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Annual Update 2004/2005 - Treatment of Neurological Disorders

(Source: Prous Science Integrity®)

Treatment of Neurological Disorders by Condition

Condition	Phase	Drug	Source
Amyotrophic lateral sclerosis	II	Arimoclomol maleate	CytRx
	II	Arundic acid[2]	Ono Pharmaceutical
	II	Edaravone[1,2]	Mitsubishi Pharma
	II	FP-0011	Faust Pharmaceuticals
	I	AEOL-10150	Aeolus Pharmaceuticals
	I	PLD-180	Pliva
	I	PYM-50018	Phytopharm
	I	TRO-19622	Trophos
	I	VP-025	Vasogen
	Discontinued	Pentoxifylline[1]	ExonHit Therapeutics
Batten disease	I	Human fetal neural stem cells	StemCells
Chronic fatigue syndrome	III	Atvogen	HemispheRx
Cognitive impairment	II	Ispronicline	Targacept
	I	IPL-455903 (HT-0712)	Helicon Therapeutics/Inflazyme
	I	N-PEP-12	Ebewe Pharma
Cognitive impairment, CABG-related	I/II	SGS-111	Saegis
	I	KTX-0101	KetoCytonyx
Cognitive impairment, schizophrenia-related	I	SGS-518	Saegis/Lilly
Dementia, Alzheimer's-type	III	Atorvastatin calcium[1,2]	Pfizer
	III	MPC-7869	Myriad Genetics
	III	Neramexane hydrochloride	Forest/Merz
	III	Phenserine tartrate[2]	Axonyx
	III	Tramiprosate	Neurochem
	III	VP-4896	Voyager Pharmaceutical
	III	Xaliproden hydrochloride[2]	Sanofi-Aventis
	II	742457	GlaxoSmithKline
	II	ABT-089	Abbott
	II	AC-1202	Accera
	II	Arundic acid[2]	Ono Pharmaceutical
	II	Bapineuzumab	Elan/Wyeth
	II	C-9136	Merck & Co.
	II	Colostrinin™	ReGen Therapeutics
	II	CX-717	Cortex
	II	Dimebolin hydrochloride[1]	Medivation
	II	FK-962	Astellas Pharma
	II	Icosapent ethyl ester[1]	Mochida
	II	Ladostigil tartrate	Teva
	II	Lecozotan hydrochloride	Wyeth
	II	LY-450139	Lilly
	II	LY-451395	Lilly
	II	MEM-1003	Memory Pharmaceuticals
	II	Mifepristone[1,2]	Corcept Therapeutics
	II	PYM-50028	Phytopharm
	II	Rasagiline mesilate[2]	Teva/Eisai

Continuation

Treatment of Neurological Disorders by Condition

Condition	Phase	Drug	Source
Dementia, Alzheimer's-type	II (EU, US)	Resequinil	Dainippon Sumitomo
	II	Rosiglitazone maleate[1,2]	GlaxoSmithKline
	II	SGS-742[2]	Saegis
	II	SL-65.0155	Sanofi-Aventis
	II	SR-57667	Sanofi-Aventis
	II	T-588[2]	Toyama
	II	ZT-1	Debiopharm/Shanghai Institute of Materia Medica
	I/II	HF-0420	Hunter-Fleming
	I	189254	GlaxoSmithKline
	I	AL-108	Allon Therapeutics
	I	Alfatradiol	Migenix
	I	AVE-1625	Sanofi-Aventis
	I	C-7617	Merck & Co.
	I	CAD-106	Novartis/Cytos Biotechnology
	I	CERE-110	Ceregene
	I	EHT-0202	ExonHit Therapeutics
	I	HCT-1026[2]	NicOx
	I	HF-0220	Hunter-Fleming
	I	MEM-3454	Memory Pharmaceuticals/Roche
	I	NGX-267	TorreyPines Therapeutics
	I	PBT-2	Prana Biotechnology
	I	(+)-Phenserine	Axonyx
	I	PRX-03140	Predix Pharmaceuticals
	I	R-1500	Roche
	I	R-1577	Roche
	I (JP)	Resequinil	Dainippon Sumitomo
	I	T-817MA	Toyama
	I	Triflusal[1,2]	Uriach
	I	VP-025	Vasogen
	Discontinued	Coluracetam	Mitsubishi Pharma
	Discontinued	NS-2330	NeuroSearch/Boehringer Ingelheim
Epilepsy	L-2004	Pregabalin[2]	Pfizer
	Prereg.	Rufinamide[2]	Eisai/Novartis
	III	Eslicarbazepine acetate	Bial
	III	Lacosamide[2]	Schwarz Pharma
	III	Retigabine[2]	Valeant
	II	Becampanel	Novartis
	II	Brivaracetam	UCB Pharma
	II	DP-VPA	D-Pharm
	II	E-2007	Eisai
	II	NS-1209	NeuroSearch
	II	RWJ-333369 (YKP-509)	Ortho McNeil (Johnson & Johnson)/SK Bio-Pharmaceuticals
	II	Safinamide mesilate[2]	Newron
	II	Seletracetam	UCB Pharma
	II	Talampanel[2]	Ivax
	I	406725	GlaxoSmithKline
	I	Isovaleramide	NPS Pharmaceuticals
	Discontinued	ICA-69673	ICAgen
Friedreich's ataxia	II	Idebenone[1,2]	Takeda/Santhera
	I	Alfatradiol	Migenix
Huntington's disease	III	Icosapent ethyl ester[1]	Amarin
	II	ACR-16	Carlsson Research
	I	TRO-19622	Trophos
	I	TV-5010	Proneuron/Teva
Mild cognitive impairment	II	Dexanabinol	Pharmos
	II	SGS-111	Saegis
	II	SGS-742[2]	Saegis
	I	AL-208	Allon Therapeutics
Multiple sclerosis	L-2005	Sativex®	GW Pharmaceuticals/Bayer
	Prereg.	Natalizumab	Elan/Biogen Idec

Continuation

Treatment of Neurological Disorders by Condition

Condition	Phase	Drug	Source
Multiple sclerosis	III	Cladribine, oral formulation	Serono/Ivax
	III	Fampridine[2]	Acorda
	III	Teriflunomide	Sanofi-Aventis
	II/III	MBP-8298	BioMS Medical
	II/III	Rituximab[1,2]	Genentech/Biogen Idec
	II - On hold	683699 (T-0047)	GlaxoSmithKline/Tanabe Seiyaku
	II	ABT-874	Abbott
	II	Alemtuzumab[1,2]	Genzyme/Schering AG
	II - On hold	ATL-1102	Antisense Therapeutics
	II	BG-12	Biogen Idec/Fumapharm
	II	C-6448	Merck & Co.
	II	CNTO-1275	Centocor (Johnson & Johnson)/Medarex
	II	Daclizumab[1,2]	Protein Design Labs/Biogen Idec
	II	E-2007	Eisai
	II	Fingolimod hydrochloride[2]	Novartis
	II	Ibudilast[1,2]	MediciNova
	II	Interferon tau	Pepgen
	II	Laquinimod[2]	Teva/Active Biotech
	II	LAX-202	Amarin
	II	MLN-1202	Millennium Pharmaceuticals
	II	MS-I.E.T.	Transition Therapeutics
	II	NeuroVax™	Immune Response
	II	Temsirolimus[2]	Wyeth
	II	Tiplimotide	Neurocrine Biosciences
	II	TV-5010	Teva
	II	Xaliproden hydrochloride[2]	Sanofi-Aventis
	I/II	BHT-3009	Bayhill Therapeutics
	I/II	Tovaxin™	PharmaFrontiers
	I	CDP-323	UCB Pharma
	I	MLN-3897 (AVE-9897)	Millennium Pharmaceuticals/Sanofi-Aventis
	I	R-1295	Roche
	I	RG-2077	Repligen
	I	SC-12267	4SC
Muscular atrophy, spinal	I	TRO-19622	Trophos
Muscular dystrophy	I/II	Stamulumab	Wyeth
Muscular dystrophy, Becker	I	MyoDys®	Transgene
Muscular dystrophy, Duchenne	II	Idebenone[1,2]	Santhera
	I	FP-0023	Faust Pharmaceuticals
	I	MyoDys®	Transgene
	I	PTC-124	PTC Therapeutics
Myasthenia gravis	III	Mycophenolate mofetil[1,2]	Aspreva
	II	Monarsen	Ester Neurosciences
Neurodegeneration	I	SSR-180575	Sanofi-Aventis
Neurological disorders	II	Glypromate®	Neuren Pharmaceuticals
Neuropathy, chemotherapy-induced	III	Xaliproden hydrochloride[2]	Sanofi-Aventis
Neuropathy, diabetic	III	Dextromethorphan/quinidine sulfate	Avanir
	III	Fidarestat	Daiichi Sankyo/Sanwa Kagaku
	III	Lacosamide[2]	Schwarz Pharma
	III (US,CA)	Ranirestat[2]	Dainippon Sumitomo/Eisai
	II	QR-333	Quigley Pharma
	II (JP)	Ranirestat[2]	Dainippon Sumitomo/Kyorin
	II	TAK-128	Takeda
	II	TAK-428	Takeda
	I	SB-509	Sangamo BioSciences
Neuropathy, peripheral	III	BNP-7787	BioNumerik/Takeda/Baxter Oncology/Aska Pharmaceutical

Continuation

Treatment of Neurological Disorders by Condition

Condition	Phase	Drug	Source
Parkinson's disease	L-2005	Rasagiline mesilate[2]	Teva/Lundbeck
	Prereg.	Melevodopa hydrochloride/carbidopa	Chiesi/Cita NeuroPharmaceuticals
	Prereg.	Rotigotine hydrochloride[2], transdermal	Schwarz Pharma/Aderis
	Prereg.	Zonisamide[1,2]	Dainippon Sumitomo
	III	Istradefylline[2]	Kyowa Hakko
	III	Safinamide mesilate[2]	Newron
	III	Sarizotan hydrochloride	EMD Pharmaceuticals/Merck KGaA
	III	SLV-308[2]	Solvay
	II	Arundic acid[2]	Ono Pharmaceutical
	II	E-2007	Eisai
	II	Fipamezole hydrochloride[2]	Juvantia
	II	FP-0011	Faust Pharmaceuticals
	II	GPI-1485	MGI Pharma/Symphony Neuro Development Company
	II	Lisuride maleate[1], transdermal	NeuroBiotec/Prestwick Pharmaceuticals
	II	NS-2330	NeuroSearch/Boehringer Ingelheim
	II	Premarin®[1]	Wyeth
	II	Spheramine®	Schering AG/Berlex/Titan
	II	SR-57667	Sanofi-Aventis
	I/II	AV-201	Avigen
	I/II	Rotigotine hydrochloride[2], nasal spray	Schwarz Pharma/Aderis
	I/II	V-2006	Biogen Idec/Vernalis
	I	ACR-16	Carlsson Research
	I	Alfatradiol	Migenix
	I	AVE-1625	Sanofi-Aventis
	I	C-6161	Merck & Co.
	I	CERE-120	Ceregene
	I	EHT-0202	ExonHit Therapeutics
	I	NLX-P101	Neurologix
	I	PYM-50028	Phytopharm
	I	VP-025	Vasogen
Peritumoral brain edema	III	Corticorelin acetate	Celtic Pharmaceutical/Neurobiological Technologies
Polyneuropathy, familial amyloid	I	Fx-1006A	FoldRx
Pseudobulbar affect	Prereg.	Dextromethorphan/quinidine sulfate	Avanir
Restless legs syndrome	III	Pramipexole hydrochloride[1,2]	Boehringer Ingelheim
	III	Rotigotine hydrochloride[2], transdermal	Schwarz Pharma/Aderis
	II/III	Lisuride maleate[1], transdermal	NeuroBiotec/Prestwick Pharmaceuticals
	II	Istradefylline[2]	Kyowa Hakko
	II	Safinamide mesilate[2]	Newron
	II	XP-13512	XenoPort/Astellas Pharma
	Discontinued	SEP-226330	Sepracor
Spasticity	I	XP-19986	XenoPort
Spinal cord injury	III	Fampridine[2]	Acorda
	II	Nerispirdine hydrochloride	Sanofi-Aventis
	II	ProCord	Proneuron
	I/II	BA-210	BioAxone
Stroke	L -2005	Losartan potassium/ hydrochlorothiazide[1]	Merck & Co.
	Prereg.	Ximelagatran[1,2]	AstraZeneca
	III	Sarpogrelate hydrochloride[1,2]	Mitsubishi Pharma
	II	AGY-94806 (SA-4503)	AGY Therapeutics/M's Science
	II	AX-200	Axaron Bioscience
	II	DP-b99	D-Pharm
	II	HPI-001	Hamilton Pharmaceuticals
	II	Microplasmin	ThromboGenics
	I	234551	GlaxoSmithKline/Shionogi
	I	813893	GlaxoSmithKline
	I	HF-0220	Hunter-Fleming
	I	NTx™-265	Stem Cell Therapeutics

Continuation

Treatment of Neurological Disorders by Condition

Condition	Phase	Drug	Source
Stroke	I	TS-011	Taisho
	IND filed	Inosine	Boston Life Sciences
Stroke, hemorrhagic	II	Clazosentan sodium	Actelion
	II	Disufenton sodium[2]	AstraZeneca
	II	Tramiprosate	Neurochem
Stroke, ischemic	III	Abciximab[1,2]	Centocor (Johnson & Johnson)/Lilly
	III	Ancrod[1]	Neurobiological Technologies
	III	Desmoteplase	Forest/Lundbeck/PAION
	III	Disufenton sodium[2]	AstraZeneca
	II/III	Arundic acid[2]	Ono Pharmaceutical/Merck & Co.
	II	MRX-815	ImaRx Therapeutics
	II	Piclozotan hydrochloride hydrate	Daiichi Asubio Pharma
	II (JP)	S-0139 (737004)	Shionogi/GlaxoSmithKline
	II	V-10153	Vernalis
	I	Enecadin hydrochloride	PAION
	I (EU)	S-0139 (737004)	Shionogi/GlaxoSmithKline
	I	SUN-N8075	Daiichi Asubio Pharma
Stroke, thrombotic	Prereg.	Fasudil hydrochloride[1,2]	Asahi Kasei
	II	Dabigatran etexilate	Boehringer Ingelheim
Subarachnoid hemorrhage	Prereg.	Nicaraven[2]	Chugai
Tardive dyskinesia	II	Talampanel[2]	Ivax
Traumatic brain injury	I/II	Oxycyte™	Synthetic Blood Intl.
	I	Anatibant mesilate	Fournier (Solvay)/Xytis
	I	DP-b99	D-Pharm
	Discontinued	Dexanabinol	Pharmos
Tremor, essential	II/III	T-2000	Taro
	II	AVE-7688	Sanofi-Aventis

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Treatment of Neurological Disorders by Source

Source	Condition	Drug	Phase
4SC	Multiple sclerosis	SC-12267	I
Abbott	Dementia, Alzheimer's-type	ABT-089	II
	Multiple sclerosis	ABT-874	II
Accera	Dementia, Alzheimer's-type	AC-1202	II
Acorda	Multiple sclerosis	Fampridine[2]	III
	Spinal cord injury	Fampridine[2]	III
Actelion	Stroke, hemorrhagic	Clazosentan sodium	II
Active Biotech	Multiple sclerosis	Laquinimod[2]	II
Aeolus Pharmaceuticals	Amyotrophic lateral sclerosis	AEOL-10150	I
Aderis	Parkinson's disease	Rotigotine hydrochloride[2], nasal spray	I/II
		Rotigotine hydrochloride[2], transdermal	Prereg.
	Restless legs syndrome	Rotigotine hydrochloride[2], transdermal	III
AGY Therapeutics	Stroke	AGY-94806 (SA-4503)	II
Allon Therapeutics	Dementia, Alzheimer's-type	AL-108	I
	Mild cognitive impairment	AL-208	I
Amarin	Huntington's disease	Icosapent ethyl ester[1]	III
	Multiple sclerosis	LAX-202	II
Antisense Therapeutics	Multiple sclerosis	ATL-1102	II - On hold
Asahi Kasei	Stroke, thrombotic	Fasudil hydrochloride[1,2]	Prereg.
Aska Pharmaceutical	Neuropathy, peripheral	BNP-7787	III
Aspreva	Myasthenia gravis	Mycophenolate mofetil[1,2]	III
Astellas Pharma	Dementia, Alzheimer's-type	FK-962	II
	Restless legs syndrome	XP-13512	II
AstraZeneca	Stroke	Ximelagatran[1,2]	Prereg.
	Stroke, hemorrhagic	Disufenton sodium[2]	II
	Stroke, ischemic	Disufenton sodium[2]	III
Avanir	Neuropathy, diabetic	Dextromethorphan/quinidine sulfate	III
	Pseudobulbar affect	Dextromethorphan/quinidine sulfate	Prereg.
Avigen	Parkinson's disease	AV-201	I/II
Axaron Bioscience	Stroke	AX-200	II
Axonyx	Dementia, Alzheimer's-type	(+)-Phenserine	I
		Phenserine tartrate[2]	III
Baxter Oncology	Neuropathy, peripheral	BNP-7787	III
Bayer	Multiple sclerosis	Sativex®	L-2005
Bayhill Therapeutics	Multiple sclerosis	BHT-3009	I/II
Berlex	Parkinson's disease	Spheramine®	II
Bial	Epilepsy	Eslicarbazepine acetate	III
BioAxone	Spinal cord injury	BA-210	I/II
Biogen Idec	Multiple sclerosis	BG-12	II
		Daclizumab[1,2]	II
		Natalizumab	Prereg.
		Rituximab[1,2]	II/III
	Parkinson's disease	V-2006	I/II
BioMS Medical	Multiple sclerosis	MBP-8298	II/III
BioNumerik	Neuropathy, peripheral	BNP-7787	III
Boehringer Ingelheim	Dementia, Alzheimer's-type	NS-2330	Discontinued
	Parkinson's disease	NS-2330	II
	Restless legs syndrome	Pramipexole hydrochloride[1,2]	III
	Stroke, thrombotic	Dabigatran etexilate	II
Boston Life Sciences	Stroke	Inosine	IND filed
Carlsson Research	Huntington's disease	ACR-16	II
	Parkinson's disease	ACR-16	I
Celtic Pharmaceutical	Peritumoral brain edema	Corticorelin acetate	III
Centocor (Johnson & Johnson)	Multiple sclerosis	CNTO-1275	II
	Stroke, ischemic	Abciximab[1,2]	III
Ceregene	Dementia, Alzheimer's-type	CERE-110	I
Ceregene	Parkinson's disease	CERE-120	I
Chiesi	Parkinson's disease	Melevodopa hydrochloride/carbidopa	Prereg.
Chugai	Subarachnoid hemorrhage	Nicaraven[2]	Prereg.
Cita NeuroPharmaceuticals	Parkinson's disease	Melevodopa hydrochloride/carbidopa	Prereg.
Corcept Therapeutics	Dementia, Alzheimer's-type	Mifepristone[1,2]	II
Cortex	Dementia, Alzheimer's-type	CX-717	II
Cytos Biotechnology	Dementia, Alzheimer's-type	CAD-106	I
CytRx	Amyotrophic lateral sclerosis	Arimoclomol maleate	II

Continuation

Treatment of Neurological Disorders by Source

Source	Condition	Drug	Phase
Daiichi Asubio Pharma	Stroke, ischemic	Piclozotan hydrochloride hydrate	II
		SUN-N8075	I
Daiichi Sankyo	Neuropathy, diabetic	Fidarestat	III
Dainippon Sumitomo	Dementia, Alzheimer's-type	Resequinil	II (EU, US)
		Resequinil	I (JP)
	Neuropathy, diabetic	Ranirestat[2]	III (US,CA)
		Ranirestat[2]	II (JP)
	Parkinson's disease	Zonisamide[1,2]	Prereg.
Debiopharm	Dementia, Alzheimer's-type	ZT-1	II
D-Pharm	Epilepsy	DP-VPA	II
	Stroke	DP-b99	II
	Traumatic brain injury	DP-b99	I
Ebewe Pharma	Cognitive impairment	N-PEP-12	I
Eisai	Dementia, Alzheimer's-type	Rasagiline mesilate[2]	II
	Epilepsy	E-2007	II
		Rufinamide[2]	Prereg.
	Multiple sclerosis	E-2007	II
	Neuropathy, diabetic	Ranirestat[2]	III (US,CA)
	Parkinson's disease	E-2007	II
Elan	Dementia, Alzheimer's-type	Bapineuzumab	II
	Multiple sclerosis	Natalizumab	Prereg.
EMD Pharmaceuticals	Parkinson's disease	Sarizotan hydrochloride	III
Ester Neurosciences	Myasthenia gravis	Monarsen	II
ExonHit Therapeutics	Amyotrophic lateral sclerosis	Pentoxifylline[1]	Discontinued
	Dementia, Alzheimer's-type	EHT-0202	I
	Parkinson's disease	EHT-0202	I
Faust Pharmaceuticals	Amyotrophic lateral sclerosis	FP-0011	II
	Muscular dystrophy, Duchenne	FP-0023	I
	Parkinson's disease	FP-0011	II
FoldRx	Polyneuropathy, familial amyloid	Fx-1006A	I
Forest	Dementia, Alzheimer's-type	Neramexane hydrochloride	III
	Stroke, ischemic	Desmoteplase	III
Fournier (Solvay)	Traumatic brain injury	Anatibant mesilate	I
Fumapharm	Multiple sclerosis	BG-12	II
Genentech	Multiple sclerosis	Rituximab[1,2]	II/III
Genzyme	Multiple sclerosis	Alemtuzumab[1,2]	II
GlaxoSmithKline	Dementia, Alzheimer's-type	189254	I
		742457	II
		Rosiglitazone maleate[1,2]	II
	Epilepsy	406725	I
	Multiple sclerosis	683699 (T-0047)	II - On hold
	Stroke	234551	I
		813893	I
	Stroke, ischemic	S-0139 (737004)	II (JP)
		S-0139 (737004)	I (EU)
GW Pharmaceuticals	Multiple sclerosis	Sativex®	L-2005
Hamilton Pharmaceuticals	Stroke	HPI-001	II
Helicon Therapeutics	Cognitive impairment	IPL-455903 (HT-0712)	I
HemispheRx	Chronic fatigue syndrome	Atvogen	III
Hunter-Fleming	Dementia, Alzheimer's-type	HF-0220	I
		HF-0420	I/II
	Stroke	HF-0220	I
ICAgen	Epilepsy	ICA-69673	Discontinued
ImaRx Therapeutics	Stroke, ischemic	MRX-815	II
Immune Response	Multiple sclerosis	NeuroVax™	II
Inflazyme	Cognitive impairment	IPL-455903 (HT-0712)	I
Ivax	Epilepsy	Talampanel[2]	II
	Tardive dyskinesia	Talampanel[2]	II
Juvantia	Parkinson's disease	Fipamezole hydrochloride[2]	II
KetoCytonyx	Cognitive impairment, CABG-related	KTX-0101	I
Kyorin	Neuropathy, diabetic	Ranirestat[2]	II (JP)
Kyowa Hakko	Parkinson's disease	Istradefylline[2]	III
	Restless legs syndrome	Istradefylline[2]	II

Continuation

Treatment of Neurological Disorders by Source

Source	Condition	Drug	Phase
Lilly	Cognitive impairment, schizophrenia-related	SGS-518	I
	Dementia, Alzheimer's-type	LY-450139	II
		LY-451395	II
	Stroke, ischemic	Abciximab[1,2]	III
Lundbeck	Parkinson's disease	Rasagiline mesilate[2]	L-2005
	Stroke, ischemic	Desmoteplase	III
Medarex	Multiple sclerosis	CNTO-1275	II
MediciNova	Multiple sclerosis	Ibudilast[1,2]	II
Medivation	Dementia, Alzheimer's-type	Dimebolin hydrochloride[1]	II
Memory Pharmaceuticals	Dementia, Alzheimer's-type	MEM-1003	II
		MEM-3454	I
Merck & Co.	Dementia, Alzheimer's-type	C-7617	I
		C-9136	II
	Multiple sclerosis	C-6448	II
	Parkinson's disease	C-6161	I
	Stroke	Losartan potassium/hydrochlorothiazide[1]	L -2005
	Stroke, ischemic	Arundic acid[2]	II/III
Merck KGaA	Parkinson's disease	Sarizotan hydrochloride	III
Merz	Dementia, Alzheimer's-type	Neramexane hydrochloride	III
MGI Pharma	Parkinson's disease	GPI-1485	II
Migenix	Dementia, Alzheimer's-type	Alfatradiol	I
	Friedreich's ataxia	Alfatradiol	I
	Parkinson's disease	Alfatradiol	I
Millennium Pharmaceuticals	Multiple sclerosis	MLN-1202	II
		MLN-3897 (AVE-9897)	I
Mitsubishi Pharma	Amyotrophic lateral sclerosis	Edaravone[1,2]	II
	Dementia, Alzheimer's-type	Coluracetam	Discontinued
	Stroke	Sarpogrelate hydrochloride[1,2]	III
Mochida	Dementia, Alzheimer's-type	Icosapent ethyl ester[1]	II
M's Science	Stroke	AGY-94806 (SA-4503)	II
Myriad Genetics	Dementia, Alzheimer's-type	MPC-7869	III
Neuren Pharmaceuticals	Neurological disorders	Glypromate®	II
Neurobiological Technologies	Peritumoral brain edema	Corticorelin acetate	III
	Stroke, ischemic	Ancrod[1]	III
NeuroBiotec	Parkinson's disease	Lisuride maleate[1], transdermal	II
	Restless legs syndrome	Lisuride maleate[1], transdermal	II/III
Neurochem	Dementia, Alzheimer's-type	Tramiprosate	III
	Stroke, hemorrhagic	Tramiprosate	II
Neurocrine Biosciences	Multiple sclerosis	Tiplimotide	II
Neurologix	Parkinson's disease	NLX-P101	I
NeuroSearch	Dementia, Alzheimer's-type	NS-2330	Discontinued
	Epilepsy	NS-1209	II
	Parkinson's disease	NS-2330	II
Newron	Epilepsy	Safinamide mesilate[2]	II
	Parkinson's disease	Safinamide mesilate[2]	III
	Restless legs syndrome	Safinamide mesilate[2]	II
NicOx	Dementia, Alzheimer's-type	HCT-1026[2]	I
Novartis	Dementia, Alzheimer's-type	CAD-106	I
	Epilepsy	Becampanel	II
		Rufinamide[2]	Prereg.
	Multiple sclerosis	Fingolimod hydrochloride[2]	II
NPS Pharmaceuticals	Epilepsy	Isovaleramide	I
Ono Pharmaceutical	Amyotrophic lateral sclerosis	Arundic acid[2]	II
	Dementia, Alzheimer's-type	Arundic acid[2]	II
	Parkinson's disease	Arundic acid[2]	II
	Stroke, ischemic	Arundic acid[2]	II/III
Ortho McNeil (Johnson & Johnson)	Epilepsy	RWJ-333369 (YKP-509)	II
PAION	Stroke, ischemic	Desmoteplase	III
		Enecadin hydrochloride	I
Pepgen	Multiple sclerosis	Interferon tau	II
Pfizer	Dementia, Alzheimer's-type	Atorvastatin calcium[1,2]	III
	Epilepsy	Pregabalin[2]	L-2004

Continuation

Treatment of Neurological Disorders by Source

Source	Condition	Drug	Phase
PharmaFrontiers	Multiple sclerosis	Tovaxin™	I/II
Pharmos	Mild cognitive impairment	Dexanabinol	II
	Traumatic brain injury	Dexanabinol	Discontinued
Phytopharm	Amyotrophic lateral sclerosis	PYM-50018	I
	Dementia, Alzheimer's-type	PYM-50028	II
	Parkinson's disease	PYM-50028	I
Pliva	Amyotrophic lateral sclerosis	PLD-180	I
Prana Biotechnology	Dementia, Alzheimer's-type	PBT-2	I
Predix Pharmaceuticals	Dementia, Alzheimer's-type	PRX-03140	I
Prestwick Pharmaceuticals	Parkinson's disease	Lisuride maleate[1], transdermal	II
	Restless legs syndrome	Lisuride maleate[1], transdermal	II/III
Proneuron	Huntington's disease	TV-5010	I
	Spinal cord injury	ProCord	II
Protein Design Labs	Multiple sclerosis	Daclizumab[1,2]	II
PTC Therapeutics	Muscular dystrophy, Duchenne	PTC-124	I
Quigley Pharma	Neuropathy, diabetic	QR-333	II
ReGen Therapeutics	Dementia, Alzheimer's-type	Colostrinin™	II
Repligen	Multiple sclerosis	RG-2077	I
Roche	Dementia, Alzheimer's-type	MEM-3454	I
		R-1500	I
		R-1577	I
	Multiple sclerosis	R-1295	I
Saegis	Cognitive impairment, CABG-related	SGS-111	I/II
	Cognitive impairment, schizophrenia-related	SGS-518	I
	Dementia, Alzheimer's-type	SGS-742[2]	II
	Mild cognitive impairment	SGS-111	II
		SGS-742[2]	II
Sangamo BioSciences	Neuropathy, diabetic	SB-509	I
Sanofi-Aventis	Dementia, Alzheimer's-type	AVE-1625	I
		SL-65.0155	II
		SR-57667	II
		Xaliproden hydrochloride[2]	III
	Multiple sclerosis	MLN-3897 (AVE-9897)	I
		Teriflunomide	III
		Xaliproden hydrochloride[2]	II
	Neurodegeneration	SSR-180575	I
	Neuropathy, chemotherapy-induced	Xaliproden hydrochloride[2]	III
	Parkinson's disease	AVE-1625	I
		SR-57667	II
	Spinal cord injury	Nerispirdine hydrochloride	II
Santhera	Friedreich's ataxia	Idebenone[1,2]	II
	Muscular dystrophy, Duchenne	Idebenone[1,2]	II
Sanwa Kagaku	Neuropathy, diabetic	Fidarestat	III
Schering AG	Multiple sclerosis	Alemtuzumab[1,2]	II
	Parkinson's disease	Spheramine®	II
Schwarz Pharma	Epilepsy	Lacosamide[2]	III
	Neuropathy, diabetic	Lacosamide[2]	III
	Parkinson's disease	Rotigotine hydrochloride[2], nasal spray	I/II
		Rotigotine hydrochloride[2], transdermal	Prereg.
	Restless legs syndrome	Rotigotine hydrochloride[2], transdermal	III
Sepracor	Restless legs syndrome	SEP-226330	Discontinued
Serono/Ivax	Multiple sclerosis	Cladribine, oral formulation	III
Shanghai Institute of Materia Medica	Dementia, Alzheimer's-type	ZT-1	II
Shionogi	Stroke	234551	I
	Stroke, ischemic	S-0139 (737004)	II (JP)
		S-0139 (737004)	I (EU)
SK Bio-Pharmaceuticals	Epilepsy	RWJ-333369 (YKP-509)	II
Solvay	Parkinson's disease	SLV-308[2]	III
Stem Cell Therapeutics	Stroke	NTx™-265	I
StemCells	Batten disease	Human fetal neural stem cells	I
Symphony Neuro Development Company	Parkinson's disease	GPI-1485	II

Continuation

Treatment of Neurological Disorders by Source

Source	Condition	Drug	Phase
Synthetic Blood Intl.	Traumatic brain injury	Oxycyte™	I/II
Taisho	Stroke	TS-011	I
Takeda	Friedreich's ataxia	Idebenone[1,2]	II
	Neuropathy, diabetic	TAK-128	II
		TAK-428	II
	Neuropathy, peripheral	BNP-7787	III
Tanabe Seiyaku	Multiple sclerosis	683699 (T-0047)	II - On hold
Targacept	Cognitive impairment	Ispronicline	II
Taro	Tremor, essential	T-2000	II/III
Teva	Dementia, Alzheimer's-type	Ladostigil tartrate	II
		Rasagiline mesilate[2]	II
	Huntington's disease	TV-5010	I
	Multiple sclerosis	Laquinimod[2]	II
		TV-5010	II
	Parkinson's disease	Rasagiline mesilate[2]	L-2005
ThromboGenics	Stroke	Microplasmin	II
Titan	Parkinson's disease	Spheramine®	II
TorreyPines Therapeutics	Dementia, Alzheimer's-type	NGX-267	I
Toyama	Dementia, Alzheimer's-type	T-588[2]	II
		T-817MA	I
Transgene	Muscular dystrophy, Becker	MyoDys®	I
	Muscular dystrophy, Duchenne	MyoDys®	I
Transition Therapeutics	Multiple sclerosis	MS-I.E.T.	II
Trophos	Amyotrophic lateral sclerosis	TRO-19622	I
	Huntington's disease	TRO-19622	I
	Muscular atrophy, spinal	TRO-19622	I
UCB Pharma	Epilepsy	Brivaracetam	II
		Seletracetam	II
	Multiple sclerosis	CDP-323	I
Uriach	Dementia, Alzheimer's-type	Triflusal[1,2]	I
Valeant	Epilepsy	Retigabine[2]	III
Vasogen	Amyotrophic lateral sclerosis	VP-025	I
	Dementia, Alzheimer's-type	VP-025	I
	Parkinson's disease	VP-025	I
Vernalis	Parkinson's disease	V-2006	I/II
	Stroke, ischemic	V-10153	II
Voyager Pharmaceutical	Dementia, Alzheimer's-type	VP-4896	III
Wyeth	Dementia, Alzheimer's-type	Bapineuzumab	II
		Lecozotan hydrochloride	II
	Multiple sclerosis	Temsirolimus[2]	II
	Muscular dystrophy	Stamulumab	I/II
	Parkinson's disease	Premarin®[1]	II
XenoPort	Restless legs syndrome	XP-13512	II
	Spasticity	XP-19986	I
Xytis	Traumatic brain injury	Anatibant mesilate	I

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Treatment of Neurological Disorders

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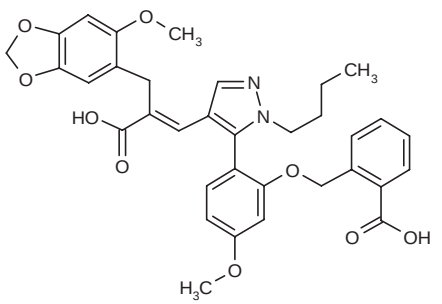
189254

Compound 189254, a histamine H_3 receptor antagonist, is currently undergoing phase I clinical trials at GlaxoSmithKline for the treatment of Alzheimer's-type dementia.

234551



An endothelin ET_A receptor antagonist, 234551 (SB-234551) is being developed by a GlaxoSmithKline/Shionogi joint venture and is currently in phase I trials for the treatment of stroke.

406725

406725 is a gap junction blocker in phase I trials at GlaxoSmithKline for the treatment of epilepsy, migraine and neuropathic pain.

683699 (T-0047)

Compound 683699, a cell adhesion inhibitor that acts as an $\alpha_4\beta_7/\alpha_4\beta_1$ integrin antagonist, is being developed by GlaxoSmithKline under license from Tanabe Seiyaku for the oral treatment of multiple sclerosis and inflammatory bowel disease. It had reached phase II trials in the U.S. and the E.U. before the FDA placed a clinical hold on studies with α_4 integrin antagonists in March 2005, due to reports of progressive multifocal leukoencephalopathy in patients who had been taking Tysabri® (natalizumab; see below) (1-3).

1. *GSK profiles CNS pipeline*. DailyDrugNews.com (Daily Essentials) Nov 26, 2004.

2. *FDA places clinical hold on studies with alpha4 integrin antagonists*. DailyDrugNews.com (Daily Essentials) March 18, 2005.

3. *Tanabe Seiyaku reports Q1 R&D highlights*. Tanabe Seiyaku Co., Ltd. Press Release 2005, May 12.

742457

The 5-HT_6 receptor antagonist 742457 is in phase II clinical trials for the treatment of Alzheimer's disease, as well as early clinical trials for use in schizophrenia. The compound shows high brain penetration and has been shown to enhance neurotransmitters and improve learning and memory in preclinical models (1, 2).

1. *GSK profiles CNS pipeline*. DailyDrugNews.com (Daily Essentials) Nov 26, 2004.

2. *A dose ranging study to investigate the efficacy and safety of SB-742457 in Alzheimer's disease (NCT00224497)*. ClinicalTrials.gov Web Site 2005, Oct 5.

813893

GlaxoSmithKline is conducting phase I clinical evaluation of 813893, a coagulation factor Xa inhibitor with potential for the prevention of stroke in atrial fibrillation.

Abciximab, New Indication

Abciximab is an anti-integrin monoclonal antibody originally launched in 1995 as ReoPro® by Centocor (Johnson & Johnson) and partner Lilly as an adjunct to

percutaneous coronary intervention (PCI) to prevent cardiac ischemic complications in patients undergoing PCI. Abciximab prevents blood clots by targeting and binding to the gpIIb/IIIa receptor on the surface of platelets and inhibiting platelet aggregation. The antibody also binds to the vitronectin and MAC-1 receptors, which play a role in smooth muscle proliferation and inflammation, respectively. Abciximab was subsequently introduced for the treatment of patients with unstable angina pectoris not responding to conventional medical therapy when PCI is planned within 24 h. Centocor and Lilly are also developing abciximab in phase III clinical trials for the treatment of acute ischemic stroke and phase III trials are under way at Centocor as combination therapy with reteplase administered prior to PCI. Lilly markets the drug outside the U.S.

Abciximab appeared to be safe when administered to patients with acute ischemic stroke in the randomized, double-blind phase II Abciximab Emergent Stroke Treatment Trial. The study included 400 patients presenting within 6 h of the onset of ischemic stroke who received abciximab (0.25 mg/kg by bolus followed by 12-h infusion of 0.125 μg/kg/min) or placebo. The incidence of symptomatic intracranial hemorrhage occurring within 5 days was 3.6% in the abciximab group compared to 1% in the placebo group (7 and 2 patients, respectively). At 3 months, the incidence of asymptomatic intracranial bleeding was higher in the placebo group (33 patients *vs*. 22 patients). In terms of outcomes, a nonsignificant trend favoring abciximab was seen in regression modeling of modified Rankin Scale scores after adjustment for stroke severity, age and interval from stroke. Further study in greater numbers of patients is required for confirmation of the efficacy results (1).

1. *Emergency administration of abciximab for treatment of patients with acute ischemic stroke. Results of a randomized phase 2 trial*. Stroke 2005, 36(4): 880.

Original monograph – Drugs Fut 1995, 20(5): 457.

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Adams, H. Jr., Cooper, J., Oemar, B., Cook, R., Leclerc, J., Hacke, W. *Association of outcome with early stroke treatment using abciximab in AbESTT: A randomized double-blind, placebo-controlled trial*. 30th Int Stroke Conf (Feb 2-4, New Orleans) 2005, Abst 8.

Al-Qasmi, M.M., Daly, S., Lu, M., Silver, B., Chopp, M., Mitsias, P. *Abciximab treatment of acute small deep infarcts: A preliminary analysis*. Neurology 2004, 62(7, Suppl. 5): Abst P06.016.

Becker, U. et al. *Abciximab beyond the 6-hour time window in patients with acute occlusion of the middle cerebral artery*. Cerebrovasc Dis 2004, 17(Suppl. 5): 104.

Becker, U., Puetz, V., Disque, C., Dzialowski, I., Gahn, G. *Combined systemic thrombolysis with recombinant tissue plasminogen activator and abciximab in patients with occlusion of the middle cerebral artery in the 3- to 6-hour time window*. 30th Int Stroke Conf (Feb 2-4, New Orleans) 2005, Abst P41.

Davalos, A., Barnathan, E.S., Oemar, B.S. et al. *Evaluation of the safety and efficacy of abciximab in subjects with "wake up" acute ischemic stroke: Insights from two randomized double-blind, placebo-controlled trials*. Stroke 2004, 35(1): Abst P185.

Deliargyris, E.N. et al. *Safety of abciximab administration during PCI of patients with previous stroke*. J Thromb Thrombolysis 2005, 19(3): 147.

Eckert, B. et al. *Aggressive therapy with intravenous abciximab and intra-arterial rtPA and additional PTA/stenting improves clinical outcome in acute vertebrobasilar occlusion. Combined local fibrinolysis and intravenous abciximab in acute vertebrobasilar stroke treatment (FAST). Results of a multicenter study*. Stroke 2005, 36(6): 1160.

Gahn, G. et al. *Recanalisation of middle cerebral artery occlusion with either rt-PA or rt-PA combined with abciximab*. Cerebrovasc Dis 2004, 17(Suppl. 5): 109.

Gahn, G., Kunz, A., Putz, V. et al. *Recanalisation of middle cerebral artery occlusion after either t-PA or t-PA combined with abciximab*. Stroke 2004, 35(1): Abst P195.

Hacke, W. et al. *CT signs of recent or remote infarction during abciximab treatment of acute ischemic stroke: An AbESTT substudy*. Cerebrovasc Dis 2004, 17(Suppl. 5): 96.

Mandava, P. et al. *Intravenous abciximab in complicated cardioembolic stroke patients with high NIHSS*. Stroke 2004, 35(6): e273.

Mitsias, P.D. et al. *Abciximab treatment of supratentorial ischemic stroke: An MRI-based open label clinical trial*. Cerebrovasc Dis 2004, 17(Suppl. 5): 105.

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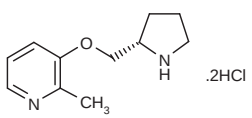
Pütz, V. et al. *Abciximab in patients with acute basilar artery occlusion or critical stenosis*. Cerebrovasc Dis 2004, 17(Suppl. 5): 105.

Sakkou, V., Tagaris, G.A., Karageorgiou, C.E. *Abciximab for the management of reocclusion after successful intravenous thrombolysis in ischemic stroke*. Neurology 2005, 64(6, Suppl. 1): Abst P02.115.

ABT-089



ABT-089 is an acetylcholine receptor modulator in phase II trials at Abbott for the treatment of attention deficit hyperactivity disorder (ADHD), Alzheimer's-type dementia and schizophrenia. Modulation of the neuronal

nicotinic acetylcholine receptor (nAChR) subtype has been shown to improve cognitive impairment and neurodegeneration in patients with CNS disorders.

ABT-874

Abbott has initiated a global phase II study of ABT-874 for the treatment of multiple sclerosis. The study will evaluate the efficacy of ABT-874 in the treatment of multiple sclerosis through its ability to reduce brain lesions caused by the disease. Patients in North America and Europe will be randomized to receive ABT-874 dosed weekly or every other week, or placebo. The trial will be 48 weeks in length —a 24-week placebo-controlled phase followed by a 24-week active open-label extension. ABT-874 is a fully human monoclonal antibody designed to target and neutralize IL-12. ABT-874 is also being studied (phase II) for the treatment of Crohn's disease. The antibody was developed at Cambridge Antibody Technology (CAT) in collaboration with Abbott and subsequently licensed to Abbott for clinical development and marketing (1, 2).

1. *New phase II study of ABT-874 for MS*. DailyDrugNews.com (Daily Essentials) June 7, 2004.

2. *Cambridge Antibody Technology reports Q3 R&D highlights*. Cambridge Antibody Technology Press Release 2004, Sept 8.

AC-1202

Accera recently received approval for a formal open-label 6-month extension to the phase IIb trial of AC-1202 (Ketasyn™) in Alzheimer's disease (AD). The ongoing double-blind, placebo-controlled phase IIb trial is being conducted at more than 15 sites across the U.S. in 100 patients diagnosed with probable mild to moderate AD. All patients who complete the trial will be given the opportunity to join the extension study, with the first patients expected to enter the study immediately. Both studies will provide safety and efficacy data based upon measures of memory, cognition and global quality of life. AC-1202 is a first-in-class therapeutic that addresses the energy deficit observed in the brain of AD patients. Numerous studies have shown that energy metabolism and lipid homeostasis are impaired in neuronal cells within the hippocampal region of the brain where memory and cognition are processed (1, 2).

1. *Accera establishes advisory boards to guide development efforts*. DailyDrugNews.com (Daily Essentials) Dec 22, 2004.

2. *Accera receives approval for Ketasyn extension study*. DailyDrugNews.com (Daily Essentials) Sept 14, 2005.

ACR-16

ACR-16, a dopaminergic stabilizer, has completed early clinical studies at Carlsson Research for the treatment of Parkinson's disease, Huntington's disease and schizophrenia, and the compound has advanced to phase II trials for Huntington's disease. Pursuant to a license agreement signed in February 2005, Astellas Pharma obtained rights to further develop, manufacture and market ACR-16 for the treatment of schizophrenia, while Carlsson Research retained full and exclusive rights for development, sales and marketing of the compound for Huntington's disease in Europe and North America. Results from the clinical trials demonstrated a good safety and pharmacokinetic profile, as well as efficacy in the treatment of schizophrenia and Parkinson's disease, with beneficial effects on psychotic symptoms, cognitive, emotional and motor functions, and sleep. Preclinical studies indicate its utility in treating the full range of symptoms of schizophrenia, including both positive and negative symptoms and impaired cognitive and social functions, coupled with a low likelihood for extrapyramidal symptoms. The compound received orphan drug designation from the European Committee for Orphan Medicinal Products (COMP) for the treatment of Huntington's disease this past summer (1, 2).

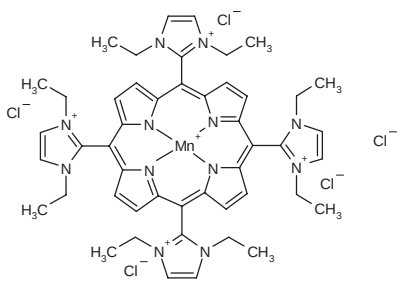
A pilot, open-label clinical trial evaluated the tolerability and clinical effects of adding once-daily ACR-16 (20 mg, titrated to 50, 70 and 100 mg during the first week) for 14 days to the regular medication of 7 patients with advanced Parkinson's disease. After titration, patients received an average dose of 57 mg/day. Most patients showed beneficial effects shortly after dosing, with increases in daily "on" time without dyskinesia, reductions in daily "on" time with dyskinesia and significant improvements in sleep. ACR-16 was well tolerated, and CNS-related adverse events were mild and transient (3).

1. *Fujisawa inlicenses ACR-16 from Carlsson Research*. DailyDrugNews.com (Daily Essentials) Feb 9, 2005.

2. *ACR-16 recommended for orphan drug status for Huntington's disease*. DailyDrugNews.com (Daily Essentials) June 3, 2005.

3. Sonesson, C., Waters, N., Waters, S., Carlsson, A., Tedroff, J. *A pilot study of the novel dopamine stabiliser ACR16 in advanced Parkinson's disease*. Mov Disord 2004, 19(Suppl. 9): Abst P565.

AEOL-10150



AEOL-10150 is a small-molecule catalytic antioxidant in phase I trials at Aeolus Pharmaceuticals (formerly

Incara) for the intravenous treatment of amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). The drug scavenges a broad range of reactive oxygen species that initiate an inflammatory cascade believed to be responsible for the degeneration of both upper and lower motor neurons in ALS. The compound has shown efficacy in treating the symptoms of ALS in preclinical animal models (1-5).

A multicenter, double-blind phase I clinical trial determined the safety and pharmacokinetics of AEOL-10150 in patients with ALS. Each patient was randomized to receive single s.c. doses of placebo or AEOL-10150 (3, 12, 30, 45, 60 or 75 mg). Data analysis revealed that all AEOL-10150 doses were well tolerated and not associated with serious adverse events or significant laboratory or cardiovascular abnormalities. Most adverse events were mild, and the most common were injection-site reactions, dizziness and headache. Pharmacokinetic parameters such as AUC and C_{max} increased with dose, and the average half-life of AEOL-10150 ranged from 2.6 h with the 3-mg dose to 6.4 h with the 75-mg dose. Evidence suggested that multiple doses would not result in accumulation of AEOL-10150. The company subsequently initiated a follow-on phase I multiple-dose study of AEOL-10150 in 18 patients with ALS who received placebo or AEOL-10150 (40, 70 or 100 mg) twice daily for 6 days, followed by a final injection on day 7. Based on initial observations in the first 3 ALS patients in the initial 6-patient cohort (40 mg of AEOL-10150 or placebo), there were no serious adverse events. The multiple-dose study is targeted for completion within the fourth quarter of this year or early in the first quarter of next year. During a meeting prior to the initiation of AEOL-10150 clinical trials, the FDA indicated that it would grant fast track status for AEOL-10150, and this is now being applied for. Following the multiple-dose study of AEOL-10150, Aeolus will request an end-of-phase I meeting with the FDA and plans to submit a request for a special protocol assessment (SPA) to review plans for a pivotal phase II/III study of AEOL-10150. AEOL-10150 also has potential for other neurological diseases, as well as radiation-related disorders (6-8).

1. *Private placement financing ensures progress of AEOL-10150 into clinic*. DailyDrugNews.com (Daily Essentials) April 22, 2004.

2. *Incara files IND to commence clinical studies of AEOL-10150 for ALS*. DailyDrugNews.com (Daily Essentials) May 7, 2004.

3. *Incara to revise phase I protocol for AEOL-10150*. DailyDrugNews.com (Daily Essentials) June 9, 2004.

4. *Aeolus cleared to begin phase I trials of AEOL-10150*. DailyDrugNews.com (Daily Essentials) Sept 10, 2004.

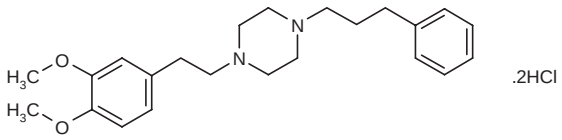
5. *AEOL-10150 enters phase I in ALS*. DailyDrugNews.com (Daily Essentials) Nov 17, 2004.

6. *Good safety profile found for single doses of AEOL-10150 in patients with Lou Gehrig's disease*. DailyDrugNews.com (Daily Essentials) April 1, 2005.

7. *Good safety and pharmacokinetics of AEOL-10150 in ALS patients*. DailyDrugNews.com (Daily Essentials) Sept 13, 2005.

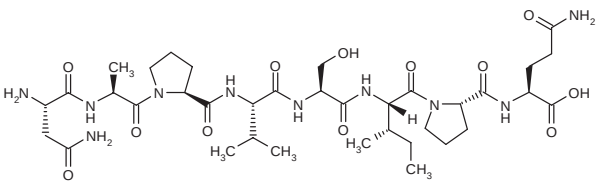
8. *Aeolus Pharmaceuticals announces initiation of multiple dose study of AEOL-10150 in patients with Lou Gehrig's disease*. Aeolus Pharmaceuticals Press Release 2005, Oct 19.

