

Therapeutic focus - Hopes fading for nicotinic receptors as Astra pill flunks



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Confirmation that the end of the road has been reached by TC-5214, AstraZeneca and Targacept's depression pill, is disappointing but not surprising given previous trial failures.

Belonging to a class of drug that has struggled to make progress, the nicotinic receptor agonist looks likely to join a growing list of similar agents that have misfired over the last decade. Targacept, which has invested heavily in this area of medical research, will have to work hard to convince shareholders further investment is warranted. Other nicotinic targeting products remain in trials but there are few viable candidates remaining – a clinical success is needed to reignite interest (see tables).

Over exposed

Expectations around TC-5214 had already collapsed following the previous failures ([Pipeline setbacks hurt AstraZeneca, December 20, 2012](#)). However, analysts had long been reluctant to ascribe substantial value to the product. At peak six months ago consensus for sales in 2016 stood at only \$379m, no doubt reflecting scepticism around this mechanism of action as well as a challenging setting in which to show effectiveness.

Astra shares were unchanged while partner Targacept was feeling the pain, its stock dropping 25% in early trade to \$5.58, valuing the company at \$185m, well below its cash balance of \$225m.

Dedicated to researching neuronal nicotinic receptors, Targacept is particularly exposed to this field of research and the failure of the most advanced clinical candidate in the class is clearly a setback. TC-5214 made it lot further than most, having been studied in more than 4,000 patients across four phase III trials and a long term safety study.

Volume knobs

Neuronal nicotinic receptors regulate nervous system activity and as such have become targets for drug research in a broad array of CNS disorders. Targacept describes them as the “volume knobs” of the nervous system, regulating and normalising brain and nervous system functions such as memory, attention, mood, pain and inflammation. The body's natural activator of these receptors is acetylcholine.

There are several subtypes of neuronal nicotinic receptors, with particular functions. TC-5214 for example was designed to block the overactive receptors implicated in depression, and was designed as an add-on therapy to other antidepressants.

Reporting data from the final two phase III studies, the companies said that although every dose group showed at least a 40% improvement on the Montgomery-Asberg Depression Rating Scale – the primary endpoint measure – statistical significance was not met. A filing in major depressive disorder will not be pursued, the companies said today.

Little progress, little value

There are several other nicotinic receptor targeting agents in development for various CNS disorders, although the class as a whole has made little real progress. Pfizer's smoking cessation pill Chantix is the only drug of this class to make it to market, a product not without its issues ([Chantix warnings strengthened but lack of competition will mitigate damage, July 3, 2009](#)).

This lack of progress probably explains why none of the remaining nicotinic receptor agonists candidates in development are attracting sales forecasts.

Most advanced nicotinic receptor targeting drugs in development for CNS disorders

Status	Product	Generic Name	Company	Originator	Indication Summary	Termination Date
Phase II	ABT-089	pozanicline	Abbott Laboratories	Abbott Laboratories	ADHD, Schizophrenia	-
	ABT-894	sofinicline	Abbott Laboratories	NeuroSearch	ADHD	-
	EVP-6124/MT-4666	-	EnVivo Pharmaceuticals/Mitsubishi Tanabe Pharma	Bayer	Schizophrenia, Alzheimer's disease	11/11/11
	RG3487/RO5313534 (MEM3454)	-	Roche	Memory Pharmaceuticals	Schizophrenia	-
	AZD3480 (TC-1734)	ispronidine	AstraZeneca	Targacept	ADHD, Alzheimer's disease, senile dementia	11/11/11
	AZD1446 (TC-6683)	-	AstraZeneca	Targacept	Alzheimer's disease, ADHD	-
	TC-5619	-	Targacept	Targacept	Schizophrenia, ADHD	11/11/11
	RPI-MN IV	-	Nutra Pharma	ReceptoPharm	Herpes, Amyotrophic lateral sclerosis	-
	RPI-78M IV	-	Nutra Pharma	ReceptoPharm	Other neurological indications	-
	NP002	nicotine dihydrate bitartrate	Neuraltus Pharmaceuticals	Neuraltus Pharmaceuticals	Parkinson's disease	-
	ND0801	-	NeuroDerm	NeuroDerm	ADHD	11/11/11

In terms of big pharma activity, Abbott's two candidates look likely abandoned; no trials are ongoing and the company has not mentioned them for a couple of years. Roche has said little about RG3487 although a trial is active, according to www.clinicaltrials.gov.

