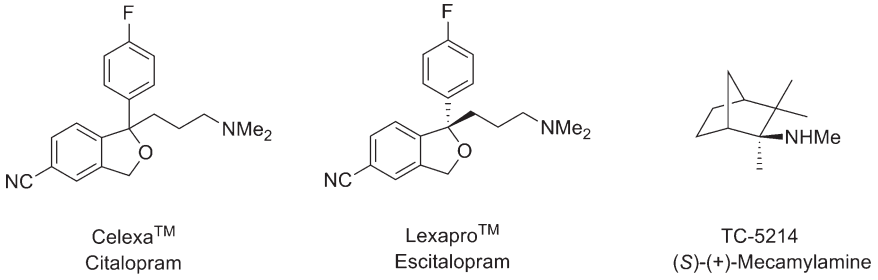


**Figure 1.** Structures of Citalopram, Escitalopram, and TC-5214.

An alternative hypothesis for depression emerged over 30 years ago and suggests that a cholinergic imbalance (hypercholinergic tone) is a major factor in depression, and both clinical and preclinical studies have implicated neuronal nicotinic cholinergic receptors (NNRs) rather than muscarinic receptors (*5*). On the basis of these data, AstraZeneca and Targacept have explored the role of NNR antagonism in depressive disorders and recently announced the initiation of a phase III trial of TC-5214, (*S*)-(+)-mecamylamine, as an adjunct therapy with Citalopram. TC-5214 is a low molecular weight (167.3 as free base, 203.8 as the HCl salt), basic ($pK_a$ = 11.5) compound, freely soluble in water. While TC-5214 displays modest selectivity among the NNRs, its antidepressive properties are presumed to be the result of inhibition of the $\alpha4\beta2$ NNRs. Preclinically, TC-5214 demonstrated robust efficacy in rodent models of depression (forced swim and behavioral despair) and anxiety (social interaction and light/dark chamber). The (*S*)-enantiomer showed a superior preclincial safety profile compared to that of either the racemic compound or the (*R*)-enantiomer. Furthermore, TC-5214 was well tolerated in both acute and chronic toxicity tests, displayed no mutagenic potential, and possessed pharmacokinetic properties suitable for development (*3*−*5*).

In 2009, Targacept conducted a double blind, placebo controlled phase IIb trial in MMD patients with TC-5214, as an adjunct treatment with Citalopram demonstrated superiority to placebo in both primary and secondary outcome measures (*3*−*5*). This positive outcome led to a license agreement in December of 2009 with AstraZeneca for the global development and commercialization of TC-5214. On June 23, 2010, AstraZeneca and Targacept announced the enrollment of the first patients in the phase III trial of TC-4214. Coined the Renaissance Program, the trial will include two fixed dose and two flexible dose phase III studies of TC-5214 as an adjunct treatment for patients with poor response to standard SSRI or SNRI therapy. Each fixed dose and flexible dose phase III study will employ an initial open label phase wherein patients diagnosed with MDD receive one of seven marketed SSRIs or SNRIs for eight weeks to assess therapeutic response. Patients that respond poorly will then be randomized into a double blind, placebo controlled second phase to receive a fixed or a flexible dose of TC-5214 or placebo, twice daily, while continuing the SSRI or SNRI therapy. A change from double blind baseline for TC-5214 on the Montgomery−Asberg Depression Rating Scale (MADRS) as compared to placebo is the primary outcome measure. The program will also include a double blind, placebo

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controlled study for long-term safety. The companies plan completion of the trial in time to file an IND with the FDA in late 2012 (*3*−*5*).

MMD is the leading cause of disability in the US for people 15−44, and the burden for MDD in the US in 2000 was in excess of $83 billion (*6*). When broken down, the workplace burden for lost time is ∼62%, treatment costs account for ∼31%, and suicide related costs average 7% (*6*). For those suffering from MDD with poor response to SSRIs and SNRIs, the phase III data is anxiously awaited.

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