AGY-94806 (SA-4503)



SA-4503 is a sigma receptor agonist in phase II trials at M's Science for the treatment of depression and phase II trials at AGY Therapeutics, where it is known as AGY-94806, for use in enhancing functional recovery from stroke. SA-4503 functions by inhibiting glutamate-induced delayed neuronal cell death. The product was originally developed at Santen and licensed to M's Science in 2000. In July 2004, AGY Therapeutics signed an agreement with M's Science to acquire exclusive development and commercialization rights for the enhancement of functional recovery after stroke. A phase I study evaluating the compound as a potential treatment for depression produced promising safety data, while preclinical data have demonstrated post-stroke recovery activity. Because the drug is delivered orally and works by stimulating functional recovery of surviving tissue to compensate for damaged areas, it potentially can be given at any time after a stroke, representing an entirely new approach for the treatment of stroke patients. The agreement also grants AGY development and commercialization rights to AGY-94806 for traumatic brain injury and spinal cord injury, as well as rights to license additional CNS indications. M's Science retains other rights and intends to continue developing SA-4503 for other CNS indications. The two companies will coordinate worldwide development for a broad range of indications.

AL-108/AL-208



AL-108

Allon Therapeutics is a drug discovery and development company focused on diseases and conditions of the CNS, with lead indications of Alzheimer's disease (AD) and cognitive impairment. Allon has four products in the pipeline, including AL-108 (NAP) and AL-208, neuropro-

tective 8-amino-acid peptides derived from ADNF (activity-dependent neuroprotective protein), a naturally occurring glial-derived neurotrophic factor, with potential in acute conditions such as cognitive impairment and ophthalmic retinopathy, as well as chronic conditions such as Alzheimer's disease and multiple sclerosis. Animal studies showed that AL-108 protects neurons against chronic diseases such as AD, multiple sclerosis and neuropathy, and acute disorders such as stroke and traumatic brain injury. AL-108 has been shown to work at the cellular level in numerous animal models of neurodegeneration and is safe, readily administered and suitable for drug development. AL-208 is the company's second product, a formulation of AL-108 that allows it to be administered intravenously. Other preclinical animal studies confirmed that AL-108 and AL-208 penetrate the blood-brain barrier and reach their target therapeutic areas in the CNS. Results confirmed the presence of AL-108, delivered intranasally, and AL-208, delivered intravenously, in the cerebrospinal fluid of animals. Allon has completed a phase Ia trial evaluating AL-108 as a treatment for AD and a phase Ib trial is planned in healthy elderly adults most at risk for AD. Results from the double-blind, randomized, dose-finding, placebo-controlled phase Ia clinical trial revealed that single doses of 1-15 mg of AL-108 were well tolerated and did not result in any serious adverse events when administered to 30 healthy volunteers aged 19-44 years. No significant differences between AL-108 and placebo were found in the patients' laboratory tests, electrocardiograms or vital signs. This program has been selected by the Alzheimer's Disease Cooperative Study (ADCS) in the U.S. to be included in its submission to receive phase II trial funding from the National Institutes of Health (NIH). A phase II trial evaluating AL-108 as a treatment for AD was one of seven projects selected by the ADCS. The company also recently commenced dosing the first patient in a phase I trial to evaluate AL-208 as an i.v. treatment for mild cognitive impairment (MCI) associated with post-coronary artery bypass graft (CABG) surgery. The double-blind, placebo-controlled, ascending-dose phase I trial is administering AL-208 to 48 healthy adults randomized to 6 dose groups to evaluate its safety, tolerability and pharmacokinetics. The study is expected to be completed in the fourth quarter of 2005 with data to follow in the first quarter of 2006 (1-11). Originally developed at the NIH and Tel Aviv University, AL-108 was subsequently licensed to Allon.

1. *Emerging companies showcased at the 12th Annual BioPartnering Europe conference: Allon Therapeutics*. DailyDrugNews.com (Daily Essentials) Oct 26, 2004.

2. *Allon Therapeutics reviews Q3 highlights*. DailyDrugNews.com (Daily Essentials) Dec 7, 2004.

3. *Allon's AL-108 and AL-208 cross blood-brain barrier in preclinical studies*. DailyDrugNews.com (Daily Essentials) June 7, 2005.

4. *Allon seeks clearance for clinical trials of AL-208*. DailyDrugNews.com (Daily Essentials) June 27, 2005.

5. *AL-208 set to enter phase I trials*. DailyDrugNews.com (Daily Essentials) Aug 16, 2005.

6. *AL-208 enters phase I trials for MCI associated with CABG*. DailyDrugNews.com (Daily Essentials) Aug 31, 2005.

7. *Allon files IND for phase I trial of AL-108 for Alzheimer's*. DailyDrugNews.com (Daily Essentials) Dec 22, 2004.

8. *Approval for phase I trial of Al-108 for Alzheimer's*. DailyDrugNews.com (Daily Essentials) Jan 26, 2005.

9. *AL-108 enters phase I trials for Alzheimer's disease*. DailyDrugNews.com (Daily Essentials) Jan 31, 2005.

10. *Alzheimer's Disease Cooperative Study selects Allon Therapeutics program*. DailyDrugNews.com (Daily Essentials) April 28, 2005.

11. *Allon Therapeutics product AL-108 successful in Phase Ia clinical trial*. Allon Therapeutics Press Release 2005, June 15.

Alemtuzumab, New Indication

Schering AG and Genzyme recently announced interim results from a phase II trial comparing alemtuzumab (Campath® in the U.S., MabCampath® in the E.U. and certain other countries) with interferon beta-1a (Rebif®) for the treatment of multiple sclerosis (MS). The results derive from a prespecified efficacy and safety interim analysis conducted after 1 year of treatment for all patients in the planned 3-year trial. Analysis of the primary endpoints after 1 year of treatment showed a large treatment effect in favor of alemtuzumab. Three confirmed cases of severe idiopathic thrombocytopenic purpura (ITP) occurred in the trial, 1 of which resulted in a fatality. In the 2 remaining cases, patients have responded to treatment. Based on these results, and after consultation with the FDA, the companies will continue to collect both efficacy and safety data from this trial while preparing to initiate a phase III trial in the first half of next year. Dosing with alemtuzumab in this trial has been suspended while the companies work to ensure that a comprehensive approach is in place to manage patient safety. Genzyme and Schering's risk management plan for ITP has included notification of regulatory authorities, trial sites and patients, and consultation with a panel of hematologists with expertise in ITP to advise on risk management. The companies have moved to implement a series of provisions in the study, including more frequent hematological monitoring and patient education about the signs and symptoms of ITP. The companies will also conduct a thorough review of patient laboratory data, and will seek indicators that might help identify those at risk for developing these types of problems. Alemtuzumab continues to be available in its current labeled indication for the treatment of B-cell chronic lymphocytic leukemia (CLL). The open-label phase II trial randomized 334 patients with active relapsing-remitting MS at 49 sites in Europe and the U.S. Patients were treated with alemtuzumab at one of two doses administered by once-a-year intravenous infusion regimens, or interferon beta-1a adminis-

tered 3 times per week as indicated in its product label. The trial compared the safety and efficacy of alemtuzumab with interferon beta-1a, examining two primary endpoints: the rate of relapse of MS symptoms and the time to progression of clinically significant disability (time to sustained accumulated disability at 6 months as measured by Expanded Disability Status Score [EDSS]). Analysis of the first co-primary endpoint showed that patients taking alemtuzumab at high and low doses experienced at least a 75% reduction in the risk for relapse after at least 1 year of follow-up when compared to patients treated with interferon beta-1a. This difference was statistically significant in favor of the alemtuzumab patients at both doses. In the other co-primary endpoint, patients treated with the high and low doses of alemtuzumab experienced at least a 60% reduction in the risk for progression of clinically significant disability when compared to patients treated with interferon beta-1a, athough this result did not achieve statistical significance. Nearly all alemtuzumab patients in the trial have received their second year's dose. In the coming months, Genzyme and Schering will evaluate the necessity and timing of the third planned dose. Because the high dose appears to offer no efficacy advantage compared to that achieved by the low dose, the companies will no longer use this dose. Alemtuzumab is a humanized monoclonal antibody that binds to CD52 on cell surfaces, directing the body's immune system to destroy malignant cells. Genzyme and Schering AG are codeveloping alemtuzumab in oncology and other indications, with Schering having exclusive responsibility for the development and commercialization of alemtuzumab for solid organ transplantation. Schering holds exclusive worldwide marketing and distribution rights to alemtuzumab. The product is marketed in the U.S. by Schering's U.S. affiliate Berlex. Alemtuzumab was originally developed by Ilex Oncology, which was subsequently acquired by Genzyme (1-11).

1. *Genzyme to acquire Ilex Oncology*. DailyDrugNews.com (Daily Essentials) March 3, 2004.

2. *Ilex Oncology reports 2003 year-end R&D highlights*. Ilex Oncology Press Release 2004, Jan 27.

3. *Ilex Oncology reports Q1 R&D highlights*. Ilex Oncology Press Release 2004, April 22.

4. *Ilex Oncology reports Q2 R&D highlights*. Ilex Oncology Press Release 2004, July 21.

5. *Merger between Genzyme and Ilex Oncology expected to close in Q4*. DailyDrugNews.com (Daily Essentials) Sept 17, 2004.

6. *Interim results for phase II study of Campath in MS*. DailyDrugNews.com (Daily Essentials) Sept 20, 2005.

7. *Genzyme Corp. reports Q3 R&D highlights*. Genzyme Corp. Press Release 2005, Oct 18.

8. *Genzyme completes acquisition of Ilex Oncology*. DailyDrugNews.com (Daily Essentials) Dec 23, 2004.

9. *FDA approval for Campath single-dose vial*. DailyDrugNews.com (Daily Essentials) Oct 20, 2004.

10. *Target enrollment met in phase III study of Campath for B-CLL*. DailyDrugNews.com (Daily Essentials) June 29, 2004.

11. *Ilex fully enrolls phase II Campath MS study*. DailyDrugNews.com (Daily Essentials) April 27, 2004.

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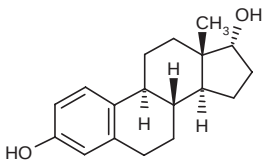
Fox, E. et al. *Open-label, single-arm phase II study of high-dose alemtuzumab in patients with active relapsing-remitting multiple sclerosis who have failed licensed beta-interferon therapies*. 21st Congr Eur Comm Treat Res Multiple Scler (Sept 28-Oct 1, Thessaloniki) 2005, Abst P 650.

Alfatradiol



Alfatradiol (MX-4509, formerly MITO-4509) is currently being evaluated in phase I clinical trials at Migenix for its potential in the treatment of neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease (AD) and Friedreich's ataxia. The orally administered drug candidate has demonstrated neuroprotective activity and reductions in β-amyloid in animal models of AD, and was well tolerated in a phase I trial. Alfatradiol has also shown potential for use in Parkinson's disease, Friedreich's ataxia, retinitis pigmentosa and mild cognitive impairment. In April, Migenix received a letter of authorization from Health Canada to begin a phase I/II trial in patients with mild to moderate AD. However, the study was postponed as part of the company's plan to reduce the cash used in its operations. As an alternative strategy, Migenix is evaluating the potential for alfatradiol in certain orphan indications. This evaluation includes ongoing nonclinical activities to support potential orphan indications, with further clinical studies to follow based on nonclinical results (1-7).

1. *Micrologix to acquire MitoKor*. DailyDrugNews.com (Daily Essentials) April 20, 2004.

2. *Micrologix Biotech completes acquisition of MitoKor*. DailyDrugNews.com (Daily Essentials) Sept 3, 2004.

3. *Recent progress at Migenix*. DailyDrugNews.com (Daily Essentials) Feb 11, 2005.

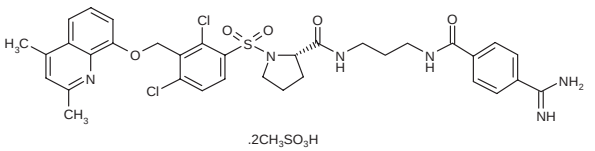
4. *Migenix receives Canadian clearance for phase I/II study of MX-4509*. DailyDrugNews.com (Daily Essentials) May 4, 2005.

5. *Migenix reports third quarter fiscal year 2005 results*. Migenix Press Release 2005, March 10.

6. *Migenix reports Q2 R&D highlights*. Migenix Press Release 2005, July 14.

7. *Migenix reports Q3 R&D highlights*. Migenix Press Release 2005, Sept 7.

Anatibant Mesilate



Anatibant mesilate (LF-16-0687MS) is a potent and selective nonpeptide antagonist of the bradykinin B_2 receptor in early clinical development for the treatment of moderate and severe traumatic brain injury (TBI). Treatment with anatibant markedly reduced cerebral edema following closed head trauma in different animal models, with a therapeutic window of 2-10 h. Anatibant also either restored or preserved the neurological functions that deteriorated after TBI. To date, a total of 101 subjects have been treated in single- and multiple-dose phase I studies in healthy volunteers and patients with severe TBI. Data from these studies together with the established rationale from preclinical experiments suggest that the drug provides a potential therapeutic approach to treating cerebral edema consecutive to brain damage. Anatibant has U.S. fast track and U.S. and E.U. orphan drug designation. Fournier, recently acquired by Solvay, granted Xytis an exclusive worldwide license for the development and commercialization of anatibant for TBI and possibly other indications. Fournier has retained full rights to manufacture the compound (1-3).

1. *European orphan drug status for anatibant*. DailyDrugNews.com (Daily Essentials) March 26, 2004.

2. *Anatibant receives orphan drug designation for severe traumatic brain injury*. DailyDrugNews.com (Daily Essentials) June 8, 2005.

3. *Fournier Pharma and Xytis Pharmaceuticals sign licensing agreement for anatibant*. Xytis Pharmaceuticals 2005, June 13.

Ancrod, New Indication

An anticoagulant that was launched over 35 years ago for the treatment of thrombosis, ancrod (Viprinex™) is currently in phase III trials at Neurobiological Technologies, through its acquisition of Empire Pharmaceuticals, for the treatment of acute ischemic stroke within 6 h of onset of symptoms. Derived from the venom of the Malayan pit viper, ancrod is a thrombin-like enzyme that is highly specific for fibrinogen, a protein involved in blood clotting. When administered systemically to stroke patients, the product has been shown to rapidly deplete plasma fibrinogen, resulting in anticoagulation, improved blood viscosity and a secondary fibrinolytic or clot-lysing action. Combined, these effects constitute a perfusion strategy that appears to restore and enhance oxygen flow to the affected area of the brain. Ancrod was granted fast track status by the FDA in February 2005 for the treatment of ischemic stroke. Studies have shown that in patients receiving ancrod within 6 h of stroke onset, blood viscosity is progressively reduced by 20-30% from pretreatment levels, resulting in an improvement in blood flow and microcirculation. After stopping treatment with ancrod, viscosity levels returned to pretreatment levels very slowly, within about 10 days. Ancrod has been studied in more than 2,000 patients in the U.S. and Europe and has the potential to double the available treatment window following the onset of stroke symptoms. A randomized, double-blind, placebo-controlled U.S. phase III study of ancrod given within 3 h after the onset of acute ischemic stroke in 500 patients showed that it was effective in preserving neurological function in this patient population. A separate randomized, double-blind, placebo-controlled phase III study in Europe enrolled patients within 6 h of onset of acute ischemic stroke. The trial was stopped after a planned interim analysis indicated lack of efficacy and an increased incidence of intracranial hemorrhage. The higher dosing levels in the European trial and the use of protocol criteria that permitted entry of patients at higher risk of hemorrhage are thought to have contributed to the trial's failure. A retrospective review of the relative strength of the positive U.S. findings *versus* the European findings has suggested the need for a revised ancrod dosing strategy, which will be one objective of further phase III studies. Empire acquired the exclusive worldwide rights to ancrod in a royalty-bearing license from Abbott in March 2002. Previous development work was conducted by Knoll prior to its acquisition by Abbott in 2001 (1-4).

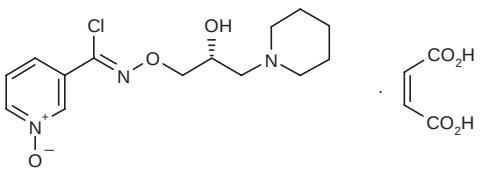
1. *Neurobiological Technologies acquires Empire Pharmaceuticals, expanding pipeline with Viprinex*. DailyDrugNews.com (Daily Essentials) July 20, 2004.

2. *Fast track status for Viprinex for ischemic stroke*. DailyDrugNews.com (Daily Essentials) Feb 1, 2005.

3. *Viprinex set for phase III in the summer*. DailyDrugNews.com (Daily Essentials) March 17, 2005.

4. *Agreement on design of phase III study for Viprinex*. DailyDrugNews.com (Daily Essentials) Aug 24, 2005.

Arimoclomol Maleate



Arimoclomol maleate is currently undergoing phase II clinical trials at CytRx for the oral treatment of ALS. Originally developed by Biorex, which was subsequently acquired by CytRx, to treat diabetic complications, the

orally active small molecule was discovered to significantly inhibit the progression of ALS in an experimental mouse model of the disease. New data also show that the drug can significantly improve nerve function in rats that have artificially had their spinal or sciatic nerves damaged by cutting or freezing. If similar effects of the drug are found in humans, it is possible that it might prevent the progression of ALS, as well as reverse some of the nerve damage caused by the disease. Arimoclomol is thought to function by activating molecular chaperone proteins that can repair or degrade the damaged proteins that are believed to cause many diseases, including ALS. The drug was well tolerated in two phase I trials in healthy volunteers. It was granted orphan drug designation by the FDA for the treatment of ALS in May 2005 and also holds fast track designation (1-8).

CytRx just recently initiated phase II trials with arimoclomol after the FDA lifted its clinical hold following review of additional information and amendments to the protocol requested by the agency. The first multicenter, double-blind, placebo-controlled study is a phase IIa trial and will include 80 ALS patients at 8-10 U.S. centers. Patients will receive either placebo or one of three dose levels of arimoclomol capsules 3 times daily for a period of 12 weeks. The primary endpoints are safety and tolerability, while secondary endpoints include a preliminary evaluation of efficacy using the revised ALS Functional Rating Scale (ALSFRS-R) and Vital Capacity (VC). The trial is powered to monitor only extreme responses in these two categories. This portion of the phase II program is expected to be completed in the first half of 2006. The subsequent phase IIb trial, which is planned to begin soon after completion of the present phase II study, subject to FDA approval, will be powered to detect more subtle efficacy responses. Although this second trial is still in the planning stages, it is expected to include 300 ALS patients recruited from 25 sites and will take approximately 18 months to complete. CytRx believes that successfully demonstrating safety and efficacy in the latter phase II trial may be sufficient to support U.S. product registration (9-11).

Therapeutic compositions containing a hydroxamic acid halide derivative such as arimoclomol maleate have been claimed for the therapeutic intervention of neurodegenerative disorders, in particular ALS (12).

1. *CytRx acquires assets of Biorex Research & Development*. DailyDrugNews.com (Daily Essentials) Oct 8, 2004.

2. *Arimoclomol demonstrates potential for type 2 diabetes*. DailyDrugNews.com (Daily Essentials) Oct 28, 2004.

3. *CytRx investigates two distinct approaches for treatment of ALS*. DailyDrugNews.com (Daily Essentials) Dec 10, 2004.

4. *Arimoclomol shows potential for type 2 diabetes in rat studies*. DailyDrugNews.com (Daily Essentials) Jan 19, 2005.

5. *Pre-IND meeting for phase II study of arimoclomol in ALS*. DailyDrugNews.com (Daily Essentials) April 21, 2005.

6. *Orphan drug designation for arimoclomol for ALS*. DailyDrugNews.com (Daily Essentials) May 9, 2005.

7. *CytRx seeks FDA approval to begin phase II clinical trials of ALS drug candidate*. DailyDrugNews.com (Daily Essentials) May 25, 2005.

8. *FDA requests information on phase II study of arimoclomol for ALS*. DailyDrugNews.com (Daily Essentials) July 27, 2005.

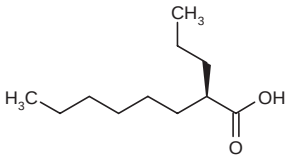
9. *FDA explains clinical hold of phase II study of arimoclomol for ALS*. DailyDrugNews.com (Daily Essentials) Aug 17, 2005.

10. *CytRx reports Q2 R&D highlights*. CytRx Corp. Press Release 2005, Aug 15.

11. *Arimoclomol begins phase II trial, receives fast track status*. DailyDrugNews.com (Daily Essentials) Sept 27, 2005.

12. Greensmith, L. et al. (Biorex Kutató és Fejlesztó Rt.) *Use of a hydroximic acid halide derivative in the treatment of neurodegenerative diseases*. WO 2005041965.

Arundic Acid



The novel neuroprotectant arundic acid (Ono-2506) is in phase II/III trials in Japan at Ono Pharmaceutical as an injectable formulation (Proglia®) for the treatment of acute ischemic stroke and in phase II trials for the oral treatment (Cereact®) of ALS, Parkinson's disease and Alzheimer's-type dementia. Partner Merck & Co. is conducting phase II trials outside Japan with the injectable formulation. It is believed to act by modulating the function of astrocytes and, through this new mechanism of action, inhibit the expansion of cerebral infarction, thereby alleviating the effects of acute stroke. Based on preclinical data, it is anticipated that the drug will show efficacy even when administered several hours after the onset of cerebral infarction and it is anticipated that there is no risk of cerebral hemorrhage since this drug has no action on the blood coagulation system. In November 2004, Ono signed a licensing agreement with Merck & Co., granting Merck an exclusive license for development and marketing of the injectable formulation of arundic acid worldwide, excluding Japan, South Korea and Taiwan. In Japan, phase II trials in stroke were discontinued by Ono in accordance with advice proffered by an independent data safety monitoring board (DSMB) after interim analysis (see below), although clinical trials for this indication are still under way in Europe (1-4).

Ono reported the results of a phase IIb study with arundic acid conducted in Japan to investigate the efficacy and safety of the agent in patients with acute cerebral infarction and to identify the optimal dose. In the randomized, double-blind study, patients received either 0.4 mg/kg/h (low-dose group), 4 mg/kg/h (medium-dose group) or 8 mg/kg/h (high-dose group) of arundic acid or

placebo by intravenous administration once daily for 7 days. The duration from the onset of stroke to admission to hospital was between 6 and 48 h in most patients. Efficacy was evaluated by means of a Modified Rankin Scale (mRS). The primary endpoint was the proportion of patients improving their ability to look after their own affairs without any assistance or better (grade 0-2). Results showed that the proportion of a patients with mRS grade 0-2 at 1 and 3 months after the start of treatment was higher by more than 10% in the high-dose group than in the placebo group and statistical significance was confirmed at 1 month, but not at 3 months. No safety issues were observed in any of the arundic acid-treated groups. Despite the positive results from this trial, however, an independent data safety monitoring board (DSMB) recommended that the subsequent phase II RREACT (Rapid REsponse with an Astrocyte modulating agent in acute Cortical sTroke) study in North America be discontinued after an interim analysis. The analysis indicated that it was highly unlikely that arudic acid for injection would have statistically significant efficacy compared to placebo according to the study design. Ono accepted the recommendation and decided to discontinue this study after consultation with Merck & Co. Ono will collect all the data from the study and share them with Merck, and, after further analysis of the data, will discuss future development plans outside Japan, Taiwan and Korea. In Japan, a phase II/III clinical study had already begun based on the results of the previously completed clinical studies conducted in Japan and this study continues as previously scheduled (5-7).

Compositions comprising a compound capable of stimulating nerve cell regeneration and preventing nerve cell death, namely arundic acid, have been claimed for the therapeutic intervention of neurodegenerative diseases. These compositions are expected to facilitate the proliferation, differentiation and functional expression of newly transplanted cells such as nerve stem cells and neurons (8).

Therapeutic compositions suitable for intravenous administration comprising arundic acid have been claimed for the treatment of neurodegenerative diseases. Such compositions contain approximately 1-5 equivalents of a basic metal to 1 equivalent of arundic acid (9, 10).

A method has been claimed for the therapeutic intervention of neurodegenerative diseases such as cerebral infarction and stroke comprising the parenteral administration of compositions containing arundic acid at doses in excess of 100 mg. The drug acts by restricting increases in S-100 beta protein activity, elevated levels of which in blood and cerebrospinal fluid are implicated in a number of neurodegenerative disorders. The use of such a medicament to stimulate neural regeneration following transplantation is also claimed (11).

1. *Ono Pharmaceuticals reports Q4 R&D highlights*. Ono Pharmaceuticals Web Site 2004, May 18.

2. *Ono and Merck & Co. in licensing agreements*. DailyDrugNews.com (Daily Essentials) Nov 12, 2004.

3. *Ono Pharmaceutical reports first-third quarter (April 1 - December 31, 2004) R&D highlights*. Ono Pharmaceutical Press Release 2005, Feb 4.

4. *Ono Pharmaceutical reports Q2 R&D highlights*. Ono Pharmaceutical Press Release 2005, Aug 4.

5. *Japanese phase IIb results for Proglia in acute cerebral infarction*. DailyDrugNews.com (Daily Essentials) Jan 3, 2005.

6. *Ono updates progress of ONO-2506 and inlicensed Merck compounds*. DailyDrugNews.com (Daily Essentials) March 4, 2005.

7. *Phase II ONO-2506 study discontinued*. DailyDrugNews.com (Daily Essentials) May 26, 2005.

8. Tateishi, N. et al. (Ono Pharmaceutical Co., Ltd.) *Nerve regeneration promoters*. WO 2005032535.

9. Sudoh, M. and Tanikawa, S. (Ono Pharmaceutical Co., Ltd.) *Drug containing (2R)-2-propyloctanoic acid as the active ingredient*. WO 2005032536.

10. Sudoh, M. and Tanikawa, S. (Ono Pharmaceutical Co., Ltd.) *Infusion preparation containing (2R)-2-propyloctanoic acid as the active ingredient*. WO 2005032538.

11. Funakoshi, Y. et al. (Ono Pharmaceutical Co., Ltd.) *Method for preventing and/or treating neurodegenerative diseases*. WO 2005032537.

Original monograph – Drugs Fut 2004, 29(5): 441.

ATL-1102

Antisense Therapeutics' ATL-1102 is a second-generation antisense inhibitor of CD49d, a subunit of VLA-4 (very late antigen-4), with potential as a treatment for multiple sclerosis (MS). The inhibition of VLA-4 may prevent white blood cells from entering sites of inflammation, thereby halting the progression of the disease. Antisense inhibition of VLA-4 has demonstrated positive effects in a number of animal models of inflammatory disease, including MS. Earlier this year, the company decided to voluntarily halt its phase IIa trial of ATL-1102 for MS and convene an advisory group following suspension of the marketing of natalizumab (see below). While Antisense Therapeutics' product is different from natalizumab and is being tested as a single agent, ATL-1102 is designed to target the same immune system protein, VLA-4, as natalizumab. Subsequently, a Medical Advisory Board (MAB) recommended that the company continue the development of ATL-1102 for relapsing-remitting MS and restart the German trial with additional safety monitoring of patients. The MAB reported that ATL-1102 appears to have significant potential as a therapeutic agent in relapsing-remitting MS. It recommended that while the risk of progressive multifocal leukoencephalopathy (PML) developing in patients in the proposed 8-week dosing trial is minimal, all patients enrolled in the trial should undergo regular monitoring for possible activation of the JC virus, for the entire duration of the trial. An independent drug safety monitoring board should be set up to assess all

safety results arising from the study. Patient enrollment criteria should be strictly followed for those who may have previously received immunomodulating drugs to eliminate any risk of a synergistic adverse effect of drug combinations, as it would appear that the 2 patients who developed PML in the natalizumab MS trial received a combination of two immunomodulating drugs. ATL-1102 is also being investigated for asthma based on encouraging results from an animal model of asthma with an inhaled form of the compound (1-4).

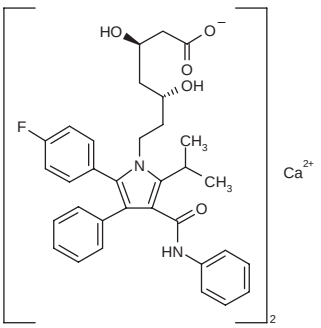
1. *Antisense Therapeutics halts phase IIa study of ATL-1102 for MS*. DailyDrugNews.com (Daily Essentials) March 16, 2005.

2. *Antisense Therapeutics to resume phase IIa study of ATL-1102*. DailyDrugNews.com (Daily Essentials) Sept 5, 2005.

3. *Antisense Therapeutics updates development status*. DailyDrugNews.com (Daily Essentials) June 3, 2005.

4. *Antisense Therapeutics reviews progress*. DailyDrugNews.com(Daily Essentials) Feb 7, 2005.

Atorvastatin Calcium, New Indication



Atorvastatin calcium is an HMG-CoA reductase inhibitor currently marketed by Pfizer and partner Astellas Pharma as Lipitor® for the treatment of hypercholesterolemia and to reduce the risk of myocardial infarction, stroke, revascularization procedures and angina in patients without clinically evident coronary heart disease but with multiple risk factors for coronary heart disease. Pfizer is also evaluating the potential of atorvastatin in phase III trials for the treatment of Alzheimer's-type dementia.

Original monograph – Drugs Fut 1997, 22(9): 956.

Atvogen

Atvogen (Ampligen®), a double-stranded RNA drug from HemispheRx, recently completed phase III clinical evaluation for chronic fatigue syndrome (CFS). Phase II clinical development is also under way for the treatment of HIV infection. Atvogen has been granted orphan drug designation by the FDA for CFS (1-3).

The therapeutic benefits of atvogen in CFS were assessed in a multicenter, double-blind, randomized, pivotal phase III clinical trial that treated 234 CFS patients with placebo or atvogen for 40 weeks. Atvogen was significantly more effective than placebo in improving the patients' exercise treadmill performance. This effect was medically and statistically significant and was associated with improvements in both maximum oxygen consumption and the Karnofsky Performance Status of the patients. Atvogen was well tolerated and induced no significant changes in either blood biochemistry or hematology parameters (1, 4).

1. *Phase III findings on Ampligen for chronic fatigue syndrome*. DailyDrugNews.com (Daily Essentials) Oct 20, 2004.

2. *Hemispherx reports preclinical studies on dsRNA*. DailyDrugNews.com (Daily Essentials) Sept 8, 2005.

3. *Japanese National Institute of Infectious Diseases to study Ampligen*. DailyDrugNews.com (Daily Essentials) Oct 5, 2005.

4. Carter, W., Stevens, S., Strayer, D., Mitchell, W. *Chronic fatigue syndrome (CFS): Phase III, randomized, double-blinded clinical trial shows significant improvement in the primary endpoint, exercise treadmill duration, with Ampligen*. 44th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Oct 30-Nov 2, Washington DC) 2004, Abst V-1248.

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Mitchell, W.M. et al. *Correlation of increased oxygen utilization with enhanced treadmill performance in patients with chronic fatigue syndrome as a function of Ampligen*. 18th Int Conf Antivir Res (April 11-14, Barcelona) 2005, Abst LB-02.

AV-201

Avigen reported encouraging results from the first patient treated in a phase I/II trial of AV-201 (AAV-AADC), the company's drug candidate for the treatment of mid- to later stage Parkinson's disease. The results from positron emission tomography (PET) brain scans obtained 6 months after AV-201 infusion indicated an increased activity of the gene product aromatic L-amino acid decarboxylase (AADC) in the targeted area of the brain, compared with pretreatment PET scans. By using the dopamine tracer [^{18}F]-fluorometatyrosine (FMT)-based PET scanning rather than conventional fluorodopa PET, clinicians were able to visualize evidence of AADC gene expression with greater specificity. FMT-PET is being evaluated in individuals with Parkinson's disease as a surrogate marker of AADC activity and gene transfer. There has been evidence of successful AADC gene transfer in the human brain for the first time. Both the apparent level and the duration of AADC expression are greater than had been anticipated, given the low dose of AV-201 with which the study began. The phase I/II trial of AV-201 in Parkinson's disease was initiated in December 2004 at the University of California at San Francisco (UCSF) and Lawrence Berkeley National Laboratory (LBNL). Levodopa, the first-line drug for treating symp-

toms of Parkinson's disease, requires AADC in order to be converted to dopamine. However, over time, AADC production in the brain also declines as the disease progresses, making levodopa less effective. AV-201, an AAV vector containing the gene for human AADC which is delivered directly to the striatum, is designed to restore the activity of AADC in the brain, thereby extending the therapeutic usefulness and life of levodopa while avoiding side effects. The patient and physician potentially can regulate the activity of AADC by raising or lowering the amount of levodopa taken. FMT-PET studies in animal models of Parkinson's disease have shown sustained AADC gene expression for more than 5 years after convection-enhanced gene delivery, along with sustained motor improvement. In April 2005, Avigen announced that it will focus on the development of traditional pharmaceutical products, particularly small molecules and biologics, and would divest its proprietary AAV technology. However, the company remains committed to ensuring the continuation of the ongoing clinical programs, including the AV-201 program in Parkinson's disease. Avigen is in advanced discussions with multiple parties to secure the long-term future of the AAV technology, including the Parkinson's trial (1-5).

1. *Avigen reports 2003 year-end R&D highlights*. Avigen Inc. Press Release 2004, Feb 11.

2. *Avigen to focus resources on neurological drug candidates*. DailyDrugNews.com (Daily Essentials) June 3, 2004.

3. *AV-201 enters phase I/II trial for Parkinson's disease*. DailyDrugNews.com (Daily Essentials) Dec 22, 2004.

4. *Avigen discontinues AAV funding to focus on traditional pharmaceuticals*. DailyDrugNews.com (Daily Essentials) April 12, 2005.

5. *Encouraging early data from phase I/II study of AV-201 for Parkinson's disease*. DailyDrugNews.com (Daily Essentials) July 22, 2005.

AVE-1625

The cannabinoid CB1 antagonist AVE-1625 is in early clinical development at Sanofi-Aventis for the treatment of Alzheimer's-type dementia, Parkinson's disease, obesity and schizophrenia.

AX-200

AX-200 is being evaluated in phase II trials at Axaron Bioscience for the treatment of stroke. The drug works in two ways after a stroke: preventing the death of nerve cells and promoting regeneration of damaged brain tissue (1, 2).

1. *AX-200 set to enter phase II for stroke*. DailyDrugNews.com (Daily Essentials) Aug 9, 2004.

2. *Axaminer demonstrates capabilities in studies*. DailyDrugNews.com (Daily Essentials) Dec 17, 2004.3

BA-210

An independent data safety monitoring board (DSMB) has recommended that BioAxone continue its phase I/IIa trial with BA-210 (Cethrin®) in acute spinal cord injury after reviewing safety data for the first 6 patients. This interim review was prospectively specified in the original protocol and was based on the review of the safety data from at least 5 patients who had completed a minimum of 3 weeks of assessments following treatment with 0.3 mg of BA-210. BioAxone is now initiating patient treatment with a higher dose (1.0 mg) of BA-210. The multinational study is designed to evaluate the safety and pharmacokinetics of escalating doses of BA-210 given as a single extradural administration during surgery for acute thoracic and cervical spinal cord injury. Up to 48 patients with acute spinal cord injury recruited from about 10 sites in Canada and the U.S. will be administered BA-210. BA-210 is a recombinant protein that acts as a Rho antagonist to promote neuroregeneration and neuroprotection in the central nervous system (CNS). It has been designed to penetrate CNS tissue and is being developed for delivery at the site of spinal cord injury during surgical intervention. It requires a single application and is noninvasive (1-4).

1. *BioAxone cleared to commence U.S. clinical development of Cethrin*. DailyDrugNews.com (Daily Essentials) Jan 14, 2005.

2. *First patient treated in acute spinal cord injury study of Cethrin*. DailyDrugNews.com (Daily Essentials) Feb 11, 2005.

3. *Phase I/IIa trial of BA-210 in acute spinal cord injury recommended to continue*. DailyDrugNews.com (Daily Essentials) June 10, 2005.

4. *A safety study for BA-210 to treat acute thoracic and cervical spinal cord injuries (NCT00104221)*. ClinicalTrials.gov Web Site 2005, Aug 29.

Additional References

Yang, F. et al. *Delivery of the Rho antagonist BA-210 by an extradural approach after acute spinal cord injury*. 34th Annu Meet Soc Neurosci (Oct 23-27, San Diego) 2004, Abst 43.7.

Bapineuzumab

Elan continues to make progress with its Alzheimer's disease (AD) immunotherapy program in collaboration with Wyeth. During the first half of 2005, Elan initiated two phase II trials with the humanized monoclonal antibody bapineuzumab (AAB-001), designed and engineered to remove the neurotoxic β-amyloid peptide that accumulates in the brains of patients with AD. The first trial is a randomized, double-blind, placebo-controlled, multiple-ascending-dose study in 180 patients with mild to moderate AD. The trial will be conducted at approximately 30 sites in the U.S. and dosing is scheduled for 18 months, with planned interim analyses. The key endpoints will include the Alzheimer's Disease Assessment Scale-

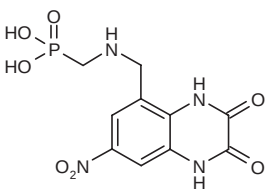
Cognitive subscale (ADAS-cog), Neuropsychological Test Battery (NTB) and Disability Assessment for Dementia (DAD) scores. The second trial is an Alzheimer's β-amyloid imaging study in 30 patients and dosing is scheduled for 18 months (1-3).

1. *U. of Pittsburgh to test AAB-001 for Alzheimer's*. DailyDrugNews.com (Daily Essentials) July 1, 2004.

2. *Elan reports Q1 R&D highlights*. Elan Corp. Press Release 2005, April 28.

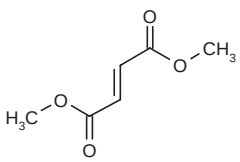
3. *Elan reports Q2 R&D highlights*. Elan Corp. Press Release 2005, July 28.

Becampanel



Becampanel (AMP-397), an AMPA antagonist, is currently being evaluated in phase II clinical trials at Novartis for the treatment of epilepsy.

BG-12



BG-12 (dimethylfumarate, Panaclar™), an NF-κB activation inhibitor, is in phase III clinical trials at Biogen Idec and Fumapharm for the oral treatment of mild to moderate psoriasis. Biogen Idec and Fumapharm are also studying the drug candidate in phase II clinical trials for the treatment of multiple sclerosis (MS). The product is a second-generation fumarate derivative with an immunomodulatory mechanism of action; the first-generation product is marketed as Fumaderm® for the treatment of psoriasis. In 2003, Biogen Idec obtained from Fumapharm exclusive worldwide rights, with the exception of Germany, to develop and market the compound for psoriasis.

The potential benefits of oral fumaric acid therapy in the treatment of relapsing-remitting MS were evaluated in an open-label clinical trial. Ten patients with relapsing-remitting MS were given increasing doses of fumaric acid esters (at a target dose of 720 mg/day p.o.) for 18 weeks, followed 4 weeks later by a second treatment period with fumaric acid esters (at a target dose of 360 mg/day p.o.) for 70 weeks. Administration of fumaric acid therapy for 12 weeks significantly decreased the number and volume of gadolinium-enhancing lesions on serial magnetic resonance imaging (MRI) scans. These effects were associated with increases in the number of $CD4^+$ T-cells producing TGF-β and interleukins IL-10 and IL-14, together with a transient increase in the apoptosis rate of T-helper cells. All patients remained clinically stable throughout the study and most adverse events were mild and transient (1-3).

1. Schimrigk, S.K. et al. *An open-label, prospective study of oral fumaric acid therapy for the treatment of relapsing-remitting multiple sclerosis (RRMS)*. Neurology 2005, 64(6, Suppl. 1): Abst S46.003.

2. Schimrigk, S., Brune, N., Hellwig, K., Rieks, M., Hoffmann, V., Pöjlau, D., Przuntek, H. *A prospective, open-label, phase II study of oral fumarate therapy for the treatment of relapsing-remitting multiple sclerosis*. Multiple Scler 2004, 10(Suppl. 2): Abst P642.

3. Brune, N., Schimrigk, S., Meier, D. et al. *Oral fumarate therapy alters cytokine production in patients with relapsing-remitting multiple sclerosis*. Multiple Scler 2004, 10(Suppl. 2): Abst P643.

Additional References

Kappos, L. et al. *A randomised, placebo-controlled phase II trial of a novel oral single-agent fumarate therapy, BG00012, in patients with relapsing-remitting multiple sclerosis*. J Neurol 2005, 252(Suppl. 2): Abst P574.

BHT-3009

Bayhill Therapeutics' lead product candidate BHT-3009 is a DNA plasmid expression vector in phase I/II clinical trials as monotherapy or in combination with atorvastatin for the treatment of MS. Bayhill licensed BHT-3009 from Stanford University. The drug candidate, delivered intramuscularly, contains the gene for full-length human myelin basic protein (MBP), which compensates for MBP lost due to MS. Preclinical studies in a murine model of MS, experimental allergic encephalomyelitis (EAE), revealed that DNA plasmids decrease mean disease score and relapse rate when given at the time of peak disease. The mechanism of action appears to be reduction of both autoimmune T-cells and antibodies to the target antigen (1).

1. *Bayhill Therapeutics raises USD 35.4 million in Series B financing*. Bayhill Therapeutics Press Release 2005, May 4.

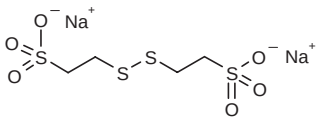
Additional References

Bar-Or, A., Jalili, F., Niino, M. et al. *Antigen-specific immunomodulation in MS patients treated with MBP encoding DNA plasmid (BHT-3009) alone or combined with atorvastatin*. 21st Congr Eur Comm Treat Res Multiple Scler (Sept 28-Oct 1, Thessaloniki) 2005, Abst P632.

Vollmer, T. et al. *Clinical trial of a MBP encoding DNA plasmid (BHT-3009) alone or combined with atorvastatin for treatment of*

multiple sclerosis. 21st Congr Eur Comm Treat Res Multiple Scler (Sept 28-Oct 1, Thessaloniki) 2005, Abst 65.

BNP-7787

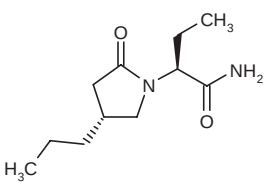


The chemoprotective agent BNP-7787 (Tavocept™) is in phase III trials in the U.S., Japan and Europe by BioNumerik and Takeda, Aska Pharmaceutical (recently formed by the merger of Grelan and Teikoku Hormone) and Baxter Oncology, respectively, for the treatment of peripheral neuropathy. BioNumerik is developing BNP-7787 as a chemotherapy supportive care drug to prevent or mitigate the incidence, severity and duration of neuropathy. Studies indicate that it has the potential to protect cells against the damage or impairment to the functions of the intracellular protein tubulin that may be associated with the neuropathy caused by the taxane and platinum classes of antitumor drugs. The drug was granted fast track status by the FDA in March 2000 for the prevention or reduction of nerve damage associated with paclitaxel (1, 2).

1. *Takeda signs agreement to market Tavocept in U.S. and Canada*. DailyDrugNews.com (Daily Essentials) Oct 13, 2004.

2. *Teikoku Hormone accelerates new drug development*. DailyDrugNews.com (Daily Essentials) June 21, 2005.

Brivaracetam



UCB Pharma's brivaracetam (UCB-34714) is a high-affinity synaptic vesicle protein SV2A ligand targeting neurological diseases, including epilepsy. Brivaracetam has shown significant antiepileptic activity in animal models of epilepsy, both *in vitro* and *in vivo,* and is currently being evaluated for the treatment of refractory patients with partial-onset seizures A first phase II study in 19 patients with photosensitive epilepsy showed that brivaracetam (single doses of 10, 20, 40 or 80 mg p.o.) provided a more potent and complete seizure suppression in these patients than seen previously in studies with levetiracetam (Keppra), UCB's marketed antiepileptic drug. The highest dose was the most effective in suppressing the induction of photoparoxysmal EEG response by intermittent photic stimulation. The product has been granted orphan medicinal product designation in Europe for the treatment of progressive myoclonic epilepsies and in the U.S. for the treatment of symptomatic myoclonus. It is also undergoing phase II clinical evaluation for post-herpetic neuralgia (1-5).

A double-blind, randomized clinical trial assessed the pharmacokinetics and safety of brivaracetam in healthy male volunteers. Compared with placebo, single doses of the drug (10, 20, 40, 80, 150, 300, 600, 1000 or 1400 mg) were associated with a dose-dependent increase in the incidence of CNS-related adverse events (*i.e.*, dizziness, somnolence, euphoria). Brivaracetam (200, 400 or 800 mg/day) given in 2 daily doses for 2 weeks was associated with a similar safety profile, adverse events also including headache, throat irritation, fatigue and nausea. Most adverse events were mild or moderate and resolved within 1 day. A crossover substudy found that food decreased the peak plasma drug concentration achieved with a single dose of 150 mg, but had no significant effect on the level of drug exposure. The maximum tolerated dose of brivaracetam was 1000 mg for a single dose and > 800 mg/day for twice-daily doses for 2 weeks (6).

1. *UCB-44212 Keppra analogue enters phase I*. DailyDrugNews.com (Daily Essentials) May 5, 2004.

2. *UCB announces positive new products results*. UCB Press Release 2004, Dec 2.

3. *Orphan drug designation recommended in Europe for brivaracetam*. DailyDrugNews.com (Daily Essentials) July 26, 2005.

4. *Brivaracetam granted orphan drug status for symptomatic myoclonus*. DailyDrugNews.com (Daily Essentials) Nov 9, 2005.

5. Kasteleijn-Nolst Trenité, D.G.A., Parain, D., Masnou, P., Genton, P., Steinhoff, B.J., Hirsch, E. *Proof of principle in the new AED ucb 34714: Use of the photosensitivity model*. Epilepsia 2004, 45(Suppl. 7): Abst 2.349.

6. Rolan, P., Pigeolet, E., Stockis, A. *Ucb 34714: Single and multiple rising dose safety, tolerability, and pharmacokinetics in healthy subjects*. Epilepsia 2004, 45(Suppl. 7): Abst 2.365.

C-6161

Phase I clinical trials are in progress at Merck & Co. to evaluate C-6161 for the treatment of Parkinson's disease.

C-9136/C-7617

Merck & Co. has two compounds in clinical development for Alzheimer's-type dementia: C-9136 in phase II and C-7617 in phase I.

C-6448

Phase II trials are under way at Merck & Co. with C-6448 for the treatment of multiple sclerosis.

CAD-106

Novartis obtained approval earlier this year from the Swedish health authority to initiate a phase I trial with the Immunodrug™ candidate CAD-106, an immunotherapeutic product for the treatment of Alzheimer's disease (AD) resulting from a collaborative program between Novartis and Cytos Biotechnology. Novartis's double-blind, placebo-controlled phase I study will include 60 patients with mild to moderate AD and will investigate safety, tolerability and β-amyloid-specific antibody responses following treatment with CAD-106. CAD-106 is designed to induce antibodies against the β-amyloid protein that would inhibit the formation of plaques in the brain of AD patients. CAD-106 consists of two components, the Immunodrug™ carrier Qb coupled with a fragment of the β-amyloid protein. Animal studies showed that treatment with CAD-106 can block the formation of β-amyloid plaques in the brain (1, 2).

1. *Swedish approval for phase I study of CAD-106 for Alzheimer's*. DailyDrugNews.com (Daily Essentials) May 20, 2005.

2. *Cytos Biotechnology reports Q2 R&D highlights*. Cytos Biotechnology Press Release 2005, July 28.

CDP-323

UCB Pharma's CDP-323, an orally active, small-molecule α_4 integrin inhibitor, has successfully completed a second phase I multiple-dose study in healthy volunteers. Good plasma exposure and potent and prolonged inhibition of ligand binding to α_4 integrins in an *in vitro* whole blood assay were demonstrated. This confirms CDP-323's antiinflammatory potential in diseases such as multiple sclerosis, allergy/respiratory diseases, rheumatoid arthritis and Crohn's disease (1, 2).

1. *UCB announces positive new products results*. UCB Press Release 2004, Dec 2.

2. *UCB: Research budget for 2005 up significantly after conversion to biopharmaceuticals*. UCB Press Release 2004, Dec 17.

CERE-110

Eight patients with early-stage probable Alzheimer's disease (AD) participated in a phase I clinical trial that evaluated the potential benefits of using a nerve growth factor (NGF) gene therapy approach for this indication. The naturally occurring NGF gene encodes the NGF protein, which maintains survival of nerve cells in the brain that are required for memory and cognitive function. Autologous fibroblasts obtained from small skin biopsies were genetically modified to secrete human NGF using CERE-110 (an adeno-associated virus [AAV2]-based vector that expresses NGF) and then stereotaxically injected into the cholinergic basal forebrain of the right brain (n=2) or both the left and right brain (n=6) of the subjects. The average annual rate of decline in the patients' Mini-Mental Status Examination (MMSE) scores, which had been 6.1 points during the last 14 months before treatment, decreased to 3.0 points during an average of 22 months after treatment; the greatest improvement was found during a time period of 6-18 months after surgery. A similar effect was found in the average annual rate of decline in the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-cog), which was 55% lower during 6-18 months after surgery compared to 1-12 months after surgery. This time effect was related to the preclinical finding that NGF gene delivery needs several months to increase cortical cholinergic terminal density in the basal forebrain of aged primates. Serial PET scans revealed that NGF therapy increased brain metabolism in the cerebellum and in most cortical regions receiving cholinergic input from nucleus basalis, but not in the striatum (which receives no input from nucleus basalis). No long-term adverse effects were reported (1).

Ceregene has confirmed that the first patient has been treated in another phase I clinical study of CERE-110. This clinical trial is the first to test the company's growth factor gene therapy delivery system in a non-patient-specific, "off-the-shelf" product formulation for patients with AD. The goal of this study is to determine the safety and efficacy of this new gene therapy system. Efficacy will be measured by memory and cognitive tests, as well as brain imaging studies (2).

1. Tuszynski, M.H. et al. *A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease*. Nat Med 2005, 11(5): 551.

2. *Ceregene begins phase I trial of novel gene therapy for Alzheimer's disease*. DailyDrugNews.com (Daily Essentials) Sept 27, 2004.