Astra still has deals in place with Targacept over two other agents being researched in Alzheimer's disease; a phase II study is ongoing with AZD3480 although no active trials are listed with AZD1446.

Targacept still owns rights to TC-5619 and started a phase IIb and phase II study late last year, in schizophrenia and ADHD respectively. Results could emerge later this year and next year.

Aside from TC-5619, EnVivo is fairly advanced with its candidate EVP-6124. The company generated strong phase IIb data on the drug last year in schizophrenia and plans to push on with phase III studies this year, focusing on improving cognition.

TC-5214 is certainly not the first and will not be the last drug to fail in depression, an incredibly hard condition to treat. The table below shows that other nicotinic receptor targeting drugs that have fallen by the wayside over the last decade, many being researched for depression or schizophrenia.

Should further flunks emerge from this class, Targacept and others will have to mount persuasive arguments to justify spending more money in this area.

Abandoned nicotinic pipeline

Abandoned Status	Pharmacological Class	Product	Company	Indication Summary	Termination Date
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Phase III	Alpha 4 & beta 2 nicotinic agonist	TC-5214	AstraZeneca/Targacept	Depression, Hypertension [Abandoned - Phase II]	20/03/2012
	Nicotinic partial agonist	Dianicline (SSR 591813)	Sanofi	Smoking cessation	31/12/2007
	Nicotinic agonist	Nicotinell TTS	Daiichi Sankyo	Smoking cessation	31/12/2006
Phase II	Nicotinic partial agonist	CP-601,927	Pfizer	Depression; Smoking cessation	11/08/2011
	Alpha-7 nicotinic agonist	TC-5619	AstraZeneca	Schizophrenia, ADHD, Alzheimer's disease [Abandoned - Phase I], General inflammatory disorders [Abandoned - Phase I]	02/05/2011
	Alpha-7 nicotinic agonist	AZD0328	Merck & Co/AstraZeneca	Alzheimer's disease	29/01/2009
	Alpha 4 & beta 2 nicotinic agonist	Mecamylamine hydrochloride	Targacept	Depression, Generalised anxiety	31/12/2008
	Alpha 4 & beta 2 nicotinic agonist	TC-2696	GlaxoSmithKline/Targacept	Post-operative pain	14/03/2008
	Nicotinic acetylcholine antagonist	ACV1	Calzada	Neuropathic pain, Diabetic neuropathy, Post-herpetic neuralgia	14/08/2007
	Nicotinic agonist	ATG002	CoMentis	Ulcers, diabetic foot	07/08/2007
	Nicotinic acetylcholine agonist	PH-399,733	Pfizer	Schizophrenia	20/12/2006
	Alpha 4 & beta 2 nicotinic agonist	TC-5231	Targacept	ADHD	31/12/2004
	Nicotinic receptor agonist	TC-2403	Targacept	Ulcerative colitis	31/12/2004
	Nicotinic acetylcholine agonist	ABT-594	Abbott Laboratories	Neuropathic pain	31/05/2003
	Nicotinic acetylcholine agonist	SIB-1508Y	Merck & Co	Parkinson's disease	-
	Nicotinic acetylcholine agonist	SIB-1553A	Merck & Co	Alzheimer's disease, ADHD, Schizophrenia	-

	Nicotinic agonist	OTS nicotine	Cephalon	Smoking cessation	-
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