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Annual Update 2004/2005 - Treatment of Cardiovascular Disorders

As in previous issues, the goal of this section is to present a balanced picture of the current status of therapies for cardiovascular disorders in the clinical stage, summarizing in a few pages the most important advances in this area over the last year or so. The therapeutic classification has changed since the publication of the last review and this therapeutic group now also includes conditions previously included in the group of drugs for hematological disorders, *i.e.*, thrombosis, acute coronary syndrome, myocardial infarction, pulmonary embolism, disseminated intravascular coagulation, coronary surgeries, peripheral and arterial vascular disorders and shock. The annual update on the treatment of hematological disorders will appear in the next issue of *Drugs of the Future*, along with a table of oncolytic drugs for hematological/blood cancers.

J.R. Prous
Editor

Treatment of Cardiovascular Disorders by Condition

Condition	Phase	Drug	Source
Acute coronary syndrome (angina pectoris, unstable)	L-2004	Atorvastatin calcium[1,2]	Pfizer
	III	Bivalirudin[1]	The Medicines Co.
	III	Fondaparinux sodium[1,2]	GlaxoSmithKline
	III	Prasugrel	Lilly/Sankyo
	III	Ranolazine[2]	CV Therapeutics
	II	DX-9065a[2]	Daiichi Pharmaceutical
	II	Otamixaban	Sanofi-Aventis
	II	rNAPc2	Nuvelo
	II	SR-123781	Sanofi-Aventis
	II	VX-702[2]	Vertex
	I	Octaparine	Sanofi-Aventis
	I	VT-111	Viron Therapeutics
Angina pectoris	II	HMR-1766	Sanofi-Aventis
	II	VEGF-2 gene therapy	Corautus Genetics/Boston Scientific
	I	AVE-9488	Sanofi-Aventis
	I	HMR-1069	Sanofi-Aventis
Angina pectoris, stable	Prereg.	Ivabradine hydrochloride[2]	Servier
	Prereg.	Ranolazine[2]	CV Therapeutics
	II	Fasudil hydrochloride[1,2]	Asahi Kasei/Schering AG
	II	Isosorbide mononitrate/L-arginine	Angiogenix
Arrhythmias, ventricular	I/II	ATI-2042	ARYx Therapeutics
Arteriosclerosis obliterans	I	K-134	Kowa
Arteriovenous graft failure	Discontinued	Edifoligide sodium	Corgentech
Atherosclerosis	III	AGI-1067[2]	AtheroGenics
	III	Atorvastatin calcium/torcetrapib	Pfizer
	II/III	Pactimibe	Sankyo/Kyoto Pharmaceutical
	II	480848	GlaxoSmithKline
	II	C-1602	Merck & Co.
	II	C-8834	Merck & Co.
	II	CETP vaccine	Avant Immunotherapeutics

Continuation

Treatment of Cardiovascular Disorders by Condition

Condition	Phase	Drug	Source
Atherosclerosis	II	ETC-216[2]	Pfizer
	I	659032	GlaxoSmithKline
	I	677116	GlaxoSmithKline
	I	681323	GlaxoSmithKline
	I	AC-3056	Amylin
	I	CRD-5	Liponex
	I	D-4F	Novartis/BruinPharma
	I	ISIS-301012	Isis Pharmaceuticals
	I	K-604	Kowa
	I	LY-674	Lilly/Ligand
	I	NV-04	Novogen
	I	RUS-3108	Dr. Reddy's Laboratories
	I	SMP-797	Sumitomo Pharmaceuticals
	I	*trans*-NV-04	Novogen
Atherothrombosis	III	S-18886	Servier
Atrial fibrillation	III	Dronedarone hydrochloride	Sanofi-Aventis
	III	Idraparinux sodium[2]	Sanofi-Aventis
	III	RSD-1235	Cardiome Pharma/Astellas Pharma
	III	Tedisamil hydrochloride	Solvay
	II	AVE-0118	Sanofi-Aventis
	II	AZD-7009	AstraZeneca
	II	Selodenoson	Aderis
	II	SSR-149744	Sanofi-Aventis
	II	Tecadenoson [2]	CV Therapeutics
	I/II	ATI-2042	ARYx Therapeutics
Cardiac surgery	II	INO-1001	Inotek
	II	TP-10	Avant Immunotherapeutics
Cardiopathy, diabetic	II	Trientine hydrochloride[1,2]	Protemix
Cardiovascular disorders	L-2004	Ibuprofen[1]	Orphan Europe
Coronary artery bypass graft (CABG)	III	Bivalirudin[1]	The Medicines Co.
	III	Pexelizumab[2]	Alexion/Procter & Gamble
	II/III	MC-1	Medicure
	II	Nesiritide[1]	Scios
	I	MLN-2222	Millennium/Xoma
	Discontinued	Edifoligide sodium	Corgentech/Bristol-Myers Squibb
Coronary artery disease	II	AdGVVEGF121.10	GenVec
	I	Motexafin lutetium	Pharmacyclics
	I	DS-992	AnGes/Daiichi Pharmaceutical
Coronary artery disease (diagnostic)	III	AI-700	Acusphere/Nycomed Pharma
	III	Binodenoson	Aderis/King Pharmaceuticals
	III	Regadenoson[2]	CV Therapeutics/Astellas Pharma
	II	BMS-068645 (ATL-146e)	Bristol-Myers Squibb/Adenosine Therapeutics
Embolism, cerebral	II	Monteplase[1]	Eisai
Embolism, pulmonary	Prereg.	Monteplase[1]	Eisai
	III	Idraparinux sodium[2]	Sanofi-Aventis
	I	Octaparine	Sanofi-Aventis
Embolism, pulmonary (treatment)	L-2004	Fondaparinux sodium[1,2]	GlaxoSmithKline
Heart failure	Prereg.	Hydralazine hydrochloride/ isosorbide dinitrate	NitroMed
	Prereg.	Nicorandil[1,2]	Chugai
	II	Alagebrium chloride	Alteon
	II	ZP-120	Zealand Pharma
Heart failure, chronic	L-2004	Candesartan cilexetil[1,2]	AstraZeneca/Takeda
	Prereg.	Celacade™	Vasogen
	III	Enoximone[1], oral	Myogen
	II	Conivaptan hydrochloride[2]	Astellas Pharma

Continuation

Treatment of Cardiovascular Disorders by Condition

Condition	Phase	Drug	Source
Heart failure, congestive	III	Irbesartan[1,2]	Sanofi-Aventis/Bristol-Myers Squibb
	III	Nolomirole hydrochloride[2]	Chiesi
	III	Tolvaptan[2]	Otsuka
	II/III	Oxypurinol	Cardiome Pharma
	II	AC-2592	Amylin
	II	Daglutril[2]	Solvay
	II	DITPA	Titan
	II	KW-3902[2]	NovaCardia
	II	Naxifylline	Biogen Idec
	II	PW-2132	Penwest
	II	SLV-320	Solvay
	I/II	MyoCell™	BioHeart
	I	AVE-9488	Sanofi-Aventis
	I	NBI-69734	Neurocrine Biosciences
Hypertension	L-2004	Amlodipine besilate/atorvastatin calcium	Pfizer
	Prereg.	Lercanidipine hydrochloride/ enalapril maleate	Recordati
	III	Aliskiren fumarate[2]	Novartis/Speedel
	III	Clevidipine[2]	The Medicines Co.
	III	PW-2101	Penwest
	II/III	MC-4232	Medicure
	II	Alagebrium chloride	Alteon
	II	Angiotensin vaccine	Protherics
	II	AVE-7688	Sanofi-Aventis
	II	Daglutril[2]	Solvay
	II	Darusentan[2]	Myogen
	II	Levamlodipine	Sepracor
	I/II	CYT006-AngQb	Cytos Biotechnology
	I	NV-04	Novogen
	I	Olmesartan medoxomil/azelnidipine	Sankyo
Hypotension	II	FK-352B[2]	Astellas Pharma
Intermittent claudication	II	NT-702 (NM-702)	Nissan Chemicals/Taisho
	II	Sarpogrelate hydrochloride[1,2]	Mitsubishi Pharma
	II	VLTS-934	Valentis
	I/II	EW-A-401	Sangamo/Edwards Lifesciences
	Discontinued	VLTS-589	Valentis
Myocardial infarction	L-2004	Atorvastatin calcium[1,2]	Pfizer
	L-2004	Valsartan[1]	Novartis
	III	Amediplase[2]	Menarini
	III	Pexelizumab[2]	Alexion/Procter & Gamble
	II	Caldaret hydrate	Mitsubishi Pharma
	II	DG-031	deCODE Genetics
	II	Staphylokinase	ThromboGenics
	II	V-10153	Vernalis
	I/II	TG-100115	TargeGen
	I/II	MyoCell™	BioHeart
Percutaneous coronary intervention (PCI)	III	Prasugrel	Sankyo/Lilly
Percutaneous transluminal coronary angioplasty (PTCA)	II	Cangrelor sodium	The Medicines Co.
	II	MC-1	Medicure
	I/II	KAI-9803	KAI Pharmaceuticals
Peripheral arterial disease (PAD)	III	Celacade™	Vasogen
	III	DS-992	AnGes/Daiichi Pharmaceutical
	II	VMDA-3601	ViroMed/Dong-A
	II	Z-335	Zeria
	I	KS-01-018	Kos Pharmaceuticals