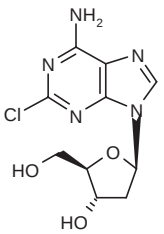
CERE-120

Patient treatment is under way in Ceregene's phase I study of CERE-120 to treat Parkinson's disease. The study is being conducted at the University of California, San Francisco Medical Center and Rush University Medical Center in Chicago. CERE-120 is a novel gene therapy product that delivers the neurturin (NTN) gene via an adeno-associated virus type 2 (AAV2) vector delivery system. The naturally occurring NTN gene encodes the NTN protein that maintains survival of dopamine-producing nerve cells which are required for normal body movement and are the nerves that degenerate in Parkinson's disease patients. The phase I study involves *in vivo* gene therapy delivery of NTN. The goal of the study is to determine the safety and efficacy of this treatment. Efficacy will be measured by standardized tests for Parkinson's patients, as well as brain imaging studies. CERE-120 has the potential to significantly slow or even halt the progression of symptoms of Parkinson's. Numerous studies

in animal models, including the most widely accepted animal models of Parkinson's disease, demonstrate that the NTN gene therapy product may be able to improve symptoms, as well as retard the progression of the disease. CERE-120 was safe and well tolerated in animals at doses hundreds of times higher than the equivalent doses being tested in humans (1).

1. *Ceregene begins phase I study of novel gene therapy for Parkinson's disease*. DailyDrugNews.com (Daily Essentials) Sept 27, 2005.

Cladribine, Oral Formulation



A proprietary oral formulation of cladribine (Mylinax®) is currently in phase III clinical trials at Serono and Ivax for the treatment of multiple sclerosis (MS). Cladribine, an adenosine deaminase inhibitor, is a purine nucleoside analogue that interferes with the behavior and the proliferation of certain white blood cells, particularly lymphocytes, which are involved in the pathological process of MS. Cladribine injection, developed by Ortho Biotech, was launched over 10 years ago for the treatment of hairy cell leukemia and is now also used for the treatment of leukemia, non-Hodgkin's lymphoma and mantle cell lymphoma. In the first quarter of this year, Serono initiated a phase III trial with oral cladribine in relapsing forms of MS. The 2-year, double-blind, placebo-controlled study of potentially the first oral treatment for MS has endpoints of clinical relapses, disability and MRI brain scans (1-5).

Oral dosage formulations comprising cladribine in combination with an amorphous cyclodextrin such as hydroxypropyl-β-cyclodextrin that are expected to augment the bioavailability of cladribine, resulting in increased therapeutic benefit to subjects with MS, rheumatoid arthritis and leukemia, have been claimed. Oral formulations of 3 and 10 mg gave respective geometric mean C_{max}, $AUC_{0-\infty}$ and AUC_t values of 5608/21,242 pg/ml, 20,159/76,690 pg.h/ml and 19,166/74,532 pg.h/ml, and corresponding t_{max} and $t_{1/2}$ values of 0.55/0.56 h and 5.85/5.6 h, when administered over 3 days in an open-label, randomized, single-dose study in 26 MS patients (6).

Formulations suitable for oral and transmucosal delivery comprising a saturated complex containing cladribine and a cyclodextrin have also been claimed. Such compositions are predicted to enhance the bioavailability of cladribine and provide improved efficacy in the treatment of MS, rheumatoid arthritis and leukemia. The oral administration of 5 mg cladribine/animal in a formulation containing hydroxypropyl-β-cyclodextrin produced a mean bioavailability of 44.8% compared with 17.3% resulting from a 5-mg i.v. bolus in male beagle dogs (7).

1. *Positive pharmacokinetic results for new oral cladribine formulation*. DailyDrugNews.com (Daily Essentials) March 24, 2004.

2. *Phase III study planned for Mylinax in MS*. DailyDrugNews.com (Daily Essentials) Jan 13, 2005.

3. *Serono reports Q1 R&D highlights*. Serono Group Press Release 2005, April 21.

4. *Product highlights at Serono*. DailyDrugNews.com (Daily Essentials) Aug 10, 2005.

5. *Serono reports Q2 R&D highlights*. Serono Group Press Release 2005, July 19.

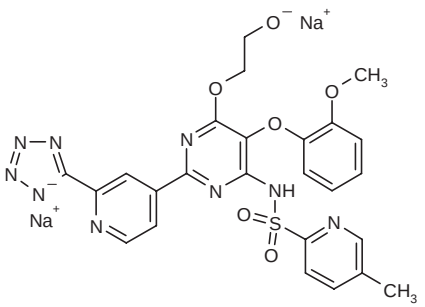
6. Bodor, N.S., Dandiker, Y. (Ivax Corp.) *Oral formulations of cladribine*. WO 2004087101.

7. Bodor, N.S. (Ivax Corp.) *Cladribine formulations for improved oral and transmucosal delivery*. WO 2004087100.

Additional References

Bartosik-Psujek, H. et al. *Interleukin-8 and RANTES levels in patients with relapsing-remitting multiple sclerosis (RR-MS) treated with cladribine*. Acta Neurol Scand 2004, 109(6): 390.

Clazosentan Sodium



Enrollment began earlier this year at the first sites in the U.S. and Canada for Actelion's phase IIb CONSCIOUS-1 (Clazosentan to Overome Neurological iSChemia and Infarct OccUrring after Subarachnoid hemorrhage) study of clazosentan sodium for preventing the occurrence of cerebral vasospasm following an aneurysmal subarachnoid hemorrhage (aSAH). The double-blind, randomized, placebo-controlled, parallel-group, dose-finding study is designed to assess the efficacy of three dose levels (1, 5 and 15 mg/h) of clazosentan, a selective endothelin ET_A receptor antagonist, in preventing the occurrence of cerebral vasospasm following aSAH. Secondary outcomes of the trial include the ability of clazosentan to reduce the occurrence of early morbidity/mortality, the effect of clazosentan on clinical outcome, and safety and tolerability. The study is expect-

ed to enroll 400 patients, with last follow-up to occur in March 2006. The study is expected to be completed in September 2006. The results of this study will be used to determine the need for, size and duration of a potential phase III trial. Actelion acquired clazosentan through its acquisition of Axovan in 2003 (1, 2). The E.U. authorities have granted orphan drug designation for the treatment of aSAH. Clazosentan was originally discovered at Roche and subsequently licensed to the former Vanguard (now Vernalis) and then to Axovan.

The potential benefits of clazosentan in the prevention of cerebral vasospasm in patients with SAH were evaluated in a multicenter phase IIa clinical trial. In the first phase of the study, 34 SAH patients were randomized to receive a continuous i.v. infusion of placebo or clazosentan (0.2 mg/kg/h) for up to 14 days after rupture, starting within 14 h of SAH and after clipping of the aneurysm. Seven clazosentan-treated patients and 12 placebo-treated patients developed cerebral vasospasm and entered the second phase of the study, when they were first stabilized and then given open-label i.v. clazosentan (0.4 mg/kg/h for 12 h, followed by 0.2 mg/kg/h) until day 14 after SAH. The first phase of the study revealed that, compared to placebo, clazosentan decreased the risk of developing cerebral vasospasm by 55% and was associated with significantly fewer severe cases of vasospasm, fewer changes in baseline transcranial Doppler and a lower incidence of new infarctions. Analysis of angiograms obtained during the second part of the study showed that open-label clazosentan induced reversal of moderate cerebral vasospasm in 50% of patients previously treated with placebo, but had no significant effects in patients previously treated with clazosentan. No significant differences were found between the safety profiles of the two study regimens (3).

1. *Actelion begins global phase IIb/III program for clazosentan.* DailyDrugNews.com (Daily Essentials) Dec 28, 2004.

2. *Phase IIb trial examines clazosentan for prevention of cerebral vasospasm.* DailyDrugNews.com (Daily Essentials) May 20, 2005.

3. Vajkoczy, P. et al. *Clazosentan (AXV-034343), a selective endothelin A receptor antagonist, in the prevention of cerebral vasospasm following severe aneurysmal subarachnoid hemorrhage: Results of a randomized, double-blind, placebo-controlled, multicenter phase IIa study*. J Neurosurg 2005, 103(1): 9.

CNTO-1275

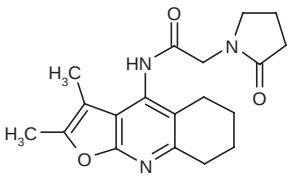
CNTO-1275 is a human anti-IL-12/IL-23 monoclonal antibody discovered by Medarex and in phase II clinical development by partner Centocor (Johnson & Johnson) for the treatment of Crohn's disease, multiple sclerosis and psoriasis (1).

1. *A safety and efficacy study of CNTO1275 in patients with multiple sclerosis (NCT00207727)*. ClinicalTrials.gov Web Site 2005, Sept 30.

Colostrinin™

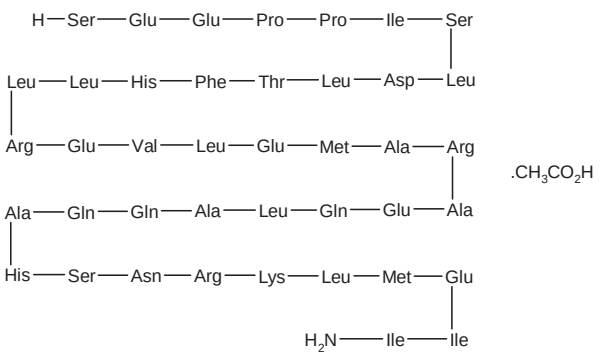
The proline-rich polypeptide complex Colostrinin™, derived from bovine and ovine colostrum, is being tested in phase II trials at ReGen Therapeutics for the treatment of Alzheimer's disease. Colostrinin™ reduces the abundance of 4-hydroxynonenal (4HNE)-protein adducts, inhibits 4HNE-mediated glutathione (GSH) depletion (important for maintenance of cellular redox status, metabolism and enzyme regulation) and inhibits 4HNE-induced activation of p53 protein and c-Jun NH_2 terminal kinase enzymes, both of which are involved in the process of apoptosis.

Coluracetam



Coluracetam, an acetylcholine release enhancer, had reached phase II clinical development at Mitsubishi Pharma for the treatment of Alzheimer's disease, but the product was discontinued earlier this year.

Corticorelin Acetate



Celtic Pharmaceutical has acquired from Neurobiological Technologies worldwide rights to corticorelin acetate (Xerecept™), a synthetic preparation of the natural human peptide corticotropin-releasing factor (hCRF), in phase III clinical trials for the treatment for peritumoral brain edema. The companies will collaborate on the clinical development of Xerecept™ in the U.S. Xerecept™, licensed from the Salk Institute in 1988, has orphan drug status in the U.S. Xerecept™ is a synthetic mimic of the naturally occurring CRF that is thought to block vascular permeability by inducing upregulation of blood-brain barrier-specific structural proteins. Clinical data suggest that Xerecept™ could be as effective as

high-dose synthetic corticosteroids, specifically dexamethasone, the current standard of care for edema. Various phase I/II trials proved Xerecept™ to be very safe and to be associated with very mild side effects such as mild flushing and some minor nausea, nasal congestion, headache and tingling. These early studies showed improvement in neurological function, as well as the ability to enhance radiation therapy for brain tumors. A subsidiary of Celtic will assume responsibility for developing Xerecept™ globally and pay all product development expenses. Notably, Xerecept™ has received orphan drug designation for peritumoral edema from the FDA. The first of two concurrent, multicenter phase III trials with Xerecept™ was initiated in April 2004 as the first controlled study in peritumoral brain swelling. The two studies include the acute protocol (Xerecept™ or dexamethasone needed immediately) and a chronic protocol or a dexamethasone-sparing trial (patients already on chronic high doses of dexamethasone but with an urgent need to dramatically lower their intake). The third study, an open-label, extended-use study of the drug candidate, began enrollment in August 2005. This study is open to all patients who participate in one of the two ongoing blinded phase III trials designed to determine the dexamethasone-sparing effects of hCRF in brain tumor patients being treated for peritumoral brain edema. This extended-use program will collect safety information and allow the treating physicians to attempt a maximum dexamethasone reduction and possible elimination altogether. Xerecept™ will be provided to enrolled patients until the drug's FDA approval and commercial launch (1-7).

1. *Phase III program commences for Xerecept in peritumoral cerebral edema*. DailyDrugNews.com (Daily Essentials) April 22, 2004.

2. *Extended-use study for Xerecept*. DailyDrugNews.com (Daily Essentials) Aug 29, 2005.

3. *Celtic Pharma acquires worldwide rights to Xerecept*. DailyDrugNews.com (Daily Essentials) Sept 22, 2005.

4. *Celtic Pharma completes acquisition of exclusive worldwide rights to Xerecept from Neurological Technologies*. Celtic Pharmaceutical Holdings Press Release 2005, Nov 29.

5. *Human corticotropin-releasing factor for patients requiring dexamethasone to treat edema associated with brain tumors (NCT00088166)*. ClinicalTrials.gov Web Site 2005, Dec 8.

6. *An open-labeled, extended-use of hCRF for patients in dexamethasone-sparing studies NTI 0302 and NTI 0303 (NCT00226655)*. ClinicalTrials.gov Web Site 2005, Sept 30.

7. *hCRF for patients requiring dexamethasone to treat peritumoral brain edema associated with primary malignant glioma (NCT00226668)*. ClinicalTrials.gov Web Site 2005, Sept 30.

CX-717

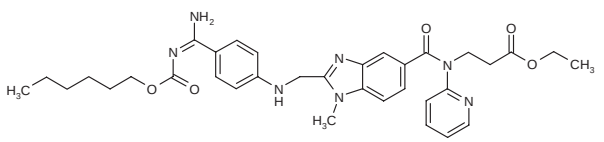
Cortex's CX-717 is an AMPA receptor modulator (Ampakine®) in phase II clinical trials for the treatment of cognition dysfunction associated with attention deficit hyperactivity disorder (ADHD), Alzheimer's disease and sleep disorders. The AMPA receptor is involved in long-term potentiation (LTP), which is believed to underlie the encoding of many types of memory. In addition to its importance in memory formation, the AMPA receptor plays a central role in excitatory communication in the brain.

Cortex recently commenced enrollment in two new CX-717 phase IIa studies, one in ADHD and the other in mild to moderate AD. These represent the second and third phase IIa studies for the compound. In May 2005, the company reported positive results from a phase IIa sleep deprivation study with CX-717, which suggested that CX-717 may provide a new approach to enhancing memory, cognition and wakefulness by cortical arousal without systemic stimulating effects. The new double-blind, randomized AD study involves the evaluation of two single doses of CX-717 (200 and 600 mg *versus* placebo) in 12 subjects with mild to moderate AD and matched controls. CX-717 is expected to positively alter regional cerebral blood flow in patients with AD during the performance of an activating task. A larger phase II study is likely to be conducted in AD. In phase I trials conducted in nearly 100 healthy volunteers who were dosed with CX-717, the compound was well tolerated across a wide range of doses and exhibited simple, linear and predictable pharmacokinetic properties. The drug had a 9-10-h half-life in these subjects, which may result in a once-a-day therapy (1, 2).

1. *Cortex cleared for phase II Alzheimer's imaging study of CX-717*. DailyDrugNews.com (Daily Essentials) Feb 3, 2005.

2. *CX-717 studied in phase IIa trials for Alzheimer's and ADHD*. DailyDrugNews.com (Daily Essentials) Aug 2, 2005.

Dabigatran Etexilate



A thrombin inhibitor from Boehringer Ingelheim, dabigatran etexilate is in phase III clinical development as an oral agent for the prevention of deep venous thrombosis (DVT) following surgery and in phase II trials for the prevention of stroke in patients with atrial fibrillation.

Daclizumab, New Indication

Biogen Idec and Protein Design Labs (PDL) have formed a broad collaboration for the joint development, manufacture and commercialization of three phase II anti-

body products. The agreement provides for shared development and commercialization of daclizumab (Zenapax®) in multiple sclerosis and indications other than transplant and respiratory diseases, and for shared development and commercialization of M-200 (volociximab) and HuZAF™ (fontolizumab) in all indications. Daclizumab is a humanized monoclonal antibody that binds to the IL-2 receptor on activated T-cells, inhibiting the binding of IL-2 and the cascade of proinflammatory events contributing to organ transplant rejection and autoimmune and related diseases. A phase II trial of daclizumab in MS is ongoing and the antibody is also in phase II testing for asthma. Rights to daclizumab in transplantation, asthma and related respiratory diseases are in partnership with Roche (1-5). Roche currently markets the antibody for induction kidney transplant therapy.

An open-label clinical trial evaluated the efficacy and safety of daclizumab (1 mg/kg i.v. once monthly, adjusted according to clinical response) in 20 patients with relapsing/remitting and secondary progressive MS. Most patients were treated for 6-22 months and only 1 discontinued treatment due to a transient adverse event. Seven patients achieved sustained clinical improvement in their Expanded Disability Status Scale (EDSS) scores and another 12 were stabilized. Daclizumab was well tolerated and the most common adverse events reported were transient nausea, paresthesia, spasms and mild rash (6).

1. *Protein Design Labs discontinues development of daclizumab for ulcerative colitis*. DailyDrugNews.com (Daily Essentials) May 19, 2004.

2. *Protein Design Labs reports Q1 R&D highlights*. Protein Design Labs Press Release 2004, May 4.

3. *Biogen Idec and PDL form collaboration for antibody products*. DailyDrugNews.com (Daily Essentials) Aug 9, 2005.

4. *Protein Design Labs reports Q2 R&D highlights*. Protein Design Labs Press Release 2005, Aug 4.

5. *Protein Design Labs reports Q1 R&D highlights*. Protein Design Labs Press Release 2005, May 2.

6. Watt, H.E., White, A., Martin, R., Rose, J.W. *Treatment of multiple sclerosis with daclizumab*. Neurology 2004, 62(7, Suppl. 5): Abst S12.002.

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Bielekova, B. et al. *Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta*. Proc Natl Acad Sci USA 2004, 101(23): 8705.

Rose, J. et al. *Daclizumab phase I/II trial in relapsing and remitting MS: MRI and clinical results*. 21st Congr Eur Comm Treat Res Multiple Scler (Sept 28-Oct 1, Thessaloniki) 2005, Abst P 590.

Desmoteplase

The plasminogen activator desmoteplase is a genetically engineered version of a clot-dissolving protein found in the saliva of the vampire bat *Desmodus rotundus*. It possesses high fibrin selectivity, allowing it to dissolve a clot locally without affecting the blood coagulation system, which is thought to potentially reduce the risk of intracranial bleeding as compared to less fibrin-specific plasminogen activators. Originally developed at Schering AG, desmoteplase was subsequently licensed to PAION. In July 2004, Forest and PAION entered into an agreement for the development and marketing of the compound in the U.S. and Canada. Lundbeck and PAION signed an exclusive partnership agreement in July 2005 for the development and marketing of desmoteplase for the treatment of stroke in Europe, Japan and the rest of the world, with the exception of the U.S. and Canada. In the U.S., desmoteplase has received fast track designation for the treatment of ischemic stroke beyond the 3-h time window. Phase III trials are in progress for the treatment of acute ischemic stroke. Pooled data from the European/Australasian DIAS (Desmoteplase in Acute Stroke) and the U.S. DEDAS (Dose Escalation study of Desmoteplase in Acute Ischemic Stroke) studies were used to confirm the therapeutic benefits of desmoteplase. Both studies were multicenter, double-blind, randomized phase II clinical trials that evaluated the effects and safety of desmoteplase (90 or 125 μg/kg) or placebo given within 3-9 h of stroke onset to 142 patients with acute ischemic stroke. Desmoteplase dose-dependently improved both clinical outcome and reperfusion rates, and the differences compared to placebo reached statistical significance at the dose of 125 μg/kg. Only 2 patients experienced symptomatic intracranial hemorrhage and mortality was low. The ongoing phase III DIAS2 study is a multicenter, multinational, randomized, parallel-design, dose-ranging study in more than 150 patients, designed to confirm the results of the earlier phase II studies, demonstrating the potential of desmoteplase to treat acute ischemic stroke patients up to 9 h after the onset of stroke symptoms, three times longer than the currently available treatment allows (1-5).

A method has been claimed for the treatment of thrombotic conditions, notably stroke, comprising the use of one or more compounds with plasminogen-activating properties and diminished lysine binding activity, in particular one with a modified/deleted kringle 2 domain or structurally homologous domain thereof, such as desmoteplase (6).

1. *Forest and PAION enter agreement for desmoteplase in U.S. and Canada*. DailyDrugNews.com (Daily Essentials) July 8, 2004.

2. *Phase IIb/III DIAS2 study begins for desmoteplase in acute ischemic stroke*. DailyDrugNews.com (Daily Essentials) Feb 14, 2005.

3. *Lundbeck and PAION partner on desmoteplase*. DailyDrugNews.com (Daily Essentials) July 13, 2005.

4. *Lundbeck reports Q2 R&D highlights*. Lundbeck Press Release 2005, Aug 17.

5. Hacke, W. *The results of the joint analysis of two phase II trials on desmoteplase in acute ischemic stroke with treatment 3 to*

9 hours after stroke onset. 14th Eur Stroke Conf (May 25-28, Bologna) 2005, Abst.

6. Söhngen, W. et al. (PAION GmbH) *Plasminogen activators having reduced lysine binding capacity*. WO 2005026341, DE 10342518.

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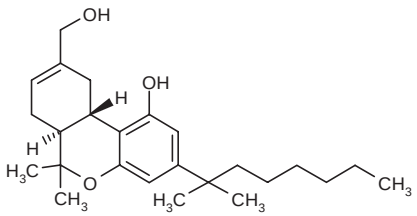
Hacke, W. et al. *The Desmoteplase In Acute Ischemic Stroke trial (DIAS). A phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase*. Stroke 2005, 36(1): 66.

Dexanabinol



Dexanabinol is a synthetic nonpsychotropic cannabinoid in phase II trials at Pharmos for the prevention of mild cognitive impairment (MCI) following coronary artery bypass graft (CABG) surgery. The drug's pharmacological activity is related to its ability to inhibit NMDA receptors and to block cyclooxygenase type 2 (COX-2), cytokines and chemokine activation, thereby acting as an antiinflammatory and neuroprotective agent. Development of the compound for traumatic brain injury (TBI) was discontinued in late 2004 based on disappointing results from a phase III study (1-3).

A multicenter, double-blind, randomized, placebo-controlled phase IIa clinical trial showed that dexanabinol may help reduce cognitive impairment after CABG surgery. A total of 202 patients aged 60 years or more who had no dementia or neurological/psychiatric symptoms at baseline received a single dose of placebo or dexanabinol (150 mg) immediately before elective CABG surgery. A series of five computerized neuropsychological tests conducted at 6 weeks and 3 months after surgery showed no significant differences between study groups. However, the results in the Stroop Color Word test, which measures selective attention and interference susceptibility, were better with dexanabinol compared to placebo, suggesting that dexanabinol may help preserve the brain's higher cognitive functions and learning mechanisms (4).

1. *Enrollment completed in phase III traumatic brain injury study of dexanabinol*. DailyDrugNews.com (Daily Essentials) March 18, 2004.

2. *Dexanabinol receives orphan drug status*. DailyDrugNews.com (Daily Essentials) Aug 17, 2004.

3. *Phase III data on the efficacy of dexanabinol in severe traumatic brain injury*. DailyDrugNews.com (Daily Essentials) Dec 29, 2004.

4. *Phase II data on the therapeutic benefits of dexanabinol in CABG-associated cognitive impairment*. DailyDrugNews.com (Daily Essentials) Nov 24, 2004.

Dextromethorphan/Quinidine Sulfate

Neurodex™ (AVP-923) is an orally administered combination of the sigma-1 receptor agonist/NMDA antagonist dextromethorphan and quinidine sulfate, a well-known, well-established antiarrhythmic agent used at low doses to inhibit the cytochrome P-450 2D6 enzyme responsible for the rapid metabolism of dextromethorphan. Neurodex™ is thought to act by binding to sigma-1 receptors, inhibiting glutamate release, and by binding to postsynaptic NMDA receptors, inhibiting glutamate-mediated responses. Avanir, which acquired rights to the product from IriSys, is currently awaiting FDA approval of the drug for the treatment of pseudobulbar affect (PBA; also known as emotional lability) associated with neurological disorders such as ALS and MS. Phase III clinical trials for the treatment of diabetic neuropathy and phase II trials for neuropathic pain are also currently under way. Avanir is currently seeking partners to outlicense Neurodex™ in Japan and Europe and the company is also exploring co-promotional opportunities in the U.S. Avanir reported positive results from its pivotal phase III trial evaluating the safety and efficacy of Neurodex™ in the treatment of PBA in patients with MS. In the double-blind study, 150 patients at 22 sites were randomized to receive either placebo or Neurodex™ on a 12-h dosing schedule for 90 days. The Center for Neurologic Study Lability Scale (CNS-LS), a validated instrument that assesses frequency and severity of PBA episodes, was utilized as the primary efficacy endpoint. A minimum CNS-LS score was required for inclusion in the study. For the primary endpoint, Neurodex™ patients had a statistically significantly greater reduction in CNS-LS than those receiving placebo. The four secondary endpoints evaluated in the trial were also statistically significant in favor of Neurodex™: number of PBA episodes, quality of life, quality of relationships and pain reduction. Neurodex™ was well tolerated. Of the side effects reported in 5% or more of the patients, a statistically significant difference between Neurodex™ and placebo was observed only for dizziness. The results of this and a phase III trial of Neurodex™ for PBA in ALS patients formed the basis of the NDA filing for the treatment of PBA. The multicenter, double-blind, controlled phase III trial in ALS patients comparing Neurodex™ to each of its two components was completed in June 2002. Data were also submitted from an open-label study evaluating the safety of long-term exposure to Neurodex™ in patients with PBA associated with a variety of neurological disorders. The company plans to submit additional safety data from the ongoing open-label clinical study, including a 120-day safety update required by FDA regulations. The open-label study is being conducted to assess the safety of

chronic exposure to Neurodex™ in patients with PBA associated with various neurological disorders, including ALS, MS, stroke, Alzheimer's disease, Parkinson's disease and traumatic brain injury (1-11).

1. *Enrollment completes in second pivotal trial for Neurodex*. DailyDrugNews.com (Daily Essentials) April 2, 2004.
2. *Treatment completed in phase III trial of Neurodex for PBA in MS patients*. DailyDrugNews.com (Daily Essentials) July 5, 2004.

3. *Positive phase III data for Neurodex for PBA in MS patients*. DailyDrugNews.com (Daily Essentials) Aug 26, 2004.

4. *Avanir Pharmaceuticals reports Q2 R&D highlights*. Avanir Pharmaceuticals Press Release 2004, May 7.

5. *Avanir commences NDA submission for Neurodex*. DailyDrugNews.com (Daily Essentials) Dec 21, 2004.

6. *Avanir completes Neurodex NDA filing*. DailyDrugNews.com (Daily Essentials) July 1, 2005.

7. *FDA decision on Neurodex NDA expected in October*. DailyDrugNews.com (Daily Essentials) Sept 5, 2005.

8. *Avanir Pharmaceuticals reports Q3 R&D highlights*. Avanir Pharmaceuticals Press Release 2005, Aug 15.

9. *Avanir Pharmaceuticals reports Q3 R&D highlights*. Avanir Pharmaceuticals Press Release 2004, Aug 13.

10. *Avanir acquires additional Neurodex rights*. DailyDrugNews.com (Daily Essentials) March 16, 2005.

11. Panitch, H. et al. *A double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of AVP-923 (dextromethorphan/quinidine) in the treatment of pseudobulbar affect in patients with multiple sclerosis*. Neurology 2005, 64(6, Suppl. 1): Abst S46.001.

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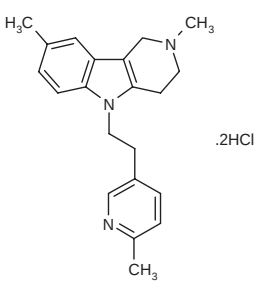
Brooks, B.R. et al. *Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine*. A randomized trial. Neurology 2004, 63(8): 1364.

Pope, L.E. et al. *Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers*. J Clin Pharmacol 2004, 44(10): 1132.

Dimebolin Hydrochloride

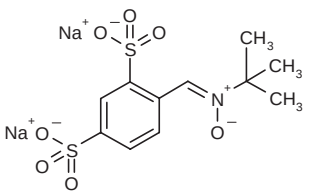


Medivation has commenced patient dosing in its phase II Alzheimer's disease (AD) study for dimebolin hydrochloride (Dimebon). This randomized, double-blind, placebo-controlled study will enroll up to 166 patients at approximately 12 sites in Russia. The study's clinical endpoints are the same as those used by the FDA to approve all of the AD drugs marketed in the U.S. Dosing is expected to be completed by the end of June 2006. Dimebolin has been approved for use in Russia as an antihistamine since 1983. More recently, it was shown to bind to cholinesterase and the NMDA receptor, two validated targets for the treatment of AD. Dimebolin also blocks a third target which has been linked to AD in published literature. Dimebolin has been shown to improve learning and memory in animal models of AD and in an open-label 14-patient pilot clinical study in AD patients. Simultaneously with the Russian phase II study, Medivation is conducting animal studies in the U.S. required to obtain FDA approval to begin U.S. clinical trials. The company expects to file an IND with the FDA for dimebolin by the end of June 2006 (1, 2).

1. *Medivation announces first patient dosed in phase II trial with Dimebon for treating Alzheimer's disease*. Medivation Press Release 2005, Sept 9.

2. *Medivation provides business update; Alzheimer's program on track; team expanded in anticipation of potential new programs*. Orion Acquisition Press Release 2005, Sept 18.

Disufenton Sodium



Disufenton sodium (NXY-059, Cerovive) is a neuroprotectant with free radical-scavenging properties in phase III clinical trials at AstraZeneca for the treatment of acute ischemic stroke. Phase II trials are also under way for the treatment of hemorrhagic stroke. Disufenton, originally discovered by the Oklahoma Medical Research Foundation and the University of Kentucky, is being developed by AstraZeneca under license from Renovis. The phase III SAINT I and II trials designed to determine the effect of disufenton on disability and neurological recovery in over 3,000 acute ischemic stroke patients are being conducted worldwide at some 400 sites in around 40 countries —Europe, Asia, Australia, New Zealand, South Africa, U.S., Canada and Latin America. The drug is also being studied in the multicenter, double-blind, randomized, placebo-controlled, parallel-group phase IIb CHANT (Cerebral Hemorrhagic And NXY-059 Treatment) study, which commenced enrollment in August 2004. CHANT, to be conducted at 140 sites in 21 countries, is assessing the safety and tolerability of 72-h i.v. infusion of disufenton in adult patients with acute intracerebral hem-

orrhage. The first data from the SAINT I study revealed that disufenton is significantly more effective than placebo in reducing disability after an acute ischemic stroke, the primary outcome, but showed no significant differences between treatments in the induction of changes in neurological impairment. The incidence of adverse events was similar in the two study groups (1-5).

1. *Cerovive phase III trials to continue*. DailyDrugNews.com (Daily Essentials) Oct 18, 2004.

2. *Enrollment completed in SAINT I study of Cerovive in stroke patients*. DailyDrugNews.com (Daily Essentials) Dec 13, 2004.

3. *NXY-059 in acute ischemic stroke: First results of the SAINT I study*. DailyDrugNews.com (Daily Essentials) May 9, 2005.

4. *Expansion of SAINT II study of Cerovive*. DailyDrugNews.com (Daily Essentials) Aug 2, 2005.

5. *AstraZeneca reports Q2 R&D highlights*. AstraZeneca Press Release 2005, July 28.

Original monograph – Drugs Fut 2002, 27(3): 240.

Additional References

Björnsson, M.A. et al. *Population pharmacokinetics of the novel neuroprotectant NXY-059: An analysis of pooled data from eight phase I studies*. 14th Eur Stroke Conf (May 25-28, Bologna) 2005, Abst.

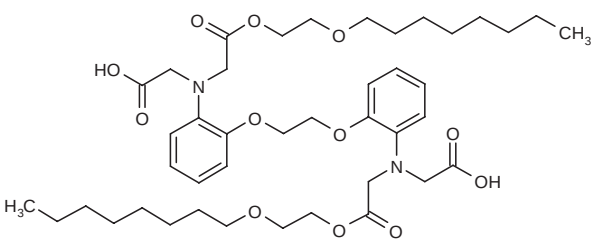
Diener, H.-C. et al. *SAINT I: A double-blind, multicentre, placebo-controlled study to assess the efficacy and safety of NXY-059 in acute ischaemic stroke*. 9th Congr Eur Fed Neurol Soc (Sept 17-20, Athens) 2005, Abst P1043.

Nilsson, D., Cheng, Y.F. *NXY-059, a novel neuroprotectant, is well tolerated in healthy volunteers: Results of a pooled analysis*. 14th Eur Stroke Conf (May 25-28, Bologna) 2005, Abst.

Reinholdsson, I. et al. *The novel neuroprotectant NXY-059 does not affect hemostasis in healthy volunteers*. 14th Eur Stroke Conf (May 25-28, Bologna) 2005, Abst.

Wang, C.X., Shuaib, A. *NXY-059: A neuroprotective agent in acute stroke*. Int J Clin Pract 2004, 58(10): 964.

DP-b99



DP-b99, designed and developed by D-Pharm using its proprietary Membrane Active Chelator (MAC) technology, is a unique neuroprotective drug that addresses the damaging processes occurring in brains of stroke patients. This includes protection against acute zinc- and calcium-mediated cell damage, as well as mitigation of neuroinflammation and edema. DP-b99 is currently undergoing early clinical evaluation at D-Pharm as first-line therapy to improve neuronal survival in traumatic brain injury (TBI; phase I) and acute stroke (phase II). The company expects to seek a partner for further development of the product following completion of phase II development.

D-Pharm has reported interim results from a confirmatory phase IIb study of DP-b99 in acute stroke. The international, multicenter, double-blind, placebo-controlled trial is designed to reconfirm the efficacy and beneficial effect of DP-b99 previously observed in stroke patients, as well as to strengthen and extend the safety data obtained from the phase IIa study. The study aims to enroll 150 acute stroke patients at sites in Europe and Israel. DP-b99 is administered intravenously over 4 days, with the first administration up to 9 h following stroke onset. The patient group is stratified into those treated within 6 and those treated within 9 h following stroke onset, so as to more clearly define the optimal therapeutic window for DP-b99. Following the recent review of safety data from the first 62 patients, the safety monitoring board recommended that the study continue. In earlier phase I and II trials, DP-b99 proved to be exceptionally safe in both healthy young and elderly volunteers and in stroke patients. Efficacy evaluation in phase IIa demonstrated noteworthy improvements in clinical stroke outcome assessed with the NIH Stroke Scale (NIHSS) 2, 7 and 30 days after stroke in drug-treated patients within a 12-h window (1, 2).

1. *Enrollment under way in confirmatory phase IIb study of DP-b99 in acute stroke*. DailyDrugNews.com (Daily Essentials) Feb 11, 2005.

2. *Phase II study of DP-b99 in acute stroke patients recommended to continue*. DailyDrugNews.com (Daily Essentials) Nov 10, 2005.

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Rosenberg, G. et al. *Clinical pharmacology of DP-b99 in healthy volunteers: First administration to humans*. Br J Clin Pharmacol 2005, 60(1): 7.

DP-VPA

D-Pharm's lead compound, DP-VPA is a unique phosphatidylcholine conjugate of valproic acid currently in phase II clinical trials for the treatment of epilepsy and in phase I clinical trials for the treatment of bipolar disorder and for the prevention of migraine. DV-VPA was designed using D-Pharm's Regulated Activation of Prodrugs (D-RAP™) technology that allows precise control of drug action at the site of pathology.

E-2007

The AMPA receptor antagonist E-2007 is being developed by Eisai for multiple indications. In the first quarter it

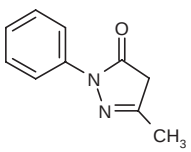
entered a phase IIb proof-of-concept study for migraine prophylaxis. It is also in a phase IIb proof-of-concept study for epilepsy, and a proof-of-concept study plan is drafted for multiple sclerosis (MS). The development of E-2007 is most advanced for adjunctive therapy with levodopa for Parkinson's disease. A briefing book has been submitted to the European Medicines Agency (EMEA) for discussion about phase III, and an end-of-phase II meeting has been scheduled with the FDA in the U.S. E-2007 is in phase I development in Japan. In Parkinson's disease, E-2007 has been shown to be similar to or better than monoamine oxidase type B (MAO-B) inhibitors and catechol *O*-methyltransferase (COMT) inhibitors in shortening the "off" time associated with the disease, and shows no worsening of dyskinesia. A regulatory filing is planned for 2006 (1-3).

1. *Eisai reports Q1 R&D highlights*. Eisai Press Release 2005, July 29.

2. *E2007 given as adjunctive therapy in patients with refractory partial seizures (NCT00144690)*. ClinicalTrials.gov Web Site 2005, Sept 29.

3. *A randomized, double-blind, placebo controlled, parallel group study to explore the safety and tolerability of doses of E2007 up to a maximum of 6 mg in patients wtih Parkinson's disease who experience end-of-dose wearing off motor fluctuations (NCT00165789)*. ClinicalTrials.gov Web Site 2005, Oct 20.

Edaravone, New Indication



An antioxidant and free radical scavenger, edaravone was launched in Japan as Radicut (injection) in 2001 by Mitsubishi Pharma for the treatment of acute cerebral infarction. It is also being evaluated in phase II trials for the treatment of amyotrophic lateral sclerosis (ALS).

Original monograph – Drugs Fut 1996, 21(10): 1014.

Additional References

Yoshino, H. *Randomized, placebo-controlled double blind study of free radical scavenger, edaravone in amyotrophic lateral sclerosis*. 15th Int Symp ALS/MND (Dec 2-4, Philadelphia) 2004, Abst C33.

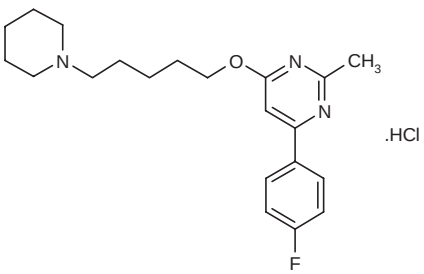
EHT-0202

EHT-0202 is a potentiator of $GABA_A$ receptor signaling and a phosphodiesterase type 4 (PDE4) inhibitor in early clinical trials at ExonHit Therapeutics as a potential new treatment for Alzheimer's disease (AD) and Parkinson's disease.

EHT-0202 has been shown to improve attention and cognition and has neuroprotective properties in animal models. Based on these findings, it is likely that EHT-0202 may prove suitable for symptom relief and as a disease-modifying agent in patients with AD. Preclinical studies with EHT-0202 have revealed protection from cell death following induction of different stresses (ischemia or toxic treatment), as well as improved learning and cognitive performance in aged rats (water-maze and Barnes' tests) and mild anxiolytic properties at higher doses (10 mg/kg). Toxicological studies have also demonstrated that EHT-0202 is well tolerated and well absorbed when given orally. A recently completed phase I single-dose study confirmed that orally administered EHT-0202 is well tolerated, with a maximum tolerated dose of 120 mg, and is well absorbed in healthy volunteers (1).

1. *EHT-0202 to enter phase IIa proof-of-concept study in Alzheimer's in 2005*. DailyDrugNews.com (Daily Essentials) Nov 24, 2004.

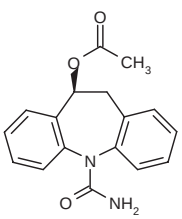
Enecadin Hydrochloride



PAION is conducting phase I clinical testing of enecadin hydrochloride, a neuroprotective Na^+/Ca^{2+} channel blocker, for the treatment of acute ischemic stroke. The compound was licensed from Nippon Shinyaku and is expected to enter phase II clinical trials this year. The company plans to develop enecadin as both monotherapy and for use in conjunction with its clot-busting stroke drug desmoteplase (see above) (1).

1. *PAION starts clinical development programme for neuroprotectant enecadin*. PAION Press Release 2005, June 15.

Eslicarbazepine Acetate



Eslicarbazepine acetate (BIA-2-093), a sodium channel blocker, is undergoing phase III clinical evaluation at

Bial for the treatment of epilepsy and phase II trials for bipolar disorder.

The potential effects of food on the pharmacokinetics of eslicarbazepine were assessed in an open-label, randomized, crossover trial involving administration of a single dose (600 mg p.o.) of the drug to 12 healthy volunteers both after a standard high-fat meal and after fasting for 10 h. Similar values were found in the fasting and fed states for mean C_{max} (11.3 and 12.8 μg/ml), AUC (243.6 and 242.5 μg.h/ml) and rate of metabolism of eslicarbazepine to BIA-2-194 and BIA-2-195 (1).

The pharmacokinetic profile of eslicarbazepine was evaluated in an open-label, nonrandomized clinical trial that included 12 elderly and 12 young healthy adult volunteers. No significant differences were found between elderly and young subjects in the C_{max} and AUC of eslicarbazepine after either a single dose of 600 mg or multiple doses of 600 mg once daily for 8 days. Eslicarbazepine was rapidly metabolized to BIA-2-194, which was the primary metabolite responsible for systemic exposure (2).

A multicenter, double-blind, randomized, placebo-controlled trial determined the potential of eslicarbazepine as add-on therapy for refractory partial epilepsy. A total of 143 adult patients treated with antiepileptic drugs and showing at least 4 partial-onset seizures per month were randomized to receive placebo or eslicarbazepine (400 mg/day, increased to 1200 mg/day) given once or twice daily for 12 weeks. Daily doses of 800 and 1200 mg of eslicarbazepine were significantly more effective than placebo in reducing the frequency of seizures. Most adverse events were mild and the most common were headache, dizziness and nausea (3).

1. Vaz-da-Silva, M., Almeida, I., Falcao, A., Maia, J., Silveira, P., Soares-da-Silva, P. *Influence of food on the pharmacokinetics of the antiepileptic agent BIA 2-093*. Epilepsia 2004, 45(Suppl. 3): Abst p408.

2. Silveira, P., Falcao, A., Almeida, L., Maia, J., Soares-da-Silva, P. *BIA 2-093 pharmacokinetics in healthy elderly subjects*. Epilepsia 2004, 45(Suppl. 3): Abst p409.

3. Maia, J., Almeida, L., Soares-da-Silva, P. *BIA 2-093 as add-on therapy for refractory partial epilepsy in adults*. Epilepsia 2004, 45(Suppl. 3): Abst p410.

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Almeida, L. et al. *Effect of gender on the pharmacokinetics of eslicarbazepine acetate (BIA 2-093), a new voltage-gated calcium channel inhibitor*. Epilepsia 2005, 46(Suppl. 6): Abst p875.

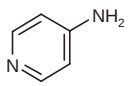
Almeida, L. et al. *Single-dose and steady-state pharmacokinetics of eslicarbazepine acetate (BIA 2-093) in healthy elderly and young subjects*. J Clin Pharmacol 2005, 45(9): 1062.

Almeida, L., Soares-da-Silva, P. *Safety, tolerability, and pharmacokinetic profile of BIA 2-093, a novel putative antiepileptic, in a rising multiple-dose study in young healthy humans*. J Clin Pharmacol 2004, 44(8): 906.

Maia, J. et al. *Effect of eslicarbazepine acetate (BIA 2-093) on the steady-state pharmacokinetics of digoxin in healthy subjects*. Epilepsia 2005, 46(Suppl. 6): Abst p876.

Nunes, T. et al. *Eslicarbazepine acetate (BIA 2-093): Relative bioavailability and bioequivalence of 50 mg/ml oral suspension and 200 mg and 800 mg tablet formulations*. Epilepsia 2005, 46(Suppl. 6): Abst p262.

Fampridine



Acorda Therapeutics is developing the selective neuronal potassium channel blocker fampridine (4-aminopyridine) as a sustained-release oral formulation designed for twice-daily administration for the treatment of spinal cord injury (SCI) and multiple sclerosis (MS), with phase III trials under way for both indications. Fampridine has been shown to restore nerve conduction by blocking the exposed potassium channels in damaged nerve fibers that have lost their insulating sheath of myelin. The product holds orphan drug designation for MS from the FDA.

Acorda reported results from trials of sustained-release fampridine, including a phase II trial in MS and two phase III trials in chronic SCI. The MS trial, which included a total of 195 patients who received doses of 10, 15 or 20 mg b.i.d. or placebo during a 2-week dose-titration phase, followed by a 12-week stable treatment period and a 1-week down-titration period, showed a strong positive trend compared to placebo in its primary endpoint: improvement in walking speed as measured by a timed 25-foot walk. There was also statistically significant improvement across dose groups in the secondary endpoint, the Lower Extremity Manual Muscle Test (LEMMT). The data are consistent with those from earlier trials in fewer subjects with shorter treatment periods. Analysis of the other secondary endpoints in the trial is ongoing. The two SCI trials did not reach statistical significance in their primary endpoints: reduction of spasticity as measured by the Ashworth score and improvement of patients' Subject Global Impression (SGI) rating. One of the SCI studies showed a positive trend toward improvement on the Ashworth score when analyzed across all observations during the double-blind study drug period, the study's prespecified plan of analysis. When analyzed based on the subjects' last observation carried forward (LOCF), the Ashworth score in that study was statistically significant. The drug groups in both studies showed a progressive mean improvement on the Ashworth score during the double-blind period, although the placebo group in one of the studies showed a more pronounced reduction than expected.The company subsequently initiated a pivotal phase III trial of fampridine in MS. The study, which is based on a special protocol assessment (SPA), will evaluate the safety and efficacy of sustained-release fampridine in improving walking ability in people with MS. The primary outcome measure will be an improvement in walking ability, while secondary outcomes will include

measurements of leg strength and muscle spasticity. The studies will enroll a total of 240 patients at approximately 30 MS centers in the U.S. and Canada (1-4).

Evaluation of data from 13 MS patients treated with fampridine showed that the number of relapses declined during treatment (mean = 1.2) compared to an equal length of time before treatment (mean = 2.9) in 9 patients (5).

1. *Mixed initial results for Fampridine-SR in MS and spinal cord injury*. DailyDrugNews.com (Daily Essentials) April 16, 2004.

2. *Acorda reaches SPA agreement on Fampridine-SR phase III study in MS*. DailyDrugNews.com (Daily Essentials) May 9, 2005.

3. *Fampridine-SR enters phase III MS study*. DailyDrugNews.com (Daily Essentials) July 4, 2005.

4. Goodman, A.D., Cohen, J., Vollmer, T., Johnson, M., Cohen, R., Katz, M., Blight, A. *Phase 2 trial of fampridine-SR in multiple sclerosis*. Multiple Scler 2004, 10(Suppl. 2): Abst P694.

5. Stefoski, D., Katsamakis, G., Ko, M. *Decreased relapses of multiple sclerosis in patients on 4-aminopyridine*. Multiple Scler 2004, 10(Suppl. 2): Abst P693.

Original monograph – Drugs Fut 1980, 5(5): 221.

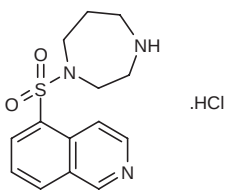
Additional References

DeForge, D. et al. *Effect of 4-aminopyridine on gait in ambulatory spinal cord injuries: A double-blind, placebo-controlled, crossover trial*. Spinal Cord 2004, 42(12): 674.

Frohman, E. et al. *A prospective, randomised, double-blind, placebo-controlled dose escalation crossover trial of sustained release fampridine (4-AP) in MS patients with internuclear ophthalmoparesis*. 21st Congr Eur Comm Treat Res Multiple Scler (Sept 28-Oct 1, Thessaloniki) 2005, Abst P 378.

Hayes, K.C., Potter, P.J., Hsieh, J.T., Katz, M.A., Blight, A.R., Cohen, R. *Pharmacokinetics and safety of multiple oral doses of sustained-release 4-aminopyridine (Fampridine-SR) in subjects with chronic, incomplete spinal cord injury*. Arch Phys Med Rehabil 2004, 85(1): 29.

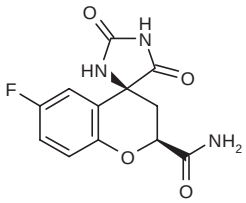
Fasudil Hydrochloride, New Indication



Fasudil hydrochloride (AT-877) is a rho kinase inhibitor that was launched in Japan as Eril™ over 10 years ago by Asahi Kasei for the treatment of vasospasm following surgery for subarachnoid hemorrhage. Asahi Kasei is awaiting marketing approval in Japan for an injectable formulation of fasudil for the treatment of acute cerebral thrombosis and is conducting phase II clinical studies with an oral fasudil formulation for the treatment of stable angina pectoris with its European partner Schering AG.

Original monograph – Drugs Fut 1989, 14(12): 1159.

Fidarestat



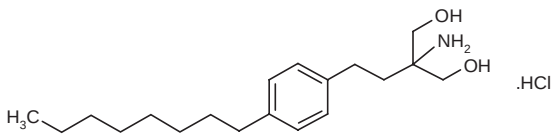
Phase III studies are in preparation for fidarestat (SNK-860), an aldose reductase inhibitor, for the treatment of peripheral diabetic neuropathy. The compound is being developed by Daiichi Sankyo and Sanwa Kagaku.

Original monograph – Drugs Fut 1996, 21(3): 261.

Additional References

Hotta, N. et al. *Effects of a novel aldose reductase inhibitor, fidarestat (SNK-860), on vibration perception threshold and subjective symptoms in patients with diabetic polyneuropathy - An open-label pilot study*. Clin Drug Invest 2004, 24(11): 671.

Fingolimod Hydrochloride



An oral immunomodulator with a novel mechanism of action, fingolimod hydrochloride (FTY-720) is currently undergoing phase III clinical trials at Novartis for the prevention of acute renal rejection in combination with ciclosporin (Neoral) or tacrolimus. The compound is also being evaluated in phase II trials for the treatment of multiple sclerosis (MS). A lysophospholipid edg1 (S1P1) receptor agonist, fingolimod appears to work by preventing lymphocytes from moving into the transplanted or other affected tissues. The compound has also exhibited apoptosis-inducing activity. Novartis acquired exclusive worldwide rights to fingolimod, with the exception of Japan, where it is co-developed by Mitsubishi Pharma and is in phase II evaluation for renal transplantation. Fingolimod demonstrated excellent efficacy and good tolerability in MS patients in a phase II study. Six-month data from the study showed a significant reduction in the relapse rate (> 50%) and in the number of brain lesions detected by MRI scan (up to 80%), as well as a longer time to first relapse. The multicenter, double-blind, ran-

domized phase II study was performed in a total of 281 patients who were treated with placebo or fingolimod (1.25 or 5 mg/day) for 6 months. The mean number of gadolinium-enhancing lesions was 14.8, 8.4 and 5.7 in the placebo, fingolimod 1.25-mg and fingolimod 5-mg treatment groups, respectively. Fingolimod also significantly reduced the number of new T2 lesions compared to placebo. The percentage of relapse-free patients at 6 months was 70%, 86% and 86% in the placebo, fingolimod 1.25-mg and fingolimod 5-mg groups, respectively, and the time to the first relapse was significantly prolonged in fingolimod-treated patients. The study was completed by 91% of patients and 89% were enrolled in an extension study in which placebo-treated patients were switched to fingolimod. While efficacy did not differ between fingolimod dose groups, more adverse events were seen in the higher dose group. Phase III studies are expected to start by the end of this year, with regulatory filings anticipated no earlier than 2008 (1-9).

1. *Novartis: Pipeline review*. DailyDrugNews.com (Daily Essentials) Jan 24, 2005.

2. *Novartis reports Q3 highlights*. Novartis Press Release 2005, Oct 18.

3. *Novartis reports phase III data and update of R&D pipeline*. DailyDrugNews.com (Daily Essentials) Sept 22, 2005.

4. *Novartis reports Q2 R&D highlights*. Novartis Press Release 2005, July 14.

5. *Novartis reflects on Q2 activities*. DailyDrugNews.com (Daily Essentials) Aug 9, 2005.

6. *FDA requests safety analysis for FTY-720*. DailyDrugNews.com (Daily Essentials) July 12, 2005.

7. *Novartis reports Q1 R&D highlights*. Novartis Press Release 2005, April 21.

8. *Novartis highlights pharmaceutical research strategy*. DailyDrugNews.com (Daily Essentials) May 6, 2005.

9. Kappos, L. et al. *FTY720 in relapsing MS: Results of a double-blind placebo-controlled trial with a novel oral immunomodulator*. J Neurol 2005, 252(Suppl. 2): Abst O141.

Original monograph – Drugs Fut 1997, 22(1): 18.

Additional References

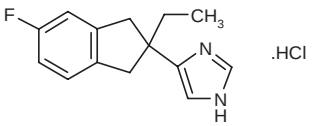
Kappos, L., Radue, E.W., Antel, J. et al. *FTY720: A novel immunomodulator under clinical investigation in multiple sclerosis*. J Neurol 2004, 251(Suppl. 3): Abst P703.

Kappos, L. et al. *Promising results with a novel oral immunomodulator - FTY720 - in relapsing multiple sclerosis*. 21st Congr Eur Comm Treat Res Multiple Scler (Sept 28-Oct 1, Thessaloniki) 2005, Abst 64.

Kovarik, J. et al. *FTY720 exposure/efficacy relationship in a 6-month phase 2 study in patients with relapsing MS*. 21st Congr Eur Comm Treat Res Multiple Scler (Sept 28-Oct 1, Thessaloniki) 2005, Abst P 578.

O'Connor, P. et al. *Phase II study with oral FTY720 in relapsing MS: Results of the dose-blinded active drug extension phase at 12 months*. 21st Congr Eur Comm Treat Res Multiple Scler (Sept 28-Oct 1, Thessaloniki) 2005, Abst 682.

Fipamezole Hydrochloride

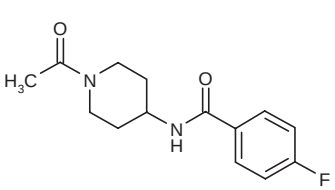


Results from a phase IIa study of Juvantia's lead product candidate fipamezole hydrochloride (JP-1730) demonstrated that it reduced levodopa-induced dyskinesias and prolonged levodopa's duration of action in advanced Parkinson's disease patients, providing proof of concept for fipamezole. The proof-of-concept study, conducted at the NIH, was designed to assess the safety and efficacy of fipamezole in suppressing dyskinesia and improving motor fluctuations in advanced Parkinson's disease patients. The double-blind, randomized, placebo-controlled study used an intravenous infusion model developed by the principal investigator. Sixteen participants who had an average of 17 years' symptom duration and an H&Y score of 2.9 received up to 90 mg of fipamezole as single doses. Preliminary analysis suggested that fipamezole (60 and 90 mg by acute oromucosal delivery) extends the duration of antiparkinsonian action of levodopa and reduces the intensity of dyskinesias. These findings are consistent with preclinical data in the MPTP-lesioned monkey and 6-OHDA-lesioned rat, where α_2-adrenoceptor antagonists show prolongation of the duration of levodopa response and a concomitant reduction in dyskinesia severity. Fipamezole did not appear to be associated with adverse events on the cardiovascular system. Common adverse events were pallor, nausea, sweating and dizziness. Fipamezole has a unique pharmacological profile, acting on α_2-adrenoceptors. Over 100 people have been exposed to fipamezole in a clinical development program conducted by Juvantia (1). The FDA granted fast track designation several years ago.

1. *Proof-of-concept for fipamezole in Parkinson's patients*. DailyDrugNews.com (Daily Essentials) July 5, 2004.

Original monograph – Drugs Fut 2003, 28(1): 14.

FK-962



FK-962 is currently undergoing phase II clinical trials at Astellas Pharma for the oral treatment of Alzheimer's-

type dementia. The compound appears to act by triggering the release of somatostatin in brain regions involved in learning and memory.

FP-0011

Faust Pharmaceuticals' FP-0011, already marketed for a non-CNS indication, is an antiglutamatergic compound in phase IIa clinical development for the treatment of amyotrophic lateral sclerosis (ALS), Parkinson's disease and migraine. The drug candidate works through presynaptic regulation of glutamate and shows strong neuroprotective activities. In animal models, FP-0011 has succeeded in reducing central glutamate levels after systemic administration.

FP-0023

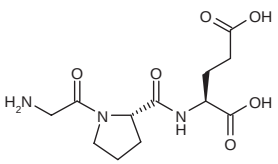
Another Faust compound, FP-0023, is in phase I trials as a potential new treatment for Duchenne muscular dystrophy.

Fx-1006A

Fx-1006A recently entered early clinical trials at FoldRx for the treatment of familial amyloid cardiomyopathy (FAC) and familial amyloid polyneuropathy (FAP). The drug is a first-in-class disease-modifying compound that is designed to inhibit the formation of amyloid deposits by preventing the misfolding and deposition of the transthyretin protein (TTR), a 127-amino-acid, 55-kDa protein primarily synthesized in the liver and secreted into the blood and cerebrospinal fluid and which acts as a carrier of thyroxin and retinol (vitamin A) binding protein. In FAP, deposition of TTR amyloid occurs in the peripheral nerve tissue and results in sensory neuropathy starting in the lower extremities. Liver transplantation is currently the only treatment available for these patients. This phase I trial will be a double-blind, placebo-controlled study of single and multiple escalating doses, enrolling approximately 55 healthy volunteers. The study will seek to evaluate the safety and tolerability of Fx-1006A and also to determine the compound's pharmacological properties and TTR-stabilizing activity (1).

1. *Phase I study for Fx-1006A to stabilize protein misfolding in hereditary amyloid disorders*. DailyDrugNews.com (Daily Essentials) Oct 17, 2005.

Glypromate®



Neuren Pharmaceuticals has initiated a phase II pharmacokinetic and safety study of its lead drug Glypromate®. The study is enrolling 30 patients at 4 sites in New Zealand and 1 site in Australia and is expected to be completed at the end of 2005. Neuren intends to file an IND with the FDA to begin a phase III study in mid-2006. The phase III study will assess the efficacy of the compound in protecting from neurocognitive disturbance following coronary artery bypass graft surgery (CABG). Glypromate® is a naturally occurring peptide fragment derived from insulin-like growth factor I (IGF-I) and found in normal brain tissue. When injected intravenously, Glypromate® has been shown to act by multiple pathways to protect brain tissue from injury (1).

The intravenous administration of an infusion comprising the neuromodulatory *N*-terminal peptide of IGF-I, namely Glypromate®, has been claimed for conferring neuroprotection in the treatment of disorders of the nervous system, including senile dementia, epilepsy, depression and schizophrenia. Direct administration via this route was found to provide rapid protection against neurodegeneration that may be sustained over an extended period of time (*e.g.*, 30 days), despite the peptide's very brief half-life. The claim further pertains to the co-administration of a peptidase/protease inhibitor that further extends the therapeutic activity by retarding its breakdown (2).

1. *Neuren initiates phase 2 trial*. Neuren Pharmaceuticals Press Release 2005, Aug 30.

2. Guan, J. et al. (Neuren Pharmaceuticals Ltd.) *Neuroprotective effects of Gly-Pro-Glu following intravenous infusion*. WO 2005042000.

GPI-1485

The neuroimmunophilin ligand (NIL) GPI-1485 is in phase II clinical trials at MGI Pharma, which acquired the drug upon its acquisition of Guilford Pharmaceuticals, and Symphony Neuro Development Company for the treatment of Parkinson's disease and postprostatectomy erectile dysfunction (PPED). The product is also being evaluated preclinically for HIV-related neuropathy and dementia. Neuroimmunophilin compounds are orally active small molecules that are able to cross the blood-brain barrier and cause regrowth of damaged nerve cells (1-4).

1. *Guilford Pharmaceuticals reports 2003 year-end R&D highlights*. Guilford Pharmaceuticals Press Release 2004, Feb 17.

2. *Guilford licenses U.S. rights to GPI-1485 to Symphony Neuro Development Company*. DailyDrugNews.com (Daily Essentials) June 22, 2004.

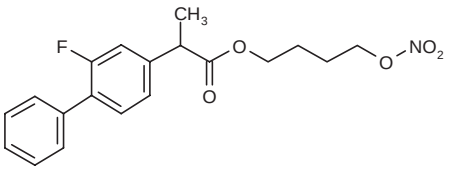
3. *2 Year study to evaluate the effects of GPI 1485 on [123I]b-CIT/SPECT scanning and clinical efficacy in patients with PD (NCT00209508)*. ClinicalTrials.gov Web Site 2005, Sept 20.

4. *NINDS Parkinson's disease neuroprotection trial of CoQ10 and GPI 1485 (NCT00076492)*. ClinicalTrials.gov Web Site 2005, Aug.

Additional References

A 2-year randomized, placebo controlled trial of the neuroimmunophilin ligand, GPI 1485 on dopamine transporter density and Parkinson's disease progression: Design and patient baseline characteristics. Mov Disord 2004, 19(Suppl. 9): Abst P492.

HCT-1026



HCT-1026, a nitric oxide (NO)-donating derivative of the nonsteroidal antiinflammatory drug flurbiprofen, is undergoing phase I clinical evaluation at NicOx for the treatment of Alzheimer's disease (AD). HCT-1026 was found to significantly reduce β-amyloid deposition in the brain in a mouse model of AD, without side effects. Early human studies demonstrated penetration of the blood-brain barrier and effective cerebrospinal fluid concentrations of the drug after repeated oral dosing.

Original monograph – Drugs Fut 1999, 24(8): 858.

HF-0220

A cytoprotective steroid, HF-0220 is a highly potent neuroprotective/cytoprotective agent in early clinical development at Hunter-Fleming for the treatment of acute and chronic neurodegenerative disorders, specifically Alzheimer's-type dementia and stroke. The company believes that the compound also holds potential for the treatment of other indications, including traumatic brain injury, spinal cord injury and coronary heart disease (myocardial infarction). Although specific pathways have yet to be determined, HF-0220 activates endogenous 7-hydroxysteroid-driven cytoprotection. The compound may be administered orally or intravenously, depending on the indication. A multiple-dose phase I study has been completed.

HF-0420

HF-0420 (heparin-derived oligosaccharide-C3, subeparin, Oligotropin) is a very-low-molecular-weight glycosaminoglycan (GAG) derived from heparin in phase I/II clinical trials at Hunter-Fleming for the oral treatment of Alzheimer's-type dementia. The formulation currently being investigated incorporates Access Pharmaceuticals' vitamin B_{12} oral drug delivery technology, which takes advantage of the body's natural transport system for vitamin B_{12}. By attaching vitamin B_{12} to HF-0420, the drug is actively transported from the gut to the bloodstream. HF-0420's size, sulfation pattern and charge suggest, and tests confirmed, that it passes through the blood-brain barrier when administered i.v., s.c. or p.o. The compound has been shown to protect neurons in three different *in vitro* and *in vivo* models of cell death, independent of the type of insult. Complementary to this general neuroprotective effect, HF-0420 has a neurotrophic action, increasing dendritic branching and the numbers of spines on the dendrites of cells in the CA1 layer of the hippocampus. This may allow those cells that survive to enhance their neuronal communications and take over the activities lost when other cells die in various neurodegenerative conditions. Originally codeveloped by Corcon (Cornelli Consulting) and the Loyola University Medical Center, where it was also studied for the treatment of vascular dementia, the product was subsequently licensed to Hunter-Fleming (1).

1. *Access and Hunter-Fleming form oral drug delivery collaboration*. DailyDrugNews.com (Daily Essentials) May 17, 2005.

HPI-001

HPI-001 (formerly HL-0812) is being prepared to enter phase IIb clinical trials at Hamilton Pharmaceuticals for the treatment of neuropsychiatric complications in post-stroke patients. Previous clinical studies of the drug have shown it to be well tolerated and indicate substantial potential for efficacy (1).

1. *Phase IIb study of Hamilton's HL-0812 supported by Series A financing*. DailyDrugNews.com (Daily Essentials) April 27, 2005.

Human Fetal Neural Stem Cells

StemCells' human neural stem cells (HuCNS-SC) are a somatic cell therapy product being developed initially for the treatment of two forms of Batten disease: infantile (CLN1) and late-infantile (CLN2) neuronal ceroid lipofuscinosis (NCL). The therapy consists of neural cells prepared under controlled conditions. Neural stem cells, a rare subset of brain cells, are isolated from the human fetal brain, purified, propagated and tested. A property of HuCNS-SC is that they spread throughout the brain and produce both of the lysosomal enzymes (palmitoyl-protein thioesterase 1, or PPT1, and tripeptidyl peptidase I, or TPP-I) missing in the two subtypes of Batten disease being studied. The company just recently received FDA clearance to begin a phase I clinical trial of HuCNS-SC. Human fetal neural stem cells may also have potential in disorders of myelination, stroke, spinal cord injury, Alzheimer's disease and Parkinson's disease, among other CNS disorders. This represents the first-ever FDA-approved clinical trial to use a purified composition of human neural stem cells as a potential therapeutic agent in humans. The trial will evaluate the safety and prelimi-

nary efficacy of HuCNS-SC for the treatment of infantile and late-infantile NCL. The safety of HuCNS-SC will be measured, and initial data will be gathered on their ability to affect the progression of the disease. Potential patients will be tested for eligibility and then evaluated for baseline disease status prior to transplantation of HuCNS-SC. Children enrolled in the study will be evaluated with standardized measures of development, cognition, behavior and language for 1 year following HuCNS-SC transplantation. The company intends to follow the long-term effects of the therapy, so patients will be asked to commit to a 4-year follow-up study. The company plans to seek Institutional Review Board (IRB) approval from a number of leading medical institutions, including the Stanford University School of Medicine (1-4).

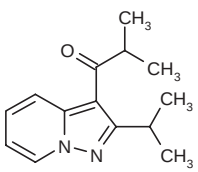
1. *StemCells files IND for human neural stem cell transplant for Batten disease*. DailyDrugNews.com (Daily Essentials) Jan 10, 2005.

2. *StemCells works to lift clinical hold on proposed phase I study of HuCNS-SC*. DailyDrugNews.com (Daily Essentials) April 5, 2005.

3. *StemCells files IND amendment to begin stem cell therapy in Batten disease*. DailyDrugNews.com (Daily Essentials) Sept 21, 2005.

4. *FDA clears phase I study of neural stem cells to treat Batten disease*. DailyDrugNews.com (Daily Essentials) Oct 25, 2005.

Ibudilast, New Indication



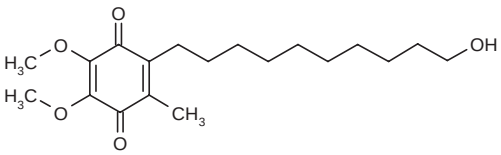
MediciNova is enrolling patients in a phase II study with MN-166 (ibudilast) for the treatment of multiple sclerosis (MS). The study is being conducted in 9 countries in Eastern Europe and will compare two oral doses of MN-166 to placebo in 300 patients with relapsing-remitting MS. It will measure reduction in MS lesions in the brain as detected by MRI, reductions in annualized relapse rates and functional status as determined by the EDSS. MN-166 is an orally administered drug with a novel mechanism of action that includes the inhibition of phosphodiesterase type 4 (PDE4). In small, open-label studies in patients with relapsing-remitting MS, MN-166 produced encouraging results. Under a licensing agreement with Kyorin, MediciNova obtained exclusive worldwide rights, except for Japan, China, Taiwan and South Korea, to develop and commercialize MN-166 for MS. For the past 16 years, MN-166 has been marketed in Japan as Ketas®, for the treatment of asthma and cerebrovascular disorders. Ibudilast was also launched in Korea in September 2002 (1, 2).

1. *Outline of products under development by MediciNova*. DailyDrugNews.com (Daily Essentials) April 5, 2005.

2. *MN-166 enters phase II study for relapsing-remitting MS*. DailyDrugNews.com (Daily Essentials) Aug 4, 2005.

Original monograph – Drugs Fut 1984, 9(2): 113.

Idebenone, New Indication



Santhera and Takeda plan to collaborate to develop and commercialize idebenone (SNT-MC17), a small-molecule drug for the treatment of Friedreich's ataxia. Idebenone for Friedreich's ataxia is about to enter a phase III study in Europe and will enter a phase III study in the U.S. shortly thereafter. The product has orphan drug designation in the U.S. and Europe for this indication. Under the collaboration, Santhera will conduct all clinical development for regulatory approval in Europe and in the U.S. Takeda will support the development work and will obtain an exclusive license to market idebenone in the E.U. and Switzerland. In the U.S., Santhera plans to market idebenone on its own. Idebenone, a small-molecule oral therapy introduced almost 20 years ago by Takeda for the treatment of Alzheimer's-type dementia, has been shown to improve mitochondrial function and/or reduce oxidative stress in muscle cells, heart cells and neurons. By protecting heart muscle cells from the oxidative stress that is mainly responsible for the deterioration of the heart muscle in Friedreich's ataxia, idebenone could offer the first therapeutic option to prolong the lives of patients. Santhera is also collaborating with the National Institute of Neurological Disorders and Stroke (NINDS) of the NIH in the U.S. on a recently initiated phase II trial in patients with Freidreich's ataxia. Santhera has also initiated a phase IIa study to evaluate idebenone in the treatment of Duchenne muscular dystrophy (DMD). The double-blind, randomized, placebo-controlled trial aims to assess the efficacy of idebenone in 10-16-year-old males with cardiac dysfunction associated with DMD. The primary endpoint is to evaluate cardiac function improvement in DMD patients after 1 year of treatment. The effect of idebenone on muscle strength in the limbs and respiratory muscles will also be assessed as secondary endpoints. This study will enroll a total of 21 patients at the University of Leuven in Belgium. Cardiac function is expected to be improved in these patients by using idebenone to protect muscle cells from oxidative stress (1-4).

1. *SNT-MC17 begins phase IIa study for Duchenne muscular dystrophy*. DailyDrugNews.com (Daily Essentials) Oct 31, 2005.

2. *Santhera and Takeda to collaborate on idebenone for Friedreich's ataxia*. DailyDrugNews.com (Daily Essentials) Aug 9, 2005.

3. *Takeda offers six-month development update*. DailyDrugNews.com (Daily Essentials) Nov 25, 2005.

4. *Santhera and the NIH collaborate to evaluate SNT-MC17 in Friedreich's ataxia*. Santhera Pharmaceuticals Press Release 2005, Nov 3.

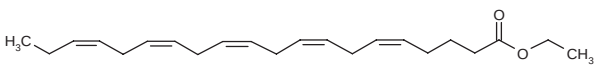
Original monograph – Drugs Fut 1983, 8(7): 583.

ICA-69673

ICA-69673 had been under development at ICAgen for the treatment of epilepsy and neuropathic pain. Results from preclinical studies indicated that the drug targets a novel ion channel involved in neuroexcitability, with mutations in the channel having been linked to a rare form of neonatal convulsions. However, results from a multiple-dose safety, tolerability and pharmacokinetic study of ICA-69673 did not support continued clinical development and ICAgen decided to discontinue development of the drug for all indications. The company is currently performing preclinical studies on other lead compounds in order to select a backup compound (1).

1. *Icagen reports fourth quarter and full year 2004 financial results and reports results of a phase Ib clinical trial of ICA69673*. ICAgen Press Release 2005, March 30.

Icosapent Ethyl Ester



The semisynthetic highly purified derivative of the n-3 fatty acid eicosapentaenoate (EPA) icosapent ethyl ester was launched by Mochida over 15 years ago for the treatment of atherosclerosis obliterans and dyslipidemia. The drug is now in phase II and III development at Amarin (Miraxion™, formerly LAX-101) for the treatment of depression and Huntington's disease (HD), respectively. Mochida is also evaluating icosapent ethyl ester (MND-21) in phase II for the treatment of Alzheimer's-type dementia. The mechanism of action of icosapent ethyl ester is believed to involve stabilization of cell membranes and of mitochondrial integrity of suffering neurons, thereby preventing or slowing progression from neuronal dysfunction to apoptosis. Fast track status has been granted in the U.S. and orphan drug designation was granted in both the U.S. and the E.U. for HD. Amarin recently signed a definitive agreement to acquire Laxdale, from which it had previously licensed the U.S. rights to icosapent ethyl ester for HD in November 2000. The acquisition will give Amarin E.U. and Japanese rights to icosapent ethyl ester for HD, plus existing licensee relationships for the major European markets and Japan, plus North American, E.U. and Japanese rights to icosapent ethyl ester in all other CNS disorders, including treatment-unresponsive depression. The initial phase III trial in 135 HD patients did not achieve statistical significance in the intent-to-treat group of patients, primarily due to a high number of patients who did not comply with the protocol. However, in those patients who complied with the protocol, a trend for statistical significance was observed. Recent additional analysis of the clinical data from the initial study also identified a subset of patients with a specific gene variant who responded to icosapent ethyl ester with statistical significance at 6 and 12 months (see below). Amarin plans to seek a partner for development of icosapent ethyl ester for treatment-unresponsive depression. Two phase II trials demonstrated with statistical significance that a dose of 1 g/day icosapent ethyl ester was effective in treating depression in patients who remained depressed despite receiving standard therapy. Amarin plans to directly commercialize its neurology products in the U.S. and outlicense or partner its rights in Europe and Japan (1).

Amarin reported results of gene variant data analysis from the initial phase III trial of icosapent ethyl ester in HD. The analysis identified a group of patients with a specific gene variant who experienced a significant response to the drug. As HD is believed to be caused by a genetic mutation of the cytosine, adenosine and guanine (CAG) polymorphic trinucleotide repeat, the possibility that treatment efficacy could be related to the number of CAG repeats was proposed as part of the prespecified analysis. Exploratory analysis was conducted after completion of the trial to examine this influence. A strong correlation between the CAG repeat number and the change in Total Motor Score-4 (TMS-4) score was detected in those patients taking icosapent ethyl ester. Patients were split into two groups based on the median number of CAG repeats, which was identified as 45. Those patients who took icosapent ethyl ester and had a CAG repeat length of less than 45 comprised the responsive group. This effect was consistent across all centers. In total, 67 of the 135 patients in the initial phase III study had this specific gene variant. The group of patients with a CAG repeat length of less than 45 in the intent-to-treat group receiving icosapent ethyl ester showed a statistically significant improvement over those patients receiving placebo. The group of patients with a CAG repeat length of less than 45 who observed the clinical trial protocol receiving icosapent ethyl ester showed a 22.7% improvement in TMS-4 score *versus* patients receiving placebo, who showed a 5.7% deterioration at the end of the 12-month study. This improvement was observed over a 6-month period and maintained for a further 6 months. In the 12-month, open-label continuation phase of the trial, this improvement continued to be maintained. At the end of the open-label phase, all patients who had taken part in the trial were offered compassionate supply. More than 3 years after the commencement of this trial, 101 of the 135 patients enrolled in the trial continue to be treated with icosapent

ethyl ester. The initial 12-month, multicenter, double-blind, randomized, placebo-controlled phase III study of icosapent ethyl ester, conducted in 2002 by Laxdale, enrolled 135 patients with HD at 6 centers in the U.S., Canada, the U.K. and Australia. The primary endpoint in the initial trial was the change over a 1-year period in the TMS-4 subscale of the Unified Huntington's Disease Rating Scale (UHDRS) (2).

The not-for-profit Huntington Study Group (HSG) has commenced dosing in the U.S. phase III trial of Amarin's icosapent ethyl ester in HD. The HSG is conducting the TREND-I study to evaluate the treatment in patients aged 35 years or older who have mild to moderate HD. The 12-month study includes a 6-month double-blind, placebo-controlled phase with research subjects being randomized to receive either icosapent ethyl ester (2 g total daily dose) or a matching placebo. This will be followed by another 6-month observation phase in which all participants will receive icosapent ethyl ester. Researchers at 43 sites in the U.S. and Canada will each enroll approximately 7-8 research subjects with early signs of HD who are independently ambulatory and fully self-sufficient in activities of daily living, such as eating, dressing and bathing. The trial aims to determine the effect of this daily dose of icosapent ethyl ester on motor signs and symptoms of HD. An earlier trial in subjects with HD indicated that icosapent ethyl ester at 2 g daily was well tolerated over 12 months. A European phase III trial (TREND-II) will be conducted at up to 28 sites in collaboration with EURO-HD and Icon, a leading global contract research organization. Both trials are expected to include up to 540 HD patients (3-6).

1. *Amarin to acquire Laxdale*. DailyDrugNews.com (Daily Essentials) July 15, 2004.

2. *Gene variant data analysis results for Miraxion in Huntington's disease*. DailyDrugNews.com (Daily Essentials) Aug 26, 2004.

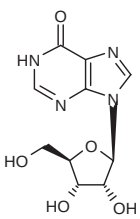
3. *Miraxion enters phase III trial for Huntington's disease*. DailyDrugNews.com (Daily Essentials) June 16, 2005.

4. *Amarin reports Q2 R&D highlights*. Amarin Press Release 2005, July 27.

5. *Amarin reaches SPA agreement for phase III trials of Miraxion*. DailyDrugNews.com (Daily Essentials) Sept 15, 2005.

6. *U.S. phase III study begins for Miraxion in Huntington's disease*. DailyDrugNews.com (Daily Essentials) Sept 28, 2005.

Inosine



Boston Life Sciences has filed an IND application with the FDA for the use of inosine (Axosine™) to enhance motor function recovery after stroke, which was subsequently put on hold by the agency pending the submission of additional pharmacology/toxicology data. The IND includes a proposed phase I study to test the safety of inosine administered to stroke patients for 28 days by continuous infusion into the cerebral ventricle (i.c.v.). The proposed study is designed to enroll 27 moderate to severe stroke patients at up to 3 academic stroke centers in the greater Boston area. The study design calls for dose escalation of inosine given to three groups of stroke patients, with the highest dose being the estimated human equivalent of the effective dose given to rats. All patients will be maintained on their initial dose of inosine for the full 28-day study period. Inosine will be administered via an implantable s.c. pump and i.c.v. catheter system that potentially allows the patient to leave the hospital at the same approximate time that they otherwise would have after such a stroke. In addition to safety monitoring, efficacy monitoring will also be performed, but the small number of patients and the short duration of treatment will probably preclude statistically valid efficacy conclusions to be drawn. Formal efficacy testing will be conducted in a phase II study. Preclinical animal testing has shown that inosine administered i.c.v. is safe, well tolerated and highly effective in promoting motor function recovery after experimentally induced strokes in rats. Studies have also demonstrated compensatory axon growth in experimental spinal cord injury. Boston Life Sciences believes that inosine is the first in a class of small-molecule (nonpeptide) axonal growth factors to enter commercial clinical development for this indication. Inosine is not a neuroprotective agent, nor is it a thrombolytic agent, and thus it does not need to be given within hours after symptoms of stroke occur. Inosine does not work by limiting or reversing the brain damage caused by the interruption of arterial blood flow that results in stroke, but instead promotes motor function recovery through the formation of new axonal branches and connections in the brain and spinal cord after the stroke is complete. This means that inosine has an extended treatment window. Rats can begin inosine treatment up to 24 h after the completed stroke and still recover motor function. If studies in treating stroke are successful, the company plans to move on to the treatment of spinal cord injury and traumatic brain injury (1, 2).

1. *Boston Life Sciences files IND for phase I study of Axosine*. DailyDrugNews.com (Daily Essentials) July 29, 2004.

2. *Boston Life Sciences' phase I Axosine study on hold pending further data*. DailyDrugNews.com (Daily Essentials) Sept 17, 2004.

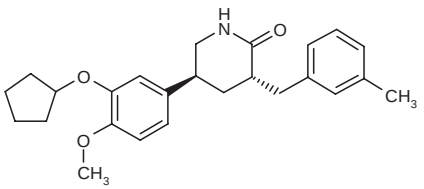
Interferon Tau

Interferon tau (Tauferon™) is a type I interferon in phase II trials at Pepgen for the oral treatment of MS. Preclinical and human clinical studies have shown that the drug is active when given orally, has an excellent

safety profile, does not generate antibodies and induces a dose-dependent Th2-biased (antiinflammatory) cytokine profile (1).

1. *Funding at Pepgen to support advancement of Tauferon*. DailyDrugNews.com (Daily Essentials) Aug 9, 2004.

IPL-455903 (HT-0712)



Inflazyme and Helicon Therapeutics are collaborating on the development of the PDE4 inhibitor IPL-455903 (HT-0712) for the treatment of learning and memory disorders. Helicon recently completed a U.S. phase I trial to assess the safety, tolerability and pharmacokinetic properties of escalating single oral doses of HT-0712 in healthy volunteers. Results showed the drug to be safe and well tolerated at all doses tested, with no serious adverse events noted. In particular, there was no evidence of nausea or vomiting often associated with other PDE4 inhibitors in development. These initial phase I studies were designed to assess the safety, tolerability and pharmacokinetic properties of a single escalating oral dose in 50 healthy volunteers aged 18-81. The subjects were administered either placebo or drug at 5-405 mg orally. Other assessments included the effect of food on the absorption of the drug, which was found to be minimal. HT-0712 also demonstrated acceptable pharmacokinetic properties. Inflazyme now plans to focus some of its activities to leverage this novel chemical series in disease areas outside of learning and memory disorders. Helicon will be continuing its phase I program with additional double-blind, placebo-controlled studies of multiple doses of HT-0712 in male and female volunteers treated for 2 weeks. These studies will further investigate the safety, tolerability and pharmacokinetic properties of the compound. HT-0712 is expected to enter phase II studies in early 2006. The orally active compound blocks the activity of PDE4, which results in increased and prolonged levels of cyclic AMP (cAMP), which may assist memory consolidation. Helicon licensed the drug from Inflazyme in January 2003 and is now developing the compound at its own cost. Inflazyme has the rights, at any time up until the successful completion of a phase IIa program, to enter into a joint venture with Helicon for the further development and commercialization of this compound in the field of learning and memory (1-4).

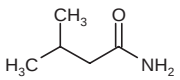
1. *Restructuring and R&D refocusing at Inflazyme*. DailyDrugNews.com (Daily Essentials) July 30, 2004.

2. *Helicon launches phase I studies of IPL-455903*. DailyDrugNews.com (Daily Essentials) Dec 15, 2004.

3. *Inflazyme charts progress from preclinical company*. DailyDrugNews.com (Daily Essentials) April 20, 2005.

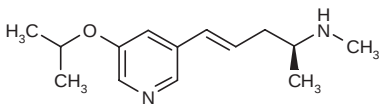
4. *Preliminary phase I results with PDE4 inhibitor IPL-455903*. DailyDrugNews.com (Daily Essentials) May 13, 2005.

Isovaleramide



Isovaleramide (NPS-1776) is a small-molecule, broad-spectrum neuromodulator that is in phase I clinical trials at NPS Pharmaceuticals for the treatment of epilepsy and other neurological and psychiatric disorders.

Ispronicline



One of Targacept's neuronal nicotinic acetylcholine receptor modulators, ispronicline (TC-1734) is a small-molecule neuroprotectant in phase II trials for the oral treatment of conditions of cognitive impairment in the elderly, including AD and age-related cognitive impairment (AAMI). Isopronicline is a nicotinic $\alpha_4\beta_2$ agonist that acts to prevent deterioration and death of neurons. Phase II trials have been performed in AAMI and mild cognitive impairment (MCI), and phase II trials are planned for next year in patients with mild to moderate AD. Targacept is also evaluating the clinical development of ispronicline for additional indications, such as cognitive impairment associated with schizophrenia, cognitive impairment following CABG, ADHD and some forms of dementia.

Data from 5 clinical trials were used to review the effects and safety profile of ispronicline, given as single (up to 320 mg) or multiple (up to 200 mg for 10 days) doses to 124 subjects. Both regimens induced pharmaco-EEG changes that in some cases were also associated with cognitive improvements. In elderly patients with AAMI, a dose of 50 mg of ispronicline significantly improved attention, speed of memory and quality of episodic memory, but had no effects on quality of working memory. Most adverse events were mild or moderate, and dose-limiting toxicities consisted of headache, dizziness, lightheadedness and occasional nausea or vomiting. No evidence of peripheral cardiovascular effects was found at any dose tested. The maximum tolerated dose was established at 320 mg for young subjects and 150 mg for elderly subjects (1).

The potential effects of ispronicline in humans were evaluated in a double-blind clinical trial that randomized

patients 60 years of age and older with MCI to receive placebo or ispronicline (50 or 100 mg) once daily for 3 weeks. Both doses improved cognition, but the higher dose was more effective in improving power of attention, episodic memory, working memory and speed of memory. All study treatments were well tolerated and the most common adverse event was lightheadedness, considered to be of central origin (2).

1. Dunbar, G.C. *TC-1734: A neuronal nicotinic acetylcholine receptor partial agonist that demonstrated an excellent safety/tolerabililty profile and cognitive enhancement in early studies in humans*. Neuropsychopharmacology 2004, 29(Suppl. 1): S127.

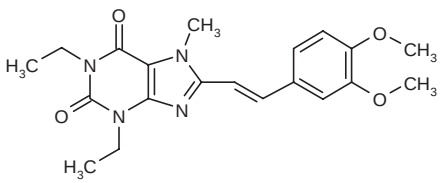
2. Dunbar, G., Wamsley, J. *Ispronicline a neuronal nicotinic receptor partial agonist in the treatment of subjects with mild cognitive impairment (MCI)*. Int Psychogeriatr 2005, 17(Suppl. 2): Abst P1:105.

Additional References

Dunbar, G. et al. *Cognitive enhancement with ispronicline (TC-1734), a partial agonist at the alpha4beta2 NNR receptor, in subjects with AAMI*. 18th Congr Eur Coll Neuropsychopharmacol (ECNP) (Oct 22-26, Amsterdam) 2005, Abst P.5.037.

Dunbar, G.C. et al. *Cognitive enhancement in early studies with TC-1734, a partial agonist at the NNR receptor*. 7th Int Conf Prog Alzheimer Parkinson Dis (March 9-13, Sorrento) 2005, Abst.

Istradefylline



Kyowa Hakko's istradefylline (KW-6002), an adenosine A_{2A} antagonist, is being studied in phase III clinical trials in the U.S. and Europe and phase IIa trials in Japan for the oral treatment of Parkinson's disease. As monotherapy or combination therapy with levodopa or dopamine agonists, it has been shown to improve the symptoms of the disease in a parkinsonian monkey model, without increasing the incidence or severity of dopaminergic-related side effects or inducing or worsening dyskinesia. Phase IIa trials are also in progress in the U.S. for restless legs syndrome (RLS).

The US-005 and US-006 clinical trials randomized 591 advanced Parkinson's disease patients with wearing-off motor responses to levodopa who were Hoehn and Yahr stages 2-4 and had at least 2 h of "off" time to receive placebo or istradefylline (20, 40 or 60 mg/day) together with other antiparkinsonian drugs for 12 weeks. The most common adverse events found were dyskinesia and nausea, but no significant differences were found in the safety profiles of the different study treatments. The combined results from these studies showed that istradefylline was more effective than placebo in reducing the "off" time of the patients (1, 2).

A multicenter, open-label clinical trial has determined the long-term effects and safety of istradefylline therapy in 496 patients with Parkinson's disease. Each patient was given an initial dose of 40 mg/day of istradefylline, which could be increased to 60 mg/day or decreased to 20 mg/day during the treatment period. Dyskinesia, dizziness and nausea were the most common adverse events found after a total exposure to open-label istradefylline of 241.8 patient exposure years. The incidence rates of adverse events were similar to those found in previous double-blind clinical trials. The continued treatment of these patients was found to be effective through 52 weeks. Patients receiving istradefylline 40 mg/day had a reduction of 1.1 h in "off" time at 12 weeks in double-blind studies; this was maintained by continued treatment for 1 year in the open-label study. Also, patients receiving placebo in the double-blind trials, or who had not received treatment for over 2 weeks before entering the long-term study, had reductions in "off" time of approximately 0.7-0.9 h within 2 weeks in the long-term study. These reductions were also maintained through 52 weeks (3, 4).

Solid formulations within which crystalline cellulose is combined with a xanthine derivative such as istradefylline have been claimed. These compositions are expected to possess favorable disintegration, release and stability profiles (5).

The administration of an adenosine A_{2A} receptor antagonist, for instance istradefylline, in combination with a dopaminergic agent, for example a dopamine receptor agonist such as pramipexole, pergolide mesilate, cabergoline or ropinirole hydrochloride, a MAO-B inhibitor such as selegiline hydrochloride or a COMT inhibitor such as entacapone has been claimed for the therapeutic intervention of disorders characterized by functional abnormality of the dopamine system. Targeted disorders include Parkinson's disease, RLS and ADHD (6).

Compositions comprising a xanthine derivative, namely istradefylline, have been claimed for use in treating conditions associated with higher brain dysfunction, including unilateral spatial neglect, apraxia, agnosia, memory impairment and learning disability (7).

1. Stacy, M.A. *Istradefylline (KW-6002) as adjunctive therapy in patients with advanced Parkinson's disease: A positive safety profile with supporting efficacy*. Mov Disord 2004, 19(Suppl. 9): Abst P605.

2. LeWitt, P.A. *"Off" time reduction from adjunctive use of istradefylline (KW-6002) in levodopa-treated patients with advanced Parkinson's disease*. Mov Disord 2004, 19(Suppl. 9): Abst P624.

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4. Mark, M.H. *Long-term efficacy of istradefylline in patients with advanced Parkinson's disease*. Mov Disord 2005, 20(Suppl. 10): Abst P310.

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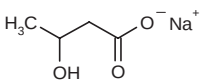
7. Kase, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Preventive and/or therapeutic agent for higher brain dysfunction*. WO 2005056016.

Original monograph – Drugs Fut 2001, 26(1): 21.

KTX-0101

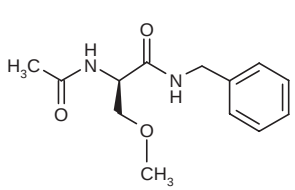


Late last year, KetoCytonyx successfully completed a phase I study of KTX-0101 (β-hydroxybutyrate), its lead therapeutic targeting prevention of cognitive impairment in patients undergoing CABG surgery. The dose-escalation study enrolled 20 healthy volunteers. KTX-0101 was found to be well tolerated by all volunteers, with no serious adverse events reported. Drug pharmacokinetics were as predicted. In addition, statistically significant changes compared to placebo in the electroencephalogram (EEG) recording indicated that KTX-0101 had a pharmacodynamic effect on the CNS. This effect was similar to that seen in patients when hypothermia was used to provide neuroprotection for patients undergoing CABG surgery and following head injury. Further phase Ib and phase II studies are being planned to confirm safety and proof of principle. KTX-0101 is one of a series of ketone bodies and acts as a superfuel, an alternative energy system for cells when ischemia reduces ATP production, as occurs in CABG surgery for example. In addition to providing ketone bodies to the mitochondria to keep the cells alive, the ketone bodies also suppress free radical production and thereby increase the cell's ability to protect itself from damage (1, 2).

1. *Phase I study for neuroprotectant KTX-0101*. DailyDrugNews.com (Daily Essentials) July 12, 2004.

2. *KetoCytonyx completes phase I study of KTX-0101*. DailyDrugNews.com (Daily Essentials) Dec 15, 2004.

Lacosamide



Schwarz Pharma is evaluating lacosamide (SPM-927, formerly harkoseride) for the treatment of epilepsy in a phase III trial, from which first results are expected in the second quarter of 2006. Lacosamide is also being tested in a phase III trial for treating chronic pain caused by diabetic neuropathy. Results from the European and U.S. phase IIb trial of lacosamide for the treatment of epilepsy demonstrated statistically significant and clinically relevant reductions in seizure frequency. The multicenter, double-blind, placebo-controlled trial had a treatment duration of 12 weeks. A total of 497 patients with partial seizures suffering from refractory epilepsy were randomized for adjunctive treatment. The primary parameters were reduction in seizure frequency and a 50% response rate. Both primary endpoints for the trial were achieved. More than 90% of patients who completed the study entered the open-label follow-up trial. First headline data from the study in diabetic neuropathic pain showed that lacosamide significantly reduced diabetic neuropathic pain and had a consistent safety profile compared to previous trials with lacosamide for the target dose of 400 mg/day. Lacosamide showed statistical significance at 400 mg/day for the primary efficacy variable of change in pain from baseline to end of treatment. Differences between placebo and lacosamide were statistically significant when compared over the entire titration period, the 12-week maintenance period and the overall treatment period. In addition, treatment with lacosamide showed significant results with respect to Patients' Global Impression of Change in pain (PGIC). In this U.S. multicenter, double-blind, placebo-controlled trial, 370 patients with painful diabetic neuropathy received either placebo, 200, 400 or 600 mg/day lacosamide for up to 20 weeks. Patients rated their perception of pain twice daily in an electronic patient diary on the Likert scale ranging from 0 to 10. In another multicenter, double-blind, placebo-controlled trial conducted across Europe, 357 patients with painful diabetic neuropathy received either placebo, 400 or 600 mg/day lacosamide for up to 20 weeks. Patients also rated their perception of pain twice daily in an electronic patient diary. The average pain scores of the patients on active drug decreased and remained stable over the entire maintenance period. Differences between placebo and lacosamide were statistically significant when compared over the entire titration period, the 12-week maintenance period and the overall treatment period. The results of this trial demonstrated a separation between both lacosamide groups and the placebo group in the primary and secondary efficacy variables, although the primary variable (change in pain from baseline to end of treatment) did not reach significance. A total of 90% of patients who completed the trials decided to continue treatment with lacosamide in open-label follow-on trials. Another double-blind, placebo-controlled clinical trial with lacosamide in patients with diabetic neuropathy is expected to report in the second quarter of 2006 (1-3).

A single-center, open-label, crossover clinical trial found bioequivalence for a single dose of 200 mg of lacosamide when administered to 24 healthy male volunteers in the form of a 30-min i.v. infusion, a 60-min i.v. infusion or an oral tablet (4).

An open-label, crossover clinical trial conducted in healthy male volunteers found no significant differences in the rate of gastrointestinal absorption of a single oral dose of 300 mg of lacosamide when given in the fasted state or at 30 min after a standard high-fat and high-calorie breakfast (5).

Analysis of pooled data from two phase I clinical trials revealed that age had no clinically relevant effects on the area under the curve and the peak plasma concentration of lacosamide (100 or 200 mg once or twice daily). Both pharmacokinetic parameters showed greater values in young and elderly women compared to young and elderly men, but this was attributed to the women's lower body weight (6).

In a randomized clinical trial, 418 patients with epilepsy who had experienced at least 8 partial seizures and no 21-day seizure-free period for 8 weeks before inclusion supplemented their stable antiepileptic drug therapy with oral lacosamide or placebo for 12 weeks. At the end of the study, lacosamide at doses of 200, 400 and 600 mg/day decreased seizure frequency by 14.6%, 28.4% and 21.3%, respectively, compared to placebo. The 50% responder rates were also higher with lacosamide (33%, 41% and 38%, respectively, for 200, 400 and 600 mg/day) than with placebo (22%). The most common adverse events included dizziness, ataxia, nystagmus, diplopia, abnormal vision and fatigue, and patients mostly discontinued the study due to adverse events involving the central and peripheral nervous system (7).

A multicenter, open-label phase II clinical trial revealed that lacosamide (50 mg b.i.d., increased to up to 300 mg b.i.d. or the maximum tolerated dose) administered for 4 weeks was effective in reducing seizure frequency in 91 patients with partial seizures under treatment with one or two antiepileptic drugs. The median maximum tolerated dose of lacosamide was established at 300 mg/day. Blood samples taken from the patients at baseline and at the end of the study showed that lacosamide had no effects on the plasma levels of concomitant antiepileptic drugs, suggesting that the lower seizure frequency was not caused by a greater exposure to these drugs (8).

Sixty patients with partial seizures who were participating in an open-label extension study of oral lacosamide plus concomitant antiepileptic drugs were enrolled in a placebo-controlled clinical trial that compared the safety of oral and intravenous lacosamide (200-600 mg/day, given for 2 days). No significant differences between groups were found in the incidence of adverse events, vital signs or ECG effects. Intravenous lacosamide was well tolerated and only 3 patients experienced injection-site reactions. Most patients completed the study, and no patients discontinued due to adverse events (9).

A multicenter, double-blind, randomized, placebo-controlled, dose-escalating clinical trial assessed the safety and analgesic effects of lacosamide given at a maximum dose of 400 mg/day to 119 patients with diabetic distal sensory polyneuropathy for 1-5 years. The clinical trial included a 4-week run-in period, a 5-week dose-escalation period, a 4-week maintenance period, a 1-week tapering-off period and a 2-week follow-up period. Lacosamide was more effective than placebo in reducing pain scores, pain interference with sleep and pain interference with function on the Likert scale. No significant differences were found between the safety profiles of the two study groups (10, 11).

The use of one or more peptides with glycine-site NMDA receptor-antagonist activity, for example lacosamide, has been claimed for therapeutic intervention in neuropathic pain, notably diabetic distal sensory polyneuropathy. The claim follows the evaluation of the drug in a clinical trial involving subjects with painful diabetic neuropathy, which resulted in the drug providing a potent analgesic effect without promoting weight gain (12).

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9. Biton, V. et al. *Safety, tolerability and pharmacokinetics of intravenous lacosamide as replacement for oral lacosamide in subjects with partial seizures*. Neurology 2005, 64(6, Suppl. 1): Abst P02.148

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11. Rauck, R., Shaibani, A., Biton, V., Simpson, J., Koch, B., Rauschkolb, C. *SPM 927, a novel anticonvulsant in painful diabetic neuropathy*. Neuropathic Pain: Chang Paradigms Diagn Treat (May 13-16, Madrid) 2004, Abst.

12. Rauschkolb-Löffler, C. and Koch, B. (Schwarz Pharma AG) *Novel use of peptide compounds for treating pain in painful diabetic neuropathy*. WO 2005092313, EP 1579858.

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Biton, V. et al. *Safety and tolerability of intravenous lacosamide as replacement for oral lacosamide in subjects with partial-onset seizures*. 9th Congr Eur Fed Neurol Soc (Sept 17-20, Athens) 2005, Abst P1324.

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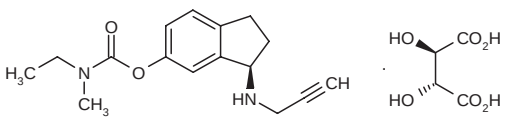
A multicenter, double-blind, randomized, placebo-controlled, parallel group trial to investigate the efficacy and safety of SPM 927 (400mg/day and 600mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization (NCT00136019). ClinicalTrials.gov Web Site 2005, Aug 29,

A multicenter, open-label trial to investigate the safety and tolerability of intravenous SPM 927 as replacement for oral SPM 927 in subjects with partial seizures with or without secondary generalization (NCT00151879). ClinicalTrials.gov Web Site 2005, Sept 26,

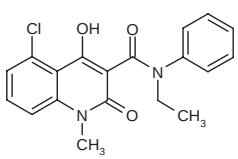
A multi-center, randomized, double-blind, placebo-controlled, parallel-group trial to assess the efficacy and safety of SPM 927 (200, 400, and 600mg/day) in subjects with painful distal diabetic neuropathy (NCT00135109). ClinicalTrials.gov Web Site 2005, Aug 29.

Ladostigil Tartrate



Teva is conducting phase II clinical trials with ladostigil tartrate (TV-3326) as a potential new treatment for AD. The drug combines in one molecule three mechanisms of action: MAO inhibition, cholinesterase inhibition and neuroprotective activity. The combination of these three activities in a single entity gives the molecule a unique profile: it targets both the cognitive impairment and the problematic behavioral disturbances, such as depression and anxiety, prevalent in AD, and also potentially modifies the course of the disease via its neuroprotective mechanism. Ladostigil tartrate was originally developed at Hebrew University and subsequently licensed to Teva.

Laquinimod



Teva, licensee of laquinimod (SAIK-MS), recently filed an IND to conduct a U.S. study on laquinimod and its interactions with other drugs. Teva is currently conducting a supplementary multicenter phase II study to establish the optimal dose for pivotal phase III studies. This study is a full-scale multicenter, double-blind, placebo-controlled phase IIb trial in several European countries that is evaluating the effect of laquinimod *versus* placebo administered once a day in tablet form at doses of 0.3 and 0.6 mg/day for 9 months. The phase III program for laquinimod in relapsing MS is expected to begin in 2006. Laquinimod's mode of action is also being studied in parallel with clinical development. Laquinimod, licensed by Active Biotech to Teva in 2004 for all markets except the Nordic and Baltic countries, is not an immunosuppressant and has the potential to become the first disease-modifying drug in tablet form for the treatment of MS. Active Biotech successfully completed a phase II trial, in which oral laquinimod at a dose of 0.3 mg/day was well tolerated and effective in suppressing the development of active lesions in relapsing MS. Treatment over 6 months with 0.3 mg/day of laquinimod resulted in a 30% decrease in MRI disease activity. Patients with disease activity at the start of the study showed a decrease of more than 40%. A 2009 market launch is being targeted (1-7).