Continuation

Treatment of Cardiovascular Disorders by Condition

Condition	Phase	Drug	Source
Peripheral arterial obstructive disease (PAOD)	III	Ecraprost	Mitsubishi Pharma/Asahi Glass
	II	Alfimeprase	Nuvelo
	II	Liprostin™	Endovasc
	II	NCX-4016[2]	NicOx
	I/II	MRX-815	ImaRx
	I	DG-041	deCODE Genetics
	I	Microplasmin	ThromboGenics
	I	SL-65.0472	Sanofi-Aventis
Peripheral bypass graft (PBG)	III	Edifoligide sodium	Corgentech/Bristol-Myers Squibb
Peripheral vascular disease (PVD)	II	Treprostinil sodium[1,2]	United Therapeutics
	II	XRP-0038	Centelion (Sanofi-Aventis)
Restenosis, arterial	II/III	AVI-4126	AVI BioPharma
	I/II	Paclitaxel, nanoparticles	American BioScience
Shock, cardiogenic	II	Tilarginine acetate	Arginox Pharmaceuticals
Shock, distributive	II	Pyridoxalated hemoglobin polyoxyethylene	Curacyte
Stenosis, arterial	II	EG-004	Ark Therapeutics
Tachycardia, paroxysmal supraventricular	III	Tecadenoson[2]	CV Therapeutics
Tachycardia, ventricular	I	ZP-123 (GAP-486)	Zealand Pharma/Wyeth
Thromboembolism, venous	II	YM-150	Astellas Pharma
	I	EMD-503982	Merck KGaA
	I	TTP-889	TransTech Pharma
Thrombosis	Prereg.	Recombinant human antithrombin III	GTC Biotherapeutics
	II	AZD-0837	AstraZeneca
	II	AZD-6140	AstraZeneca
	II	AZD-9684	AstraZeneca
	II	DU-176b	Daiichi Pharmaceutical
	II	Odiparcil	GlaxoSmithKline
	II	Org-42675	Organon
	II	Rivaroxaban	Bayer
	II	SSR-182289	Sanofi-Aventis
	I	AJW-200	Ajinomoto
	I	INS-50589	Inspire Pharmaceuticals
	I	LB-30870	LG Life Sciences
	I	PAI-749	Wyeth
	I	SSR-126517	Sanofi-Aventis
	I	TGN-167	Trigen/Eurand
	I	TGN-255	Trigen
Thrombosis, antibody-mediated (antiphospholipid syndrome)	I/II	LJP-1082	La Jolla Pharmaceutical
Thrombosis, deep venous	L-2004 (EU)	Ximelagatran[2]	AstraZeneca
	III	Dabigatran etexilate	Boehringer Ingelheim
	III	Idraparinux sodium[2]	Sanofi-Aventis
	III	Oral heparin	Emisphere Technologies
	II	ART-123	Asahi Kasei
	II	MCC-977	Mitsubishi Pharma
	II	Odiparcil	GlaxoSmithKline
	II	Razaxaban hydrochloride	Bristol-Myers Squibb
	II	YM-150	Astellas Pharma
	I/II	MRX-815	ImaRx
	I	KFA-1982	Kissei
	I	Octaparine	Sanofi-Aventis
Thrombosis, deep venous (treatment)	L-2004	Fondaparinux sodium[1,2]	GlaxoSmithKline
Vascular graft occlusion	II	Pegmusirudin	Speedel

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

Treatment of Cardiovascular Disorders by Source

Source	Condition	Drug	Phase
Acusphere	Coronary artery disease (diagnostic)	AI-700	III
Adenosine Therapeutics	Coronary artery disease (diagnostic)	BMS-068645 (ATL-146e)	II
Aderis	Atrial fibrillation	Selodenoson	II
	Coronary artery disease (diagnostic)	Binodenoson	III
Ajinomoto	Thrombosis	AJW-200	I
Alexion	Coronary artery bypass graft (CABG)	Pexelizumab[2]	III
	Myocardial infarction	Pexelizumab[2]	III
Alteon	Heart failure	Alagebrium chloride	II
	Hypertension	Alagebrium chloride	II
American BioScience	Restenosis, arterial	Paclitaxel, nanoparticles	I/II
Amylin	Atherosclerosis	AC-3056	I
	Heart failure, congestive	AC-2592	II
AnGes	Coronary artery disease	DS-992	I
	Peripheral arterial disease (PAD)	DS-992	III
Angiogenix	Angina pectoris, stable	Isosorbide mononitrate/L-arginine	II
Arginox Pharmaceuticals	Shock, cardiogenic	Tilarginine acetate	II
Ark Therapeutics	Stenosis, arterial	EG-004	II
ARYx Therapeutics	Arrhythmias, ventricular	ATI-2042	I/II
	Atrial fibrillation	ATI-2042	I/II
Asahi Glass	Peripheral arterial obstructive disease (PAOD)	Ecraprost	III
Asahi Kasei	Angina pectoris, stable	Fasudil hydrochloride[1,2]	II
	Thrombosis, deep venous	ART-123	II
		YM-150	II
Astellas Pharma	Atrial fibrillation	RSD-1235	III
	Coronary artery disease (diagnostic)	Regadenoson[2]	III
	Heart failure, chronic	Conivaptan hydrochloride[2]	II
	Hypotension	FK-352B[2]	II
	Thromboembolism	YM-150	II
	Thrombosis, deep venous	YM-150	II
AstraZeneca	Atrial fibrillation	AZD-7009	II
	Heart failure, chronic	Candesartan cilexetil[1,2]	L-2004
	Thrombosis	AZD-0837	II
		AZD-6140	II
		AZD-9684	II
	Thrombosis, deep venous	Ximelagatran[2]	L-2004 (EU)
AtheroGenics	Atherosclerosis	AGI-1067[2]	III
Avant Immunotherapeutics	Atherosclerosis	CETP vaccine	II
	Cardiac surgery	TP-10	II
AVI BioPharma	Restenosis, arterial	AVI-4126	II/III
Bayer	Thrombosis	Rivaroxaban	II
Biogen Idec	Heart failure, congestive	Naxifylline	II
BioHeart	Heart failure, congestive	MyoCell™	I/II
	Myocardial infarction	MyoCell™	I/II
Boheringer Ingelheim	Thrombosis, deep venous	Dabigatran etexilate	III
Boston Scientific	Angina pectoris	VEGF-2 gene therapy	II
Bristol-Myers Squibb	Coronary artery bypass graft (CABG)	Edifoligide sodium	Discontinued
	Coronary artery disease (diagnostic)	BMS-068645 (ATL-146e)	II
	Heart failure, congestive	Irbesartan[1,2]	III
	Peripheral bypass graft (PBG)	Edifoligide sodium	III
	Thrombosis, deep venpus	Razaxaban hydrochloride	II
BruinPharma	Atherosclerosis	D-4F	I
Cardiome Pharma	Atrial fibrillation	RSD-1235	III
	Heart failure, congestive	Oxypurinol	II/III
Centelion (Sanofi-Aventis)	Peripheral vascular disease (PVD)	XRP-0038	II
Chiesi	Heart failure, congestive	Nolomirole hydrochloride[2]	III
Chugai	Heart failure	Nicorandil[1,2]	Prereg.
Corautus Genetics	Angina pectoris	VEGF-2 gene therapy	II
Corgentech	Arteriovenous graft failure	Edifoligide sodium	Discontinued
	Coronary artery bypass graft (CABG)	Edifoligide sodium	Discontinued
	Peripheral bypass graft (PBG)	Edifoligide sodium	III
Curacyte	Shock, distributive	Pyridoxalated hemoglobin polyoxyethylene	II
CV Therapeutics	Acute coronary syndrome (angina pectoris, unstable)	Ranolazine[2]	III
	Angina pectoris, stable	Ranolazine[2]	Prereg