A total of 209 patients with relapsing MS participated in a double-blind, randomized, placebo-controlled clinical trial that determined the safety and therapeutic effects of laquinimod (0.1 and 0.3 mg/day p.o.) in this condition. After 24 weeks of treatment, laquinimod was significantly more effective than placebo in inhibiting the development of active lesions (assessed in gadolinium-enhanced MRI scans). Laquinimod was especially effective in the subgroup of patients who had at least one active lesion at baseline. No significant differences between study groups were found for disability or relapse during the study period. Analysis of gadolinium-enhanced brain MRI scans obtained during the treatment period and at 8 weeks after the last dose showed that, compared to placebo, 0.3 mg/day of laquinimod decreased the cumulative number of active lesions by 44% in the whole study population, and by 52% in the subgroup of patients with at least one active lesion at baseline. All study regimens were well tolerated, and although laquinimod tended to increase the erythrocyte sedimentation rate and liver function measurements, these effects were generally mild, transient and clinically irrelevant. The pharmacokinetics of laquinimod were not changed when compared with previous data from single and repeated dosing in healthy volunteers and patients with secondary progressive disease. Linear pharmacokinetics were seen and clearance was 17% lower in females compared to males. Clearance decreased with increasing EDSS scores and systemic exposure was correlated with response, with fewer active lesions developing in patients with greater drug exposure. The study findings indicate that greater exposure, and therefore higher laquinimod doses, may provide greater activity (5, 9-11).

1. *Active Biotech discontinues discovery projects, focuses on development*. DailyDrugNews.com (Daily Essentials) March 3, 2004.

2. *Active Biotech reports 2003 year-end R&D highlights*. Active Biotech Web Site 2004, Feb 12.

3. *Active Biotech reports Q1 R&D highlights*. Active Biotech Web Site 2004, March 13.

4. *Active Biotech reports Q2 R&D highlights*. Active Biotech Press Release 2004, Aug 12.

5. *IND submission for MS drug laquinimod*. DailyDrugNews.com (Daily Essentials) June 30, 2005.

6. *Active Biotech reports Q2 R&D highlights*. Active Biotech Press Release 2005, Aug 11.

7. *Teva and Active Biotech sign laquinimod licensing deal*. DailyDrugNews.com (Daily Essentials) June 16, 2004.

9. Nordle, O., Sparre, B., Linde, A., Nederman, T., Gunnarsson, P.O. *Pharmacokinetic evaluation in a double blind, randomised, phase II study of oral laquinimod versus placebo in patients with relapsing multiple sclerosis*. Multiple Scler 2004, 10(Suppl. 2): Abst P644.

10. Barkhof, F., Polman, C.H., Sandberg-Wollheim, M., Linde, A., Nederman, T. *Oral treatment with laquinimod reduces development of active MRI lesions in relapsing MS*. Neurology 2004, 62(7, Suppl. 5): Abst S12.005.

11. Polman, C. et al. *Treatment with laquinimod reduces development of active MRI lesions in relapsing MS*. Neurology 2005, 64(6): 987.

Original monograph – Drugs Fut 2003, 28(11): 1059.

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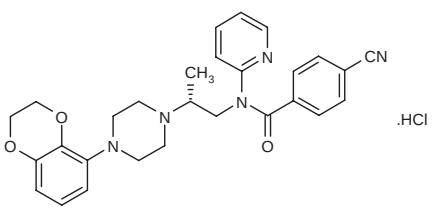
Polman, C. et al. *Oral treatment with laquinimod reduces development of active MRI lesions in relapsing multiple sclerosis*. J Neurol 2004, 251(Suppl. 3): Abst 189.

Sandberg-Wollheim, M. et al. *48-week open safety study with a high-dose oral laquinimod in MS patients*. 21st Congr Eur Comm Treat Res Multiple Scler (Sept 28-Oct 1, Thessaloniki) 2005, Abst P 587.

LAX-202

The orally delivered combination of lofepramine and L-phenylalanine, known as LAX-202, is in phase II trials at Amarin for the treatment of fatigue associated with MS. The company is currently seeking development partners for this drug candidate.

Lecozotan Hydrochloride



Phase II clinical trials are under way for lecozotan hydrochloride (SRA-333), an orally available, potent and selective 5-HT_{1A} antagonist in development by Wyeth Pharmaceuticals for the treatment of Alzheimer's-type dementia.

A randomized, double-blind, placebo-controlled clinical trial evaluated the safety, pharmacokinetics and pharmacodynamics of single doses of lecozotan (2, 5 and 10 mg) in 24 healthy volunteers. The time to peak plasma concentration was 0.5 h and the half-life was 6-8 h, indicating the feasibility of a twice-daily dosing regimen. Plasma drug concentrations increased with dose and all three doses were well tolerated, although the highest dose was associated with dose-limiting mild to moderate CNS adverse events (lightheadedness, sensorial disturbances, dizziness) (1, 2).

The effects of age and gender on the pharmacokinetic profile of a single dose of 3 mg of lecozotan were assessed in another double-blind, randomized, placebo-controlled clinical trial that enrolled 48 healthy volunteers. Elderly subjects showed a lower oral clearance and a higher mean half-life compared to young subjects. Peak plasma concentration was 17% higher in women compared to men, which may be associated with weight differences between gender groups. Lecozotan was not associated with adverse effects on attention, vigilance, sensorimotor tasks, working memory or episodic memory (3).

A double-blind, randomized, placebo-controlled clinical trial determined the safety and pharmacokinetics of multiple doses of lecozotan in 41 young adults and 8 elderly volunteers who were randomized to receive placebo or lecozotan (0.1, 0.25, 0.5, 1 or 5 mg b.i.d.) for 14 days. Plasma drug levels increased with dose, and findings suggested a linear accumulation when multiple doses were administered. All dose levels were well tolerated and were not associated with severe or dose-related adverse events. Elderly subjects showed peak plasma concentration and AUC values that were 48% and 42% greater, respectively, than the corresponding values found in young volunteers. The maximum tolerated dose was established at 5 mg twice daily (4, 5).

1. Patat, A.A., Parks, V., Raje, S., Plotka, A., Chassard, D. *Safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ascending single doses of SRA-333 in healthy subjects*. Clin Pharmacol Ther 2004, 75(2): Abst PI-70.

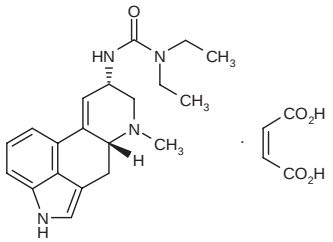
2. Plotka, A., Parks, V., Raje, S., Patat, A., Chassard, D. *Safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ascending single doses of SRA-333 in healthy subjects*. Neurobiol Aging 2004, 25(Suppl. 2): Abst P1-401.

3. Patat, A., Parks, V., Raje, S., Plotka, A., Dietrich, B. *Age-gender study of SRA-333, a novel 5-HT1A antagonist*. Clin Pharmacol Ther 2005, 77(2): Abst PI-79.

4. Raje, S.V., Plotka, A., Parks, V., Patat, A., Chassard, D. *Safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ascending multiple doses of SRA-333 in healthy subjects*. Neurobiol Aging 2004, 25(Suppl. 2): Abst P1-410.

5. Patat, A.A., Parks, V., Raje, S., Plotka, A., Chassard, D. *Safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ascending multiple doses of SRA-333 in healthy subjects*. Clin Pharmacol Ther 2004, 75(2): Abst PI-71.

Lisuride Maleate, Transdermal



Lisuride maleate, a dopamine D2 agonist, was initially launched by Schering-Plough more than 20 years ago for the oral treatment of advanced Parkinson's disease. The Schering AG spin-off NeuroBiotec has licensed all nonoral formulations of lisuride and is evaluating a transdermal formulation in phase II/III trials for the treatment of restless legs syndrome (RLS). Phase II trials are also under way in combination with levodopa for the treatment of Parkinson's disease. The lisuride transdermal system shows high efficacy for Parkinson's and RLS patients, providing continuous dopaminergic stimulation. Prestwick Pharmaceuticals, the American licensee of NeuroBiotec's technology, has started parallel development and clinical studies in the U.S. and Canada. NeuroBiotec intends to seek a first submission for marketing authorization by the European Medicines Agency in 2006 (1).

A proof-of-concept study evaluated the use of transdermal lisuride in 10 patients with RLS. All but 1 patient showed remarkable improvement under open-label treatment with lisuride patches, while patients taking placebo showed worsened RLS. Adverse events were mild to moderate nausea and vomiting. Based on the results, further studies for lisuride patches in patients with RLS were recommended (2).

Medicaments suitable for transdermal application comprising stabilized formulations of an ergolin compound, namely the dopamine D2 receptor agonist lisuride, have been claimed for the treatment of Parkinson's disease, RLS, hyperprolactinemia and migraine. The claim embodies the protection from oxidation of such compounds via the inclusion of a liposoluble antioxidant with free radical-scavenging activity, for instance tocopherol, and a basic polymer (3).

1. *NeuroBiotec raises EUR 10 million in financing*. NeuroBiotec Press Release 2005, Jan 28.

2. Benes, H. *Efficacy and tolerance of transdermal lisuride TTS patches in patients with severe restless-legs-syndrome: A proof-of-concept study*. Sleep 2004, 27(Suppl.): Abst 684.

3. Horowski, R. et al. (NeuroBiotec GmbH) *Agent containing ergolin for transdermal application*. WO 2005025546, DE 10341317.

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Benes, H. *Transdermal lisuride in patients with idiopathic restless legs syndrome: Results from a placebo-controlled, double-blind, randomized, multicenter, 12-week dose-finding study*. 1st Congr World Assoc Sleep Med (WASM) (Oct 15-18, Berlin) 2005, Abst P 089.

Woitalla, D. et al. *Transdermal lisuride delivery in the treatment of Parkinson's disease*. J Neural Transm Suppl 2004, (68): 89.

Losartan Potassium/ Hydrochlorothiazide, New Indication

Losartan potassium/hydrochlorothiazide (Hyzaar®) is a fixed-dose combination of the angiotensin II receptor blocker (ARB) losartan potassium (Cozaar®; 100 mg) and the diuretic hydrochlorothiazide (25 mg) launched more than 10 years ago by Merck & Co. for the treatment of severe hypertension. Earlier this year, the FDA approved a new indication for Hyzaar®. Hyzaar® is now indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy (LVH). This new indication is based on the landmark LIFE (Losartan Intervention For Endpoint reduction in hypertension) study in which 4,605 patients were randomized to receive once-daily losartan 50 mg and 4,588 patients to receive once-daily atenolol 50 mg. If goal blood pressure (< 140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. If necessary, other antihypertensive treatments were added to the treatment regimen to reach the goal blood pressure. Patients in the LIFE trial were followed for an average of 4.8 years. The results showed that in patients treated with losartan, the risk of first occurrence of cardiovascular death, nonfatal stroke or nonfatal myocardial infarction (primary endpoint) was reduced by a statistically significant 13% compared to patients treated with atenolol. This difference was primarily the result of an effect on fatal and nonfatal stroke. At least one of the components of the primary composite endpoint occurred in 508 patients in the group taking losartan and in 588 patients in the atenolol arm. Treatment with a regimen based on losartan significantly reduced the risk of stroke (fatal and nonfatal) by 25% in patients with hypertension and LVH *versus* treatment with a regimen based on the β-blocker atenolol. There were 232 fatal and nonfatal strokes in the group treated with losartan compared to 309 in the atenolol group. There was no significant difference between the treatment groups in the risk of heart attack or cardiovascular death. At the end of the study or at the last visit before a primary endpoint, the mean blood pressure was 144.1/81.3 mmHg for the losartan-based group and 145.4/80.9 mmHg for the atenolol-based group. The difference in systolic blood pressure of 1.3 mmHg was significant, while the difference of 0.4 mmHg in diastolic blood pressure was not significant. The LIFE study did not provide evidence that the benefits of Cozaar® in reducing the risk of cardiovascular events in hypertensive patients with LVH apply to black patients. Merck demonstrated that the losartan and hydrochlorothiazide tablets used in the LIFE study were bioequivalent to the marketed Hyzaar® tablets. Along with Merck's

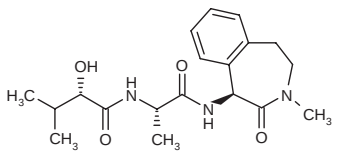
Cozaar® (losartan potassium), approved in March 2003, Hyzaar® is now the only ARB indicated to reduce the risk of stroke in patients with hypertension and LVH. Hyzaar® is also the only combination antihypertensive product that is indicated for initial use in appropriate patients with severe hypertension (1-3).

1. *New indication approved for Hyzaar*. DailyDrugNews.com (Daily Essentials) April 18, 2005.

2. *Merck & Co.*, Inc. reports Q1 R&D highlights. Merck & Co., Inc. Press Release 2005, April 21.

3. *Hyzaar 100-12.5 mg now available*. DailyDrugNews.com (Daily Essentials) Oct 26, 2005.

LY-450139



The γ-secretase inhibitor LY-450139 is in phase II trials at Lilly for the treatment of Alzheimer's disease (AD) (1).

Multiple doses of LY-450139 were administered to 37 healthy volunteers in an early assessment of the suitability of the drug for the treatment of AD. Study subjects received placebo or LY-450139 (5, 20, 40 or 50 mg p.o.) once daily for up to 14 days. Plasma concentrations were linearly related to LY-450139 doses, although drug exposure decreased after 14 days of dosing in the highest dose group. Plasma β-amyloid (Aβ) concentrations decreased dose-dependently over 6 h after LY-450139 administration and transiently increased after returning to baseline. Cerebrospinal fluid (CSF) Aβ concentrations were not altered at 6 h after LY-450139 dosing, although the higher doses tended to reduce CSF Aβ levels. LY-450139 had a plasma half-life of about 2.5 h. Adverse events were similar for placebo and LY-450139 at doses up to 40 mg, while 2 patients given the 50-mg dose experienced clinically significant adverse events (diarrhea and high serum amylase and lipase levels). Further studies are required to determine if adverse events increase with higher LY-450139 doses and if reductions in CSF Aβ can be achieved with the drug (2, 3).

The efficacy of LY-450139 against the production of Aβ was investigated in a randomized, double-blind, placebo-controlled study in 70 patients with mild to moderate AD. LY-450139 was well tolerated at a dose of 40 mg/day, with diarrhea and loose stools being the only adverse events that differed between treatment groups. Lumbar punctures performed at baseline and after 6 weeks of treatment showed a maximum decrease of 39.4 ± 5.6% in plasma concentrations of Aβ compared to patients taking placebo, whereas Aβ concentrations in CSF in treated and untreated patients did not show significant differences. LY-450139 treatment induced a small but significant reduction in serum phosphorus and uric acid, as well as a small increase in eosinophil count, compared to placebo. Higher doses resulted in plasma Aβ concentrations too low for accurate measurement. There were no differences observed between drug- and placebo-treated patients on cognitive measures including ADAS-cog and a battery of neuropsychological tests (4).

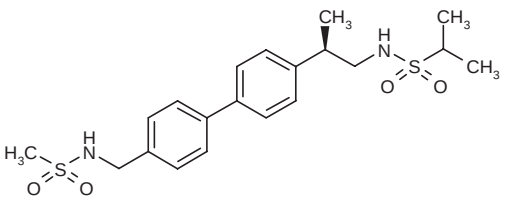
1. *Effects of LY450139 dihydrate on subjects with mild to moderate Alzheimer's disease (NCT00244322)*. ClinicalTrials.gov Web Site 2005, Nov 10.

2. Siemers, E. et al. *Safety, tolerability, and changes in amyloid beta concentrations after administration of a gamma-secretase inhibitor in volunteers*. Clin Neuropharmacol 2005, 28(3): 126.

3. Siemers, E., Dean, R.A., Satterwhite, J., Farlow, M.R., Skinner, M., Ness, D., May, P.C. *Safety, tolerability, and changes in plasma and cerebrospinal fluid amyloid beta concentrations after administration of a functional gamma-secretase inhibitor in healthy volunteers*. Neurobiol Aging 2004, 25(Suppl. 2): Abst P4-333.

4. Siemers, E.R., Quinn, J.F., Kaye, J., et al. *Effect of LY450139, a functional gamma-secretase inhibitor, on plasma and cerebrospinal fluid concentrations of Abeta and cognitive functioning in patients with mild to moderate Alzheimer's disease*. Neurology 2004, 62(7, Suppl. 5): Abst S17.001.

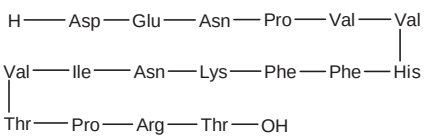
LY-451395



Lilly's LY-451395 is an AMPA receptor potentiator in phase II trials as a potential new treatment for Alzheimer's-type dementia (1).

1. *Efficacy and safety of LY451395 in patients with probable Alzheimer's disease (NCT00051909)*. ClinicalTrials.gov Web Site 2005, June 30.

MBP-8298



Enrollment is under way in BioMS Medical's pivotal phase II/III trial of MBP-8298, a proprietary synthetic peptide that consists of 17 amino acids linked in a sequence

identical to that of a portion of human myelin basic protein (MBP), for the treatment of secondary progressive multiple sclerosis. The apparent mechanism of action of MBP-8298 is the induction or restoration of immunological tolerance. The international, multicenter, double-blind, placebo-controlled trial is expected to enroll up to 553 patients. Patients will be administered either MBP-8298 or placebo intravenously every 6 months for a period of 2 years. The primary endpoint is defined as a statistically and clinically significant increase in the time to progression of disease as measured by the EDSS in the previously identified responder group, patients with immune response genes HLA-DR2 or HLA-DR4. Patients with the immune response genes HLA-DR2 or HLA-DR4 account for up to 75% of the MS patient population (1-8).

1. *BioMS Medical seeks clearance to begin pivotal trial of MBP-8298 in Canada*. DailyDrugNews.com (Daily Essentials) May 21, 2004.

2. *Pivotal phase II/III trial of MBP-8298 cleared by Health Canada*. DailyDrugNews.com (Daily Essentials) June 10, 2004.

3. *Enrollment under way in pivotal MS study of MBP-8298*. DailyDrugNews.com (Daily Essentials) Dec 13, 2004.

4. *BioMS Medical provides multiple sclerosis trial update*. BioMS Medical Press Release 2004, Oct 26.

5. *Progression of pivotal study of MBP-8298 for secondary progressive MS*. DailyDrugNews.com (Daily Essentials) April 25, 2005.

6. *U. of Alberta sells BioMS Medical shares*. DailyDrugNews.com (Daily Essentials) May 20, 2005.

7. *Pivotal study of MBP-8298 expands into Europe*. DailyDrugNews.com (Daily Essentials) July 27, 2005.

8. *Phase II/III MS study of MBP-8298 to be extended to Sweden*. DailyDrugNews.com (Daily Essentials) Aug 25, 2005.

Melevodopa Hydrochloride/ Carbidopa

Melevodopa hydrochloride/carbidopa (CHF-1512, CNP-1512, formerly GT-1512) is currently awaiting registration in Italy as effervescent, controlled-release tablets for the treatment of Parkinson's disease. Originally discovered by Chiesi, the combination is being developed in collaboration with Cita NeuroPharmaceuticals (formerly GB Therapeutics). Phase III development for Parkinson's disease has been completed in Europe and led to registration in Italy. Additional phase III trials to meet FDA and ICH guidelines targeting motor fluctuations are expected to commence in the first quarter of 2006 (1, 2).

1. *GB Therapeutics acquires CHF-1512 for Parkinson's disease*. DailyDrugNews.com (Daily Essentials) Jan 31, 2005.

2. *GB Therapeutics changes name to Cita NeuroPharmaceuticals*. DailyDrugNews.com (Daily Essentials) April 19, 2005.

MEM-1003

Memory Pharmaceuticals has commenced dosing of the first patient in a phase IIa trial of MEM-1003 in patients with mild to moderate Alzheimer's disease (AD). The multicenter, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of two dose levels of MEM-1003 in approximately 180 patients with mild to moderate AD at approximately 50 centers under a U.S. IND. Patients will be randomized to one of three treatment groups: 30 mg MEM-1003 twice a day, 90 mg MEM-1003 twice a day or placebo twice a day. During the double-blind treatment segment of the study, patients will receive MEM-1003 or placebo for a period of 12 weeks, which will be followed by a 4-week single-blind placebo treatment. The primary outcome measure of the trial is a 12-week change in the ADAS-cog score. Secondary measures will assess changes in activities of daily living, behavior and global function. Memory is obligated to make a USD 1 million milestone payment to Bayer as a result of the commencement of this trial. In September 2005, Memory completed dosing in a single-center, randomized, double-blind, placebo-controlled safety and tolerability study of MEM-1003 in 81 AD patients. The company has also completed a phase I trial in 125 healthy volunteers in the U.K. to evaluate the potential cardiovascular impact and side effect profile produced by single and multiple doses of MEM-1003. MEM-1003 is a neuronal L-type calcium channel modulator under development at Memory for AD, and with additional potential for use in vascular dementia and mild cognitive impairment. By blocking L-type calcium channels, MEM-1003 may regulate the flow of calcium and re-establish normal levels of calcium, thereby enhancing cognition and reducing progression of the disease (1-4).

1. *MEM-1003 enters U.S. safety and tolerability study for Alzheimer's*. DailyDrugNews.com (Daily Essentials) Jan 17, 2005.

2. *Memory extends timeline for safety and tolerability study of MEM-1003*. DailyDrugNews.com (Daily Essentials) April 15, 2005.

3. *Memory Pharmaceuticals completes safety and tolerability study of MEM-1003*. Memory Pharmaceuticals Press Release 2005, Sept 26.

4. *Phase IIa study begins for MEM-1003 in Alzheimer's disease*. DailyDrugNews.com (Daily Essentials) Nov 23, 2005.

MEM-3454

Memory Pharmaceuticals commenced a phase I study of MEM-3454, a partial agonist of the nicotinic $\alpha 7$ receptor, in healthy volunteers earlier this year. The single-center, double-blind, placebo-controlled study is being conducted in Toronto, Canada, under a Canadian clinical trial application (CTA). The study will evaluate the safety, tolerability and pharmacokinetics of single

ascending doses of MEM-3454. Compounds acting on the nicotinic $\alpha 7$ receptor could be beneficial in the treatment of schizophrenia and Alzheimer's disease, as well as other psychiatric and neurological disorders. Roche has the right to obtain an exclusive license for MEM-3454 following the completion of phase IIa clinical trials under Memory's 2003 collaboration with Roche (1, 2).

1. *MEM-3454 studied in phase I trial*. DailyDrugNews.com (Daily Essentials) March 2, 2005.

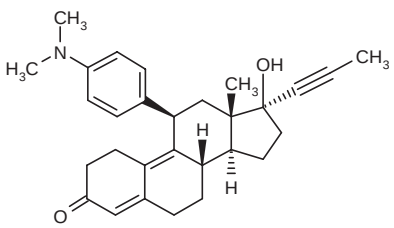
2. *Roche makes milestone payment to retain option to MEM-3454*. DailyDrugNews.com (Daily Essentials) May 5, 2005.

Microplasmin

Systemically administered recombinant microplasmin, a truncated form of the human protein plasmin, is in phase II trials at ThromboGenics for the treatment of stroke and in early clinical development as a potential therapy for the treatment of peripheral arterial obstructive disease (PAOD); an intravitreal injection formulation is also in phase II development for vitreoretinal disorders (1).

1. *Intravenous administration of microplasmin for treatment of acute ischemic stroke (NCT00123305)*. ClinicalTrials.gov Web Site 2005, 2005, Dec 8.

Mifepristone, New Indication



First launched in 1989 in France as Mifeprex™ by the former Roussel Uclaf for the termination of pregnancy, mifepristone (RU-486), a dual glucocorticoid and progesterone receptor antagonist, is in phase II clinical evaluation at Corcept Therapeutics (Corlux®) for the treatment of Alzheimer's disease and phase II trials for the treatment of psychotic features associated with major depression.

In September, Corcept announced plans to close enrollment in its clinical study evaluating the safety and efficacy of mifepristone to improve cognition in patients with mild to moderate Alzheimer's disease. Ongoing review of blinded safety data has not revealed any serious safety findings. Patients in this trial were dosed with an acetylcholinesterase inhibitor and mifepristone or placebo. The study protocol prohibited the concomitant use of Namenda® (memantine), which was commercialized after the trial was initiated. Because a majority of AD patients are now treated with the combination of Namenda® and an acetylcholinesterase inhibitor, enrollment in the Corcept study slowed significantly. To date the study has enrolled 80 of the planned 160 patients. The study is not powered to show statistically significant results with only 80 patients, but the company intends to analyze the data and will report any findings in the first quarter of 2006 (1).

1. *Corcept closes enrollment in Corlux study in Alzheimer's patients*. DailyDrugNews.com (Daily Essentials) Sept 29, 2005.

Original monograph – Drugs Fut 1984, 9(10): 755.

MLN-1202

Millennium Pharmaceuticals has initiated a multicenter phase II trial of MLN-1202 in approximately 40 patients with relapsing-remitting multiple sclerosis (MS). MLN-1202, a novel humanized monoclonal antibody, is designed to block chemokine CCR2 receptors and prevent the infiltration of immune cells into inflammatory sites. The chemokine CCR2 pathway is believed to play a central role in a number of inflammatory conditions, including MS. This proof-of-concept study will assess the safety and tolerability of the molecule and determine the effect of MLN-1202 on disease activity using MRI. Participants will receive multiple doses of MLN-1202 in two dosing regimens over the course of 4 months. The study will be conducted at sites in Canada and Europe. Millennium is also evaluating MLN-1202 in a multicenter phase II trial involving approximately 30 patients with rheumatoid arthritis. The first three cohorts have been fully enrolled and MLN-1202 appears to be well tolerated, with favorable pharmacokinetic and pharmacodynamic profiles. A fourth cohort has been added with data anticipated in 2006. A randomized, double-blind, placebo-controlled phase II trial of MLN-1202 is also under way in patients at risk for atherosclerotic cardiovascular disese. Further studies of MLN-1202 are planned, including a phase II trial in patients with scleroderma (1-4).

1. *Millennium reviews 2004 milestones, looks forward to 2005*. DailyDrugNews.com (Daily Essentials) Jan 13, 2005.

2. *MLN-1202 enters phase II study for relapsing-remitting MS*. DailyDrugNews.com (Daily Essentials) July 13, 2005.

3. *MLN-1202 begins new phase II study for atherosclerotic cardiovascular disease*. DailyDrugNews.com (Daily Essentials) Aug 24, 2005.

4. *Millennium Pharmaceuticals reports Q2 R&D highlights*. Millennium Pharmaceuticals Press Release 2005, July 28.

MLN-3897 (AVE-9897)

MLN-3897 (AVE-9897) is an orally active chemokine CCR1 antagonist in early clinical development by Millennium Pharmaceuticals and Sanofi-Aventis for the

treatment of rheumatoid arthritis (RA) and multiple sclerosis (MS) (1, 2).

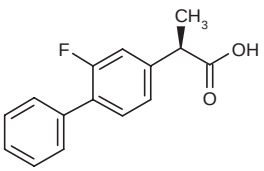
1. *Millenium Pharmaceuticals reports 2003 year-end R&D highlights*. Millennium Pharmaceuticals Press Release 2004, Jan 27.

2. *Millennium reviews 2004 milestones, looks forward to 2005*. DailyDrugNews.com (Daily Essentials) Jan 13, 2005.

Monarsen

The antisense oligonucleotide monarsen (EN-101) is in phase II trials at Ester Neurosciences for the treatment of myasthenia gravis, an acquired immunological disorder in which neuromuscular transmission is damaged as a result of destruction of functioning acetylcholine receptors (AChR) by the immune system. Since ACh action is regulated by acetylcholinesterase (AChE) hydrolyzing activity, therapies aimed at inhibiting AChE have been shown to be effective in treating the disorder. Monarsen, a short chain of 20 nucleic acids, inhibits the translation of AChE by interfering with the correct reading of the protein from the mRNA. In November 2003, the FDA granted monarsen orphan drug designation for the treatment of myasthenia gravis, and the EMEA followed suit in May 2004.

MPC-7869



Myriad Genetics is evaluating MPC-7869 ([*R*]-flurbiprofen, Flurizan™), an NF-κB modulator and antiamyloidogenic agent, in phase III clinical trials for the prevention and treatment of Alzheimer's disease and in phase IIb trials for the treatment of prostate cancer. The drug has been shown to reduce levels of the toxic peptide β-amyloid 42 (Aβ42) in cultured human cells and animal models. In addition to improving spatial learning and memory, MPC-7869 may reduce accumulated plaques in the brains of AD patients. Enrollment in the phase III trial of MPC-7869 in patients with mild stages of AD is proceeding on schedule. An amended protocol was reviewed by the FDA without any changes or request for modification, and the central investigational review board covering a majority of the investigational sites has given its approval of the modified protocol. More than 120 U.S. sites have been enlisted and most are now screening and enrolling patients. Enrollment for the 12-month study is expected to be completed during the first half of 2006, with results to follow in the third calendar quarter of 2007. Results of a phase II trial of MPC-7869 (see below) were used to amend the protocol. Phase II results indicated that patients with mild AD treated with 800 mg twice daily experienced the greatest benefit, with a 34% slowing in the rate of cognitive decline. This finding also guided Myriad to size the study to show statistical significance given a 30% improvement *versus* placebo with 90% confidence (1-8).

A total of 207 patients with mild to moderate AD participated in a multicenter, double-blind, randomized phase II clinical trial that evaluated the efficacy and safety of MPC-7869 in this indication. Each patient was randomized to receive placebo or MPC-7869 (400 or 800 mg b.i.d.) for 12 months. An interim analysis showed that MPC-7869 induced no significant improvement in the whole patient population. However, a subanalysis of data from the group of patients with mild AD at baseline revealed that a twice-daily dose of 800 mg was associated with a 44% slowing of decline in daily living activities, a 41% slowing of decline in global function and a 29% slowing of cognitive decline during the treatment period. These preliminary results suggested that MPC-7868 may be effective in the management of early AD (9, 10).

A method has been claimed for the prophylaxis and/or treatment of neurodegenerative conditions such as AD, dementia and moderate damage to cognitive function. The claim embodies the preparation and administration of pharmaceutical compositions comprising at least one (*R*)-enantiomer nonsteroidal antiinflammatory drug, such as (*R*)-flurbiprofen, in conjunction with at least one HMG-CoA reductase inhibitor, such as atorvastatin, simvastatin, lovastatin, fluvastatin, pravastatin, cerivastatin, rosuvastatin or pitavastatin, or pharmaceutically acceptable salts or esters thereof (11).

1. *Phase II trial of MPC-7869 progresses on schedule*. DailyDrugNews.com (Daily Essentials) April 22, 2004.

2. *Myriad Genetics reports Q2 R&D highlights*. Myriad Genetics Press Release 2004, Feb 3.

3. *Myriad Genetics reports Q3 R&D highlights*. Myriad Genetics Press Release 2004, May 4.

4. *Enrollment begins in phase III Alzheimer's study of Flurizan*. DailyDrugNews.com (Daily Essentials) Jan 14, 2005.

5. *Myriad Genetics reports Q1 R&D highlights*. Myriad Genetics Press Release 2005, May 4.

6. *Myriad Genetics reports Q2 R&D highlights*. Myriad Genetics Press Release 2005, Aug 23.

7. *Phase III Flurizan trial enrolling on schedule*. DailyDrugNews.com (Daily Essentials) Aug 8, 2005.

8. *Myriad Genetics reports Q4 R&D highlights*. Myriad Genetics Press Release 2004, Aug 18.

9. *Preliminary data on the efficacy of Flurizan in Alzheimer's disease*. DailyDrugNews.com (Daily Essentials) May 5, 2005.

10. Wilcock, G.K. et al. *A placebo-controlled, double-blind trial of the selective Abeta-42 lowering agent, Flurizan (MPC-7869, (R)-flurbiprofen) in patients with mild to moderate Alzheimer's disease*. Alzheimer's Assoc Int Conf Prev Dement (June 18-21, Washington DC) 2005, Abst O2-01-05.

11. Hobden, A. and Roch, J.-M. (Myriad Genetics, Inc.) *Method and composition for treating neurodegenerative disorders*. WO 2004028456.

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MRX-815

A multicenter, randomized, blinded, 40-patient phase II trial is evaluating the safety and efficacy of SonoLysis™ for the treatment of acute ischemic stroke. SonoLysis™, which combines external ultrasound and ImaRx Therapeutics' proprietary MRX-815 nanobubbles, is designed to clear blood clots quickly and without the use of invasive surgery or potentially dangerous lytic drugs. SonoLysis™ nanobubbles are injected intravenously to accumulate at the site of a blood clot. With the application of ultrasound, the bubbles are designed to pulsate and break apart to physically impact and destroy the clot. An earlier study at the University of Texas at Houston, which set out to determine whether ultrasound could safely enhance the clot-dissolving ability of tissue-type plasminogen activator (t-PA), found that 38% of patients who received ultrasound and t-PA had complete clearance of their clots within 2 h of treatment, compared with only 13% of those who received t-PA alone. Incorporating ImaRx's nanobubbles into the treatment may result in further improved results. A study using t-PA, ultrasound and off-label diagnostic bubbles against t-PA and ultrasound in 103 stroke patients showed that 55% of the t-PA, ultrasound and microbubble group had complete recanalization at 2 h compared to 41% in the t-PA and ultrasound group. SonoLysis™ is also in early clinical evaluation for the treatment of peripheral arterial occlusive disease (PAOD) (1, 2).

1. *ImaRx studies Sonolysis in phase II stroke study*. DailyDrugNews.com (Daily Essentials) April 8, 2005.

2. *Phase I/II trial begins for SonoLysis in PAOD*. DailyDrugNews.com (Daily Essentials) April 15, 2005.

MS-I.E.T.

Transition Therapeutics is conducting a phase II clinical trial with its MS-I.E.T. multiple sclerosis interferon-enhancing therapy for the treatment of relapsing-remitting MS. MS-I.E.T. combines interferon beta with Transition's enhancing agent EMZ-701 to inhibit disease symptoms and slow the progression of MS. In a phase I trial, EMZ-701 was well tolerated and showed a good safety profile. Preclinical studies demonstrated that MS-I.E.T. is significantly more effective than interferon beta alone in reducing both symptoms and pathologies associated with MS in multiple animal models (1-6).

1. *Canadian approval for initiation of phase II study of I.E.T. for MS*. DailyDrugNews.com (Daily Essentials) July 7, 2004.

2. *Transition Therapeutics announces first quarter fiscal 2006 financial results*. Transition Therapeutics Press Release 2005, Nov 4.

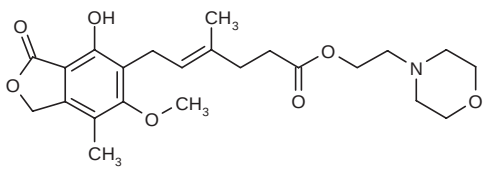
3. *Transition Therapeutics announces fiscal 2005 year end financial results*. Transition Therapeutics Press Release 2005, Sept 9.

4. *Transition Therapeutics announces third quarter fiscal 2005 financial results*. Transition Therapeutics Press Release 2005, May 12.

5. *Transition Therapeutics updates progress of lead programs*. DailyDrugNews.com (Daily Essentials) May 10, 2005

6. *Enrollment begins in phase II study of MS-I.E.T*. DailyDrugNews.com (Daily Essentials) Feb 2, 2005.

Mycophenolate Mofetil, New Indication



Aspreva has completed enrollment of 176 patients in a global phase III study to assess the safety and efficacy of mycophenolate mofetil (CellCept®) to maintain or improve symptom control with reduced corticosteroids in patients with myasthenia gravis. The randomized, double-blind, placebo-controlled trial is designed to evaluate the efficacy and safety of mycophenolate mofetil to maintain or improve symptom control with reduced corticosteroids in patients with myasthenia gravis over a treatment period of 36 weeks. The primary endpoint of responder status in the trial encompasses both minimal disease activity and low steroid dose. The company expects to complete the trial in late 2006. Aspreva signed a collaboration agreement in 2003 with Roche for the exclusive worldwide rights (excluding Japan) to develop and commercialize mycophenolate mofetil, Roche's leading immunosuppressant, for all autoimmune disease applications (1-3). Aspreva is also conducting phase III trials of mycophenolate mofetil in lupus nephritis and pemphigus vulgaris.

1. *Private equity financing to fund CellCept clinical trials for autoimmune diseases*. DailyDrugNews.com (Daily Essentials) March 16, 2004.

2. *New phase III study of CellCept for myasthenia gravis*. DailyDrugNews.com (Daily Essentials) June 10, 2004.

3. *Enrollment completed in phase III study of CellCept*. DailyDrugNews.com (Daily Essentials) Dec 1, 2005.

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CellCept(R) (mycophenolate mofetil) in myasthenia gravis, optional double-blind treatment continuation of protocol WX17798 (NCT00231088). ClinicalTrials.gov Web Site 2005, Oct 7.

MyoDys®

Transgene's gene therapy product MyoDys® (formerly TG5001), a plasmid that contains a full-length human dystrophin gene under the control of a muscle-specific promoter, is in phase I clinical trials at Transgene for the treatment of Duchenne muscular dystrophy and Becker muscular dystrophy. The program is being financed by the French Muscular Dystrophy Association (1).

1. *Transgene has new strategy in therapeutic vaccines*. DailyDrugNews.com (Daily Essentials) Feb 25, 2005.

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Natalizumab

Natalizumab, the first in a new class of drugs known as SAM (selective adhesion molecule) inhibitors, is a humanized monoclonal antibody that binds to a specific adhesion molecule on the immune cell surface known as α_4 integrin and subsequently inhibits the movement of immune cells to the inflamed gut, as in Crohn's disease, or to brain tissue, as in multiple sclerosis (MS). Natalizumab was launched in the U.S. in 2004 as Tysabri® by Elan and co-development partner Biogen Idec for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical relapses. However, early in 2005, the companies voluntarily withdrew the product from the U.S. market and suspended dosing in all clinical trials based on reports of progressive multifocal leukoencephalopathy (PML), a rare and frequently fatal demyelinating disease of the central nervous system, in 2 patients treated with natalizumab in combination with Avonex® (interferon beta-1a). All regulatory applications, including those filed in Canada and the E.U. for MS and in the E.U. for the treatment of Crohn's disease, were withdrawn. Following an extensive safety evaluation of the product, in September 2005, Elan and Biogen Idec submitted a supplemental BLA for the product with the FDA seeking approval for use in MS. The filing included final 2-year data from the phase III AFFIRM monotherapy trial and SENTINEL add-on trial with Avonex® (interferon beta-1a) in MS, integrated safety assessment of patients treated with natalizumab in clinical trials, and a revised label and risk management plan. The companies have requested priority review status for the sBLA. Biogen Idec and Elan have submitted a similar data package to the EMEA (1-26).

The potential benefits of combining natalizumab with interferon beta-1a (Avonex®) therapy in the treatment of MS were evaluated in the SENTINEL study. This multicenter, double-blind clinical trial randomized 1,171 MS patients to supplement their baseline Avonex® therapy with placebo or natalizumab for 2 years. A recent analysis has shown that, compared to Avonex® alone, supplementation with natalizumab decreased the risk of disability progression by 24% and the rate of clinical relapses by 56% at the end of the treatment period. SENTINEL also met all secondary endpoints, including MRI measures. The most frequent adverse events were headache, nasopharyngitis, limb pain, depression, flu-like symptoms, diarrhea, insomnia, sinusitis, influenza, nausea, muscle pain, anxiety and cough. No significant differences between study groups were found in the incidence of infections (13, 22).

The phase III AFFIRM monotherapy trial achieved the 2-year primary endpoint of slowing the progression of disability in patients with relapsing forms of MS. Natalizumab treatment led to a 42% reduction in the risk of disability progression relative to placebo. The data also demonstrated a 67% reduction in the rate of clinical relapses over 2 years, which was sustained and consistent with 1-year results. Other data from AFFIRM at 2 years, including MRI measures and immunogenicity, were similar to previously reported results. AFFIRM was a 2-year, multicenter, randomized, double-blind, placebo-controlled study in 942 patients conducted at 99 sites worldwide, evaluating the effect of natalizumab on the progression of disability as measured by the EDSS and the rate of clinical relapses. Patients were randomized to receive either placebo or a 300-mg i.v. infusion of natalizumab every 4 weeks (21, 22).

Analysis of both the above trials indicated a low level of immunogenicity associated with natalizumab. Patients were tested for antibodies every 12 weeks; antibodies were detected in approximately 10% of patients at least once during treatment, with 6% of patients remaining persistently positive. Persistently positive antibodies were associated with a substantial decrease in efficacy and an increase in certain infusion-related adverse events. Almost all patients who tested positive for antibodies did so within the first 12 weeks of treatment (22).

A single-patient study assessed the effects of natalizumab given once monthly to a 5-year-old girl with MS unresponsive to interferon beta-1a, methylprednisolone and cyclophosphamide. The patient was quadriplegic and blind as a result of disease progression, and natalizumab

(3 mg/kg once monthly for 4 months, followed by 6 mg/kg once monthly) was given as rescue therapy. The clinical condition of the patient improved after she began receiving natalizumab, and at 29 weeks she had become fully ambulatory, had partially recovered vision in her right eye and disease activity was minimal. No changes in liver function tests or drug-related adverse events were found (27).

A multicenter, double-blind, randomized, placebo-controlled clinical trial evaluated the effects of natalizumab in the treatment of MS relapses. A total of 180 patients with mild to moderate MS and symptoms of acute relapse were given single doses of natalizumab (1 or 3 mg/kg i.v.) or placebo and were followed for up to 14 weeks postdose. Natalizumab induced no significant effects on the short-term clinical course of the patients. Most of them showed clinical improvements during the follow-up period regardless of treatment. The volume of gadolinium-enhancing lesions of the patients decreased significantly with natalizumab compared to placebo at weeks 1 and 3 postdose. Natalizumab showed a good safety profile, and the most common adverse events were headache, pharyngitis, dizziness, nausea, pain, insomnia and asthenia. The MRI improvements found in this clinical trial support the clinical evaluation of multiple doses of natalizumab in MS (28).

1. *European filing for Antegren for MS planned for summer*. DailyDrugNews.com (Daily Essentials) March 25, 2004.

2. *Biogen Idec reports 2003 year-end R&D highlights*. Biogen Idec Press Release 2004, March 2.

3. *Elan and Biogen Idec to file for approval of Antegren for Crohn's disease in Europe*. DailyDrugNews.com (Daily Essentials) May 20, 2004.

4. *Elan Corp. reports 2003 year-end R&D highlights*. Elan Corp. Press Release 2004, Feb 18.

5. *Priority review and accelerated approval designations for Antegren BLA*. DailyDrugNews.com (Daily Essentials) July 2, 2004.

6. *Antegren submitted for approval in Canada*. DailyDrugNews.com (Daily Essentials) Aug 19, 2004.

7. *Elan reports Q1 R&D highlights.* Elan Corp. Press Release 2004, May 13.

8. *New head-to-head study compares Tysabri to Rebif*. DailyDrugNews.com (Daily Essentials) Dec 23, 2004.

9. *Biogen Idec and Elan suspend Tysabri*. DailyDrugNews.com (Daily Essentials) March 1, 2005.

10. *Biogen Idec reports Q2 R&D highlights*. Biogen Idec Press Release 2005, July 26.

11. *Elan reports Q2 R&D highlights*. Elan Corp. Press Release 2005, July 28.

12. *Tysabri safety evaluation update*. DailyDrugNews.com (Daily Essentials) Aug 11, 2005.

13. *Natalizumab reported to improve the effects of interferon beta-1a in multiple sclerosis*. DailyDrugNews.com (Daily Essentials) July 21, 2005.

14. *Phase III Crohn's disease study of Tysabri meets endpoints*. DailyDrugNews.com (Daily Essentials) July 4, 2005.

15. *Biogen reports Q1 R&D highlights*. Biogen Press Release 2005, April 27.

16. *Elan reports Q1 R&D highlights.* Elan Corp. Press Release 2005, April 28.

17. *Past Tysabri patient had PML*. DailyDrugNews.com (Daily Essentials) April 4, 2005.

18. *Tysabri investigator confirms case of PML*. DailyDrugNews.com (Daily Essentials) March 9, 2005.

19. *Tysabri safety evaluation completed with no new cases of PML*. DailyDrugNews.com (Daily Essentials) Oct 19, 2005.

20. *Supplemental BLA submitted for Tysabri for MS*. DailyDrugNews.com (Daily Essentials) Sept 28, 2005.

21. *Tysabri approved for multiple sclerosis*. DailyDrugNews.com (Daily Essentials) Nov 25, 2004.

22. *Phase III Tysabri study in MS meets two-year endpoint*. DailyDrugNews.com (Daily Essentials) Feb 22, 2005.

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24. *Antegren BLA for MS accepted for review*. DailyDrugNews.com (Daily Essentials) July 28, 2004.

25. *European MAA submission for Antegren for MS*. DailyDrugNews.com (Daily Essentials) June 8, 2004.

26. *Elan and Biogen Idec announce Antegren(R) (natalizumab) phase III maintenance trial in Crohn's disease met its primary endpoint.* Elan Corp. Press Release 2004, Jan 29.

27. Choudry, S., Maxwell, S., Jeffery, D.R., Panzara, M., Roach, E.S. *Single-patient study for the emergency use of natalizumab (Antegran) in the treatment of pediatric multiple sclerosis*. Neurology 2004, 62(7, Suppl. 5): Abst P06.082.

28. O'Connor, P.W., Goodman, A., Wilmer-Hulme, A.J. et al. *Randomized multicenter trial of natalizumab in acute MS relapses*. Clinical and MRI effects. Neurology 2004, 62(11): 2038.

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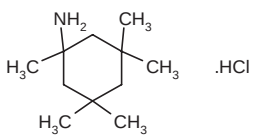
Neramexane Hydrochloride



Neramexane hydrochloride is a low-to-moderate-affinity, uncompetitive NMDA receptor antagonist that is being co-developed by Forest Laboratories and Merz for the treatment of Alzheimer's disease (AD). Evidence suggests that neramexane selectively blocks the excitotoxic effects caused by an abnormal transmission of the neurotransmitter glutamate, which is involved in the neural pathways associated with learning and memory. A multicenter, double-blind, proof-of-concept phase III trial compared the effects of placebo *vs.* neramexane given for 24 weeks to 198 patients with moderate to severe AD not receiving any other treatment for dementia. Daily function, which was evaluated using the Alzheimer's Disease Cooperative Study Inventory - Activities of Daily Living (ADCS-ADL) scale, significantly improved with neramexane compared to placebo at the end of the study. Patients given neramexane also showed significant improvements in the Severe Impairment Battery (SIB) cognition scores at week 12, but not at week 24. No significant differences were found between the safety profiles of the two study treatments. Based on these findings, Forest announced that it would continue developing neramexane in this indication (1, 2).

A preliminary analysis of data from the first phase III study of neramexane failed to achieve statistical significance. The 6-month, double-blind, parallel-group study

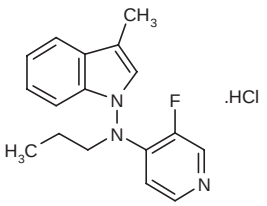
was designed to evaluate the safety and efficacy of combination therapy with neramexane and any of the three most widely prescribed acetylcholinesterase inhibitors (AChEI) compared to an AChEI alone in 415 outpatients with moderate to severe AD. Early analysis of data indicated that patients receiving neramexane and an AChEI did not achieve a statistically significant difference compared to patients on an AChEI alone on the study's primary endpoints of cognition and function. The primary endpoints were the SIB and the ADCS-ADL scale modified for severe dementia (ADCS-ADLsev). The secondary endpoint, the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), also failed to show statistical significance. There were no safety issues identified in the study (3).

1. *Forest Laboratories reports Q4 R&D highlights*. Forest Laboratories, Inc. Press Release 2004, April 20.

2. *Update on the effects of neramexane in Alzheimer's disease*. DailyDrugNews.com (Daily Essentials) July 21, 2005.

3. *Neramexane fails to reach statistical significance in phase III Alzheimer's study*. DailyDrugNews.com (Daily Essentials) Sept 3, 2004.

Nerispirdine Hydrochloride



Nerispirdine hydrochloride (HP-184), an acetylcholine release enhancer and dual Na^+/K^+ ion channel blocker, is under phase II clinical testing at Sanofi-Aventis for the treatment of spinal cord injury.

NeuroVax™

The Immune Response Corporation is conducting phase II clinical evaluation of NeuroVax™, its T-cell receptor (TCR) peptide vaccine for the treatment of relapsing or secondary progressive multiple sclerosis (MS), in collaboration with Oregon Health & Science University (OSHU). It is comprised of a mixture of three TCR peptides selected to represent three TCR families overexpressed in MS patients (BV5S2, BV6S5 and BV13S1), combined with incomplete Freund's adjuvant to improve immune response rates. Immune Response is seeking a partner for commercialization of this program. The company recently announced a new phase II study to investigate the long-term safety, mechanism of action and utility of a quarterly dosing regimen of NeuroVax™. The open-label study will enroll 40 patients with relapsing-remitting or secondary progressive MS, of whom approximately 30 will be rollover patients from a previous study. Patients in this new study will receive 3 monthly NeuroVax™ injections followed by 3 quarterly injections. Results are expected in 2006. Previous data demonstrated that NeuroVax™ produced a peptide-specific immune response in 94% of patients treated in a phase I/II trial in MS. A separate open-label rollover study has now completed enrollment and is following those patients to evaluate the long-term safety of NeuroVax™. The new phase II study will build on the knowledge acquired in these studies. While the first completed controlled study was not designed to evaluate clinical benefit, the investigators observed a trend favoring decreased MRI activity among patients who responded to NeuroVax™ immunologically. Data from the phase II trial of NeuroVax™ in MS demonstrated that monthly NeuroVax™ injections given during a 1-year period increased the FOXP3 marker and regulatory T-cell functional activity in MS patients to a level equivalent to that seen in healthy controls (1-6).