Continuation

Treatment of Cardiovascular Disorders by Source

Source	Condition	Drug	Phase
CV Therapeutics	Atrial fibrillation	Tecadenoson[2]	II
	Coronary artery disease (diagnostic)	Regadenoson[2]	III
	Tachycardia, paroxysmal supraventricular	Tecadenoson[2]	II
Cytos Biotechnology	Hypertension	CYT006-AngQb	I/II
Daiichi Pharmaceutical	Acute coronary syndrome (angina pectoris, unstable)	DX-9065a[2]	II
	Coronary artery disease	DS-992	I
	Peripheral arterial disease (PAD)	DS-992	III
deCODE Genetics	Myocardial infarction	DG-031	II
	Peripheral arterial obstructive disease (PAOD)	DG-041	I
Dong-A	Peripheral arterial disease (PAD)	VMDA-3601	II
Dr. Reddy's Laboratories	Atherosclerosis	RUS-3108	I
Edwards Lifesciences	Intermittent claudication	EW-A-401	I/II
Eisai	Embolism, cerebral	Monteplase[1]	II
	Embolism, pulmonary	Monteplase[1]	Prereg.
Emisphere Technologies	Thrombosis, deep venous	Oral heparin	III
Endovasc	Peripheral arterial obstructive disease (PAOD)	Liprostin™	II
Eurand	Thrombosis	TGN-167	I
GenVec	Coronary artery disease	AdGVVEGF121.10	II
GlaxoSmithKline	Acute coronary syndrome (angina pectoris, unstable)	Fondaparinux sodium[1,2]	III
	Atherosclerosis	480848	II
		659032	I
		677116	I
		681323	I
	Embolism, pulmonary (treatment)	Fondaparinux sodium[1,2]	L-2004
	Thrombosis	Odiparcil	II
	Thrombosis, deep venous	Odiparcil	II
	Thrombosis, deep venous (treatment)	Fondaparinux sodium[1,2]	L-2004
GTC Biotherapeutics	Thrombosis	Recombinant human antithrombin III	Prereg.
ImaRx	Peripheral arterial obstructive disease (PAOD)	MRX-815	I/II
	Thrombosis, deep venous	MRX-815	I/II
Inotek	Cardiac surgery	INO-1001	II
Inspire Pharmaceuticals	Thrombosis	INS-50589	I
Isis Pharmaceuticals	Atherosclerosis	ISIS-301012	I
KAI Pharmaceuticals	Percutaneous transluminal coronary angioplasty (PTCA)	KAI-9803	I/II
King Pharmaceuticals	Coronary artery disease (diagnostic)	Binodenoson	III
Kissei	Thrombosis, deep venous	KFA-1982	I
Kos Pharmaceuticals	Peripheral arterial disease (PAD)	KS-01-018	I
Kowa	Arteriosclerosis obliterans	K-134	I
	Atherosclerosis	K-604	I
Kyoto Pharmaceutical	Atherosclerosis	Pactimibe	II/III
La Jolla Pharmaceutical	Thrombosis, antibody-mediated (antiphospholipid syndrome)	LJP-1082	I/II
LG Life Sciencies	Thrombosis	LB-30870	I
Ligand	Atherosclerosis	LY-674	I
Lilly	Acute coronary syndrome (angina pectoris, unstable)	Prasugrel	III
	Atherosclerosis	LY-674	I
	Percutaneous coronary intervention (PCI)	Prasugrel	III
Liponex	Atherosclerosis	CRD-5	I
Medicure	Coronary artery bypass graft (CABG)	MC-1	II/III
	Hypertension	MC-4232	II/III
	Percutaneous transluminal coronary angioplasty (PTCA)	MC-1	II
Menarini	Myocardial infarction	Amediplase[2]	III
Merck & Co.	Atherosclerosis	C-1602	II
		C-8834	II
Merck KGaA	Thromboembolism, venous	EMD-503982	I
Millennium	Coronary artery bypass graft (CABG)	MLN-2222	I

Continuation

Treatment of Cardiovascular Disorders by Source

Source	Condition	Drug	Phase
Mitsubishi Pharma	Intermittent claudication	Sarpogrelate hydrochloride[1,2]	II
	Myocardial infarction	Caldaret hydrate	II
	Peripheral arterial obstructive disease (PAOD)	Ecraprost	III
	Thrombosis, deep venous	MCC-977	II
Myogen	Heart failure, chronic	Enoximone[1], oral	III
	Hypertension	Darusentan[2]	II
Neurocrine Biosciences	Heart failure, congestive	NBI-69734	I
NicOx	Peripheral arterial obstructive disease (PAOD)	NCX-4016[2]	II
Nissan Chemicals	Intermittent claudication	NT-702 (NM-702)	II
NitroMed	Heart failure	Hydralazine hydrochloride/isosorbide dinitrate	Prereg.
NovaCardia	Heart failure, congestive	KW-3902[2]	II
Novartis	Atherosclerosis	D-4F	I
	Hypertension	Aliskiren fumarate[2]	III
	Myocardial infarction	Valsartan[1]	L-2004
Novogen	Atherosclerosis	NV-04	I
		trans-NV-04	I
	Hypertension	NV-04	I
Nuvelo	Acute coronary syndrome (angina pectoris, unstable)	rNAPc2	II
	Peripheral arterial obstructive disease (PAOD)	Alfimeprase	II
Nycomed Pharma	Coronary artery disease (diagnostic)	AI-700	III
Organon	Thrombosis	Org-42675	II
Orphan Europe	Cardiovascular disorders	Ibuprofen[1]	L-2004
Otsuka	Heart failure, congestive	Tolvaptan[2]	III
Penwest	Heart failure, congestive	PW-2132	II
	Hypertension	PW-2101	III
Pfizer	Acute coronary syndrome (angina pectoris, unstable)	Atorvastatin calcium[1,2]	L-2004
	Atherosclerosis	Atorvastatin calcium/torcetrapib	III
		ETC-216[2]	II
	Hypertension	Amlodipine besilate/atorvastatin calcium	L-2004
	Myocardial infarction	Atorvastatin calcium[1,2]	L-2004
Pharmacyclics	Coronary artery disease	Motexafin lutetium	I
Procter & Gamble	Coronary artery bypass graft (CABG)	Pexelizumab[2]	III
	Myocardial infarction	Pexelizumab[2]	III
Protemix	Cardiopathy, diabetic	Trientine hydrochloride[1,2]	II
Protherics	Hypertension	Angiotensin vaccine	II
Recordati	Hypertension	Lercanidipine hydrochloride/enalapril maleate	Prereg.
Sangamo	Intermittent claudication	EW-A-401	I/II
Sankyo	Acute coronary syndrome (angina pectoris, unstable)	Prasugrel	III
Sankyo	Atherosclerosis	Pactimibe	II/III
	Hypertension	Olmesartan medoxomil/azelnidipine	I
	Percutaneous coronary intervention (PCI)	Prasugrel	III
Sanofi-Aventis	Acute coronary syndrome (angina pectoris, unstable)	Octaparine	I
		Otamixaban	II
		SR-123781	II
	Angina pectoris	AVE-9488	I
		HMR-1069	I
		HMR-1766	II
	Atrial fibrillation	AVE-0118	II
		Dronedarone hydrochloride	III
		Idraparinux sodium[2]	III
		SSR-149744	II
	Embolism, pulmonary	Idraparinux sodium[2]	III
		Octaparine	I
	Heart failure, congestive	AVE-9488	I
		Irbesartan[1,2]	III
	Hypertension	AVE-7688	II

Continuation

Treatment of Cardiovascular Disorders by Source

Source	Condition	Drug	Phase
Sanofi-Aventis	Peripheral arterial obstructive disease (PAOD)	SL-65.0472	I
	Thrombosis	SSR-126517	I
		SSR-182289	II
	Thrombosis, deep venous	Idraparinux sodium[2]	III
		Octaparine	I
Schering AG	Angina pectoris, stable	Fasudil hydrochloride[1,2]	II
Scios	Coronary artery bypass graft (CABG)	Nesiritide[1]	II
Sepracor	Hypertension	Levamlodipine	II
Servier	Angina pectoris, stable	Ivabradine hydrochloride[2]	Prereg.
	Atherothrombosis	S-18886	III
Solvay	Atrial fibrillation	Tedisamil hydrochloride	III
	Heart failure, congestive	Daglutril[2]	II
		SLV-320	II
	Hypertension	Daglutril[2]	II
Speedel	Hypertension	Aliskiren fumarate[2]	III
	Vascular graft occlusion	Pegmusirudin	II
Sumitomo Pharmaceuticals	Atherosclerosis	SMP-797	I
Taisho	Intermittent claudication	NT-702 (NM-702)	II
Takeda	Heart failure, chronic	Candesartan cilexetil[1,2]	L-2004
TargeGen	Myocardial infarction	TG-100115	I/II
The Medicines Co.	Acute coronary syndrome (angina pectoris, unstable)	Bivalirudin[1]	III
	Coronary artery bypass graft (CABG)	Bivalirudin[1]	III
	Hypertension	Clevidipine[2]	III
	Percutaneous transluminal coronary angioplasty (PTCA)	Cangrelor sodium	II
ThromboGenics	Myocardial infarction	Staphylokinase	II
	Peripheral arterial obstructive disease (PAOD)	Microplasmin	I
Titan	Heart failure, congestive	DITPA	II
TransTech Pharma	Thromboembolism	TTP-889	I
Trigen	Thrombosis	TGN-167	I
		TGN-255	I
United Therapeutics	Peripheral vascular disease (PVD)	Treprostinil sodium[1,2]	II
Valentis	Intermittent claudication	VLTS-589	Discontinued
		VLTS-934	II
Vasogen	Heart failure, chronic	Celacade™	Prereg.
	Peripheral arterial disease (PAD)	Celacade™	III
Vernalis	Myocardial infarction	V-10153	II
Vertex	Acute coronary syndrome (angina pectoris, unstable)	VX-702[2]	II
ViroMed	Peripheral arterial disease (PAD)	VMDA-3601	II
Viron Therapeutics	Acute coronary syndrome (angina pectoris, unstable)	VT-111	I
Wyeth	Tachycardia, ventricular	ZP-123 (GAP-486)	I
	Thrombosis	PAI-749	I
Xoma	Coronary artery bypass graft (CABG)	MLN-2222	I
Zealand Pharma	Heart failure	ZP-120	II
	Tachycardia, ventricular	ZP-123 (GAP-486)	I
Zeria	Peripheral arterial disease (PAD)	Z-335	II