1. *Development of NeuroVax supported by ITN grant*. DailyDrugNews.com (Daily Essentials) April 8, 2004.

2. *Immune Response Corporation expands MS development program*. DailyDrugNews.com (Daily Essentials) Dec 13, 2004.

3. *New phase II study for NeuroVax*. DailyDrugNews.com (Daily Essentials) March 4, 2005.

4. *The Immune Response Corporation reports update on HIV and MS clinical programs*. DailyDrugNews.com (Daily Essentials) Sept 22, 2005.

5. Vandenbark, A., Bartholomew, R., Bourdette, D. *Boosting regulatory T-cells in multiple sclerosis: Immunogenicity and safety of a trivalent BV5S2, BV6S5 and BV13S1 CDR2 vaccine in incomplete Freund's adjuvant*. J Neurol 2004, 251(Suppl. 3): Abst 184.

6. Offner, H. et al. *Expression of the Treg cell associated FOXP3 gene is decreased in MS patients and increases following immunisation with a T cell receptor peptide vaccine*. J Neurol 2005, 252(Suppl. 2): Abst O62.

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Bourdette, D., Guttmann, C.R.G., Nagy, Z.P. et al. *Boosting regulatory T cells with T cell receptor peptides: A tripeptide vaccine in incomplete Freund's adjuvant is highly immunongenic in multiple sclerosis patients*. Neurology 2004, 62(7, Suppl. 5): Abst S40.001.

Vandenbark, A. et al. *TCR peptide vaccination in MS induces high levels of IL-10 and restores decreased FOXP3 levels*. 21st Congr Eur Comm Treat Res Multiple Scler (Sept 28-Oct 1, Thessaloniki) 2005, Abst P 652.

NGX-267

NGX-267, a selective cholinergic muscarinic M_1 receptor agonist, is TorreyPines Therapeutics' (formerly Neurogenetics) lead Alzheimer's disease (AD) product candidate and is presently in phase I clinical trials. The compound was licensed from Life Science Research Israel. NGX-267 may be simultaneously effective in treat-

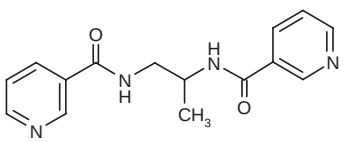
ing the memory and cognitive disturbances experienced by AD patients and in reducing the formation of neurotoxic proteins, thereby delaying disease progression. Compared to other cholinergic agonists, the properties of NGX-267 suggest exceptional pharmacological specificity, and as a result, it may exhibit fewer adverse side effects at doses that improve memory and potentially lower β-amyloid (Aβ) production and deposition. The M_1 receptor plays an important role in memory and cognitive processing. Its activation has also been linked to decreases in Aβ production and tau protein phosphorylation, both of which are involved in the formation of the neurofibrillary tangles and amyloid plaques that are major histopathological hallmarks of AD. The phase I trial will be conducted at a single U.S. center and will enroll approximately 55 healthy volunteers. The single-dose trial will assess the tolerance, safety and pharmacokinetics of NGX-267. If successful, this trial will be followed by a second phase I trial to be conducted in an age-appropriate population that more closely emulates AD patients (1-3).

1. *Neurogenetics changes name to TorreyPines Therapeutics*. DailyDrugNews.com (Daily Essentials) March 22, 2005.

2. *TorreyPines Therapeutics files IND for Alzheimer's drug NGX-267*. DailyDrugNews.com (Daily Essentials) June 9, 2005.

3. *NGX-267 for Alzheimer's disease enters phase I study*. DailyDrugNews.com (Daily Essentials) Aug 10, 2005.

Nicaraven



A free radical-scavenging antioxidant from Chugai, nicaraven (AVS, Antevas®) injection is awaiting registration in Japan for the treatment of subarachnoid hemorrhage.

Original monograph – Drugs Fut 1983, 8(6): 485.

NLX-P101

Positive interim results were reported in September from Neurologix's landmark phase I gene therapy trial of NLX-P101 (AAV-GAD) for the treatment of Parkinson's disease. The open-label dose-escalation trial uses a viral vector (the adeno-associated virus, or AAV) to transfer the gene encoding glutamic acid decarboxylase (GAD) and involves 4 patients in each of 3 escalating-dose cohorts. The third cohort of 4 patients receives 10 times the dose of the first cohort. The 12 patients participating in the trial were diagnosed with severe Parkinson's disease of at least 5 years' duration no longer adequately responding to current medical therapies. The vector was injected unilaterally into the subthalamic nucleus, a deep brain structure known to function abnormally in Parkinson's patients, to transfer the gene encoding GAD, an enzyme that synthesizes GABA, the major brain inhibitory neurotransmitter. Twelve patients in total have undergone gene transfer; 7 of the 8 repesenting the low- and mid-dose cohorts have now been evaluated 1 year following treatment, 3 of the remaining 5 have been followed for 6 months and the other 2 for more than 4 months. The primary outcome measure of this phase I study is safety. According to interim findings, the treatment appears to be safe and well tolerated. Moreover, patients exhibited a statistically significant improvement (27%) in motor function on the side of the body corresponding to the treated part of the brain, as measured by the UPDRS, whereas no significant improvement was seen on the untreated side. Activities of daily living also showed a strong trend for improvement. PET scans at 1 year revealed that the treated side of the brain exhibited a statistically significant decrease in abnormal metabolism, whereas the untreated side showed a further increase. Pending final results, Neurologix intends to submit a pivotal trial protocol to the FDA for the use of the therapy in the treatment of Parkinson's disesae (1-3).

1. *Phase I gene therapy study for Parkinson's nears completion*. DailyDrugNews.com (Daily Essentials) May 3, 2005.

2. *Diamyd's comments on GAD-gene therapy*. DailyDrugNews.com (Daily Essentials) May 20, 2005.

3. Feigin, A. et al. *Gene therapy for Parkinson's disease with AAV-GAD: An open-label, dose escalation, safety-tolerability trial*. 19th Annu Symp Etiol Pathog Treat Parkinson Dis Other Mov Disord (Sept 25, San Diego) 2005, Abst.

N-PEP-12

Ebewe Pharma's N-PEP-12, a derivative of Cerebrolysin®, is a dietary supplement consisting of neuropeptides and amino acids. In animal experiments, the compound has been shown to enhance cognitive function and reduce neurodegenerative events associated with aging. The effects of a single oral dose of N-PEP-12 (180 mg) on brain bioelectrical activity and cognitive performance were examined in a study in healthy elderly subjects. N-PEP-12 induced a significant increase in relative α-activity power 6 h after administration. This enhancement was accompanied by a generalized decrease in slow δ activity. Significant improvement in memory performance subtests was also seen 6 h after N-PEP-12 administration in some but not all tests. Taken together, these data suggest that N-PEP-12 might be a reliable dietary supplement worth investigating for improving and perhaps maintaining brain function among healthy older adults (1).

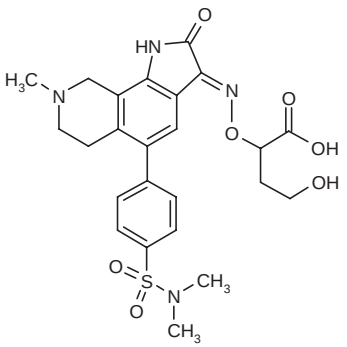
1. Álvarez, X.A., Corzo, L., Laredo, M., Sampedro, C., Cacabelos, R., Windisch, M., Moessler, H., Crook, T.H.

Neuropeptide dietary supplement N-PEP-12 enhances cognitive function and activates brain bioelectrical activity in healthy elderly subjects. Methods Find Exp Clin Pharmacol 2005, 27(7): 483.

Additional References

Crook, T.H. et al. *Effects of N-PEP-12 on memory among older adults*. Int Clin Psychopharmacol 2005, 20(2): 97.

NS-1209



NeuroSearch is conducting two phase II studies of the AMPA antagonist NS-1209 in approximately 60 patients with refractory status epilepticus at 10 centers in Denmark, Sweden and Finland. Positive clinical effects have been seen to date in the open-label epilepsy studies. The goal of the studies is to develop NS-1209 for emergency treatment of severe, prolonged seizures. NeuroSearch has also decided to initiate a limited phase I/II study in neuropathic pain following nerve damage, where the compound has demonstrated good effect in preclinical models. Based on the neuroprotective effect of NS-1209, other potential indications are also being assessed (1-5).

1. *NeuroSearch reports 2003 year-end R&D highlights*. NeuroSearch A/S Web Site 2004, March 10.

2. *NeuroSearch initiates phase II studies of NS-1209 for refractory status epilepticus*. DailyDrugNews.com (Daily Essentials) July 22, 2004.

3. *NeuroSearch A/S reports Q1 R&D highlights*. NeuroSearch A/S Web Site 2004, April 28.

4. *NeuroSearch A/S reports Q1 R&D highlights*. NeuroSearch A/S Press Release 2005, April 27.

5. *NeuroSearch A/S reports Q2 R&D highlights*. NeuroSearch A/S Press Release 2005, Aug 31.

NS-2330

NeuroSearch and Boehringer Ingelheim have been collaborating on the development of NS-2330, a compound that inhibits the reuptake of the three neurotransmitters 5-HT, norepinephrine and dopamine, as a potential therapy for Parkinson's disease and Alzheimer's disease. However, results from three recently completed phase II studies of NS-2330 in Alzheimer's disease (AD) and Parkinson's disease did not meet Boehringer Ingelheim's efficacy criteria to proceed with phase III development. As such, Boehringer Ingelheim decided to terminate development for the AD indication, while remaining options for Parkinson's disease are still being assessed. In AD the decision was based on the results of a 14-week phase II proof-of-concept trial in 430 patients with mild to moderate AD. In Parkinson's disease, the decision was based on the results of two 14-week phase II proof-of-concept trials in 515 patients diagnosed with advanced or early-stage Parkinson's disease. NS-2330 has now been tested in more than 1,000 humans. All relevant preclinical safety testing has been completed with satisfactory results. Based on the safety profile and the mechanism of action of the compound, Boehringer Ingelheim and partner NeuroSearch are assessing possible options for development of NS-2330 in additional indications. Boehringer Ingelheim is responsible for financing the development of NS-2330 (1-8).

Results from a 4-week, randomized, double-blind, placebo-controlled clinical trial involving 9 patients with relatively advanced Parkinson's disease found that treatment with NS-2330 (1.5 mg 3 times/week for 8 doses) was ineffective. Following a 1-week placebo run-in period, patients received placebo, NS-2330 alone or NS-2330 in combination with optimal-dose i.v. levodopa infusion + oral carbidopa (50 mg every 3 h). Parkinsonian scores of patients receiving NS-2330 alone or in combination with levodopa were not altered at the end of the treatment period. Moreover, the severity of dyskinesia and the duration of antiparkinsonian response to levodopa were not affected by NS-2330 treatment (9).

1. *NeuroSearch reports 2003 year-end R&D highlights*. NeuroSearch A/S Web Site 2004, March 10.

2. *NeuroSearch A/S reports Q1 R&D highlights*. NeuroSearch A/S Web Site 2004, April 28.

3. *Enrollment completed in three phase II trials of NS-2330*. DailyDrugNews.com (Daily Essentials) Nov 11, 2004.

4. *NeuroSearch A/S reports Q2 R&D highlights*. NeuroSearch A/S Press Release 2004, Aug 18.

5. *NS-2330 results do not warrant phase III studies in Alzheimer's, Parkinson's*. DailyDrugNews.com (Daily Essentials) Aug 16, 2005.

6. *NeuroSearch A/S reports Q2 R&D highlights*. NeuroSearch A/S Press Release 2005, Aug 31.

7. *NeuroSearch A/S reports Q1 R&D highlights*. NeuroSearch A/S Press Release 2005, April 27.

8. *Neurosearch receives payment for NS-2330 development*. DailyDrugNews.com (Daily Essentials) Jan 27, 2005.

9. Bara-Jimenez, W., Dimitrova, T., Sherzai, A., Favit, A., Mouradian, M.M., Chase, T.N. *Effect of monoamine reuptake inhibitor NS 2330 in advanced Parkinson's disease*. Mov Disord 2004, 19(10): 1183.

NTx™-265

Patient dosing has been completed in the phase I clinical study of Stem Cell Therapeutics' NTx™-265 stroke program. The clinical trial, conducted in Denmark, is expected to characterize the pharmacokinetic profile of two currently marketed drug candidates, identified by SCT as effective in preclinical models of stroke. NTx™-265, the company's lead therapeutic product, has been shown to increase the number of innate adult stem cells that grow in place when this therapeutic approach is applied to test animals. The company then plans to conduct a phase II trial to evaluate the safety and efficacy in stroke patients (1-4).

1. *Stem Cell Therapeutics retains Medicon for phase I trial of NTx-265*. DailyDrugNews.com (Daily Essentials) Aug 30, 2005.

2. *Phase I protocol submitted for Stem Cells Therapeutics' stroke program*. DailyDrugNews.com (Daily Essentials) Oct 6, 2005.

3. *Dosing begins in phase I study of NTx-265 for stroke*. DailyDrugNews.com (Daily Essentials) Dec 2, 2005.

4. *Approval for phase I study in Stem Cell Therapeutics' stroke program*. DailyDrugNews.com (Daily Essentials) Nov 11, 2005.

Oxycyte™

Synthetic Blood International plans to initiate phase II clinical trials with its proprietary perfluorocarbon (PFC) blood substitute and therapeutic oxygen carrier Oxycyte™ in patients with traumatic brain injury and sickle cell anemia. In an effort to expedite the advancement of Oxycyte™ and gain phase II data, it has temporarily suspended enrollment in its phase II trial in patients with hip revision surgery to allocate resources to the smaller, faster phase II studies. Synthetic Blood believes that recruitment in the 8-patient traumatic brain injury trial and the 20-patient sickle cell trial will be rapid. The company submitted an amendment to its Oxycyte™ IND in August 2005 to initiate a phase II proof-of-concept study to evaluate the safety and biological effects of Oxycyte™ in patients with traumatic brain injury. In this 8-patient, open-label phase II pilot study, Oxycyte™ will be administered to patients with severe traumatic brain injury and a Glasgow Coma Scale score of 3-9 within 24 h of the injury's occurrence. The primary purpose of this study will be to demonstrate Oxycyte™'s ability to increase brain oxygen tension and favorably affect other brain chemistries that impact clinical outcome in patients suffering severe head injury. Additionally, the study will further assess the safety of Oxycyte™ when given by i.v. infusion. Recently reported preclinical study data suggest that Oxycyte™ improves cognitive recovery following traumatic brain injury in a fluid percussion injury model, a widely accepted rat model that simulates moderate head injury with prolonged cognitive deficits sustained in humans. Cognitive recovery was determined by performance in a standard water maze test. In the study, rats administered Oxycyte™ at 4.5 and 9.0 ml/kg showed significantly better performance in the water maze test and had fewer dying neurons in the brain than control animals treated with a saline solution. Additionally, the group receiving Oxycyte™ at the higher dose maintained mean arterial blood pressure at a relatively higher level, which could indicate a further improvement in the cerebral blood flow after traumatic brain injury (1, 2).

1. *Phase II studies planned for Oxycyte*. DailyDrugNews.com (Daily Essentials) Oct 6, 2005.

2. *Oxycyte produces positive results in preclinical traumatic brain injury study*. DailyDrugNews.com (Daily Essentials) Oct 26, 2005.

PBT-2

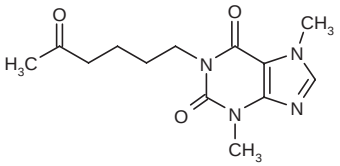
Positive results were reported from a phase I trial of Prana Biotechnology's PBT-2 in a total of 55 healthy volunteers. This double-blind, placebo-controlled study determined the safety and pharmacokinetics of single doses of PBT-2. The results of the study showed that drug exposure increased linearly with dose, and that the incidence of adverse events in patients treated with PBT-2 was very similar to that found in placebo-treated patients. Prana Biotechnology is developing PBT-2 for the treatment of Alzheimer's disease (AD). PBT-2, a metal-protein-attenuating compound (MPAC), is the successor to PBT-1 (clioquinol) for the treatment of AD and is designed to have an improved safety and efficacy profile. MPACs bind specific metals, such as copper, zinc and iron, to decrease the interaction of these metals with proteins. The compound has demonstrated significantly greater efficacy in lowering plaque in the transgenic mouse model in both preclinical *in vitro* and *in vivo* testing. It appears to be better than PBT-1 at decreasing the toxicity of plaques through improved peroxide inhibition, and also appears to have superior pharmaceutical characteristics, such as improved solubility. An ongoing dose-escalation trial is assessing the pharmacokinetics and safety of multiple doses of PBT-2 in elderly healthy volunteers (1-3).

1. *Prana begins phase I trial for PBT-2*. DailyDrugNews.com (Daily Essentials) March 18, 2005.

2. *Prana completes review of development program*. Prana Biotechnology Press Release 2005, June 16.

3. *Good safety profile of single-dose PBT-2 in healthy volunteers*. DailyDrugNews.com (Daily Essentials) Nov 8, 2005.

Pentoxifylline, Sustained-Release

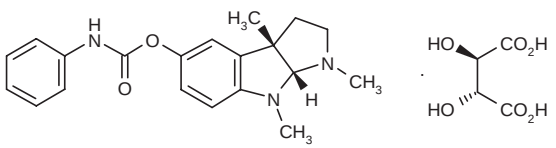


ExonHit Therapeutics' phase III trial of sustained-release pentoxifylline (Ikomio®) in amyotrophic lateral sclerosis (ALS, Charcot's disease, Lou Gehrig's disease) failed to demonstrate any benefit in survival compared to placebo. The double-blind, randomized, placebo-controlled study enrolled 400 participants at 12 European sites in Belgium, France, Germany and the U.K. Pentoxifylline or placebo was administered in addition to Rilutek® (riluzole), the only currently approved treatment for ALS. Patients were treated for 18 months and the primary endpoint was survival at this time point. Both treatment groups were strictly comparable at the start of the study and no imbalance in prognostic factors was observed (1, 2).

1. *ExonHit develops improved formulation of Ikomio*. DailyDrugNews.com (Daily Essentials) June 23, 2004.

2. *Phase III trial of Ikomio for ALS fails to show survival benefit*. DailyDrugNews.com (Daily Essentials) Oct 6, 2004.

Phenserine Tartrate



Axonyx recently decided not to commit further resources to the development of phenserine tartrate, its dual acetylcholinesterase and β-amyloid inhibitor developed for the treatment of Alzheimer's disease, after evaluating the whole development program, including the results from the first phase III trial, the results of the curtailed and combined analysis of the second and third phase III trials and the interim analyses of the β-amyloid trial, as well as recent additional patient data. None of the trials achieved statistical significance for the primary endpoints, although positive signals were observed in all the clinical trials to date, including the interim analyses of the phase IIb β-amyloid trial. The results of this trial to date appear to show a difference between phenserine 15 mg and placebo on the levels of β-amyloid 1-42. The magnitude of this difference and the variability of these data show that a larger investigation than planned would be needed to demonstrate a statistically significant effect. The company believes that a reformulated phenserine providing potentially higher drug exposure may improve the efficacy profile and potential amyloid-lowering effects. Axonyx plans to use data collected to date to produce a marketing package for potential licensees (1-9).

1. *Axonyx updates pipeline status*. DailyDrugNews.com (Daily Essentials) Nov 10, 2005.

2. *Higher doses of phenserine may be efficacious in mild to moderate Alzheimer's disease*. DailyDrugNews.com (Daily Essentials) Dec 2, 2005.

3. *Second phase III trial of phenserine for Alzheimer's disease*. DailyDrugNews.com (Daily Essentials) June 18, 2004.

4. *Phenserine fails to achieve significant efficacy in phase III Alzheimer's study*. DailyDrugNews.com (Daily Essentials) Feb 9, 2005.

5. *Second interim analysis of phenserine tartrate study in Alzheimer's disease*. DailyDrugNews.com (Daily Essentials) Aug 4, 2005.

6. *Axonyx reports Q2 R&D highlights*. Axonyx Press Release 2005, Sept 8.

7. *Axonyx announces results of interim analysis of beta-amyloid trial; data meet pre-defined criteria for continuing trial enrollment in top dose group*. Axonyx Press Release 2005, March 11.

8. *Treatment completed in phase III phenserine trial*. DailyDrugNews.com (Daily Essentials) Dec 30, 2004.

9. *Progression of Axonyx phase IIb trial of phenserine*. DailyDrugNews.com (Daily Essentials) May 11, 2004.

Original monograph – Drugs Fut 2003, 28(1): 18.

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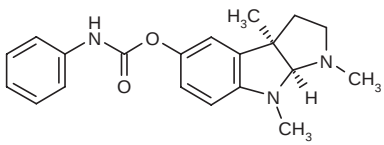
Giacobini, E. *Safety, tolerability, and pharmacokinetics of phenserine in the treatment of mild-to-moderate Alzheimer's disease*. 7th Int Conf Prog Alzheimer Parkinson Dis (March 9-13, Sorrento) 2005, Abst.

Winblad, B. *The efficacy of phenserine in the treatment of mild-to-moderate Alzheimer's disease*. 7th Int Conf Prog Alzheimer Parkinson Dis (March 9-13, Sorrento) 2005, Abst.

(+)-Phenserine



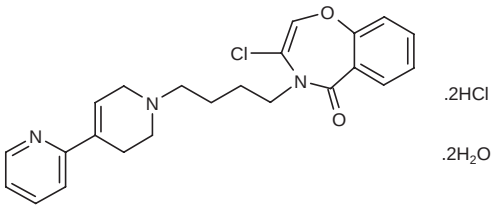
Following FDA approval of Axonyx's IND application, submitted in June 2005, the company began phase I testing of (+)-phenserine (Posiphen™), in development for the treatment of Alzheimer's disease (AD) progression. This first phase I study will primarily evaluate the safety of Posiphen™ in healthy volunteers. In preclinical studies, it has been shown to lower β-amyloid precursor protein (APP) and β-amyloid (Aβ) levels in rodents, as well as demonstrating a favorable side effect rate. Posiphen™ is

the positive isomer of phenserine (see above), which had been in development for the treatment of mild to moderate AD. Axonyx has worldwide patent rights to Posiphen™ with the NIH/National Institute on Aging (NIA) (1, 2).

1. Posiphen given green light to begin phase I. DailyDrugNews.com (Daily Essentials) Aug 4, 2005.

2. Axonyx updates pipeline status. DailyDrugNews.com (Daily Essentials) Nov 10, 2005.

Piclozotan Hydrochloride Hydrate



Piclozotan hydrochloride hydrate (SUN-N4057) is a 5-HT_{1A} receptor agonist in phase II trials overseas at Daiichi Asubio Pharma for the treatment of acute ischemic stroke. Through its 5-HT_{1A} receptor-agonist effect, piclozotan attenuates glutamate-mediated toxicity by inducing hyperpolarization, while avoiding the side effects associated with glutamate antagonists and NMDA receptor modulators.

A multicenter, double-blind, randomized, placebo-controlled clinical trial is under way to determine the effects and safety of piclozotan in patients with acute ischemic stroke and a measurable penumbra within 9 h of onset. In the first stage of the study, 112 patients will be given a 72-h i.v. infusion of placebo or piclozotan (80 or 120 ng/ml) and will be monitored for up to 90 days. Study endpoints will include changes in stroke lesion volume, clinical outcome (evaluated using the Modified Rankin Scale, the Barthel Index and the National Institutes of Health Stroke Scale) and all-cause mortality at 28 and 90 days. Another 94 patients will participate in the second stage of the study and will receive one of the two piclozotan doses used in the first stage (1).

1. Zimmerman, T.R. et al. *Double-blind, placebo-controlled, multicenter, study of SUN N4057 administered for 72 hours by intravenous infusion in subjects with acute ischemic stroke and MRI penumbra*. 14th Eur Stroke Conf (May 25-28, Bologna) 2005, Abst.

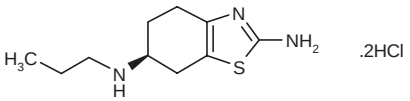
PLD-180

Pliva is pursuing negotiations with third parties for the divesture of its CNS franchise, which includes its phase I pipeline product candidate PLD-180 for the treatment of amyotrophic lateral sclerosis (ALS) (1, 2).

1. *PLIVA terminates agreements with Legacy Pharma*. PLIVA Press Release 2005, Oct 3.

2. *PLIVA divests CNS franchise from proprietary portfolio*. PLIVA Press Release 2005, Aug 1.

Pramipexole Hydrochloride, New Indication



The dopamine agonist pramipexole hydrochloride (Mirapex®, Mirapexin®, Sifrol®, BIoSifrol®) is marketed by Boehringer Ingelheim for the treatment of the signs and symptoms of idiopathic Parkinson's disease, as monotherapy or in combination with levodopa. It is also being studied in phase II and III trials for the treatment of restless legs syndrome (RLS) (1, 2), and the National Institute of Mental Health is conducting studies in major depressive disorder.

The safety and efficacy of pramipexole were evaluated in a 3-week, double-blind, placebo-controlled, dose-finding study in 109 patients with RLS who were randomized to receive one of three doses of pramipexole or placebo. Results showed that pramipexole was effective at doses of 0.125-0.75 mg/day within 3 weeks of therapy, with the most prominent response in patients taking 0.5 and 0.75 mg. Treatment was safe and tolerable in all dose groups (3).

Pramipexole was evaluated in a randomized, double-blind, placebo-controlled trial in 345 patients with RLS who underwent dose titration from 0.125 to 0.75 mg once daily over 4 weeks and received stable doses for 2 more weeks. Analysis of visual analog scale (VAS) symptom severity ratings from the study showed that pramipexole was effective during the night and during the day, reducing RLS severity significantly compared to placebo in both time periods ($p < 0.0001$). The severity of RLS symptoms was significantly reduced at the time of getting to sleep with pramipexole (–31.1) compared to placebo (–13.8). Satisfaction with sleep was also rated significantly higher in pramipexole-treated patients. Analysis of Patient Global Impression scores measured each week in the study showed that 31.2% of patients were much or very much improved after 1 week of treatment with pramipexole 0.125 mg/day. Significantly more patients with an initial response had a response lasting up to week 6 in the pramipexole group (19.8%) as compared to the placebo group (3.74%). At 6 weeks, the mean change in the RLS rating scale score was –12.4 with pramipexole and –5.8 with placebo, and 64.4% of patients responded to pramipexole therapy. Of the patients included in the study, 59 had a severe mood disturbance due to RLS symptoms at baseline. After 6 weeks, 79% of those in the pramipexole group and 35% of those in the placebo group had no mood disturbance or mild mood distur-

bance. Pramipexole was generally well tolerated, with headache, nausea and fatigue being the most common adverse effects (4-8).

The administration of an adenosine A_{2A} receptor antagonist, for instance istradefylline, in combination with a dopaminergic agent, for example a dopamine receptor agonist such as pramipexole, pergolide mesilate, cabergoline or ropinirole hydrochloride, a MAO-B inhibitor such as selegiline hydrochloride or a COMT inhibitor such as entacapone, has been claimed for therapeutic intervention in disorders characterized by functional abnormality of the dopamine system. Targeted disorders include Parkinson's disease, RLS and ADHD (9).

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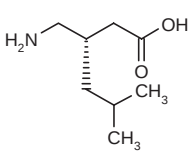
Pregabalin



The GABA analogue pregabalin acts as a voltage-dependent calcium channel $\alpha 2$-δ subunit ligand and possesses analgesic, anticonvulsant and anxiolytic proper-

ties. Developed by Pfizer, the drug was launched in the U.K. and Germany in 2004 and in Italy in 2005 as Lyrica™ for the treatment of peripheral neuropathic pain and as adjunctive therapy for partial seizures resulting from epilepsy, following E.U. approval in July 2004. Also in 2004, the drug received FDA approval for the treatment of postherpetic neuralgia and for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, the first FDA-approved treatment for both of these neuropathic pain states. In 2005, a revised label was approved by the FDA for the add-on indication of partial seizures due to epilepsy. Pregabalin was launched for these indications in the U.S. in September 2005. The drug is undergoing regulatory review in the E.U. for the treatment of generalized anxiety disorder (GAD), although a nonapprovable letter for this indication was issued by the FDA in 2004. Pfizer is also studying pregabalin in phase III trials in patients with neuropathic pain associated with spinal cord injury and for the treatment of fibromyalgia (1-14).

Pharmacokinetic studies of pregabalin in healthy volunteers and patients with renal disease revealed little potential for drug-drug interactions as there was no hepatic metabolism and excretion was primarily renal. Renal function was therefore a determinant of pregabalin clearance. Dose-proportional exposure was seen after single and multiple doses, and pregabalin pharmacokinetics were linear and predictable (15).

Pharmacokinetic profiling revealed significant differences between pregabalin and gabapentin. While pregabalin was absorbed rapidly, reaching peak plasma concentrations within less than 1 h and increasing linearly with dose, gabapentin was absorbed slowly, reaching peak plasma levels between approximately 3 and 4 h. Pregabilin bioavailability was always over 90% (irrespective of dose), whereas gabapentin bioavailability decreased with increasing dose. Recommended drug administration, based on renal clearance, is b.i.d. or t.i.d. for pregabalin and t.i.d. for gabapentin (16).

The pharmacokinetics of pregabalin in healthy subjects were determined in 5 studies in which single and multiple doses of 1-300 mg were investigated. The drug was rapidly absorbed and demonstrated linear, dose-proportional pharmacokinetics after both single- and multiple-dose administration. Food did not affect the extent of pregabalin absorption. Repeated administration led to the achievement of steady state after 1-2 days. The primary means of elimination was by renal clearance (17).

A total of 46 healthy male volunteers aged 18-55 years were included in a multicenter, double-blind trial and received placebo or pregabalin (200 mg t.i.d.) for 14 weeks. No significant differences were found in the percentage of sperm with normal motility, sperm concentration and semen volume of the two study groups at the end of the treatment period and after an 8-week washout phase. No evidence suggesting that pregabalin may have adverse effects on male reproductive function (*e.g.,* changes in the metabolism and binding of sex hormones) was found (18).

A multicenter, double-blind, placebo-controlled clinical trial compared the antiepileptic efficacy of a fixed-dose regimen and a flexible-dose regimen (intended for dose optimization) of pregabalin in 341 patients with refractory partial seizures. Each patient was randomized to receive placebo, fixed-dose pregabalin (600 mg/day b.i.d.) or flexible-dose pregabalin (150 mg/day for 2 weeks, followed by 300 mg/day for 2 weeks, 450 mg/day for 4 weeks and 600 mg/day for 4 weeks) for a total of 12 weeks. Patients randomized to receive a flexible-dose pregabalin regimen could adjust their daily dose based on tolerability. At the end of the study, the number of seizures decreased by 49.3% with fixed-dose pregabalin, by 35.4% with flexible-dose pregabalin and by 10.6% with placebo. The percentages of patients who withdrew from the study due to adverse events were, respectively, 32.8%, 12.2% and 6.8%, and most adverse events were mild or moderate. The flexible-dose regimen was the most effective and safest overall (19, 20). Analysis of data from this and another similar study (total of 794 patients) confirmed that flexible-dose regimens were at least as effective as fixed-dose regimens and better tolerated, with fewer discontinuations due to adverse events (21).

Spanish researchers used stochastic simulation techniques and data from 3 randomized clinical trials to compare the cost-effectiveness of add-on therapy with pregabalin (300 mg/day) and levetiracetam (2000 mg/day) in a hypothetical cohort of 1,000 patients with partial refractory epilepsy. Pregabalin was associated with a greater increase in the number of seizure-free days (40.9 days *vs*. 24.4 days), greater improvements in quality of life and lower treatment cost scores (22).

Pooled data from 4 double-blind, randomized, placebo-controlled clinical trials were used to study the efficacy and safety of add-on pregabalin in 1,174 refractory patients suffering from partial seizures with or without secondary generalizations. Seizure frequency decreased by 3.5% with placebo and by 27.1%, 43.5% and 49.7%, respectively, with 150, 300 and 600 mg/day of pregabalin. Response to treatment, which was defined as a reduction of at least 50% in seizure frequency, increased dose-dependently with pregabalin (22.2%, 40.0% and 46.1%, respectively, *vs.* 10.1% with placebo). Most pregabalin-related adverse events were mild or moderate (23).

A double-blind trial examined the effects of add-on pregabalin in 15 patients with well-controlled partial seizures and sleep disturbance while receiving antiepileptic drug monotherapy. Compared to placebo, a dose of 300 mg/day of pregabalin given for 4 weeks significantly improved sleep efficiency and reduced the number of awakenings. Evidence suggested that this effect was independent of the drug's anticonvulsant efficacy (24).

Analysis of data from 4 open-label add-on clinical trials in which pregabalin (maximum dose of 600 mg/day) was administered to 1,480 patients with partial seizures for up to 1,989 days found that, compared to baseline, seizure frequency improved by an average of 41.3% at the end of the treatment period. Depending on the clinical trial, the percentage of seizure-free patients was 7.4-24.2% over

the last 6 months of treatment, and 4.5-18.4% over the last year. Long-term administration of pregabalin had no adverse effects on the drug's safety profile (25-27).

Pooled data from 3 double-blind, randomized, placebo-controlled clinical trials revealed that the antiepileptic effects of add-on therapy with pregabalin (150-600 mg/day for 12 weeks) in patients refractory to two antiepileptic drugs (AEDs) were not affected by either duration of epilepsy or number of concomitant AEDs (28).

The efficacy of pregabalin in reducing seizures of different types in patients with refractory disease was evaluated in a *post hoc* analysis of data from 3 multicenter, double-blind, randomized, placebo-controlled studies. Study subjects were treated with 150, 300 or 600 mg/day b.i.d. or t.i.d. for 12 weeks. Dose-related efficacy, which was significant with the 600 mg/day dose, was seen in patients with simple and complex partial and secondarily generalized seizures. Pregabalin was also well tolerated (29, 30).

Dose-related efficacy was observed in an analysis of data from 3 randomized, double-blind, placebo-controlled trials in which patients with refractory partial seizures were treated with pregabalin for 12 weeks. Increasing pregabalin doses were associated with decreases in seizure frequency in 75% of the 1,042 patients evaluated. Seizures were reduced by as much as 100% in women and by 78% in men by a dose of approximately 186 mg/day (31).

The pharmacological interaction between pregabalin and oral contraceptives was assessed in a study in healthy female volunteers in which an oral contraceptive (Ortho-Novum 1/35 tablet once daily) for the first 21 days of 3 consecutive menstrual cycles was combined with pregabalin (200 mg t.i.d.) during the first 21 days of the third menstrual cycle. Pregabalin had no significant effects on the pharmacokinetic profile of norethindrone and ethinylestradiol, and no ovulations took place during oral contraceptive therapy, either alone or combined with pregabalin (32, 33).

Pooled data from 3 double-blind, randomized, placebo-controlled clinical trials in a total of 484 patients were used to study whether the efficacy and tolerability of add-on pregabalin is affected by oral contraceptive use or menopausal status. In the oral contraceptive group, 27%, 40% and 43% of patients administered pregabalin doses of 150, 300 and 600 mg/day, respectively, experienced decreases of 50% or more in seizure frequency compared to 21%, 43% and 53%, respectively, of patients not using contraceptives. The anticonvulsant effects of pregabalin were not affected by either menopausal status or by the concomitant administration of oral contraceptives. The most common adverse events were dizziness and somnolence (34).

A method has been claimed for promoting improved absorption of the anticonvuslant drugs gabapentin and pregabalin in the treatment of epilepsy and neuropathic pain comprising the inclusion of a functional transport component, for instance an alkyl sulfate group, in pharmaceutical compositions containing such drugs. The claim pertains to the inference that sustained concentrations of either drug within the bloodstream without resorting to regular (*e.g.*, 3 or 4 doses/day) dosing would be highly beneficial. Such compositions are expected to be compatible with once-daily dosing and are predicted to accentuate absorption within the gastrointestinal tract, especially the lower gastrointestinal tract, between 10 and 24 h following administration (35).

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Premarin®, New Indication

Premarin®, conjugated equine estrogens developed by Wyeth and marketed for the treatment and prevention of a variety of postmenopausal symptoms, is being evaluated in the phase II POETRY study as a potential therapy for Parkinson's disease in postmenopausal women (1).

1. *POETRY (NCT00234676)*. ClinicalTrials.gov Web Site 2005, Oct 6.

ProCord

ProCord, Proneuron's autologous activated macrophage cell therapy, is currently being examined in phase II clinical trials for the treatment of acute complete spinal cord injury. ProCord consists of macrophages isolated from the patient's blood, activated through a proprietary process and then injected directly into the patient's injured spinal cord. The therapy involves the induction of nerve regeneration by enhancing the natural macrophage response in injured spinal cord tissue. ProCord, which was originally developed at the Weizmann Institute of Science and licensed to Proneuron, was granted orphan drug designation by the FDA in 2004 (1-4).

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PRX-03140

Predix Pharmaceuticals reported positive findings from the second of two phase Ib multiple-dose studies with PRX-03140, its highly selective 5-HT_4 receptor agonist intended to treat Alzheimer's disease (AD) and other disorders of memory and cognition. The study was the first Predix study in patients with AD. In this double-blind, placebo-controlled trial, patients with mild to moderate AD received a once-daily dose of the study drug. The trial investigated the effects of PRX-03140 on cognitive function and memory, electroencephalograms and biochemical markers of AD pathology. The results suggested that PRX-03140 produced the desired alterations in brain wave activity in the patients, and was well tolerated. The primary objectives of the phase Ib studies in both healthy subjects and patients with AD were to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of the compound over a 14-day period. PRX-03140 was previously well tolerated in healthy volunteers for 14 days at concentrations that were associated with beneficial effects in animal models. In single- and multiple-ascending-dose studies in healthy volunteers, the drug concentrations in humans increased in proportion to increases in dose, and results indicate that the drug can be administered once daily. Results suggest that at well-tolerated doses, PRX-03140 is active at the 5-HT_4 receptor in humans and elicits central nervous system effects. PRX-03140 has a selective receptor binding profile, and preclinical studies have shown that it improves cognitive function, as well as increasing levels of acetylcholine (ACh), soluble amyloid precursor protein (sAPP) and brain-derived neurotrophic factor (BDNF) in regions of the brain known to be important for memory. Phase II trials are expected to commence early next year (1-4).

1. *PRX-03140 enters phase I for Alzheimer's*. DailyDrugNews.com (Daily Essentials) Dec 23, 2004.

2. *PRX-03140 enters phase Ib studies for Alzheimer's*. DailyDrugNews.com (Daily Essentials) April 5, 2005.

3. *PRX-03140 enters phase Ib study in Alzheimer's patients*. DailyDrugNews.com (Daily Essentials) July 18, 2005.

4. *Predix Pharmaceuticals announces positive findings from first clinical trial in Alzheimer's disease patients*. Predix Pharmaceuticals Press Release 2005, Nov 14.

PTC-124

PTC-124 is an orally available small-molecule drug developed at PTC Therapeutics for the treatment of genetic defects resulting from nonsense mutations. Phase I trials have been conducted with a view to its application initially in the treatment of Duchenne muscular dystrophy and cystic fibrosis (CF), and phase II clinical trials were recently initiated in patients with CF. Results from phase I studies confirmed that PTC-124 is orally bioavailable, generally well tolerated, achieves target plasma concentrations that have been associated with activity in preclinical models and does not induce ribosomal readthrough of normal stop codons. Other potential indications under consideration for PTC-124 include hemophilia, neurofibromatosis, retinitis pigmentosa, bullous skin diseases and lysosomal storage diseases. PTC-124 allows the cellular machinery to bypass the nonsense mutation and continue the translation process, restoring the production of full-length functional protein. The product holds orphan drug designation for both indications in the U.S. and the E.U. and the FDA has granted fast track designation for the treatment of CF (1-8).

1. *PTC-124 enters phase I for cystic fibrosis and Duchenne muscular dystrophy*. DailyDrugNews.com (Daily Essentials) July 15, 2004.

2. *PTC-124 awarded orphan drug status for cystic fibrosis*. DailyDrugNews.com (Daily Essentials) Dec 13, 2004.

3. *Further phase I study evaluates PTC-124*. DailyDrugNews.com (Daily Essentials) Dec 29, 2004.

4. *PTC-124 receives fast track status for cystic fibrosis*. DailyDrugNews.com (Daily Essentials) April 5, 2005.

5. *PTC-124 receives orphan drug designations in Europe*. DailyDrugNews.com (Daily Essentials) July 12, 2005.

6. *Orphan drug status for PTC-124 for Duchenne muscular dystrophy*. DailyDrugNews.com (Daily Essentials) Feb 1, 2005.

7. Hirawat, S. et al. *Phase 1 multiple-dose safety and PK study of PTC124 for nonsense mutation suppression therapy of Duchenne musuclar dystrophy (DMD)*. Neurology 2005, 64(6, Suppl. 1): Abst EVG.009.

8. *PTC Therapeutics initiates phase 2 study of PTC124 in cystic fibrosis*. PTC Therapeutics Press Release 2005, Dec 6.

PYM-50018

Phytopharm's second lead neurodegeneration compound, PYM-50018 (Myogane™), is being developed for the oral treatment of amyotrophic lateral sclerosis (ALS). In preclinical models, the plant-derived compound has been shown to protect against neuronal damage, increase neurite outgrowth, reverse oxidative damage and reverse neuronal apoptosis. It was also shown to delay the loss of muscle strength and extend survival time following oral administration in a transgenic preclinical model of ALS. In 2004, PYM-50018 received fast track designation and orphan drug designation in the U.S. for the treatment of ALS. A phase Ia clinical trial evaluating the safety, tolerability and pharmacokinetics of PYM-50018 has been successfully completed, confirming that it was well absorbed and had a good safety profile (1-5).

Forty healthy male subjects participated in a double-blind, randomized, placebo-controlled clinical trial that evaluated the pharmacokinetics and safety of single doses of PYM-50018 (80, 240, 480 or 960 mg p.o.). The level of drug exposure increased with dose and when administered after a high-fat breakfast. All dose levels were well tolerated (6).

1. *R&D highlights from the 3rd Annual Global Biotech Forum for Investing & Partnering: Phytopharm*. DailyDrugNews.com (Daily Essentials) April 27, 2004.

2. *PYM-50018 successfully completes phase I*. DailyDrugNews.com (Daily Essentials) May 6, 2004.

3. *Orphan drug status for PYM-50018 for ALS*. DailyDrugNews.com (Daily Essentials) Aug 4, 2004.

4. *PYM-50018 awarded fast track status for ALS*. DailyDrugNews.com (Daily Essentials) Nov 12, 2004.

5. *Preliminary results for the year ended 31 August 2005*. Phytopharm Press Release 2005, Nov 2.

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PYM-50028

Phytopharm's lead comopund PYM-50028 (Cogane™) is an orally active, synthetic product with neuroprotective and neuroregenerative properties that is being developed for treating patients with Alzheimer's disease (AD; phase II) and Parkinson's disease (phase I). PYM-50028 has been shown in preclinical studies to reverse both the decrease in neuronal growth factors and the neuronal degeneration seen in the aging brain, restoring protein levels to those seen in the young and producing beneficial outgrowth and branching of neurites. It has also been shown to reverse the free radical neurotoxicity produced by MPP+ in neurons, as well as the decrease in dopamine receptors in the brain. An ongoing double-blind, randomized, placebo-controlled phase II clinical trial is evaluating the cognitive effects and safety of PYM-50028 given orally once daily for 12 weeks to AD patients. Interim analysis of data from the first 60 patients to complete the study revealed that PYM-50028 was well tolerated and was not associated with any safety concerns. Pending a positive phase II study outcome, Phytopharm plans to seek global multinational partners in the first half of 2006. Following a portfolio review arising out of its merger with Fujisawa to form Astellas Pharma, Yamanouchi terminated its licensing agreement with Phytopharm for this compound covering Japan and certain other Asian countries (1-5).

1. *R&D highlights from the 3rd Annual Global Biotech Forum for Investing & Partnering: Phytopharm*. DailyDrugNews.com (Daily Essentials) April 27, 2004.

2. *Good safety profile found for PYM-50028 in AD patients*. DailyDrugNews.com (Daily Essentials) Jan 24, 2005.

3. *Yamanouchi may terminate PYM-50028 licensing agreement with Phytopharm*. DailyDrugNews.com (Daily Essentials) March 11, 2005.

4. *Yamanouchi confirms termination of Cogane licensing agreement*. DailyDrugNews.com (Daily Essentials) April 1, 2005.

5. *Preliminary results for the year ended 31 August 2005*. Phytopharm Press Release 2005, Nov 2.

QR-333

Quigley Pharma's QR-333 is a topical compound combining quercetin, ascorbyl palmitate and vitamin D_3, designed and formulated to decrease the oxidative stress that contributes to diabetic peripheral neuropathy and

thereby alleviate the symptoms. The results of a proof-of-principle phase II study of QR-333 in patients with symptomatic diabetic peripheral neuropathy supported further investigation of the drug in this indication. In the randomized, double-blind trial, 34 patients applied topical QR-333 or placebo 3 times daily to each foot where symptoms were noted. At 4 weeks, the severity of numbness, jolting pain and irritation were significantly improved from baseline with QR-333, which also improved overall and specific quality-of-life measures. Adverse events were reported by 11 QR-333-treated patients and 4 placebo-treated patients. Diarrhea was the only event reported by more than 1 QR-333-treated patient, but the 2 cases seen were not thought to be related to the study drug. The only adverse event considered related to QR-333 was a pricking sensation reported twice by 1 patient (1-4).

1. *Quigley completes pre-IND meeting for QR-333*. DailyDrugNews.com (Daily Essentials) April 1, 2004.

2. *Quigley Pharma advances R&D programs*. DailyDrugNews.com (Daily Essentials) Jan 27, 2005.

3. Valensi, P. et al. *A multicenter, double-blind, safety study of QR-333 for the treatment of symptomatic diabetic peripheral neuropathy. A preliminary report*. J Diabetes Complications 2005, 19(5): 247.

4. *Journal of Diabetes and Its Complications publishes favorable study addressing Quigley Pharma's diabetic neuropathy formu*lation QR-333. Quigley Pharma Press Release 2005, Sept 7.

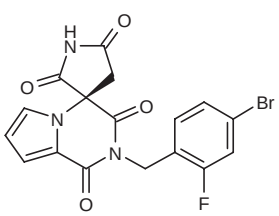
R-1295

R-1295 is a small-molecule integrin receptor antagonist in early clinical development by Roche for the treatment of autoimmune diseases including rheumatoid arthritis and multiple sclerosis

R-1500/R-1577

Roche has two enzyme inhibitor compounds in early clinical development for the treatment of Alzheimer's disease: R-1500 and R-1577.

Ranirestat



Dainippon Sumitomo Pharma and Eisai have signed an exclusive licensing agreement for ranirestat (AS-3201), a potential new treatment for diabetic neuropathy that was discovered and is being developed by Dainippon. Under the agreement, Eisai will assume the exclusive rights to further develop, manufacture and market this compound worldwide outside Japan, while Dainippon retains rights to Japan and to co-promote the compound with Eisai in major countries. Ranirestat is designed to improve the symptoms of diabetic neuropathy by suppressing the accumulation of sorbitol within cells by strongly inhibiting aldose reductase. Dainippon is currently conducting phase III trials in the U.S. and Canada, and phase II trials in Japan with partner Kyorin. In close coordination, Eisai will continue the development currently being conducted by Dainippon and proceed with subsequent trials, seeking early application for approval in the U.S. and other countries (1, 2).

A double-blind phase IIa trial enrolled 101 patients with low-grade to moderate diabetic sensorimotor polyneuropathy who received 12 weeks of treatment with either placebo or ranirestat administered once a day at doses of 5 or 20 mg. There was a dose-related increase in drug concentrations in sural nerve and a dose-related decrease in sorbitol and fructose concentrations in sural nerve cells. Inhibition of the accumulation of sorbitol and fructose was 65% and 44%, respectively, at 5 mg, and 84% and 68%, respectively, at 20 mg. At 20 mg, medial and sural sensory nerve conduction velocity was improved significantly. A dose-related increase in sensory examination score was also observed. There were no significant side effects observed in the liver or kidney (3-5).

In a 48-week extension study, a dose of 20 mg/day of ranirestat was associated with significant improvements in sural and medial sensory nerve conduction velocity and vibration perception thresholds. The lower dose of 5 mg/day of ranirestat induced inconsistent improvements and was considered to be subtherapeutic. Both ranirestat doses were well tolerated (6).

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2. *Eisai assumes development of Dainippon's AS-3201 for diabetic neuropathy*. DailyDrugNews.com (Daily Essentials) Oct 3, 2005.

3. *Phase IIa results for diabetic complication drug AS-3201*. DailyDrugNews.com (Daily Essentials) March 25, 2004.

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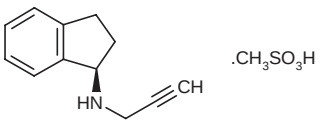
Rasagiline Mesilate



A potent and selective, irreversible monoamine oxidase type B (MAO-B) inhibitor, rasagiline mesilate (TVP-1012, Agilect®) was launched in 2005 in Israel by Teva as monotherapy for the treatment of early Parkinson's disease and as adjuvant treatment in moderate to advanced disease. The product was also launched in the U.K. by Teva and European development partner Lundbeck following the issuance of a marketing authorization by the European Commission early in 2005. Regulatory applications have been filed in Canada and the U.S.; an approvable letter was issued by the FDA. Developed by Teva based on research originating from the Technion - Israel Institute of Technology, rasagiline is also in phase II clinical trials in the U.S. by partners Teva and Eisai for the treatment of Alzheimer's disease (1-9).

Data from two double-blind, randomized, placebo-controlled clinical trials were used to determine the pharmacokinetics and safety of rasagiline. Thirty-six healthy male volunteers received placebo, single doses of rasagiline (1, 2, 5, 10 or 20 mg p.o.) or multiple doses of rasagiline (2, 5 or 10 mg p.o. once daily for 10 days). Rasagiline was rapidly absorbed, time to peak plasma levels ranging from 0.36 to 0.54 h, and both peak plasma concentrations and AUC increased with dose. All rasagiline doses were well tolerated and inhibited platelet MAO-B activity for more than 7 days after the last administration (10).