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

Treatment of Cardiovascular Disorders

N.E. Mealy, M. Bayés
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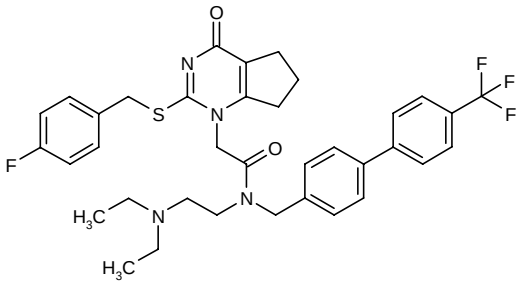
480848/659032/677116



480848

480848 (SB-480848) is a small-molecule drug arising from a Human Genome Sciences-GlaxoSmithKline agreement. It is an inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA_2), an enzyme associated with the development of atherosclerotic plaques. GlaxoSmithKline has completed a phase II trial of 480848 and has indicated that it plans to advance 480848 to phase III trials for the treatment of cardiovascular disease in the coming months. Under the agreement signed in 1993, Human Genome Sciences is entitled to receive clinical development milestone payments and royalties for compounds discovered by GSK through the use of Human Genome Sciences' technology and intellectual property. Human Genome Sciences will receive a milestone payment if 480848 moves into registration, and will receive royalties if the compound is commercialized. Human Genome Sciences also has an option to copromote an approved drug in the North American and European markets. GSK has also advanced two other small-molecule Lp-PLA_2 inhibitors discovered under this collaboration into early clinical development for the treatment of atherosclerosis: 659032 (SB-659032) and 677116 (1-3).

1. *GlaxoSmithKline advances new Lp-PLA_2 inhibitor into the clinic.* DailyDrugNews.com (Daily Essentials) April 5, 2004.

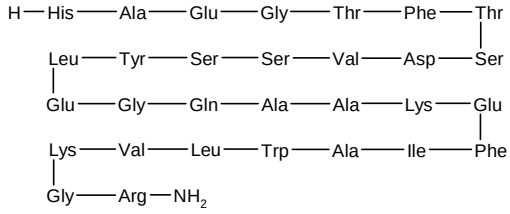
2. *Human Genome Sciences reports Q1 R&D highlights.* Human Genome Sciences Press Release 2004, April 28.

3. *Human Genome Sciences updates 2004 progress.* DailyDrugNews.com (Daily Essentials) Jan 27, 2005.

681323

In addition to the above-mentioned compounds, GlaxoSmithKline is also developing an MAP (mitogen-activated protein) p38 kinase inhibitor, 681323, which is undergoing phase I testing for atherosclerosis, as well as rheumatoid arthritis and chronic obstructive pulmonary disease (COPD).

AC-2592



Amylin recently initiated a double-blind, placebo-controlled phase II study of AC-2592, a recombinant form of glucagon-like peptide-1 (GLP-1) licensed from Restoragen in 2003, in its development program for congestive heart failure (CHF). This program utilizes continuous infusion of GLP-1. The study will include approximately 180 subjects, and will test two doses of AC-2592. The primary endpoint will be peak oxygen consumption. The secondary endpoints will include various measures of quality of life and cardiac function (1).

1. *Amylin Pharmaceuticals provides update on clinical development programs.* Amylin Pharmaceuticals Press Release 2004, Dec 5.

AC-3056

AC-3056 is an antioxidant currently in early clinical development at Amylin for the oral treatment of atherosclerosis-related cardiovascular disease. The compound was licensed from the former Aventis Pharma (now Sanofi-Aventis) in 1997.

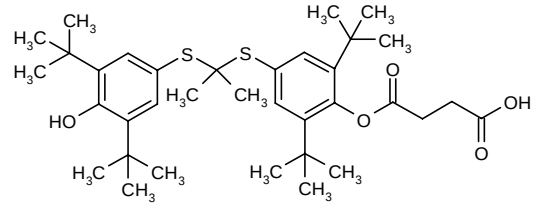
AdGVVEGF121.10

GenVec has initiated a randomized, placebo-controlled phase IIb trial of its AdGVVEGF121.10 (BioBypass®) angiogen, an adenovirus vector containing the gene for vascular endothelial growth factor-121 (VEGF-121), for the treatment of severe coronary artery disease (CAD). The NOVA (NOGA delivery of VEGF for Angina) trial will evaluate the effects of AdGVVEGF121.10 on exercise tolerance, heart function, symptoms and quality of life in approximately 129 patients suffering from moderate to severe chest pain due to advanced CAD. Two medical centers in Denmark have begun enrollment. Approximately 15 centers in Europe and Israel will ultimately participate. The NOVA trial is being conducted under a research collaboration between GenVec and the cardiology division of Cordis, a Johnson & Johnson company. AdGVVEGF121.10 will be administered using the Cordis NOGA® technology with the Nogastar® Mapping Catheter and Myostar™ Injection Catheter. AdGVVEGF121.10 promotes the production of GenVec's proprietary form of VEGF to stimulate the growth of new blood vessels in areas of the heart lacking sufficient blood flow. In an earlier multicenter, randomized, controlled phase II trial known as the REVASC study, AdGVVEGF121.10 was administered during surgery. The AdGVVEGF121.10-treated group showed significant clinical benefits, including an increased ability to exercise (1, 2). GenVec obtained an exclusive worldwide license to the VEGF-121 gene for all gene therapy applications from Scios in 1999. GenVec and former development partner Pfizer had also been studying BioBypass® for the treatment of peripheral vascular disease (PVD).

1. *GenVec reports Q1 R&D highlights.* GenVec Press Release 2004, April 29.

2. *Phase IIb study for Biobypass.* DailyDrugNews.com (Daily Essentials) March 7, 2005.

AGI-1067



AGI-1067, an antioxidant capable of inhibiting monocyte chemoattractant protein-1 (MCP-1) and vascular cell adhesion molecule-1 (VCAM-1) expression, is currently undergoing phase III development by AtheroGenics for the treatment of atherosclerosis in patients with CAD. AGI-1067 is the first in the new vascular protectant (v-protectant) class that aims to reduce inflammation in blood vessel walls.

The double-blind, randomized, placebo-controlled CART-1 (Canadian Antioxidant Restenosis Trial-1) trial evaluated the effects of AGI-1067 in 305 patients scheduled to undergo percutaneous coronary intervention (PCI). Each patient was treated with placebo, probucol (500 mg twice daily) or AGI-1067 (70, 140 or 280 mg once daily) for 2 weeks before and 4 weeks after PCI. The results of the study revealed that AGI-1067 had positive effects on restenosis and atherosclerotic control segments. A reassessment of the study data showed that patients treated with AGI-1067 had lower plasma fibrinogen levels and circulating white blood cell counts compared to those receiving placebo or probucol (1) (Table I).

The CART-2 study was a multicenter, randomized, placebo-controlled clinical trial that evaluated the benefits of AGI-1067 (280 mg p.o. once daily) in the treatment of coronary atherosclerosis. A total of 469 patients scheduled to undergo an angioplasty procedure received standard care supplemented with placebo for 14 days, placebo for 11 days followed by AGI-1067 for 3 days, or AGI-1067 for 14 days. All patients underwent surgery at the end of the 14-day treatment period, and then continued receiving AGI-1067 for 12 months. Final data from this trial showed significantly greater average reductions in plaque volume with AGI-1067 compared to standard of care alone after 1 year of treatment, both in the overall study population (2.3% *vs.* 0.8%) and in the subgroup of most severely diseased patients. AGI-1067 also significantly reduced the levels of myeloperoxidase, an inflammatory biomarker associated with a greater risk of heart attack (2, 3).

The FDA has approved AtheroGenics' proposed amendment to the ARISE (Aggressive Reduction of Inflammation Stops Events) phase III trial protocol. The trial is testing the company's lead compound AGI-1067 for the oral treatment of atherosclerosis at leading cardiovascular research centers throughout the U.S., Canada, the U.K. and South Africa. The study is designed to evaluate the effect of AGI-1067 on important clinical outcome measures, including death due to cardiovascular disease,

Table I: Clinical studies of AGI-1067 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Atherosclerosis, Coronary artery disease	Randomized Double-blind Multicenter	AGI-1067, 70 mg o.d. x 6 wks [from 2 wks before to 4 wks after intervention] AGI-1067, 140 mg o.d. x 6 wks [from 2 wks before to 4 wks after intervention] AGI-1067, 280 mg o.d. x 6 wks [from 2 wks before to 4 wks after intervention] Probucol, 500 mg b.i.d. [from 2 wks before to 4 wks after intervention] Placebo	305	AGI-1067 induced antiatherosclerotic and antiinflammatory effects in patients undergoing percutaneous coronary interventions	1

myocardial infarction, stroke, coronary revascularization and unstable angina, in patients who have CAD. It will assess the incremental benefits of AGI-1067 over current standard-of-care therapies in this patient population. Eligible patients are randomized to receive oral AGI-1067 300 mg or placebo once daily, in addition to receiving other appropriate heart disease medications, which may include statins and other cholesterol-lowering therapies, high blood pressure medications and anticlotting agents. The changes to the ARISE protocol are intended to enhance the trial, as well as to accelerate its pace, without adversely affecting its special protocol assessment (SPA). The approved changes include increasing the trial's enrollment figure from 4,000 to 6,000. With this increase, the study will now accumulate 10,000 patient-years of exposure over the course of the trial. AtheroGenics estimates that ARISE will complete full enrollment by mid-2005. Given the increased size and longer duration of the trial, the FDA has approved the elimination of the minimum 12-month follow-up period for patients. The FDA also gave the company approval to decrease the trial's target number of clinical events from 1,160 to 990. This revised target number will continue to yield greater than 95% statistical power to detect a 20% difference in clinical events between the study arms. ARISE is expected to be completed by the end of the first quarter of 2006, and an NDA filing will follow shortly thereafter (4-6).

1. L'Allier, P.L., Reeves, F., Guertin, M.-C., Gregoire, J., Laramee, L., Lavoie, J., Tardif, J.-C., Schwartz, L., Title, L. *Anti-Inflammatory effects of the V-protectant AGI-1067 in the Canadian Antioxidant Restenosis Trial (CART-1).* 53rd Annu Sci Sess Am Coll Cardiol (March 7-10, New Orleans) 2004, Abst 1023-93.

2. *Preliminary data support the use of AGI-1067 in coronary atherosclerosis.* DailyDrugNews.com (Daily Essentials) Sept 30, 2004.

3. *Clinical data confirm the benefits of AGI-1067 in atherosclerosis.* DailyDrugNews.com (Daily Essentials) Nov 24, 2004.

4. *AtheroGenics proposes amendments to ARISE trial of AGI-1067.* DailyDrugNews.com (Daily Essentials) Jan 5, 2005.

5. *FDA approves amendments to ARISE study of AGI-1067.* DailyDrugNews.com (Daily Essentials) Feb 24, 2005.

6. *Target enrollment reached in ARISE study of AGI-1067 for atherosclerosis.* DailyDrugNews.com (Daily Essentials) Nov 26, 2004.

Original monograph – Drugs Fut 2003, 28(5): 421.

AI-700

Acusphere has entered into a collaboration, license and supply agreement with Nycomed Pharma for the European development and marketing rights to AI-700, an ultrasound contrast agent in phase III trials for assessing myocardial perfusion in the diagnosis of CAD. AI-700-enhanced ultrasound is being developed as a cost-effective and convenient alternative to nuclear imaging. Nycomed will be responsible for sales, marketing and regulatory submissions in its sales territory, which includes the member states of the E.U., as well as Russia/CIS and Turkey. The phase III program for AI-700 has enrolled 300 patients and includes a pilot phase for training of new clinical sites, and two simultaneous pivotal trials. More than 20 medical centers in the U.S., Europe and Australia are actively enrolling in the pivotal phase of the phase III program. An estimated 600 patients in total will be required to complete enrollment in the pivotal trials, anticipated for the second half of 2005. Regulatory filings in the U.S. and the E.U. are expected in the first half of 2006 (1-3).

1. *Acusphere enrolls 300 in pivotal program for AI-700.* DailyDrugNews.com (Daily Essentials) Dec 21, 2004.

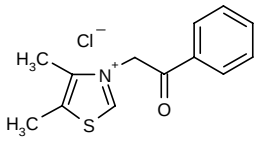
2. *Acusphere's AI-700 pilot study exceeds expectations.* Acusphere Press Release 2005, Jan 6.

3. *Acusphere and Nycomed in European partnership for AI-700.* DailyDrugNews.com (Daily Essentials) July 9, 2004.

AJW-200

A humanized monoclonal antibody to von Willebrand factor (vWF) that specifically inhibits the interaction between vWF and gpIb receptors, AJW-200 is under early clinical evaluation at Ajinomoto as an antithrombotic agent.

Alagebrium Chloride



Alteon's lead advanced glycation end product (AGE) crosslink breaker alagebrium chloride (ALT-711) is the first in a new class of compounds that have been shown *in vitro* and *in vivo* to reverse AGE crosslinking, thereby restoring more normal function to tissues, vessels and organs that have lost flexibility. Alagebrium's mechanism of action is believed to be new and novel, and unrelated to that of any pharmaceutical agent. Alagebrium does not disrupt the natural enzymatic glycosylation sites or peptide bonds that are responsible for maintaining the normal integrity of the collagen chain. In preclinical studies, alagebrium consistently demonstrated the ability to reverse the upregulation of genes for proteins and growth factors known to be associated with the pathological hypertrophy of tissues. Alagebrium has demonstrated safety and efficacy in several phase II trials and is being developed for systolic hypertension, heart failure and erectile dysfunction (1, 2).

The company recently temporarily suspended enrollment in its ongoing clinical trials of alagebrium pending additional preclinical data and discussions with the FDA. Patients already enrolled in the clinical trials are continuing treatment. The company took this action voluntarily after findings of a 2-year toxicity study indicated that male Sprague-Dawley rats exposed to high doses of alagebrium over their natural lifetime developed dose-related increases in liver cell alterations and tumors, and that the liver tumor rate was slightly over the expected background rate in this gender and species of rat. The company is conducting a series of preclinical experiments to explore the mechanism by which the liver tumors developed and the relevance of such tumors to human exposure. Results are expected by mid-year. Earlier preclinical toxicity studies found no mutagenic or carcinogenic activity in either rats or mice. Four key genotoxicity studies to help determine potential toxicities of alagebrium in man also did not indicate any potential carcinogenic risk. A review of the cumulative human safety profile and previous preclinical experience of alagebrium does not demonstrate an association with the lifetime carcinogenicity study in rats (3).

The ongoing phase IIb SPECTRA (Systolic Pressure Efficacy and Safety Trial of Alagebrium) trial is on target to complete enrollment (approximately 390 patients) during the first half of 2005, with data expected in the second half of 2005. SPECTRA is designed to evaluate alagebrium's ability to lower systolic blood pressure (SBP) in patients with a reading of 145 mmHg or greater (by 24-h ambulatory blood pressure measurement). Patients are randomized to receive alagebrium tablets or placebo in addition to hydrochlorothiazide once a day for 12 weeks. Approximately 70 sites are enrolling patients in the trial.

Previous trials demonstrated alagebrium's safety and ability to lower SBP and pulse pressure in aging patients, especially in a difficult-to-treat hypertensive patient population (see below). Alagebrium's beneficial effects in previous phase II trials were demonstrated over and above current hypertension therapy, and data to date suggest a mechanism of action unlike any existing blood pressure agent. Positive findings have also been reported from an interim analysis of PEDESTAL (Patients with Impaired Ejection Fraction and Diastolic Dysfunction: Efficacy and Safety Trial of ALagebrium). The ongoing open-label, exploratory phase IIa study is being conducted at Baylor Heart Clinic to evaluate alagebrium's effects on diastolic function and ventricular mass in patients with significant heart failure. Preliminary data from the initial 14 (of the planned 20) patients indicate trends consistent with positive data from the phase IIa DIAMOND (Distensibility Improvement and Remodeling in Diastolic Heart Failure) trial and preclinical studies in heart failure. Despite the differences in patient groups —patients in PEDESTAL have impaired ejection fraction, larger hearts and are sicker overall— treatment with alagebrium appears to have important and consistent effects in both patient groups. Enrollment is ongoing in PEDESTAL and final data are expected in 2005. Furthermore, Alteon reported during last year positive findings from an interim analysis of the phase IIa open-label trial in endothelial function conducted at Johns Hopkins under grants from the National Heart, Lung and Blood Institute and the Society of Geriatric Cardiology. The trial aimed to determine whether increasing arterial elasticity by breaking AGE crosslinks improves endothelial function as assessed by evaluating vessel relaxation and biomarkers of endothelial function in patients with systolic hypertension. Patients received 210 mg of alagebrium twice daily for 8 weeks, preceded by 3 weeks of twice-daily placebo run-in dosing. The study was designed to extend and confirm positive findings from the phase IIa DIAMOND trial in patients with diastolic heart failure, in which alagebrium treatment over 16 weeks demonstrated a statistically significant reduction in left ventricular mass and a marked improvement in left ventricular diastolic filling, as well as statistically significant improvements in multiple quality-of-life measurements. These data show strong trends in key measures relating to improvements in carotid artery stiffness based on a series of advanced noninvasive measurements. Data from the phase IIb SAPPHIRE/SILVER (Systolic And Pulse Pressure Hemodynamic Improvement by Restoring Elasticity/Systolic Hypertension Interaction with Left Ventricular Remodeling) trial of alagebrium in systolic hypertension were published in December, detailing the ability of alagebrium to significantly reduce systolic blood pressure in patients with a baseline 24-h ambulatory systolic blood pressure of 140 mmHg or greater. In a difficult-to-treat patient population with a baseline 24-h ambulatory SBP of 150 mmHg or greater and on 2 or more background medications, patients had an average drop in their 24-h ambulatory SBP of 18 mmHg *versus* placebo (4-8).