The potential benefits of rasagiline in advanced Parkinson's disease were evaluated in the LARGO (Lasting effect in Adjunct therapy with Rasagiline Given Once daily) study, a multicenter, double-blind, randomized clinical trial that compared the efficacy and safety of rasagiline (1.0 mg once daily), entacapone (200 mg with each levodopa dose) and placebo for 18 weeks in 687 advanced Parkinson's disease patients with motor fluctuations who were taking levodopa. The reduction in the daily "off" time of the patients after 18 weeks of treatment was significantly greater with rasagiline and entacapone (both 1.2 h) compared to placebo (0.4 h). Patients treated with rasagiline or entacapone showed significant improvements in the UPDRS total score and in the Clinical Global Improvement score, and were able to reduce their levodopa dose by 24.3 and 19.2 mg/day, respectively, whereas placebo-treated patients increased theirs by 5.5 mg/day. Only patients receiving rasagiline showed significant improvements in their UPDRS-Motor score during "off" periods. Comparison of the UPDRS-Motor scores during "off" periods at baseline and after 18 weeks of therapy revealed that these scores decreased by 4.38 units with rasagiline and by 1.95 units with entacapone, whereas they increased by 1.27 units with placebo. The UPDRS-Tremor score of patients treated with rasagiline improved significantly compared to baseline from week 10 to the end of the study. Improvements over placebo were also found when rasagiline was given to patients with severe tremor. Adverse event rates were similar among rasagiline, entacapone and placebo groups and serious adverse events occurred in 12, 12 and 17 patients in these groups, respectively (11-16).

An ancillary study to the LARGO trial revealed that both rasagiline (1 mg/day) and entacapone (200 mg with each levodopa dose) significantly improved freezing of gait in patients with advanced Parkinson's disease and motor fluctuations. At 10 weeks after the beginning of the study, the baseline Freezing Of Gait Questionnaire (FOG-Q) score of the patients decreased by 1.2 points with rasagiline, by 1.1 points with entacapone and by 0.5 points with placebo. The effects of rasagiline were significant in patients with mild to moderate FOG at baseline, but not in patients with severe FOG. A weak correlation was found between this effect and the reduction in "off" periods also induced by the two drugs (17-19).

The potential benefits of adding rasagiline to Parkinson's disease therapy were assessed in the multicenter, randomized, double-blind, placebo-controlled PRESTO study. At baseline, the 472 patients studied were experiencing a minimum of 2.5 h of poor motor function ("off" time) daily while receiving optimized and stable levodopa and other treatments. During 26 weeks of treatment with either rasagiline 0.5 or 1 mg/day or placebo, daily "off" time decreased by 1.41, 1.85 and 0.91 h, respectively. Both doses of rasagiline were also associated with significant improvements in Investigator's Clinical Impression of Improvement, the UPDRS Activities of Daily Living subscale during "off" periods and the UPDRS Motor subscale during "on" periods. No evidence for adverse interactions between rasagiline and selective serotonin reuptake inhibitors (SSRIs) was obtained in the 77 patients receiving stable SSRI therapy at baseline. Rasagiline was well tolerated, with gastrointestinal adverse events and dyskinesias occurring more frequently in the rasagiline groups compared to placebo (20-22).

Pooled data from the double-blind, placebo-controlled PRESTO and LARGO trials were used to define the therapeutic benefits of rasagiline in levodopa-treated patients with Parkinson's disease and motor fluctuations. Rasagiline (1.0 mg once daily for 18 or 26 weeks) was significantly more effective than placebo in reducing total day "off" time and increasing total daily "on" time of the patients. All active treatments (including once-daily rasagiline monotherapy, once-daily rasagiline plus levodopa therapy, or 200 mg of entacapone plus levodopa therapy) were associated with greater improvements in symptoms compared to placebo. Once-daily rasagiline was well tolerated, and few patients experienced troublesome dyskinesia (23).

The effects of rasagiline on progression of disability were evaluated in the double-blind, placebo-controlled TEMPO trial that randomized 404 patients with early Parkinson's disease and not requiring dopaminergic therapy to receive rasagiline (1 or 2 mg/day) for 1 year, or

placebo for 6 months followed by rasagiline (2 mg/day) for 6 months. Rasagiline-treated patients showed improvements in their UPDRS scores after 4 and 8 weeks of treatment. At 26 weeks, the percentage of patients with improvements in their baseline UPDRS scores was 47% in the rasagiline group and 28.3% in the placebo group. At the end of the study period, the average increase in the UPDRS score compared to baseline in each study group was 3.01 with 1 mg/day, 1.97 with 2 mg/day and 4.17 with delayed 2 mg/day. The percentage of patients who responded to treatment in each group was, respectively, 52.5%, 63.8% and 52.3%. Rasagiline was also more effective than placebo in maintaining and even slightly improving the quality of life of the patients. No significant differences were found among the adverse event profiles of the three study groups; the most common adverse events were infection, headache, unintentional injury and dizziness. Moreover, no significant differences among study groups were found in the incidence of cognitive and behavioral adverse events (*e.g.,* hallucinations, confusion, depression and somnolence) (24-27).

An open-label extension study that enrolled 85% of the Parkinson's disease patients who completed the TEMPO trial found that the difference between the functional decline of patients who received rasagiline for 1 year immediately after inclusion and those who did not start receiving rasagiline until 6 months after inclusion was still maintained after the patients had been given rasagiline (1.0 mg once daily) with or without additional antiparkinsonian drugs for an average of 3.6 years. The annual rate of decline of patients who received rasagiline monotherapy throughout the open-label extension study was significantly lower than that reported elsewhere for placebo-treated patients. In patients followed for up to 6.5 years, the mean difference in total UPDRS change from baseline was 2.5 between the early- and delayed-start treatment groups. At 2 years, 46% of the patients achieved adequate control of Parkinson's disease symptoms without needing any additional antiparkinsonian drugs. Long-term rasagiline was generally well tolerated (28-31).

Safety data gathered from the TEMPO and PRESTO studies indicated that rasagiline treatment was safe and well tolerated. Total adverse effects, total serious adverse effects and symptomatic hypotension did not differ significantly between rasagiline and placebo and did not differ between older and younger patients. Although hallucinations were infrequent, they were more often experienced by elderly patients given rasagiline and levodopa, suggesting that vigilance is required in elderly patients given this treatment combination (32).

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7. *Eisai reports Q1 R&D highlights*. Eisai Press Release 2005, July 29.

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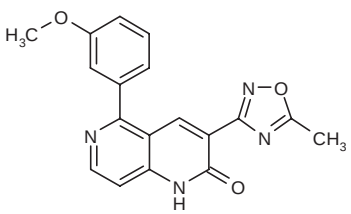
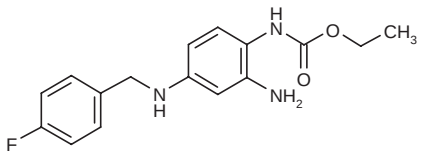
Resequinil



Dainippon Sumitomo Pharma is conducting phase I trials in Japan and phase II trials in the U.S. and the E.U.

with resequinil (AC-3933), a $GABA_A$ receptor benzodiazepine-site partial inverse agonist, for the oral treatment of dementia.

Retigabine



Retigabine has entered phase III trials at Valeant Pharmaceuticals as adjunctive therapy in refractory epilepsy patients with partial-onset seizures. The compound represents an entirely new mechanism of action for this indication as both a potassium channel opener and a GABA potentiator. Valeant acquired the product upon its acquisition in March 2005 of Xcel Pharmaceuticals. Phase III trials will consist of two global studies, the first in the U.S., Mexico and South America with up to 45 sites, and the second in other major markets around the world with up to 60 sites. Combined enrollment in both studies is expected to be approximately 800 patients. The first study will have two treatment arms: placebo and 1200 mg/day retigabine; the second study will have three arms: placebo, 600 mg/day retigabine and 900 mg/day retigabine. The multicenter, randomized, double-blind, placebo-controlled, parallel-group studies will assess the efficacy and safety of retigabine compared to placebo in patients with epilepsy who are receiving one, two or three antiepileptic drugs (AEDs). The two co-primary endpoints are the percentage change in total partial seizure frequency per 4 weeks from baseline to the double-blind period, and the proportion of responders, defined as a patient experiencing at least a 50% reduction in total partial seizure frequency per 4 weeks from baseline to the double-blind period. Results are anticipated to be available in the second half of 2007 and retigabine could be launched in 2008. A large phase II trial of retigabine that consisted of four treatment groups (a placebo group and retigabine 600, 900 and 1200 mg/day) showed that the median monthly seizure rates decreased by 13% in the placebo group and by 23%, 29% and 35%, respectively, in the retigabine groups. Results were statistically significant for the two higher doses compared to placebo (1-5).

Seventy-three patients with partial-onset seizures were enrolled in a randomized clinical trial that compared the safety profile of three different dosing schedules of retigabine. All patients started receiving 300 mg/day of retigabine, but this was gradually increased until a target drug dose of 1200 mg/day was reached after 13 (fast titration), 25 (medium titration) or 42 (slow titration) days of treatment. The percentage of patients who discontinued the study due to adverse events was 43.5% with fast titration, 31.8% with medium titration and 13.0% with slow titration (6).

The benefits of retigabine were evaluated in a double-blind, randomized clinical trial in which placebo or retigabine (200, 300 or 400 mg t.i.d.) was given together with concomitant AEDs to 399 patients with refractory partial-onset seizures. A total of 222 of these patients completed the trial and participated in an open-label extension study in which retigabine (300 mg t.i.d., later decreased or increased to a maximum dose of 1200 mg/day) plus concomitant AEDs was administered. Compared to baseline, the monthly total partial seizure frequency of the patients decreased by a median of 48.3% during the open-label period. Overall, 8% and 18% of patients withdrew from the study at 3 and 6 months, respectively, the main reason being adverse events associated with the CNS (7).

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5. *Retigabine efficacy and safety trial for partial onset refractory seizures in epilepsy (NCT00235755)*. ClinicalTrials.gov Web Site 2005, Dec 8.

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RG-2077

Early clinical development is in progress at Repligen for RG-2077 (CTLA4-Ig), a recombinant protein consisting of CTLA4 fused to the heavy-chain constant region of human immunoglobulin of the IgG_4 isotype, as a potential treatment for multiple sclerosis (MS).

An open-label, phase I clinical trial revealed that single doses of CTLA4-Ig (2, 10, 20 or 35 mg/kg i.v.) were well tolerated and induced biological effects in 16 patients with relapsing-remitting MS (1).

1. Khoury, S.J. et al. *A phase I trial of CTLA4Ig treatment in MS*. Neurology 2005, 64(6, Suppl. 1): Abst S46.004.

Rituximab, New Indication

Initially launched in 1997 in the U.S. by Biogen Idec and Genentech as Rituxan® and in Switzerland by Roche

as MabThera® for the treatment of relapsed or refractory low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL), rituximab is a chimeric monoclonal antibody targeting the CD20 antigen on B-cells. It was the first monoclonal antibody approved by the FDA for the treatment of cancer. The antibody continues in active development for several new indications. In 2005, Biogen Idec and Genentech submitted rituximab for approval in the U.S. and Roche in the E.U. for the treatment of rheumatoid arthritis. Phase III trials are under way to evaluate the potential of the antibody for the treatment of chronic lymphocytic leukemia (CLL) and Genentech and Biogen Idec are conducting phase II/III trials for the treatment of primary progressive multiple sclerosis. Additional phase II/III and phase III trials are under way at Genentech for the treatment of vasculitis and lupus nephritis, respectively, as are phase II trials at Genentech for idiopathic thrombocytopenic purpura (ITP).

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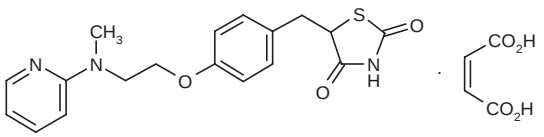
Rosiglitazone Maleate, New Indication



Currently used as an antidiabetic, rosiglitazone maleate (Avandia®) is a peroxisome proliferator-activated receptor (PPAR-γ) agonist that was first launched in the U.S. in 1999 by GlaxoSmithKline and partner Bristol-Myers Squibb. The drug is also under development at GSK for a variety of other indications, including Alzheimer's disease (AD), rheumatoid arthritis and ulcerative colitis (phase II).

Twenty-one patients with MCI or early AD were randomized to receive placebo or rosiglitazone (4 mg once daily) for 24 weeks. Compared with baseline, the plasma levels of β-amyloid 1-40 and 1-42 were maintained throughout the study with rosiglitazone but progressively decreased with placebo. The authors concluded that rosiglitazone was able to normalize the decline in plasma β-amyloid usually found in patients with AD (1).

The effects of rosiglitazone on cognitive function were evaluated in a clinical trial that included 23 patients with amnesic MCI or early AD. Compared with placebo, rosiglitazone (4 mg once daily for 24 weeks) improved delayed word list recall and frontal-executive skills, and was associated with a lower number of errors in the Stroop color-word interference test (2).

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2. Watson, G.S., Reger, M.A., Cholerton, B.A. et al. *Rosiglitazone preserves cognitive functions in patients with early Alzheimer's disease*. Neurobiol Aging 2004, 25(Suppl. 2): Abst O4-05-05.

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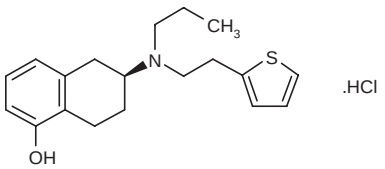
Rotigotine Hydrochloride



Rotigotine hydrochloride (SPM-962, Neupro®) is a nonergot dopamine agonist that was originally developed by Aderis and is licensed to Schwarz Pharma, which obtained all remaining rights to the product last year. More than 1,500 patients with Parkinson's disease have been treated with rotigotine in 15 clinical trials. Regulatory submissions are under review in the U.S. and the E.U. for a once-daily transdermal patch (CDS – constant delivery system) for the treatment of early Parkinson's disease, and a nasal spray formulation of the compound has completed phase I trials for Parkinson's disease and is expected to enter phase II clinical testing soon. Phase III trials with rotigotine CDS in patients with advanced-stage Parkinson's disease demonstrated statistically significant and clinically relevant reductions in "off" time. The reduction in "off" time following adjunctive therapy with rotigotine was not associated with an increase in undesirable dyskinesias. A European phase III trial of rotigotine as adjunctive therapy in patients with advanced-stage Parkinson's disese started in the second quarter of 2004. A total of 470 patients are planned for this double-blind, placebo- and active comparator-controlled trial, with results expected in early 2006. A lower dose rotigotine transdermal patch is also in phase III trials for the treatment of restless legs syndrome (RLS). A multinational phase IIb trial of rotigotine for the treatment of RLS showed a statistically significant and clinically relevant reduction in RLS symptoms. The improvement was measured using the International Restless Legs Study Group (IRLSSG) scale and a meaningful clinical effect was observed within the first 7 days of treatment. The patch was well tolerated. The multicenter, double-blind, place-

bo-controlled trial had a treatment duration of 6 weeks and 310 patients with idiopathic moderate to very severe RLS completed the trial (1-13).

Seventy patients with early-stage Parkinson's disease participated in a multicenter, open-label clinical trial that determined the pharmacokinetics of transdemal rotigotine administered at doses of 4.5-18 mg/day applied to 6 different areas of the body (abdomen, shoulder, upper arm, hip, thigh and flank). The average 24-h plasma concentration of rotigotine was 0.79 ng/ml, and this value was not significantly affected by age, gender or application site (14).

Dose titration of rotigotine delivered via transdermal patches was evaluated in an open-label study in 31 Parkinson's disease patients. Study subjects had Parkinson's disease for < 5 years and received rotigotine patches of 10 or 20 cm^2 (4.5 or 9 mg of rotigotine, respectively), with up to 3 patches applied to the upper abdomen. The maximum dose of 18 mg was achieved by 25 of 29 patients who completed the trial; 24 of 25 patients were maintained at the maximum dose. The treatment was well tolerated, with 11 patients experiencing application-site reactions, 10 of which consisted of barely perceptible, minimal erythema. Nausea was seen in 10 patients and 4 severe, treatment-related adverse events were observed in 2 patients (nausea and vomiting in 1 patient and nausea and dyskinesia in another). UPDRS scores on parts I, II and III were significantly improved from baseline in patients completing the trial. All three subscores were significantly improved in patients achieving the maximum rotigotine dose, while changes were not significant in those with a lower final dose (15, 16).

A multicenter, double-blind clinical trial randomized 351 patients with advanced Parkinson's disease to receive transdermal rotigotine (18 or 27 mg/day) or placebo during a 5-week titration phase and a 24-week maintenance phase. The patients' "off" time decreased significantly more with rotigotine (–2.7 h with 18 mg/day, –2.1 h with 27 mg/day) compared to placebo (–0.9 h). No patients showed an increase in the time "on with troublesome dyskinesias". Rotigotine was well tolerated, and the most common adverse events were application-site reactions, somnolence, nausea and dizziness (17).

Patients with early-stage idiopathic Parkinson's disease (n=273) were treated with placebo or the rotigotine transdermal patch titrated weekly from 10 cm^2 (4.5 mg/day) to an optimal dose of 30 cm^2 (13.5 mg/day). After 6 months, the active treatment significantly improved UPDRS subtotal scores compared to placebo in the overall group of patients, and the efficacy of the treatment was independent of age, gender, disease severity or disease duration at baseline. The drug was equally safe in subgroups based on age, gender, disease severity and disease duration at baseline (18-20).

Additional evidence for the benefits of rotigotine in Parkinson's disease was provided by a double-blind clinical trial in which patients with early-stage Parkinson's disease were randomized to receive placebo or rotigotine (up to 13.5 mg/day) using a transdermal system for 6 months, followed by open-label rotigotine for another 6 months. At the end of the study, the average improvement in the UPDRS scores was greater in patients given rotigotine throughout the study than in patients who switched from placebo to rotigotine at 6 months (4.1 points *vs*. 2.4 points). The authors conclude that rotigotine may reduce the rate of progression of disability in early-stage Parkinson's disease (21).

The effects and safety of transdermal rotigotine were evaluated in a multicenter, double-blind clinical trial that randomized 340 patients with moderate to severe idiopathic RLS to receive placebo or rotigotine (1.125, 2.25, 4.5, 6.75 or 9 mg/day) for 7 weeks. Compared to baseline, rotigotine-treated patients achieved greater reductions in the adjusted International RLS Scale (IRLS) score than placebo-treated patients at 6 weeks. The difference compared to placebo was significant at all rotigotine dose levels save for 1.125 mg/day, and the greatest reduction was achieved with a dose of 6.75 mg/day. The most common adverse events were application-site reactions, nausea, fatigue, headache and influenza-like symptoms (22).

A 1-week multicenter, double-blind, randomized pilot study produced results indicating that the administration of rotigotine via a patch is well tolerated and effective in treating patients with moderate to severe RLS. A total of 63 patients were randomized to rotigotine 1.125, 2.25 or 4.5 mg or placebo. Total IRLS Scale scores were dose-dependently improved by rotigotine compared with placebo; the difference between placebo and the highest rotigotine dose was significant (15.7 points *vs.* 8 points). Rotigotine 4.5 mg was also significantly superior to placebo in improving symptoms throughout the day and night according to the RLS-6 scale. Clinical Global Impression scores also revealed increased benefit with all rotigotine doses over placebo. The rotigotine patch was well tolerated and associated with a similar rate of adverse events as placebo. No serious adverse events were noted, and most adverse events were mild and transient application-site reactions (23).

A phase I trial evaluated the pharmacokinetics of rotigotine (9 mg/20 cm^2) with and without levodopa/carbidopa (100/25 mg b.i.d.) n 24 patients with RLS. Combined treatment did not alter mean concentration-time profiles for levodopa/carbidopa or rotigotine (24).

Compositions containing one or more substituted 2-aminotetraline compounds, for example the dopamine D2/D3 receptor agonist rotigotine hydrochloride, have been claimed for use in treating Parkinson's disease (25).

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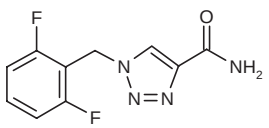
Rufinamide



The broad-spectrum anticonvulsant rufinamide (Inovelon®) is awaiting registration in the U.S. and the

E.U. as adjunctive therapy for the oral treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children 4 years and older, and a submission is also under review by the FDA for the treatment of partial-onset seizures in adults and adolescents. Originally developed at Novartis, rufinamide, a sodium channel modulator, was licensed on an exclusive worldwide basis to Eisai in 2004. It has received orphan drug designation in both the U.S. and the E.U. for the treatment of LGS (1-4).

A multicenter, double-blind clinical trial randomized 138 patients aged 4-37 years with inadequately controlled LGS to receive adjunctive placebo or rufinamide (median dose of 1800 mg/day) for 84 days. At the end of the study period, rufinamide-treated patients showed greater median reductions in total seizure frequency (32.7% *vs.* 11.7%) and tonic-clonic seizure frequency (42.5% *vs*. 1.4%), and also improvements in seizure frequency (53.4% *vs.* 30.6%) compared to placebo-treated patients. A total of 124 patients participated in an open-label extension phase and received adjunctive rufinamide for a median of 432 days. The efficacy of rufinamide was maintained during the extension phase and no evidence for tolerance was found. The most common adverse events were vomiting, pyrexia and somnolence (5).

The safety and efficacy of adjunctive rufinamide therapy were assessed in a multicenter, double-blind trial that enrolled 155 adult and pediatric patients with inadequately controlled primary generalized tonic-clonic seizures (PGTCS) despite receiving antiepileptic therapy. Each patient was randomized to receive placebo or rufinamide (800 mg/day) for 140 days. At the end of the treatment, the median reduction in PGTCS frequency was greater with rufinamide than with placebo (36.4% *vs.* 25.6%), although the difference between study treatments was not significant. The most frequent adverse events reported by patients in the rufinamide group were headache, somnolence, nausea and dizziness (6).

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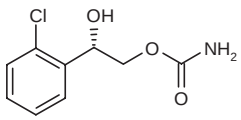
RWJ-333369 (YKP-509)



RWJ-333369 (YKP-509), a novel broad-acting antiepileptic agent, is currently undergoing phase II development for the treatment of epilepsy. It is also being evaluated in phase II trials as second-line therapy for the treatment for migraine. Originally discovered by SK Bio-Pharmaceuticals, the compound is licensed to Ortho-McNeil, a subsidiary of Johnson & Johnson, for further development (1-3).

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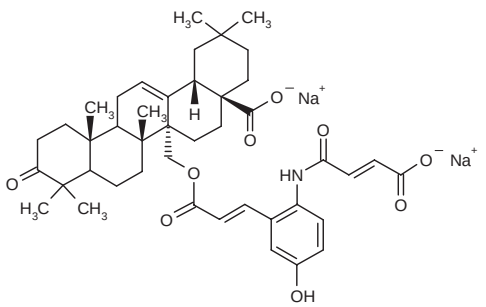
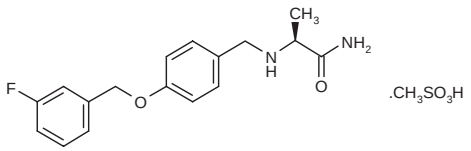
S-0139 (737004)



A joint venture between Shionogi and GlaxoSmithKline is developing S-0139 (737004), an

endothelin ET_A receptor antagonist, as a potential therapy for ischemic stroke. Phase II trials are in progress in Japan and phase I trials are under way in Europe.

Safinamide Mesilate



Newron's lead product safinamide mesilate, an anticonvulsant and neuroprotectant, is in phase III trials as adjunctive treatment with a dopamine agonist for Parkinson's disease. Phase II trials are also under way for the treatment of epilepsy and RLS. Safinamide is a unique molecule with multiple mechanisms of action and a very high therapeutic index. It combines inhibition of dopamine uptake and potent, selective and reversible inhibition of MAO-B with potent sodium (Na^+) channel blockade and calcium (Ca^{2+}) channel modulation. The Na^+ channel blockade selectively affects those neurons with abnormal firing patterns and leaves normal activity unaltered. Data from phase II trials in Parkinson's disease showed safinamide to have an excellent safety profile and initial efficacy as monotherapy, as well as unique results when added to levodopa or dopamine agonists. Treatment with safinamide also resulted in significant improvement in all efficacy parameters studied when administered to patients with RLS in a phase II pilot study. A total of 10 patients with RLS were enrolled in the single-center, open study of safinamide at the Sleep Disorders Center, San Raffaele Hospital in Milan. Each patient was administered safinamide (100 mg/day orally) at bedtime for 2 weeks. Safinamide was well tolerated and did not exhibit any clinically relevant side effects. Sleep architecture was not modified, while sleep fragmentation was positively influenced (1-4).

Oral safinamide incrementally improved motor function in Parkinson's disease patients. Doses of the drug (100, 150 and 200 mg) were increased every 2 weeks in a 6-week open-label trial and were added to treatment with a single dopamine agonist (n=14) or levodopa (n=11). None of the 7 adverse events believed to be related to treatment were serious. Reductions on the UPDRS-III of 1.5 and 4.1 points were obtained in levodopa- and dopamine agonist-treated patients, respectively (5-7).

The effects of safinamide on motor function were evaluated in a double-blind clinical trial that randomized 168 patients with early Parkinson's disease to receive placebo or safinamide (0.5 or 1 mg/kg/day) for 12 weeks. At the end of the study period, the percentage of patients who responded to treatment was 21.4% with placebo, 30.9% with low-dose safinamide and 37.5% with high-dose safinamide. Motor function improvements in the UPDRS-III scores of these groups were, respectively, 3.4%, 15.8% and 20%. Patients who were also receiving stable treatment with a single dopamine agonist achieved the greatest motor function improvements. All study treatments were well tolerated (8). Withdrawal of safinamide was found to result in worsening of motor function (9).

A pilot study was conducted in 43 epilepsy patients with at least 2 seizures per month who were receiving treatment with as many as 3 AEDs. A starting dose of safinamide 50 mg p.o. was increased every 2 weeks up to 300 mg. Adverse events were mild to moderate in intensity and were reported by 18 patients. The highest dose was reached by 37 of the 38 patients finishing the trial. The pharmacokinetic variables of concomitant medications were not affected by safinamide. Evidence of efficacy was also seen, as 41% of patients had a reduction of at least 50% in seizure frequency (10, 11).

A method for treating or alleviating the symptoms of Parkinson's disease has been described. The claim pertains to the use of the potent dopamine reuptake and MAO-B inhibitor safinamide, or derivatives thereof, or an additional MAO-B inhibitor, such as selegiline, in combination with antiparkinsonian agents, such as levodopa/carbidopa, or a dopamine agonist, such as bromocriptine. In a multicenter, randomized, double-blind, placebo-controlled phase II trial over 12 weeks in 167 patients with idiopathic early Parkinson's disease, safinamide (1 mg/kg p.o. once daily) was generally safe and demonstrated a 30% or greater therapeutic improvement compared with placebo, as measured by the UPDRS. This outcome appeared to arise primarily from a synergistic response in patients undergoing therapy with a single dopamine agonist (12).

1. *R&D highlights from the 3rd Annual Global Biotech Forum for Investing & Partnering: Newron*. DailyDrugNews.com (Daily Essentials) April 28, 2004.

2. *Safinamide studied in phase III trial for Parkinson's*. DailyDrugNews.com (Daily Essentials) Sept 15, 2004.

3. *Safinamide shows promise in restless legs syndrome pilot study*. DailyDrugNews.com (Daily Essentials) Jan 14, 2005.

4. *Phase III Parkinson's disease study of safinamide completes enrollment*. DailyDrugNews.com (Daily Essentials) July 25, 2005.

5. Stocchi, F., Vacca, L., Grassini, P., Battaglia, G., Altibrandi, M., Ruggieri, S.A. *Safinamide add-on to levodopa and dopamine agonist treatment in Parkinson disease: An open, escalating dose study*. Mov Disord 2004, 19(Suppl. 9): Abst P631.

6. Stocchi, F., Vacca, L., Grassini, P., Battaglia, G., Altobrandi, M., Ruggieri, S. *Safinamide add-on to L-dopa and dopamine agonist in Parkinson's disease. An open escalating dose 6-week trial*. J Neurol 2004, 251(Suppl. 3): Abst P339.

7. Stocchi, F., Vacca, L., Grassini, P., Battaglia, G., Altobrandi, M.G., Ruggieri, S. *Safinamide add-on to levodopa and dopamine agonist in Parkinson disease. An open escalating dose six week trial*. J Neural Transm - Gen Sect 2004, 111(5): Abst 128.

8. Fariello, R., Stocchi, F., Arnold, G. et al. *Improvement of motor function in early Parkinson's disease by safinamide, a new neuroprotectant anticonvulsant*. J Neurol 2004, 251 (Suppl. 3): Abst P236.

9. Thomas, A., Cattaneo, C., Besana, C. et al. *Motor function: Follow-up in patients affected by Parkinson's disease treated previously with safinamide*. J Neural Transm - Gen Sect 2004, 111(5): Abst 133.

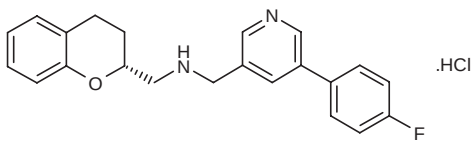
10. Fariello, R., Perucca, E., Avanzini, G. et al. *A pilot study of safinamide in medically intractable epilepsy. Tolerability, drug-drug interaction and preliminary efficacy data*. J Neurol 2004, 251(Suppl. 3): Abst P358.

11. Perucca, E., Avanzini, G., Onofrj, M. et al. *A pilot study of safinamide in medically intractable epilepsy. Tolerability, drug-drug interaction and efficacy data*. J Neural Transm - Gen Sect 2004, 111(5): Abst 89.

12. Ruggero, F. et al. (Newron Pharmaceuticals SpA) *Methods for treatment of Parkinson's disease*. WO 2004089353.

Original monograph – Drugs Fut 2001, 26(8): 745.

Sarizotan Hydrochloride



Sarizotan (EMD-128130) is a 5-HT_{1A} receptor agonist and a dopamine D2 antagonist in phase III clinical trials at EMD Pharmaceuticals/Merck KGaA for the treatment of dyskinesia associated with Parkinson's disease (1).

The SPLENDID study was a multicenter, open-label clinical trial that evaluated the safety and efficacy of sarizotan in patients younger than 80 years with idiopathic Parkinson's disease and levodopa-induced dyskinesia who received stable doses of antiparkinsonian drugs for at least 1 month before inclusion. Sarizotan was administered at an initial dose of 2 mg b.i.d., which was increased to up to 10 mg b.i.d. over a 3-week titration phase; this dose was maintained for another 9 weeks and was only reduced in the event of adverse events. Sarizotan significantly increased the percentage of "on" time without dyskinesia and reduced that of "on" time with dyskinesia during waking time. The percentage of patients suffering from moderate to severe dyskinesia decreased from 81.2% at baseline to 38.5% at the end of the treatment period. The most common adverse event was worsening parkinsonism, which led to 9 patients withdrawing from the study and another 35 patients requiring dose reductions (2).

1. *Sarizotan HCl in patients with Parkinson's disease suffering from treatment-associated dyskinesia (NCT00105521)*. ClinicalTrials.gov Web Site 2005, Oct 25.

2. Olanow, C.W., Damier, P., Goetz, C.G. et al. *Multicenter, open-label, trial of sarizotan in Parkinson disease patients with levodopa-induced dyskinesias (the SPLENDID study)*. Clin Neuropharmacol 2004, 27(2): 58.

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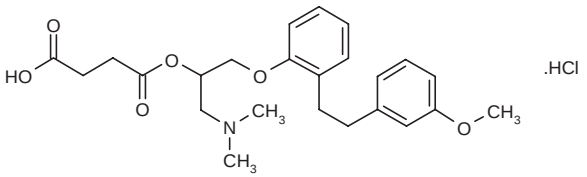
Kuenzel, H.E. et al. *Changes in sleep electroencephalogram and nocturnal hormone secretion after administration of the antidyskinetic agent sarizotan in healthy young male volunteers*. Psychopharmacology (Berlin) 2005, 180(2): 327.

Sarpogrelate Hydrochloride, New Indication



Available since 1993 from Mitsubishi Pharma in Japan as Anplag for the treatment of ischemic symptoms, including pain, ulcers and cold sensation, due to chronic arterial obstruction, sarpogrelate hydrochloride, a selective oral 5-HT_{2A} receptor antagonist, is being evaluated in phase III trials for the prevention of the recurrence of stroke and in phase II trials for the treatment of chronic pain.

Original monograph – Drugs Fut 1992, 17(12): 1093.

Sativex®

Sativex® is a whole-plant medicinal cannabis extract containing Δ-9-tetrahydrocannabinol (THC, dronabinol) and cannabidiol (CBD) as its principal components. In 2005, GW Pharmaceuticals and marketing partner Bayer launched Sativex® oromucosal spray in Canada as adjunctive treatment for the symptomatic relief of neuropathic pain in adults with multiple sclerosis (MS), the product's first market. The company is awaiting approval in the U.K. for its use in debilitating symptoms of MS, including neuropathic pain and spasticity. The Medicines Commission, the senior advisory body to the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA), declined GW Pharmaceuticals' appeal against a previous request for a further clinical study in MS spasticity to support U.K. licensure for Sativex®. The Committee on Safety of Medicines (CSM), an advisory body to the MHRA, advised that a further clinical study would be required prior to the granting of a U.K. product license for Sativex®, but said that there were no quality or safety issues preventing authorization. A 280-patient study to determine the efficacy of Sativex® in MS spasticity is under way and is due to report results in the spring of 2006. Clinical trials are also under way for the treatment of various types of pain (1-10).

Positive preliminary results were reported from a phase III trial assessing the effects of Sativex® on spasticity in 189 patients with MS. A statistically significant improvement in comparison with placebo was seen in spasticity as measured on a numerical rating scale, the primary endpoint. Other secondary outcome measures, such as the Ashworth scale, were in favor of Sativex® but did not reach statistical significance. The safety profile

was consistent with that shown in previous studies. The multicenter, double-blind, randomized, placebo-controlled, parallel-group study allowed patients to remain on their existing medication in addition to the study medication. Previous phase III trials in patients with MS have shown Sativex® to reduce pain and sleep disturbances and improve quality of life. A further phase III trial is ongoing in patients with bladder dysfunction due to MS (11).

In a randomized, double-blind, placebo-controlled study, 66 MS patients took self-titrated doses of Sativex® for 4 weeks and 63 continued in a long-term, open-label extension. Mean pain scores and sleep disturbances were significantly reduced with the active treatment compared to placebo. Adverse events were seen in 88.2% and 68.8% of patients in the Sativex® and placebo groups, respectively, but no serious adverse events were recorded. Pain score improvements were sustained in 34 patients treated for 52 weeks, and no significant intoxication was observed (12, 13).

Data from a large long-term extension study including 404 patients with MS or chronic pain included in randomized trials showed the therapeutic potential of Sativex® in this indication. Treatment-related adverse events were seen in 84.4% of patients, but only 2.7% of patients experienced serious adverse events. Adverse events were the cause of withdrawal in 57 (14%) patients. Patients treated for 1 year had sustained improvements in numerical rating scale symptom scores, including those for spasticity, central neuropathic pain and peripheral neuropathic pain. No evidence of tolerance to the treatment or serious intoxication was noted (14).

Analysis of data from double-blind, randomized, placebo-controlled phase I-III trials revealed that Sativex® significantly improved sleep quality in patients with MS, neurogenic symptoms, neuropathic pain and lower urinary tract symptoms. In 8 healthy volunteers, Sativex® was also associated with less sedation and residual effects than a dronabinol preparation. No patients experienced fundamental changes in EEG sleep architecture after receiving Sativex®. Evidence from safety extension studies suggested that the improvements induced by Sativex® were maintained after more than 1 year of administration (15).

1. *GW Pharmaceuticals to submit more information for U.K. review of Sativex*. DailyDrugNews.com (Daily Essentials) May 4, 2004.

2. *NDS submission for Sativex in Canada*. DailyDrugNews.com (Daily Essentials) May 13, 2004.

3. *Sativex produces positive results in phase II rheumatoid arthritis study*. DailyDrugNews.com (Daily Essentials) June 11, 2004.

4. *Positive preliminary phase III results for Sativex in neuropathic pain*. DailyDrugNews.com (Daily Essentials) June 17, 2004.

5. *GW receives Qualifying Notice for Sativex in Canada*. DailyDrugNews.com (Daily Essentials) Dec 28, 2004.

6. *Canadian approval for Sativex*. DailyDrugNews.com (Daily Essentials) April 21, 2005.

7. *GW and Bayer amend Sativex marketing agreement*. DailyDrugNews.com (Daily Essentials) May 13, 2005.

8. *Sativex launched in Canada*. DailyDrugNews.com (Daily Essentials) June 21, 2005.

9. *Further study required for Sativex approval in U.K.*. DailyDrugNews.com (Daily Essentials) June 14, 2005.

10. *Positive preliminary phase III results for Sativex in severe cancer pain*. DailyDrugNews.com (Daily Essentials) Jan 21, 2005.

11. *Sativex improves spasticity in MS patients in phase III trial*. DailyDrugNews.com (Daily Essentials) June 23, 2004.

12. Young, C. et al. *A randomised controlled trial of cannabis based medicinal extract in central neuropathic pain due to multiple sclerosis*. 24th Annu Sci Meet Am Pain Soc (March 30-April 2, Boston) 2005, Abst 718.

13. Rog, D.J. et al. *Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis*. Neurology 2005, 65(6): 812.

14. Serpell, M. et al. *Sativex® in the treatment of pain of neurological origin or symptoms of multiple sclerosis: Interim analysis of a long-term, open label, safety and tolerability study*. 24th Annu Sci Meet Am Pain Soc (March 30-April 2, Boston) 2005, Abst 722.

15. Russo, E.B. *Sativex cannabis based medicine maintains improvements in sleep quality in patients with multiple sclerosis and neuropathic pain*. Neurology 2005, 64(6, Suppl. 1): Abst P01.061.

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Serpell, M.G., Smith, E.J., Sarantis, N. *Sativex in the treatment of pain of neurological origin or symptoms of multiple sclerosis: Interim analysis of a long-term, open label, safety and tolerability study*. 8th Congr Eur Fed Neurol Soc (Sept 4-7, Paris) 2004, Abst P1431.

Vaney, C. et al. *Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: A randomized, double-blind, placebo-controlled, crossover study*. Multiple Scler 2004, 10(4): 417.

Wade, D.T. et al. *Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients*. Multiple Scler 2004, 10(4): 434.

Wein, A.J. *An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis*. J Urol 2005, 173(4): 1262.

Young, C.A. et al. *A randomised controlled trial of sativex, a cannabis based medicine (CBM), in central neuropathic pain due to multiple sclerosis, followed by an open-label extension*. 11th World Congr Pain (August 21-26, Sydney) 2005, Abst 661-P267.

SB-509

Sangamo BioSciences has initiated a phase I trial of SB-509, a novel therapeutic designed to protect and stimulate the regeneration of peripheral nerve function in diabetics suffering from peripheral neuropathy. The multicenter study is designed to evaluate the clinical safety of

SB-509 in diabetics with mild to moderate diabetic peripheral sensorimotor neuropathy in the legs. The FDA cleared an IND filing for the single-blind, placebo-controlled, dose-escalation trial in February 2005. The trial began with the screening and treatment of the first patient at the Diabetes and Glandular Disease Clinic in San Antonio, Texas. A total of 4 sites are expected to take part and some 12 patients will be treated in the trial. Subjects will receive injections in a distribution that targets the major peripheral nerves in the legs and feet. The first dose level will be injected in a distribution to treat nerves in the foot, the second will be distributed to include nerves in the outside of the lower leg and foot, the third for the whole lower leg and foot, and the fourth for the major nerves in the whole leg from the thigh down. Patient safety will be monitored throughout the study, and visits at 1, 2, 3 and 6 months will include neurological examination and electrophysiological testing. The trial is expected to take approximately 12 months to screen and enroll patients and 6 months for patient follow-up. SB-509 is an injectable formulation of plasmid DNA that encodes a zinc finger DNA-binding protein transcription factor (ZFP TF™) and is designed to upregulate the vascular endothelial growth factor A (VEGF-A) gene. In a diabetic rat model, SB-509 proved effective in protecting motor and sensory nerve function from disease-induced nerve damage. VEGF-A has been shown to be effective for maintenance of nerve function in this condition and this approach of activating the patient's own VEGF-A gene directly may have advantages over introducing a cloned gene or recombinant protein (1-3).

1. *Sangamo updates ZFP programs*. DailyDrugNews.com (Daily Essentials) Sept 16, 2004.

2. *Sangamo submits IND for SB-509 to treat diabetic neuropathy*. DailyDrugNews.com (Daily Essentials) Jan 12, 2005.

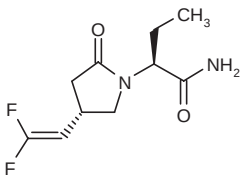
3. *SB-509 enters new phase I trial for diabetic neuropathy*. DailyDrugNews.com (Daily Essentials) May 9, 2005.

SC-12267

4SC has successfully concluded phase I studies for the small-molecule product candidate SC-12267 for the treatment of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. A safe and well-tolerated dose was determined in these studies, which did not cause any relevant side effects after 14 days of once-daily application of SC-12267. The substance demonstrated a very good pharmacokinetic profile, suitable for once-daily dosing. 4SC has now begun preparations for a phase IIa study in rheumatoid arthritis. SC-12267 is a novel, small-molecule disease-modifying antirheumatic drug (DMARD). Through highly selective inhibition of pyrimidine biosynthesis, via inhibition of dihydroorotate dehydrogenase (DHODH), it controls the growth of rapidly proliferating cells, especially lymphocytes. SC-12267 has shown excellent effects in animal studies of rheumatoid arthritis and multiple sclerosis. SC-12267 is orally bioavailable and demonstrates a half-life in man that allows a once-daily dose in therapeutic use (1).

1. *4SC concludes phase I studies for SC-12267*. DailyDrugNews.com (Daily Essentials) April 5, 2005.

Seletracetam



UCB Pharma's seletracetam (UCB-44212), a high-affinity SV2A ligand and a more potent analogue of the antiepileptic levetiracetam (Keppra), is undergoing phase II clinical trials in epilepsy patients and phase III trials are in preparation (1-4).

1. *Open label study with subjects 18-65 years old with partial onset seizures who are currently taking levetracetam (NCT00152503)*. ClinicalTrials.gov Web Site 2005, Sept 12.

2. *Open-label study with seletracetam (Ucb 44212) in adult subjects (18 to 65 years) with partial onset seizures (NCT00152451)*. ClinicalTrials.gov Web Site 2005, Sept 13.

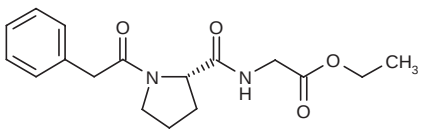
3. *Open label study (everyone who participates receives drug) to further determine how safe and effective oral treatment with seletracetam is in patients with refractory epilepsy (NCT00175864)*. ClinicalTrials.gov Web Site 2005, Nov 21.

4. *Open label trial to study the long-term safety and efficacy of seletracetam for the treatment of epilepsy (NCT00175851)*. ClinicalTrials.gov Web Site 2005, Nov 21.

SEP-226330

Sepracor completed a phase II study with SEP-226330, a norepinephrine and dopamine reuptake inhibitor (NDRI), for the treatment of restless legs syndrome (RLS) in the third quarter of 2005. Based on preliminary analysis of data, the compound did not meet the company's standards for efficacy. Preclinical evaluation continues, however, of its potential for the treatment of other CNS disorders, such as Parkinson's disease.

SGS-111



The nootropic drug SGS-111 is being assessed by Saegis in phase II trials for the treatment of age-related mild cognitive impairment (MCI) and in early clinical trials

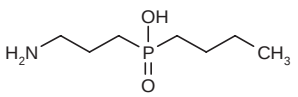
for the treatment of cognitive impairment resulting from CABG surgery. SGS-111 is a small molecule designed to mimic the molecular properties of piracetam, an approved memory-enhancing drug. In numerous models of brain injury, SGS-111 acts as a neuroprotectant and facilitates the survival of neurons. Saegis acquired SGS-111 from the Russian Academy of Medical Sciences in 1999. The company is actively seeking a partner specialized in cognitive impairment as a result of CABG surgery.

SGS-518

Earlier this year, Saegis successfully completed a first-in-man phase I study of SGS-518, in development as a treatment for cognitive impairment associated with schizophrenia (CIAS). The primary objective of the placebo-controlled, blinded study was to evaluate safety and tolerability, as well as pharmacokinetics, of SGS-518. The study was conducted in 2 cohorts of healthy volunteers, including a dose-ranging arm followed by a multiple-dose study. The conclusion of both arms of the study found SGS-518 to be safe and well tolerated. SGS-518 is a selective 5-HT_6 receptor antagonist believed to act by enhancing transmission of chemicals in the brain. Preclinical evaluation of SGS-518 has shown it to be effective in behavioral studies of learning and memory. Saegis is developing SGS-518 in cooperation with Lilly (1).

1. *SGS-518 safe, well tolerated in phase I study*. DailyDrugNews.com (Daily Essentials) April 1, 2005.

SGS-742



SGS-742 (formerly CGP-36742) is a selective, orally active $GABA_B$ antagonist in phase II clinical development by Saegis for the treatment of mild to moderate Alzheimer's disease and ADHD in adults. Positive findings were reported from a previously completed phase II trial in mild cognitive impairment (MCI), demonstrating that patients treated with SGS-742 showed improvement in multiple cognitive domains, including psychomotor skills, memory and attention. SGS-742, discovered by Novartis and licensed to Saegis in 2001, is a phosphoamino acid derivative that is highly water-soluble and readily crosses the blood-brain barrier (1).

A multicenter, double-blind clinical trial randomized 110 patients with MCI but no dementia to receive placebo or SGS-742 (600 mg p.o.) 3 times daily for 8 weeks. No significant differences between groups were found for the Hopkins Verbal Learning Test-Revised (HVLT) scores. Compared with placebo, patients receiving SGS-742 showed greater improvements in both immediate and delayed paragraph recall, psychomotor speed, attention and memory, mean reaction time and rapid visual information processing at the end of the treatment period. A preliminary analysis suggested that SGS-742 tended to improve the overall mental ability of the patients and was well tolerated (2).

Controlled-release therapeutic compositions suitable for once-daily oral administration containing the $GABA_B$ antagonist SGS-742 have been claimed for the treatment of cognitive impairment and associated disorders. The claim embodies the preparation of compositions that additionally comprise a functional transport moiety, for instance a C12-alkyl sulfate salt, which ensure predominantly zero-order drug release, resulting in improved absorption, particularly in the lower gastrointestinal tract (3).

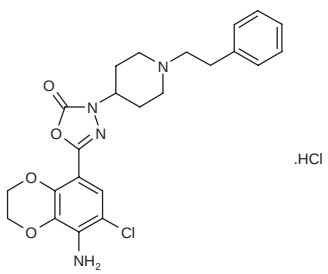
1. *SGS-742 evaluated in new phase II study for adult ADHD*. DailyDrugNews.com (Daily Essentials) March 29, 2005.

2. Tomlinson, J., Cummins, H., Wendt, J. et al. *SGS742, a novel GABAB receptor antagonist, improves cognition in patients with mild cognitive impairment*. Neurology 2004, 62(7, Suppl. 5): Abst P02.053.

3. Wong, P.S.L. et al. (Alza Corp.) *Compositions and dosage forms for enhanced absorption of 3-amino-n-butyl-phosphinic acid*. WO 2005041926.

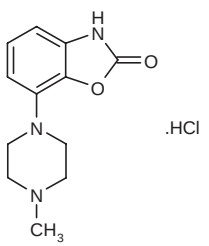
Original monograph – Drugs Fut 2005, 30(3): 248.

SL-65.0155



Sanofi-Aventis is conducting phase II clinical testing with SL-65.0155, a 5-HT_4 partial agonist, for the treatment of Alzheimer's disease and urge incontinence.

SLV-308



Solvay has advanced SLV-308 into a full phase III development program. SLV-308 is an oral therapy for the

treatment of Parkinson's disease that combines partial dopamine D2-agonist activity with 5-HT_{1A} receptor-agonist and noradrenergic properties. Registration submissions are intended for 2007, with the product anticipated to become available from 2008 (1).

1. *Solvay advances SLV-308 into phase III*. DailyDrugNews.com (Daily Essentials) Feb 7, 2005.

Original monograph – Drugs Fut 2001, 26(2): 128.

Spheramine®

Spheramine® is a cell therapy in phase II clinical trials at Schering AG and its U.S. affiliate Berlex for the treatment of Parkinson's disease. The product consists of human retinal pigment epithelial (RPE) cells adhered to microscopic, inert matrices which allow the long-term survival and function of hRPE cells implanted into the mammalian central nervous system. Preclinical studies have revealed that these cells, which produce L-Dopa, are effective in reversing motor deficits in an experimental model of Parkinson's disease. Spheramine® was developed at Titan and the company subsequently established a corporate partnership with Schering AG for the worldwide development, manufacture and commercialization of the product. The FDA has granted Spheramine® both orphan drug designation and fast track designation for the treatment of advanced Parkinson's disease. Spheramine® is currently being evaluated in a double-blind, placebo-controlled phase IIb study. The multicenter, double-blind, controlled STEPS study is determining the effects and safety of bilateral implantation of Spheramine® into the postcommissural putamen of 68 Parkinson's disease patients (1-6).

The long-term effects and safety of Spheramine® were determined in an open-label clinical trial that enrolled 6 patients with advanced Parkinson's disease. A procedure consisting of MRI-guided stereotaxic surgery and implantation of 325,000 hRPE cells in the postcommissural putamen contralateral to the most affected side was well tolerated, did not result in any serious surgery-related adverse events, and improved the UPDRS-Motor score in the "off" state of all patients. At 48 months, the patients showed significant improvements in their UPDRS-Motor "off" scores (43%), total UPDRS scores (30%), UPDRS-Motor "on" scores (45%), Dyskinesia Rating Scale scores (38%) and PDQ39 quality of life scores (30%) compared to baseline (7).

1. *Spheramine granted fast track status for advanced Parkinson's disease*. DailyDrugNews.com (Daily Essentials) July 15, 2004.

2. *Titan Pharmaceuticals reports Q1 R&D highlights*. Titan Pharmaceuticals, Inc. Press Release 2004, May 6.