1. *Alagebrium chloride approved as generic name for ALT-711.* DailyDrugNews.com (Daily Essentials) March 9, 2004.

2. *Phase II trial investigates alagebrium chloride for erectile dysfunction.* DailyDrugNews.com (Daily Essentials) Jan 21, 2005.

3. *Alteon suspends enrollment in alagebrium trials.* DailyDrugNews.com (Daily Essentials) March 1, 2005.

4. *New phase II trial studies effects of ALT-711 on endothelial function.* DailyDrugNews.com (Daily Essentials) Feb 13, 2004.

5. *New phase IIb trial evaluates alagebrium chloride for systolic hypertension.* DailyDrugNews.com (Daily Essentials) March 15, 2004.

6. *Alteon updates progress.* DailyDrugNews.com (Daily Essentials) Dec 29, 2004.

7. *PEDESTAL trial evaluates alagebrium for diastolic dysfunction.* DailyDrugNews.com (Daily Essentials) April 22, 2004.

8. *Alteon's ALT-711 shows highly significant reduction in systolic blood pressure in detailed analysis of SAPPHIRE/SILVER clinical trial.* Alteon Inc. Press Release 2004, Feb 23.

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Bakris, G.L., Bank, A.J., Kaas, D.A., Neutel, J.M., Preston, R.A., Oparil, S. *Advanced glycation end-product cross-link breakers: A novel approach to cardiovascular pathologies related to he aging process.* Am J Hypertens 2004, 17(12, Part 2): 23S.

Bakris, G.L. et al. *A clinical trial of an AGE cross-link breaker, ALT-711, in systolic hypertension.* Am J Hypertens 2004, 17(5, Part 2): Abst P-261.

Alfimeprase

The thrombolytic alfimeprase is a recombinant modified fibrolase that directly degrades fibrin when delivered through a catheter at the site of a blood clot. It is up to 6 times faster in dissolving clots than traditional plasminogen activators. Preliminary testing suggests that its lytic activity is localized to the site of delivery. Alfimeprase is inhibited within seconds of moving away from the clot and into the general circulation by α_2-macroglobulin, a naturally occurring protein in blood. This clearance mechanism helps focus the thrombolytic activity to the site of delivery and appears to minimize bleeding side effects. Alfimeprase has orphan drug designation for peripheral arterial occlusion (PAO). Nuvelo signed an agreement with Amgen last year to gain worldwide rights to develop and commercialize alfimeprase, originally identified through Amgen's internal research program. Based on recent discussions with the FDA, Nuvelo is finalizing the design of and preparing to initiate an international, randomized, double-blind, placebo-controlled phase III program to determine the efficacy and safety of alfimeprase for the treatment of patients with acute PAO. This NAPA-2 (Novel Arterial Perfusion with Alfimprase-2) program is expected to consist of two overlapping trials that will include a total of approximately 700 patients who will be randomized to receive either 0.3 mg/kg of alfimeprase or placebo. The primary endpoint will be avoidance of open vascular surgery at 30 days, while secondary endpoints will include restoration of arterial blood flow and increase in ankle-brachial index. The phase III program is targeted to begin in the first quarter of 2005. Results of the multinational, open-label, dose-escalating phase II NAPA-1 study in 113 patients with acute PAO indicated that, based on intention-to-treat analysis, alfimeprase was associated with thrombolysis rates of up to 76% and restoration of arterial flow rates of up to 60%. All thrombolytic activity and restoration of flow was recorded within 4 h of initiation of dosing. From 52% to 69% of study patients were able to avoid vascular surgical intervention. Among the 113 patients enrolled, there were no intracerebral hemorrhages or deaths at 30 days. There were 7 major bleeding events reported, of which 1 major bleed was categorized by the investigator as possibly related to alfimeprase (a groin hematoma). Nuvelo is also preparing to meet with the FDA to discuss the initiation of an additional phase III program for alfimeprase in central venous catheter occlusion. Nuvelo closed its phase II alfimeprase trial in patients with occluded central venous catheters sooner than expected in order to accelerate the program. The trial concluded with 56 patients dosed. This multicenter, randomized, double-blind study began in June 2003 and compared three doses of alfimeprase (0.3, 1.0 and 3.0 mg) against the approved dose of Cathflo® Activase® (alteplase). The study was designed to treat up to 100 patients and was conducted at 32 U.S. sites. The data safety and monitoring board (DSMB) analysis suggested there were no safety concerns in any of the alfimeprase dose groups, with two of these groups demonstrating efficacy warranting further study. Compared to Cathflo® Activase®, patients treated with 3.0 mg of alfimeprase showed greater patency rates at 15 min after the first dose (50% *vs.* 0%), at 120 min after the first dose (60% *vs.* 46%) and at 120 min after the second dose (80% *vs.* 62%). No patients experienced major bleeding, and only 1 had a catheter-related infection (1-8) (see Table II).

1. *Nuvelo reports 2003 year-end R&D highlights.* Nuvelo Press Release 2004, Feb 5.

2. *Phase II alfimeprase study in venous catheter occlusion completes interim analysis.* DailyDrugNews.com (Daily Essentials) June 11, 2004.

3. *Nuvelo reports Q1 R&D highlights.* Nuvelo Press Release 2004, May 6.

4. *Nuvelo reports preliminary data from phase II study of alfimeprase in PAO.* DailyDrugNews.com (Daily Essentials) July 7, 2004.

5. *Nuvelo closes phase II alfimeprase study early.* DailyDrugNews.com (Daily Essentials) July 15, 2004.

6. *Nuvelo phase 2 clinical trial results show potential of alfimeprase to treat acute peripheral arterial occlusion, also known as 'leg attack'.* Nuvelo Press Release 2004, Sept 30.

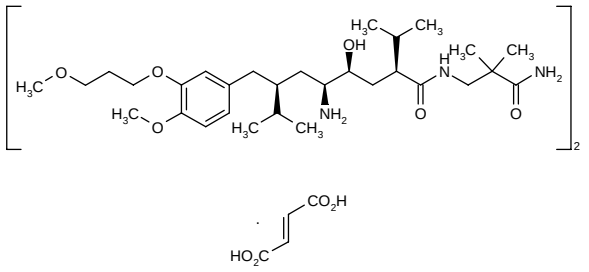
Table II: Clinical studies of alfimeprase (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Peripheral arterial occlusion	Open Multicenter	Alfimeprase, 0.1 mg/kg i.v. Alfimeprase, 0.3 mg/kg i.v. Alfimeprase, 0.6 mg/kg i.v.	113	A single dose of alfimeprase was effective in inducing thrombolysis and restoring arterial flow in patients with acute peripheral arterial occlusion. These benefits were detected within 4 h of administration	6
Central venous catheter occlusion	Randomized Double-blind Multicenter	Alfimeprase, 0.3 mg intraluminal x 2 (n=13) Alfimeprase, 1.0 mg intraluminal x 2 (n=14) Alfimeprase, 3.0 mg intraluminal x 2 (n=9) Alteplase, 2.0 mg intraluminal x 2 (n=12)	48	Intraluminal alfimeprase was more effective than alteplase in restoring catheter patency in patients with occluded central venous catheters	8

7. *Nuvelo to gain worldwide rights to alfimeprase.* DailyDrugNews.com (Daily Essentials) Nov 4, 2004.

8. Deitcher, S.R., Moll, S., Homesley, H.D., Bertoli, L., Kenyon, P., Swischuk, P., Pena, L. *Safety and efficacy of alfimeprase for restoring function in occluded central venous catheters: Interim results of a phase 2, multicenter, randomized, double-blind study (NuCath).* Blood 2004, 104(11, Part 1): Abst 1768.

Aliskiren Fumarate



Aliskiren fumarate (SPP-100) is the first in a new class of antihypertensive agents called renin inhibitors which offers a once-daily treatment with efficacy and safety comparable to angiotensin receptor blockers (ARBs). In contrast to other antihypertensive agents, aliskiren lowers renin enzyme activity in the bloodstream and may have the potential to better protect against myocardial infarction and kidney disease. Phase III trials are ongoing in the U.S., the E.U. and Japan and the first regulatory submission is planned for early 2006. Aliskiren was originally licensed by Speedel from Novartis in 1999. Speedel successfully completed 18 clinical trials through phase I and II in about 500 patients and healthy volunteers before Novartis exercised a license-back option in 2002 (1, 2).

The first results of a phase III study (Study 2203) of aliskiren in 1,064 hypertensive patients confirmed the blood pressure-lowering effect and safety profile of the renin inhibitor as monotherapy compared to placebo and valsartan. The data are consistent with a previous phase II study in 650 patients conducted by Novartis comparing aliskiren with irbesartan and are also consistent with the original phase II study in 200 patients conducted by Speedel comparing the drug with losartan. Phase II results from the same study (Study 2203) in which patients were treated with a combination of aliskiren and valsartan suggested a trend towards additive benefits and a dose-response relationship for the combination, which are to be confirmed in a follow-up study. The combination data build on Speedel's clinical findings on the benefits of combination therapy in pilot clinical studies with aliskiren in combination with ramipril, hydrochlorothiazide and irbesartan. All three studies showed the potential for beneficial effects of aliskiren with these different classes of blood pressure modulators while maintaining a promising safety profile (3).

An 8-week, multicenter, double-blind, randomized, placebo-controlled trial compared the antihypertensive efficacy of irbesartan and aliskiren in 652 patients with mild to moderate hypertension. Patients entered a 2-week single-blind placebo run-in period and were then treated with aliskiren (150, 300 or 600 mg p.o.), irbesartan (150 mg p.o.) or placebo once daily. All three aliskiren doses were more effective than placebo in reducing both the mean sitting diastolic blood pressure (DBP) and the mean sitting systolic blood pressure (SBP) of the patients. The decreases in baseline DBP at the end of the treatment were 9.5, 12.0 and 11.7 mmHg with aliskiren 150, 300 and 600 mg, respectively, and 6.5 mmHg with placebo. The corresponding reductions in baseline SBP were 10.8, 15.5, 15.6 and 5.1 mmHg. The effects induced by 150 mg/day of aliskiren were similar to those with 150 mg/day of irbesartan. No significant differences were found among the safety profiles and rates of serious adverse events of the study groups (4) (Table III).

1. *Novartis reports Q1 R&D highlights.* Novartis Press Release 2004, April 22.

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

3. *New phase III and II data for SPP-100 for hypertension.* DailyDrugNews.com (Daily Essentials) Jan 25, 2005.

4. Gradman, A.H., Schmieder, R.E., Lins, R.L., Chiang, Y., Bedigian, M.P. *Aliskiren, a novel orally effective renin inhibitor, provides antihypertensive efficacy and placebo-like tolerability similar to an AT1-receptor blocker in hypertensive patients.* Am J Hypertens 2004, 17(5, Part 2): Abst P-204.

Table III: Clinical studies of aliskiren fumarate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hypertension	Randomized Double-blind Multicenter	Aliskiren, 150 mg p.o. o.d. x 6 wks Aliskiren, 300 mg p.o. o.d. x 6 wks Aliskiren, 600 mg p.o. o.d. x 6 wks Irbesartan, 150 mg p.o. o.d. x 6 wks Placebo	652	Aliskiren was well tolerated and as effective as irbesartan in reducing blood pressure in patients with mild to moderate hypertension	4

Original monograph – Drugs Fut 2001, 26(12): 1139.

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Gradman, A.H., Schmieder, R.E., Lins, R.L., Nussberger, J., Chiang, Y., Bedigian, M.P. *Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients.* Circulation 2005, 111(8): 1012.

Amediplase

Amediplase is a recombinant chimeric protein composed of tissue plasminogen activator (t-PA) and a single-chain urokinase-type plasminogen activator (scu-PA). The protein, originally developed by Novartis, is currently in phase III development by Menarini as a thrombolytic given as a single bolus for the treatment of myocardial infarction.

Original monograph – Drugs Fut 2002, 27(6): 533.

Amlodipine Besilate/ Atorvastatin Calcium

In January of 2004. the FDA approved Pfizer's dual therapy medicine amlodipine besilate/atorvastatin calcium (Caduet®) for the simultaneous treatment of high blood pressure and high cholesterol. Launch took place in May. The dual therapy combines the long-acting calcium channel antagonist amlodipine and the HMG-CoA reductase inhibitor atorvastatin. Recent results of clinical studies have shown that many patients taking the combination successfully reached both their recommended blood pressure and cholesterol goal levels. Amlodipine/atorvastatin was well tolerated by patients and has been administered with a variety of antihypertensive medications, including thiazide diuretics, β-blockers and angiotensin-converting enzyme (ACE) inhibitors. More than 3,700 patients with high blood pressure and high cholesterol are enrolled in the Caduet® clinical trial program. A European regulatory submission is also under review (1-4).

The GEMINI study was a multicenter, open-label clinical trial that assessed the efficacy and safety of the combination of amlodipine besilate and atorvastatin calcium administered as a single pill in the management of concomitant hypertension and dyslipidemia. Overall, 1,220 patients with uncontrolled hypertension and concomitant dyslipidemia introduced lifestyle modifications and were treated with different doses of amlodipine/atorvastatin (5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80 and 10/80 mg) for 14 weeks. Physicians adjusted the combination dose given to the patients during the study in order to reduce their blood pressure and LDL cholesterol levels to pre-established target levels, depending on the presence of cardiovascular risk factors or coronary heart disease at baseline. Target blood pressure and LDL cholesterol levels were achieved by 57.7% of the patients at the end of the treatment period, while another 4.8% discontinued due to adverse events. The most frequent adverse events were respiratory tract infection (11.9%), peripheral edema (8.8%), headache (5.4%) and myalgia (4.2%) (5) (Table IV).

The results of the GEMINI study also indicated that treatment of diabetic patients with concomitant hypertension and dyslipidemia with the combination is safe and effective. Of 227 treated patients, 28.4% achieved both their blood pressure and LDL cholesterol goals, 43.8% achieved their blood pressure goal alone and 55.8% achieved their LDL cholesterol goal alone. Systolic blood pressure was reduced by a mean 15.5 ± 0.8 mmHg and LDL cholesterol was reduced by a mean 27.5 ± 1.3% from baseline. Among patients not previously treated with lipid-lowering therapy but who had received antihypertensive therapy (n=80), 35.4% achieved both their blood pressure and LDL cholesterol goals (6).

1. *Caduet receives FDA approval.* DailyDrugNews.com (Daily Essentials) Feb 5, 2004.

2. *Pfizer reports 2003 year-end R&D highlight*s. Pfizer Press Release 2004, Jan 22.

3. *Pfizer reports Q1 R&D highlights.* Pfizer Press Release 2004, April 20.

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

5. Blank, R., LaSalle, J., Reeves, R., Piper, B.A., Sun, F. *Amlodipine/atorvastatin single pill dual therapy improves goal attainment in the treatment of concomitant hypertension and*

Table IV: Clinical studies of amlodipine besilate/atorvastatin calcium (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hyperlipidemia, Hypertension	Open Multicenter	Amlodipine, 5 mg p.o. o.d. + Atorvastatin, 10 mg p.o. o.d. x 14 wks Amlodipine, 10 mg p.o. o.d. + Atorvastatin, 10 mg p.o. o.d. x 14 wks Amlodipine, 5 mg p.o. o.d. + Atorvastatin, 20 mg p.o. o.d. x 14 wks Amlodipine, 10 mg p.o. o.d. + Atorvastatin, 20 mg p.o. o.d. x 14 wks Amlodipine, 5 mg p.o. o.d. + Atorvastatin, 40 mg p.o. o.d. x 14 wks Amlodipine, 10 mg p.o. o.d. + Atorvastatin, 40 mg p.o. o.d. x 14 wks Amlodipine, 5 mg p.o. o.d. + Atorvastatin, 80 mg p.o. o.d. x 14 wks Amlodipine, 10 mg p.o. o.d. + Atorvastatin, 80 mg p.o. o.d. x 14 wks	1220	A single-pill combination of amlodipine and atorvastatin was well tolerated and effective in improving the condition of patients with hypertension and dyslipidemia	5

dyslipidemia: The GEMINI study. 53rd Annu Sci Sess Am Coll Cardiol (March 7-10, New Orleans) 2004, Abst 1008-190.

6. LaSalle, J., Hershon, K., Berman, L., Gibson, E., Gillen, D., Maroni, J. *Utility of amlodipine/atorvastatin single-pill therapy in patients with diabetes mellitus: Results from the GEMINI study.* 40th Annu Meet Eur Assoc Study Diabetes (Sept 5-9, Munich) 2004, Abst 1140.