3. *Titan Pharmaceuticals reports Q2 R&D highlights*. Titan Pharmaceuticals, Inc. Press Release 2005, Aug 9.

4. Reissig, E. *The STEPS trial*. 16th Int Congr Parkinson's Dis Relat Disord (June 5-9, Berlin) 2005, Abst IS005-05.

5. *Spheramine® in advanced Parkinson's disease (The STEPS Trial) (NCT00059007)*. ClinicalTrials.gov Web Site 2005, Sept 30.

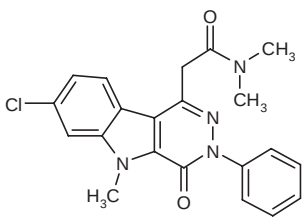
6. *STEPS Trial - Spheramine safety and efficacy study (NCT00206687)*. ClinicalTrials.gov Web Site 2005, Sept 30.

7. Watts, R. et al. *48-month follow-up of Spheramine protocol 101: A pilot study in six advanced Parkinson's disease patients*. 16th Int Congr Parkinson's Dis Relat Disord (June 5-9, Berlin) 2005, Abst IS005-04.

SR-57667

The neurotrophic agent SR-57667 is undergoing phase IIb clinical trials at Sanofi-Aventis for the treatment of Alzheimer's disease and Parkinson's disease.

SSR-180575



Sanofi-Aventis is evaluating SSR-180575, a peripheral benzodiazepine receptor (PBR) ligand, in early clinical trials for its potential in the treatment of neurodegenerative diseases, arthritis and chronic heart failure.

Stamulumab

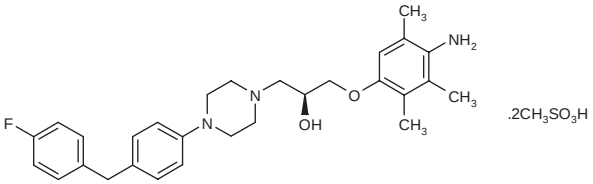
Stamulumab (MYO-029) is a recombinant fully human monoclonal antibody discovered at Cambridge Antibody Technology and developed by Wyeth, presently in phase I/II trials for the treatment of adult muscular dystrophy. The drug inhibits growth and differentiation factor-8 (GDF-8), also known as myostatin, a protein involved in the regulation of skeletal muscle mass, and is expected to be useful for increasing muscle mass and/or bone strength (1-3).

1. *Cambridge Antibody Technology reports Q3 R&D highlights*. Cambridge Antibody Technology Press Release 2004, Sept 8.

2. *MYO-029 studied in new phase I/II trial for muscular dystrophy*. DailyDrugNews.com (Daily Essentials) March 9, 2005.

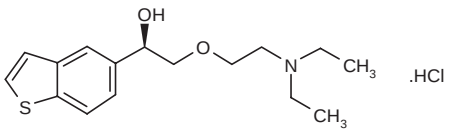
3. *Study evaluating MYO-029 in adult muscular dystrophy (NCT00104078)*. ClinicalTrials.gov Web Site 2005, Dec 8.

SUN-N8075



SUN-N8075 is a neuroprotectant in early clinical testing at Daiichi Asubio Pharma for the treatment of acute ischemic stroke. The drug acts by blocking Na^+ and T-type Ca^{2+} channels and also exerts antioxidant effects.

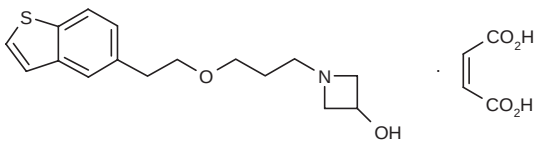
T-588



Toyama's T-588, a compound with neuroprotective and neurite outgrowth-promoting properties, has demonstrated promising results in phase II clinical trials for the treatment of Alzheimer's disease. Toyama is seeking a partner for the co-development of the compound. T-588 is also expected to be effective in the treatment of glaucoma, as it prevented optic nerve degeneration in animal models of glaucoma.

Original monograph – Drugs Fut 1997, 22(4): 386.

T-817MA



A successor compound to T-588 with more robust neuroprotective properties, T-817MA has entered phase I clinical development at Toyama for the oral treatment of Alzheimer's disease. The drug inhibits the progression of Alzheimer's dementia by inhibiting nerve cell death and stimulating neurite growth (1, 2).

1. *Toyama Chemical commences clinical study with T-817*. DailyDrugNews.com (Daily Essentials) June 8, 2004.

5. *Toyama Chemical begins U.S. phase I study of T-817MA*. DailyDrugNews.com (Daily Essentials) July 22, 2005.

T-2000

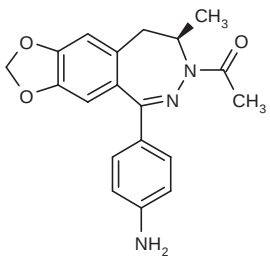
T-2000, a long-acting, nonsedating barbiturate in development by Taro Pharmaceutical, has been cleared for phase III clinical trials in Canada for the treatment of essential tremor (1).

1. *Taro reports third quarter and nine month 2005 results*. Taro Pharmaceutical Press Release 2005, Nov 17.

TAK-128/TAK-428

Takeda has two compounds in phase II development for diabetic neuropathy. TAK-128 is a myelin formation enhancer that enhances nerve regeneration and has shown potent and long-lasting efficacy against diabetic complications in the sensory, motor and autonomic nervous systems. The product was licensed from Mitsubishi Pharma (Y-128) several years ago for exclusive worldwide development and marketing. The company is also developing the neurotrophic factor production accelerator TAK-428 for the treatment of diabetic neuropathy.

Talampanel



Talampanel is an AMPA receptor antagonist in phase II trials at Ivax for the treatment of epilepsy (Ampanel). Phase II trials are also under way in conjunction with the National Institute of Neurological Disorders and Stroke (NINDS) for the treatment of Parkinson's disease-associated dyskinesia (Kinampa) and together with the National Cancer Institute (NCI) for the treatment of brain cancer (1-7).

Talampanel was used in a placebo-controlled clinical trial that evaluated the effects of AMPA blockade on human neurophysiological parameters. Six healthy volunteers were given single doses of placebo or talampanel (25 or 50 mg p.o.). Electroencephalogram recordings obtained for up to 3 h after administration showed that talampanel dose-dependently increased β activity and had no effect on α activity. Talampanel also increased resting and active motor thresholds and decreased the recruitment curve gradient in a series of transcranial magnetic stimulation studies (8).

An open-label clinical trial determined the potential effects of sodium valproate (250 mg p.o. b.i.d. for 5 days) on the pharmacokinetics of a single oral dose of 25 mg of the novel antiepileptic drug talampanel in 10 healthy adult volunteers. No significant differences were found in the area under the curve, the peak plasma concentration and the time to peak plasma concentration of talampanel

when given alone or after 4 days of sodium valproate administration (9).

1. *Talampanel, radiation therapy, and temozolomide in treating patients with newly diagnosed glioblastoma multiforme (NCT00082992)*. ClinicalTrials.gov Web Site 2005, Dec 8.

2. *Investigating the use of talampanel in patients with recurrent high-grade gliomas (NCT00061685)*. ClinicalTrials.gov Web Site 2005, Sept 28.

3. *Talampanel to treat Parkinson's disease (NCT00108667)*. ClinicalTrials.gov Web Site 2005, Dec 22.

4. *Effect of talampanel (an AMPA receptor blocker) on brain activity (NCT00057460)*. ClinicalTrials.gov Web Site 2005, Aug 22.

5. *Safety and efficacy of talampanel in glioblastoma multiforme (NCT00267592)*. ClinicalTrials.gov Web Site 2005, Dec 20.

6. *Phase 2 trial using talampanel in patients with recurrent high-grade gliomas (NCT00062504)*. ClinicalTrials.gov Web Site 2005, Dec 8.

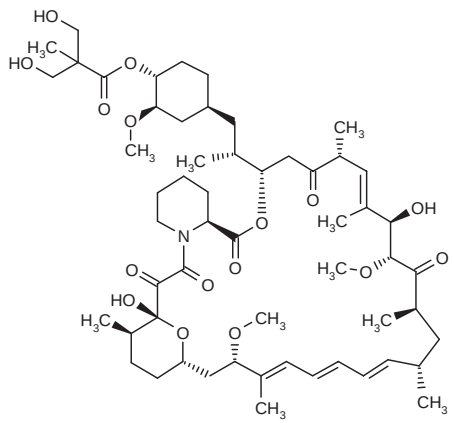
7. *Multicenter trial for adults with partial epilepsy (NCT00034814)*. ClinicalTrials.gov Web Site 2005, Dec 8.

8. Danielsson, I., Su, K.G., Kauer, L. et al. *Talampanel and human cortical excitability: EEG and TMS*. Epilepsia 2004, 45(Suppl. 7): Abst 1.314.

9. Gidal, B.E. et al. *Evaluation of the potential pharmacokinetic interaction between sodium valproate and the investigational antiepileptic drug talampanel*. Neurology 2005, 64(6, Suppl. 1): Abst P03.107.

Original monograph – Drugs Fut 2001, 26(8): 754.

Temsirolimus



Phase III trials are under way for Wyeth's temsirolimus (CCI-779), an mTOR inhibitor, in several cancers including renal cell carcinoma, advanced metastatic breast cancer and mantle cell lymphoma. Phase II trials are also investigating whether it may have therapeutic utility in other diseases such as rheumatoid arthritis and multiple sclerosis (MS) (2, 3).

The potential benefits of temsirolimus in MS were assessed in a multicenter, double-blind, randomized phase II clinical trial that enrolled 296 patients aged 19-57 years with relapsing-remitting MS or secondary progressive MS with relapses. Each patient was given placebo or temsirolimus (2, 4 or 8 mg) orally once daily for 9 months. Compared to placebo, patients receiving a daily dose of 8 mg of temsirolimus showed a 47.8% reduction in the cumulative number of new gadolinium-enhancing MRI lesions, a significant volume reduction in brain atrophy and a 51% decrease in the number of relapses per patient. Other effects included improvements in the number of relapse-free patients and a reduced progression of disability. The highest dose of temsirolimus was associated with an increase in the incidence of adverse events (*e.g.*, aphthous stomatitis, hyperlipidemia, rash and menstrual dysfunction) compared to placebo, but the risk/benefit ratio was considered to be acceptable (1).

Twelve healthy male volunteers participated in an open-label clinical trial that evaluated the effects of the cytochrome P-450 CYP3A4 inhibitor ketoconazole on the pharmacokinetics of temsirolimus. Co-administration of ketoconazole (200 mg p.o. once daily on study days 16-25) with a single dose of temsirolimus (2 mg p.o. on study day 20) significantly increased the peak plasma concentration and the area under the curve of both temsirolimus and its major active metabolite sirolimus. The authors concluded that the *in vivo* metabolism of temsirolimus may be inhibited by the use of CYP3A4 inhibitors (2).

Solutions containing the mTOR inhibitor temsirolimus in conjunction with an appropriate solvent have been claimed for use in the manufacture of lyophilized formulations. Such compositions are expected to have potential for treating, among others, cancer, multiple sclerosis and rheumatoid arthritis while surmounting various problems associated with previous formulations of the drug, including chemical instability and poor solubility (3).

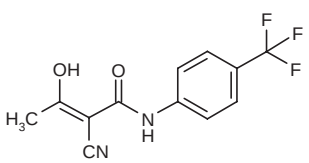
1. Kappos, L. et al. *The effect of temsirolimus on new magnetic resonance imaging scan lesions, brain atrophy, and the number of relapses in multiple sclerosis: Results from a randomised, controlled clinical trial*. J Neurol 2005, 252(Suppl. 2): Abst O158.

2. Shu, C. et al. *Effect of ketoconazole on the temsirolimus pharmacokinetic profile in healthy subjects*. Clin Pharmacol Ther 2005, 77(2): Abst PI-100.

3. Rubino, J.T. (Wyeth) *CCI-779 lyophilized formulations*. WO 2005011688, US 2005020615.

Original monograph – Drugs Fut 2002, 27(1): 7.

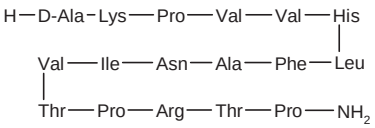
Teriflunomide



Sanofi-Aventis is evaluating teriflunomide, a dihydroorotate dehydrogenase inhibitor, in phase III clinical

trials for the treatment of multiple sclerosis (MS) (see monograph this issue).

Tiplimotide



The altered peptide ligand (APL) tiplimotide (NBI-5788) is in phase II trials at Neurocrine Biosciences for the treatment of relapsing-remitting multiple sclerosis (RRMS). The drug directly targets and regulates autoreactive and destructive immune cells thought to cause demyelination. Neurocrine scientists have taken the same amino acids that comprise a portion of myelin basic protein (MBP) and adjusted them to generate an APL that drives the pathogenic immune cells to shift to a nonpathogenic antiinflammatory response. The company completed enrollment of over 150 patients in the multicenter U.S., Canadian and Eastern European phase II trial earlier this year, with results expected in early 2006 (1-4).

1. *Neuroscrine Biosciences reports 2003 year-end R&D highlights*. Neurocrine Biosciences Press Release 2004, Jan 29.

2. *Neurocrine Biosciences reports Q1 R&D highlights*. Neurocrine Biosciences Press Release 2004, May 3.

3. *Neurocrine Biosciences reports Q1 R&D highlights*. Neurocrine Biosciences Press Release 2005, April 28.

4. *Neurocrine Biosciences reports Q2 R&D highlights*. Neurocrine Biosciences Press Release 2005, Aug 3.

Tovaxin™

Tovaxin™, a T-cell therapeutic vaccine, is in phase I/II trials at PharmaFrontiers for the treatment of relapsing-remitting and progressive multiple sclerosis (MS). The vaccine is a trivalent formulation of attenuated myelin peptide-reactive T-cells (MRTCs) derived from peripheral blood and produced *ex vivo*. The immune response elicited by Tovaxin™ is directed against autologous T-cells that are self-reactive with myelin. This immune response, directed against a specific subset of autoreactive T-cells, greatly reduces the number of these autoreactive cells in MS patients. Rights to Tovaxin™ were originally obtained by Opexa Pharmaceuticals, subsequently acquired by PharmaFrontriers, under an exclusive worldwide license from Baylor College of Medicine (1, 2).

Recent data from two open-label phase I/II clinical trials have shown that Tovaxin™ is well tolerated and may be effective in the treatment of MS. All the patients included in these studies had previously been given standard therapy for MS and were in the relapsing-remitting or secondary progressive stages of the disease. A dose-escalation study showed that both low-dose (6-9 million cells) and intermediate-dose (30-45 million cells) Tovaxin™ therapy decreased MRTC levels in peripheral blood, improved disability scores and significantly reduced the exacerbation rate over 6 months in 6 evaluable MS patients. Similar results were found in an extension study that administered two Tovaxin™ doses of 30-45 million cells to 9 MS patients. All adverse events were mild or moderate, and the most common were injection-site pain, muscle weakness, abnormal vision, anorexia, pharyngitis, neuropathy and paresthesia. Based on these promising results, PharmaFrontiers intends to begin phase IIb/III trials with Tovaxin™ by the end of 2005 or early 2006 (3).

1. *PharmaFrontiers closes acquisition of the multiple sclerosis focused Opexa Pharmaceuticals*. DailyDrugNews.com (Daily Essentials) Nov 11, 2004.

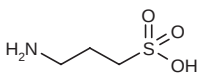
2. *PharmaFrontiers updates recent progress*. DailyDrugNews.com (Daily Essentials) April 19, 2005.

3. *Preliminary results on the efficacy of Tovaxin in multiple sclerosis*. DailyDrugNews.com (Daily Essentials) June 8, 2005.

Additional References

Loftus, B. et al. A*utologous T cell therapy in multiple sclerosis: An open-label safety and dose-range study*. 21st Congr Eur Comm Treat Res Multiple Scler (Sept 28-Oct 1, Thessaloniki) 2005, Abst P 618.

Tramiprosate



Tramiprosate (NC-531) is an orally active small-molecule antiamyloidogenic agent in phase III trials at Neurochem for the oral treatment of mild to moderate Alzheimer's disease (AD; Alzhemed™) and phase II trials for the treatment of hemorrhagic stroke due to cerebral amyloid angiopathy (CAA; Cerebril™). Tramiprosate is expected to act at three levels: preventing and stopping the formation and deposition of amyloid fibrils in the brain by binding to soluble Aβ prior to fibril formation; favoring the clearance of soluble Aβ from the brain, thereby lowering the risk of fibril formation; and inhibiting the inflammatory response associated with amyloid build-up (1-8).

The efficacy, safety and pharmacokinetics of tramiprosate were evaluated in a double-blind, randomized phase II clinical trial. Overall, 58 patients with mild to moderate AD were treated with placebo or tramiprosate (50, 100 or 150 mg p.o.) twice daily for 3 months. The analysis of adverse events suggested that tramiprosate was well tolerated and mostly associated with dose-dependent and transient nausea and vomiting. Patients treated with doses of 100 and 150 mg showed the greatest reductions in Aβ levels in the cerebrospinal fluid. Forty-two patients entered an open-label extension study

and received tramiprosate (150 mg p.o. twice daily) for another 21 months. The preliminary results of this study suggested that tramiprosate may be effective in stabilizing the cognitive function of patients with mild AD (1, 9).

1. *Positive interim reports on cognitive function in Alzhemed trial*. DailyDrugNews.com (Daily Essentials) April 19, 2004.

2. *Neurochem updates clinical pipeline progress*. DailyDrugNews.com (Daily Essentials) May 21, 2004.

3. *North American phase III trial initiated for Alzhemed*. DailyDrugNews.com (Daily Essentials) June 25, 2004.

4. *Alzhemed phase III trial recommended to continue*. DailyDrugNews.com (Daily Essentials) April 29, 2005.

5. *Alzhemed begins European phase III trial*. DailyDrugNews.com (Daily Essentials) Sept 16, 2005.

6. *Neurochem receives third positive recommendation from Independent Safety Review Board to continue phase III clinical trial for Alzhemed*. Neurochem Press Release 2005, Oct 5.

7. *Neurochem reports Q2 R&D highlights*. Neurochem Press Release 2005, Aug 10.

8. *Neurochem reports Q1 R&D highlights*. Neurochem Press Release 2004, May 11.

9. Mehran, M., Aisen, P., Poole, R. et al. *Safety, pharmacokinetic (PK) and pharmacological activity of Alzhemed™ in mild to moderate Alzheimer disease (AD) patients*. 8th Int Montreal/Springfield Symp Adv Alzheimer Ther (April 14-17, Montreal) 2004, Abst 57F.

Additional References

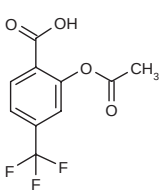
Aisen, P. et al. *Clinical data on Alzhemed(TM) after 20 months of follow-up in patients with mild to moderate Alzheimer's disease (AD)*. 7th Int Conf Prog Alzheimer Parkinson Dis (March 9-13, Sorrento) 2005, Abst.

Aisen, P.A., Mehran, M., Poole, R., Lavoie, I., Gervais, F., Laurin, J., Briand, R., Garceau, D. *Clinical data on Alzhemed after 12 months of treatment in patients with mild to moderate Alzheimer's disease*. Neurobiol Aging 2004, 25(Suppl. 2): Abst O1-05-06.

Greenberg, S.M. et al. *Phase II study of Cerebril, a candidate treatment for intracerebral hemorrhage related to cerebral amyloid angiopathy*. Neurology 2004, 62(7, Suppl. 5): Abst S13.006.

Vellas, B. et al. *A 21-month open-label study of the safety and efficacy of Alzhemed(TM) in patients with Alzheimer's disease: Preliminary results*. J Neurol 2004, 251(Suppl. 3): Abst 137.

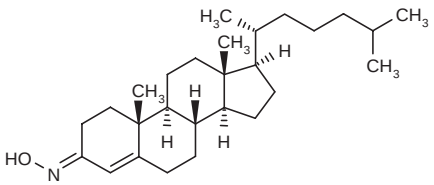
Triflusal, New Indication



A known antiplatelet agent introduced by Uriach over 20 years ago for the treatment and prevention of thromboembolic diseases, triflusal is now in early clinical trials for the treatment of Alzheimer's disease.

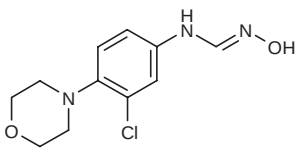
Original monograph – Drugs Fut 1978, 3(3): 225.

TRO-19622



The most advanced compound in Trophos' pipeline, TRO-19622 is a cholesterol-like small molecule with neuroprotective properties that interacts with the mitochondrial permeability transition pore (MPTP), preventing the release of apoptotic factors. An oral formulation was developed and entered phase I clinical trials in healthy volunteers in late 2004. It is being developed as a potential treatment for neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), spinal muscular atrophy and Huntington's disease.

TS-011



TS-011 is a 20-hydroxyeicosatetraenoic acid (20-HETE) synthesis inhibitor in early clinical development at Taisho for the treatment of acute stroke.

TV-5010

TV-5010, a high-molecular-weight copolymer, is currently in phase II trials at Teva for the treatment of Crohn's disease and relapsing-remitting multiple sclerosis (MS). Early clinical trials are also in progress under a collaboration with Proneuron for the treatment of various neurodegenerative diseases, including Huntington's disease and glaucoma, and it may also have potential in amyotrophic lateral sclerosis (ALS). The drug is comprised of the same amino acids present in glatiramer acetate, the active substance in Copaxone®. TV-5010 has a dual mechanism of action, affecting both inflammation and neurodegeneration.

V-2006

The adenosine receptor A_{2A} receptor antagonist V-2006 is in early clinical trials at Biogen Idec for the

treatment of Parkinson's disease. In June 2004, originator Vernalis granted Biogen Idec exclusive worldwide rights to develop and commercialize the compound. Vernalis completed five phase I trials of V-2006, including single- and multiple-ascending-dose studies and studies in healthy elderly volunteers. The company also studied the effects of V-2006 taken with and without food, and the potential for V-2006 to interact with standard dopamine therapy. Results from a phase I study demonstrated a mean plasma half-life consistent with a simple, once-daily dosing regimen. Biogen Idec anticipates filing an IND to commence phase II studies of V-2006 (1-5).

1. *Vernalis reports Q2 and Q3 R&D highlights*. Vernalis Group Press Release 2004, Jan 27.

2. *Vernalis and Biogen Idec collaborate on adenosine A2A receptor antagonists*. DailyDrugNews.com (Daily Essentials) July 1, 2004.

3. *Vernalis reports Q2 R&D highlights*. Vernalis Group Press Release 2004, Sept 17.

4. *Vernalis to acquire Ionix*. DailyDrugNews.com (Daily Essentials) July 8, 2005.

5. *Vernalis reports Q2 R&D highlights*. Vernalis Group Press Release 2005, Sept 22.

V-10153

A thrombolytic protein developed at Vernalis, V-10153 is a recombinant modified version of human plasminogen that has been altered so that it is activated to plasmin by thrombin rather than by the natural plasminogen activators. V-10153 represents a novel approach to blood clot destruction, taking advantage of the fact that active thrombin is only found at sites of ongoing clotting. It persists in the blood as an inactive prodrug and can be selectively activated by thrombin present in newly formed thrombi. This novel activation mechanism results in localized plasmin generation to remove thrombi and prevent them from forming or reforming. Therefore, in addition to lysis of existing thrombi, V-10153 can prevent reocclusion and reduce or remove the need for administration of a separate antithrombotic agent. It recently entered phase II clinical development for the treatment of acute ischemic stroke. The multicenter trial aims to determine whether the novel thrombolytic can safely benefit patients who have recently experienced an acute ischemic stroke up to 9 h after the stroke has occurred. The trial is being conducted in two parts, with Part A expected to be completed in the first half of 2006. This first part of the study is designed to identify a safe and potentially effective dose of V-10153, while the second part will be a placebo-controlled extension of the study to confirm the initial indications of efficacy from Part A. V-10153 was initially evaluated by the TIMI Study Group in a phase IIa ascending-dose study to establish proof of concept in patients who had suffered acute myocardial infarction (AMI). V-10153 was found to be well tolerated throughout the dose range of 1-10 mg/kg in patients with AMI. Restoration of blood flow was observed in blocked coronary arteries in up to 40% of patients after 60 min following doses of 5 mg/kg and greater (1-5).

1. *Vernalis reports Q2 and Q3 R&D highlights*. Vernalis Group Press Release 2004, Jan 27.

2. *Vernalis reports Q2 R&D highlights*. Vernalis Group Press Release 2004, Sept 17.

3. *Vernalis to acquire Ionix*. DailyDrugNews.com (Daily Essentials) July 8, 2005.

4. *Vernalis reports Q2 R&D highlights*. Vernalis Group Press Release 2005, Sept 22.

5. *Safety and efficacy study in acute ischaemic stroke (NCT00144014)*. ClinicalTrials.gov Web Site 2005, Oct 5.

VP-025

Vasogen has developed a new class of synthetic phospholipid-based drugs targeting chronic inflammation and designed to interact with antigen-presenting cells of the immune system to regulate tissue levels of cytokines and control inflammation. The company's first drug candidate in this class, VP-025, is being developed for the treatment of neuroinflammatory conditions such as Alzheimer's disease, Parkinson's diasese and amyotrophic lateral sclerosis (ALS). Preclinical research findings demonstrated the ability of VP-025 to significantly reduce key measures of inflammation and cell death in the brain and to improve physiological measurements that correlate with memory and learning. Vasogen has successfully completed a phase I trial of VP-025. The double-blind, placebo-controlled, dose-escalating phase I trial examined the safety and tolerability of three doses of VP-025 in 24 healthy volunteers. Multiple administrations of either low, intermediate or high doses of VP-025 were shown to be safe and well tolerated when compared to placebo and no drug-related serious adverse events were reported. Vasogen is now preparing to advance VP-025 into phase II in patients with neuroinflammatory disorders (1-8).

1. *Vasogen reports 2003 year-end R&D highlights*. Vasogen Press Release 2004, Feb 9.

2. *Vasogen reports Q2 R&D highlights*. Vasogen Press Release 2004, July 14.

3. *Canadian clearance for phase I trial of VP-025 for neuroinflammatory disease*. DailyDrugNews.com (Daily Essentials) Jan 26, 2005.

4. *VP-025 for neuroinflammatory disorders enters phase I study*. DailyDrugNews.com (Daily Essentials) Feb 8, 2005.

5. *Positive phase I results for VP-025*. DailyDrugNews.com (Daily Essentials) July 7, 2005.

6. *Vasogen reports Q1 R&D highlights*. Vasogen Press Release 2005, April 13.

7. *Vasogen reports Q2 R&D highlights*. Vasogen Press Release 2005, July 13.

8. *Vasogen reports Q3 R&D highlights*. Vasogen Press Release 2005, Oct 12.

VP-4896

A novel polymer-based formulation of the gonadotropin-releasing hormone (GnRH, LHRH) agonist leuprolide acetate, VP-4896 (Durin™-leuprolide, Memryte™) is currently undergoing phase III clinical trials for the treatment of Alzheimer's-type dementia at Voyager Pharmaceutical. The product employs Durect's Durin™ biodegradable implant technology as a platform for parenteral delivery of leuprolide acetate for extended periods. The pivotal program will consist of approximately 1,100 patients in two randomized, double-blind, placebo-controlled, 56-week trials using VP-4896 as adjunctive therapy with acetylcholinesterase inhibitors for the treatment of mild to moderate Alzheimer's disease. The first study –ALADDIN (Antigonadotropin-Leuprolide in Alzheimer's Disease Drug INvestigation)– is recruiting patients (1-5).

1. *DURIN leuprolide acetate IND accepted*. DailyDrugNews.com (Daily Essentials) Dec 23, 2004.

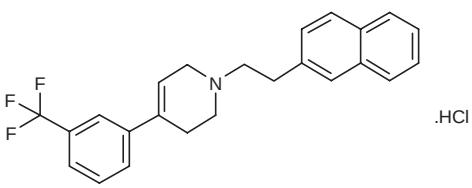
2. *Enrollment completed in study of Durin-leuprolide implant for Alzheimer's*. DailyDrugNews.com (Daily Essentials) Feb 1, 2005.

3. *Voyager completes phase II Alzheimer's study*. DailyDrugNews.com (Daily Essentials) Feb 22, 2005.

4. *Phase III program under way for Memryte implant*. DailyDrugNews.com (Daily Essentials) Oct 18, 2005.

5. *ALADDIN study – Phase III: Antigonadogropin-Leuprolide in Alzheimer's Disease Drug INvestigation (VP-AD-301) (NCT00231946)*. ClinicalTrials.gov Web Site 2005, Oct 7.

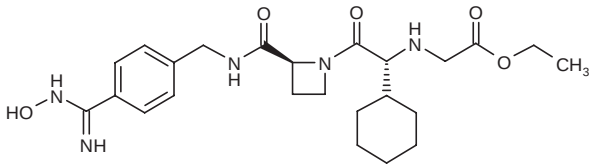
Xaliproden Hydrochloride



Phase III trials are in progress at Sanofi-Aventis with xaliproden hydrochloride (SR-57746), a 5-HT_{1A} receptor agonist and neurotrophic agent, for the treatment of Alzheimer's disease and chemotherapy-induced neuropathy. Phase II trials are also under way at the company for the treatment of multiple sclerosis (MS). The drug is reported to promote motoneuron phenotypic survival and neuritogenesis, while protecting the blood-brain barrier from disruption, which may be due to inhibition of the production of proinflammatory cytokines.

Original monograph – Drugs Fut 1998, 23(6): 616.

Ximelagatran



Ximelagatran (Exanta™), an oral prodrug of the direct thrombin inhibitor melagatran, was initially launched by AstraZeneca in Germany in June 2004, followed by several other European markets, for the prevention of venous thromboembolism (VTE) in elective hip or knee replacement surgery. The drug was also submitted in the E.U. for the treatment of VTE and for the prevention of stroke in patients with atrial fibrillation, and in the U.S. for the prevention of stroke and VTE. However, early this year, the French regulatory authority, which is acting as the reference member state for the European mutual recognition procedure, requested further clinical data on the efficacy and safety of ximelagatran in atrial fibrillation, and rejected its use in the treatment of VTE. The FDA did not grant approval for either indication. The compound is also undergoing phase II development for the prevention of arterial thrombosis following myocardial infarction (1-6).

The SPORTIF (Stroke Prevention by ORal Thrombin Inhibitor in atrial Fibrillation) III and V clinical trials compared the efficacy and safety of ximelagatran and warfarin in a total of 7,332 patients with atrial fibrillation and at least one risk factor. The pooled results of these studies revealed that ximelagatran (36 mg b.i.d.) was as effective as well-controlled warfarin (adjusted to an anticoagulation intensity of INR 2-3) in preventing stroke and systemic embolic events in these patients. The incidence of stroke and systemic embolism was similar with ximelagatran (2.2% per year in women and 1.4% per year in men) compared with warfarin (2.0% per year in women and 1.5% per year in men). Warfarin was associated with a greater incidence of minor and major hemorrhage in both women (42.6% per year *vs*. 33.8% per year) and men (36.9% per year *vs.* 30.6% per year). In the 2,804 patients enrolled who were more than 75 years old, the incidence of stroke or systemic embolism was 2.23% per year with ximelagatran and 2.27% per year with warfarin. The incidence of minor and major hemorrhage with each treatment was, respectively, 40.0% per year and 45.0% per year, suggesting that the benefits associated with ximelagatran were maintained in elderly patients (7, 8).

1. *AstraZeneca reports 2003 year-end R&D highlights*. AstraZeneca Press Release 2004, Jan 29.

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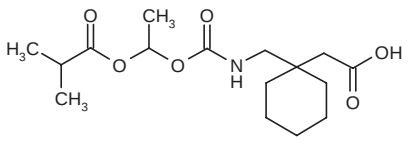
XP-13512



XP-13512 is a proprietary Transported Prodrug™ of gabapentin in phase II clinical trials at XenoPort for the oral treatment of postherpetic neuralgia and restless legs syndrome (RLS). The drug was designed to address gabapentin's deficiencies, specifically its limited and variable absorption rate, by targeting a different, high-capacity transporter mechanism expressed throughout the entire gastrointestinal tract. In this manner, XP-13512 is able to achieve blood levels of gabapentin that are unattainable after oral administration of gabapentin itself. Phase IIa studies of a tablet formulation in both indications were commenced following positive phase I results. Study XP018 was a randomized, placebo-controlled, ascending-multiple-dose study of the safety, tolerability and pharmacokinetics of the capsule formulation of XP-13512 in healthy adult subjects. A total of 38 subjects received one of four dose levels of XP-13512 or placebo administered twice a day for up to 10 days. Steady-state concentrations of gabapentin in blood were reached by the third day at the targeted dose. Pharmacokinetic analysis indicated that XP-13512 was rapidly absorbed and converted to gabapentin. Exposure to gabapentin after oral XP-13512 was dose-proportional. Exposure to the intact prodrug was low and transient at all XP-13512 doses. Bioavailability of oral XP-13512, determined by urinary recovery of gabapentin, was approximately 70% or better across the entire dose range. Side effects were mild to moderate and similar to those reported from gabapentin (Neurontin®) administration. Another phase I

study (Study 019) was a randomized, open-label, crossover study investigating the safety, tolerability and pharmacokinetics of three different tablet formulations of XP-13512 compared to the immediate-release capsules used in previous phase I studies. The different XP-13512 formulations were given 1 week apart to 12 healthy adult male subjects. A third phase I study (Study 022) was a randomized, open-label, crossover study investigating the safety, tolerability and pharmacokinetics of an optimized tablet formulation of XP-13512 under fasted and fed conditions compared to an equivalent dose of Neurontin® under fasted conditions. The study was conducted in 12 healthy subjects and the doses were administered 1 week apart. The side effects reported after dosing of all XP-13512 formulations in studies XP019 and XP022 were mild or moderate and similar to those previously reported from Neurontin® administration. Preliminary analysis of the results from Study XP022 indicated that dosing of the tablet formulation of XP-13512 under both fasted and fed conditions resulted in higher and more sustained gabapentin exposure than an equivalent dose of Neurontin®. Higher gabapentin exposure was observed after XP-13512 dosing under fed conditions in this study. Following promising results from a phase IIa trial, a multicenter, double-blind, randomized, placebo-controlled phase IIb clinical trial evaluated the potential benefits of XP-13512 in the treatment of RLS. A total of 95 RLS patients were randomized to receive placebo or XP-13512 (600 or 1200 mg) once daily with the evening meal for 14 days. Patients given 600 mg/day showed no statistical benefits compared to placebo-treated patients. In contrast, patients given 1200 mg/day of XP-13512 achieved greater average improvements in the IRLS score compared to placebo both at 1 week and at the end of the treatment period (–16.1 points *vs*. –8.9 points with placebo). A dose of 1200 mg/day of XP-13512 was also associated with significant improvements in the quality of sleep, number of awakenings per night due to RLS symptoms and severity of RLS symptoms, and resulted in more patients who were “much improved” or “very much improved” at the end of the study (81% *vs.* 48% with placebo). XP-13512 was generally well tolerated, and the most common adverse events were somnolence and dizziness. No patients experienced serious adverse events. A phase III trial with XP-13512 in RLS is expected to begin in the first half of 2006. Xenoport just recently entered into a license agreement with Astellas Pharma, whereby the latter obtains exclusive rights to develop and commercialize XP-13512 in Japan, Korea, the Philippines, Indonesia, Thailand and Taiwan, and plans to initiate phase I trials in the middle of next year (1-5).

1. *New phase IIa trials for XP-13512, additional phase I results*. DailyDrugNews.com (Daily Essentials) July 19, 2004.

2. *XP-13512 enters phase IIb study for restless legs syndrome*. DailyDrugNews.com (Daily Essentials) Feb 14, 2005.

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4. *Therapeutic benefits found for XP-13512 in RLS*. DailyDrugNews.com (Daily Essentials) Aug 4, 2005.

5. *Astellas licenses rights for XP-13512 in Asia and Japan*. DailyDrugNews.com (Daily Essentials) Dec 5, 2005.

XP-19986

XenoPort has developed a Transported Prodrug™ of the muscle relaxant and antispastic agent (*R*)-baclofen, XP-19986, which is currently in phase I trials for the treatment of spasticity and just recently entered phase II trials for the treatment of gastroesophageal reflux disease (GERD). XP-19986 is designed to enter the bloodstream thanks to the natural nutrient transport mechanisms present on the intestinal cell membranes. Once in the bloodstream, it is quickly converted to (*R*)-baclofen by high-capacity enzymes.

A phase I clinical trial has determined the safety and pharmacokinetics of one immediate-release and two sustained-release formulations of XP-19986 in healthy volunteers. A first double-blind, randomized, placebo-controlled, crossover stage administered single doses of 2, 4 or 8 mg of immediate-release XP-19986 to 30 fasted subjects, and the second stage administered single doses of 8 mg of each formulation to the same subjects with or without food. The results confirmed that XP-19986 is well absorbed and quickly converted to (*R*)-baclofen, and revealed that the pharmacokinetic profile of the sustained-release formulations suggested that they were suitable for twice-daily dosing. All adverse events were mild and similar to those reported for baclofen in previous studies (1, 2).

1. *XenoPort advances XP-19986 into phase I trials*. DailyDrugNews.com (Daily Essentials) March 31, 2005.

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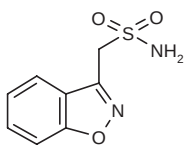
Zonisamide, New Indication



Zonisamide is a sodium channel and T-type calcium channel blocker launched over 15 years ago under the tradename Exegran by Dainippon for the oral treatment of epilepsy. The drug (Tremode) has been submitted for approval in Japan by Dainippon Sumitomo for the treatment of Parkinson's disease. Zonisamide was licensed for sales and marketing to Elan in the U.S., Canada, Mexico and Europe, but Elan sold its interest in North America and Europe to Eisai in 2004. Eisai sells the drug in these markets as Zonegran®.

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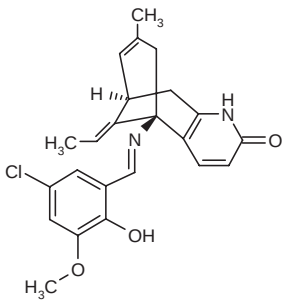
ZT-1



Debiopharm has signed a license agreement with the Shanghai Institute of Materia Medica (SIMM) for the development of ZT-1, a novel cholinesterase inhibitor for the treatment of Alzheimer's disease. ZT-1 is a huperzine A prodrug with a dual pharmacological mechanism of action that offers potential neuroprotective properties on top of its cholinergic effects, which could reduce the progression of the disease. Debiopharm has the exclusive license to develop and commercialize ZT-1 worldwide, while SIMM retains the rights in China. Debiopharm started the development of ZT-1 in 2000 and is conducting phase II clinical trials with a once-daily oral formulation. Debiopharm has also obtained positive results in animals with a sustained-release formulation. Thus far, Debiopharm has conducted approximately 60 preclinical studies and seven phase I/II clinical studies with ZT-1 and is in the process of seeking codevelopment and commercial partnerships with pharmaceutical companies (1).

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Annual Update 2004/2005 - Treatment of Neurological Cancers

(Source: Prous Science Integrity®)

More than 20 types of neurological cancer have been described. Primary brain tumors are classified depending on which cells they arise from. Brain tumors that originate from glial cells (gliomas), such as astrocytes (astrocytomas), oligodendrocytes (oligodendrogliomas) and ependymal cells (ependymomas), are the most common. Gliomas are graded according to their tendency to infiltrate, from grade I to grade IV tumors. Glioblastoma multiforme, a grade IV tumor, is the most prevalent and deadly of astrocytomas. Other varieties of neurological cancer include primitive neuroectodermal tumors, *e.g.*, medulloblastomas and neuroblastomas. Metastases to the brain from a primary tumor located outside the central nervous system are more common than primary tumors of the brain.

In the U.S., the death and incidence rates for brain cancer decreased among men and women of all races between 1975 and 2002 (1). However, malignant primary brain tumors are the second most common cause of cancer death in children up to 15 years old (2). The rate of survival 5 years after diagnosis varies with cancer grade: patients with low-grade brain tumors live an average 6-8 years, while the average survival for individuals with glioblastoma multiforme is only 1 year (3).

Currently, only three drugs are approved by the U.S. FDA for the treatment of neurological cancers: temozolomide, lomustine and carmustine (4).

In the table that follows, treatments under active development for neurological cancer are shown (*Source: Prous Science Integrity*®).

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2. American Brain Tumor Association (hope.abta.org)

3. American Association for Cancer Research (www.aacr.org)

4. U.S. Food and Drug Administration (www.fda.gov)

Pepi Hurtado, PhD

Treatment of Neurological Cancers

Condition	Phase	Drug	Target	Source
Neurological cancer	I	Valproic acid[1]	HDAC1	National Cancer Institute (US)
Brain cancer	I	Arsenic trioxide[1]		National Cancer Institute (US)
	I	GliAtak		Advantagene
	I	Lenalidomide	TNF-α	National Cancer Institute (US)
	I	Lonafarnib	Farnesyltransferase	EORTC
	I	Erlotinib hydrochloride[1]	EGFR	National Cancer Institute (US)
	I/II	Lapatinib	EGFR, HER2	National Cancer Institute (US)
	II	81C6		Duke University
	II	Antineoplaston A10		Burzynski Research Institute
	II	Antineoplaston AS2-1		Burzynski Research Institute
	II	Lucanthone	DNA topoisomerase II	Albert Einstein College of Medicine/Spectrum Pharmaceuticals
	III	Carboplatin[1]	DNA	National Cancer Institute (US)
Glioma	I	Atrasentan	ETA receptor	National Cancer Institute (US)
	I	Enzastaurin hydrochloride	PKCβ	National Cancer Institute (US)
	I	G-207		MediGene/University of Alabama at Birmingham/National Cancer Institute (US)

Continuation

Treatment of Neurological Cancers

Condition	Phase	Drug	Target	Source
Glioma	I	h-R3-(Re188)	EGFR	YM BioSciences
	I	Paclitaxel[1]	Microtubule	Children's Hospital of Philadelphia
	I	PAGRIT		Sigma-Tau
	I/ II	Erlotinib hydrochloride[1]	EGFR	National Cancer Institute (US)
	I/II	BNP-1350	DNA topoisomerase I	BioNumerik
	I/II	CC-8490	ER	Celgene/National Cancer Institute (US)
	I/II	Reolysin		Oncolytics Biotech
	I/II	Temsirolimus	mTOR	National Cancer Institute (US)
	I/II	Tipifarnib	Farnesyltransferase	National Cancer Institute (US)
	II	Antineoplaston A10		Burzynski Research Institute
	II	Antineoplaston AS2-1		Burzynski Research Institute
	II	AP-12009	TGF-β2	Antisense Pharma
	II	Bortezomib[1]	NF-κB, Proteasome	National Cancer Institute (US)
	II	Carboplatin[1]	DNA	National Cancer Institute (US)
	II	Efaproxiral sodium		Allos
	II	Gefitinib[1]	EGFR	National Cancer Institute (US)
	II	Gimatecan	DNA topoisomerase I	Sigma-Tau
	II	Imatinib mesilate[1]	Abl kinase, c-Kit, PDGFRα	National Cancer Institute (US)/EORTC
	II	Irofulven	Caspase-8 and -9	National Cancer Institute (US)
	II	Thalidomide[1]	TNF-α	National Cancer Institute (US)
	II	VNP-40101M	DNA	Vion
	Prereg.	EG-009		Ark Therapeutics
Astrocytoma	I	Arsenic trioxide[1]		National Cancer Institute (US)
	I	Lonafarnib	Farnesyltransferase	EORTC
	I/II	COL-3	MMP-2 (gelatinase A), MMP-9 (gelatinase B)	National Cancer Institute (US)
	I/II	Ixabepilone	Tubulin	National Cancer Institute (US)
	I/II	L-Alanosine	Purine	Salmedix
	II	Antineoplaston A10		Burzynski Research Institute
	II	Antineoplaston AS2-1		Burzynski Research Institute
	II	Nimotuzumab	EGFR	Oncoscience/YM BioSciences
	III	Imatinib mesilate[1]	Abl kinase, c-Kit, PDGFRα	Novartis
	L-2005	Procarbazine hydrochloride[1]	DNA	Chugai
Astrocytoma, anaplastic	I	Bortezomib[1]	NF-κB, Proteasome	National Cancer Institute (US)
	I	Cintredekin besudotox		NeoPharm
	I	Motexafin gadolinium		Pharmacyclics
	I	Sorafenib	Raf kinase, VEGFR-2, VEGFR-3, PDGFRβ, c-Kit, Flt3	National Cancer Institute (US)
	I/II	Erlotinib hydrochloride[1]	EGFR	National Cancer Institute (US)
	II	Antineoplaston A10		Burzynski Research Institute
	II	Cotara		Peregrine Pharmaceuticals
	II	Talampanel	AMPA	Ivax
	II	Thalidomide[1]	TNF-α	National Cancer Institute (US)
Glioblastoma	I	Advexin		Introgen
	I	Sorafenib	Raf kinase, VEGFR-2, VEGFR-3, PDGFRβ, c-Kit, Flt3	National Cancer Institute (US)
	I/II	CC-8490	ER	Celgene/National Cancer Institute (US)
	I/II	Ixabepilone	Tubulin	National Cancer Institute (US)
	I/II	L-Alanosine	Purine	Salmedix
	II	Enzastaurin hydrochloride	PKCβ	Lilly
	II	Nimotuzumab	EGFR	Oncoscience/YM BioSciences
	II	Thalidomide[1]	TNF-α	National Cancer Institute (US)
Glioblastoma multiforme	I	AP-23573	mTOR	Ariad Pharmaceuticals
	I	Arsenic trioxide[1]		National Cancer Institute (US)
	I	Irinotecan hydrochloride[1]	DNA topoisomerase I	St. Jude Children's Research Hospital
	I	Motexafin gadolinium		Pharmacyclics
	I/II	AEE-788	VEGFR-2, EGFR, HER2	Novartis

Continuation

Treatment of Neurological Cancers

Condition	Phase	Drug	Target	Source
Glioblastoma multiforme	I/II	COL-3	MMP-2 (gelatinase A), MMP-9 (gelatinase B)	National Cancer Institute (US)
	I/II	INO-1001	PARP	Inotek
	I/II	OV-001		OVCure
	I/II	Tipifarnib	Farnesyltransferase	M.D. Anderson Cancer Center/National Cancer Institute (US)
	II	Carboxyamidotriazole		National Cancer Institute (US)
	II	Celecoxib[1]	Cyclooxygenase type 2	National Cancer Institute (US)
	II	Cilengitide	Integrin $\alpha v\beta 3$ and $\alpha v\beta 5$	Merck KGaA/National Cancer Institute (US)
	II	Erlotinib hydrochloride[1]	EGFR	Genentech/OSI Pharmaceuticals/Roche/National Cancer Institute (US)
	II	Gefitinib[1]	EGFR	National Cancer Institute (US)
	II	Lapatinib	EGFR, HER2	National Cancer Institute (US)
	II	Motexafin gadolinium		Pharmacyclics
	II	Talampanel	AMPA	Ivax/National Cancer Institute (US)
	II	TP-38		Ivax
	III	Cintredekin besudotox		NeoPharm
	III	I-131 ch-TNT-1/B		Peregrine Pharmaceuticals
	III	Imatinib mesilate[1]	Abl kinase, c-Kit, PDGFRα	Novartis
	III	TransMID		Nycomed Pharma/Xenova
	II	DCVax-Brain		Northwest Biotherapeutics
Ependymoma	II	Antineoplaston A10		Burzynski Research Institute
Oligodendroglioma	I	Bortezomib[1]	NF-κB, Proteasome	National Cancer Institute (US)
	I	Lonafarnib	Farnesyltransferase	EORTC
	I	Sorafenib	Raf kinase, VEGFR-2, VEGFR-3, PDGFRβ, c-Kit, Flt3	National Cancer Institute (US)
	I/II	COL-3	MMP-2 (gelatinase A), MMP-9 (gelatinase B)	National Cancer Institute (US)
	I/II	Erlotinib hydrochloride[1]	EGFR	National Cancer Institute (US)
	I/II	Imatinib mesilate[1]	Abl kinase, c-Kit, PDGFRα	National Cancer Institute (US)
	I/II	Ixabepilone	Tubulin	National Cancer Institute (US)
	II	Antineoplaston A10		Burzynski Research Institute
	II	Talampanel	AMPA	Ivax
	II	Thalidomide[1]	TNF-α	National Cancer Institute (US)
	L-2005	Procarbazine hydrochloride[1]	DNA	Chugai
Medulloblastoma	II	Carboplatin[1]	DNA	National Cancer Institute (US)
	II	Oxaliplatin[1]	DNA	National Cancer Institute (US)
Neuroblastoma	I	Buthionine sulphoximine		National Cancer Institute (US)
	I	Edodekin alfa		National Cancer Institute (US)
	I	Irinotecan hydrochloride[1]	DNA topoisomerase I	St. Jude Children's Research Hospital
	I	Lestaurtinib	Flt3, TRKA	National Cancer Institute (US)
	I	Pyrazoloacridine	DNA topoisomerase I and II, DNA	National Cancer Institute (US)
	I	Temozolomide[1]	DNA	National Cancer Institute (US)
	I	TPI-287	Microtubule	Tapestry Pharmaceuticals
	II	Carboplatin[1]	DNA	National Cancer Institute (US)
	II	Oxaliplatin[1]	DNA	National Cancer Institute (US)
	II	Thalidomide[1]	TNF-α	National Cancer Institute (US)
	III	MAb-14.18		National Cancer Institute (US)

[1] Launched for another indication. AMPA: 1-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EGFR: Epidermal growth factor receptor; EORTC: European Organization for Research and Treatment of Cancer; ER: Estrogen receptor; ETA: Endothelin A; Flt3: FMS-like tyrosine kinase 3; HDAC: Histone deacetylase; HER: Human epidermal growth factor receptor; MMP: Matrix metalloproteinase; mTOR: Mammalian target of rapamycin; PARP: Poly(ADP-ribose)polymerase; PDGFR: Platelet-derived growth factor receptor; PKC: Protein kinase C; TGF-β2: Transforming growth factor-β2; TNF: Tumor necrosis factor; TRKA: Tyrosine receptor kinase A; VEGFR: Vascular endothelial growth factor receptor