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Fogari, R., Derosa, G., Malacco, E., Ciccarelli, L., Rinaldi, A., Preti, P., Mugellini, A. *Atorvastatin-amlodipine combination and fibrinolytic balance in hypertensive hypercholesterolemic insulin-resistent patients.* Am J Hypertens 2004, 17(5, Part 2): Abst P-89.

Fogari, R. et al. *Effect of amlodipine-atorvastatin combination on fibrinolysis in hypertensive hypercholesterolemic patients with insulin resistance.* Am J Hypertens 2004, 17(9): 823.

Neutel, J. et al. *Dual goal attainment with amlodipine/atorvastatin single pill in a broad range of patients: Results from the GEMINI study.* Am J Hypertens 2004, 17(5, Part 2): Abst P-410.

Preston, R.A. et al. *The efficacy and safety of fixed-dose combinations of amlodipine and atorvastatin in the treatment of patients with concomitant hypertension and dyslipidemia.* Am J Hypertens 2004, 17(5, Part 2): Abst P-413.

Angiotensin Vaccine

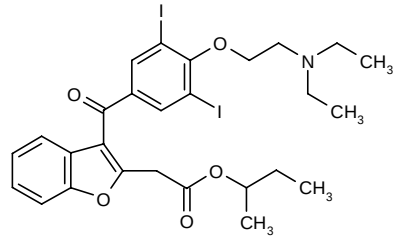
Protherics has initiated a new clinical program (phase I) to assess improved formulations of its angiotensin vaccine using third-party proprietary vaccine adjuvants which have generated encouraging antibody titers in preclinical models. The angiotensin vaccine, a therapeutic vaccine aimed at stimulating the immune system to neutralize angiotensin, is designed to regulate blood pressure. A first-generation formulation showed promising results in phase II clinical trials in patients with mild to moderate hypertension. Enrollment has commenced in a randomized, double-blind study in healthy volunteers in which vaccine formulations both with and without a novel adjuvant are being evaluated for safety and antibody titers. Secondary endpoints include blood pressure changes in response to angiotensin infusions and to dietary salt depletion. Protherics plans to advance the formulation that produces the highest antibody titers into a proof-of-concept study in hypertensive patients this year (1).

1. *New program for Protherics' angiotensin vaccine.* DailyDrugNews.com (Daily Essentials) Feb 24, 2004.

ART-123

ART-123, a recombinant human thrombomodulin developed by Asahi Kasei, is presently under evaluation in phase III clinical trials for disseminated intravascular coagulation, as well as in phase II trials for deep vein thrombosis (DVT).

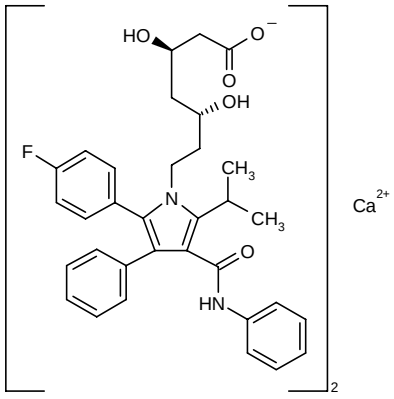
ATI-2042



ATI-2042, ARYx Therapeutics' proprietary analogue of amiodarone, is currently in early clinical trials for its

potential in the oral treatment of atrial fibrillation and the i.v. treatment of ventricular arrhythmias. ATI-2042 is designed to be equally effective but safer than amiodarone, with a more rapid onset of action, minimal tissue accumulation and more rapid elimination from the body in the form of a nontoxic, water-soluble, inactive metabolite.

Atorvastatin Calcium



Pfizer's atorvastatin calcium is an HMG-CoA reductase inhibitor originally launched in the U.S. in 1997 as Lipitor® as an adjunct to diet to treat hypercholesterolemia. Since its introduction, the safety and efficacy of atorvastatin have been supported through the Atorvastatin Landmark Program™, an extensive clinical program with more than 400 ongoing and completed trials involving over 80,000 patients. In 2004, the FDA and Health Canada approved a new indication for atorvastatin calcium: the treatment of adult patients without clinically evident coronary heart disease (CHD), but with multiple risk factors for CHD, to reduce the risk of myocardial infarction and to reduce the risk for revascularization procedures and angina. Approval was based on the landmark ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) trial in over 10,000 patients demonstrating that patients taking the lowest dose of atorvastatin had significantly fewer heart attacks than those on placebo, with a relative risk reduction of 36% (1, 2). Pfizer is also currently evaluating the potential of atorvastatin calcium for the treatment of Alzheimer's-type dementia. The product is licensed to Astellas Pharma for Japan.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study was a multicenter, double-blind, randomized, placebo-controlled clinical trial that evaluated the effects of atorvastatin on the risk of recurrent cardiovascular events in 2,908 patients with acute coronary syndrome (ACS). Each patient was given placebo or atorvastatin (80 mg/day) for 16 weeks, starting between 24 and 96 h after hospital admission due to unstable angina or non-Q wave acute myocardial infarction. High baseline plasma levels of the prothrombotic, proinflammatory cytokine C40 ligand (sCD40L) were found to be a risk factor for recurrent cardiovascular events in placebo-treated patients. Atorvastatin reduced the risk associated with high baseline sCD40L levels by 48%, but had only moderate effects on plasma sCD40L levels. These results suggested a potential role for early statin therapy in some ACS patients (3).

The Collaborative Atorvastatin Diabetes Study (CARDS) was terminated 2 years earlier than expected after a second interim analysis reported a significant reduction in the risk of first cardiovascular disease events, including stroke, in patients with type 2 diabetes. The study, conducted at 132 centers in the U.K. and Ireland, administered atorvastatin calcium (10 mg) or placebo once daily to 2,838 patients aged 40-75 years with no previous history of cardiovascular disease, and without elevated LDL cholesterol. Patients were considered at high risk for CHD by the presence of at least one of the following risk factors: retinopathy, albuminuria, current smoking or hypertension. In the median follow-up period of 3.9 years, there was a significant reduction in the risk of occurrence of a major cardiovascular event in patients receiving treatment with atorvastatin. This translated into reductions in acute CHD, coronary revascularization and rate of stroke by 36%, 31% and 48%, respectively. The risk of death from any cause was also reduced by 27% (4). The results from this and the following studies are described in Table V.

The REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study was a multicenter, double-blind, randomized clinical trial that compared the effects of a moderate lipid-lowering regimen (pravastatin sodium 40 mg/day) and an intensive lipid-lowering regimen (atorvastatin calcium 80 mg/day) in 654 patients who required coronary angiography and had at least one obstruction with luminal diameter narrowing of at least 20%. A "target segment" of at least 30 mm with luminal narrowing of not more than 50% was selected for each patient in a vessel not previously treated with angioplasty. After 18 months of treatment, the atheroma volume increased by an average of 27% in patients receiving pravastatin and decreased by 0.7% in those receiving atorvastatin. The atorvastatin regimen was more effective than pravastatin in reducing the plasma levels of total cholesterol, LDL cholesterol, triglycerides, apolipoprotein B100 (apoB100) and C-reactive protein (CRP), while pravastatin was associated with greater increases in the plasma levels of HDL cholesterol. Both study treatments were well tolerated, and no significant differences were found between their safety profiles. The authors suggested that the reduced progression of coronary atherosclerosis found with intensive atorvastatin therapy may be related to the induction of a greater reduction in the levels of atherogenic lipoproteins and CRP (5).

A total of 4,162 adult patients who had been admitted to hospital for acute myocardial infarction or high-risk unstable angina during the previous 10 days and had a total cholesterol level of 240 mg/dl or less were randomized to complement their standard treatment for ACS with pravastatin (40 mg/day) or atorvastatin (80 mg/day) for a

Table V: Clinical studies of atorvastatin calcium (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Diabetes, type 2	Randomized Double-blind Multicenter	Atorvastatin, 10 mg p.o. o.d. x 3.9 [median] y (n=1429) Placebo (n=1412)	2841	Once-daily atorvastatin was well tolerated and reduced the risk of a first cardiovascular adverse event in patients with type 2 diabetes without elevated LDL cholesterol levels	4
Atherosclerosis, Coronary artery disease	Randomized Double-blind Multicenter	Atorvastatin, 80 mg o.d. x 18 mo (n=327) Pravastatin, 40 mg o.d. x 18 mo (n=327)	654	Atorvastatin was well tolerated and more effective than pravastatin in reducing the progression of coronary atherosclerosis	5
Angina pectoris, unstable, Myocardial infarction	Randomized Double-blind Multicenter	Atorvastatin, 80 mg o.d. x 24 [mean] mo (n=2099) Pravastatin, 40 mg o.d. x 24 [mean] mo (n=2063)	4162	High-dose atorvastatin was more effective than standard-dose pravastatin in reducing LDL cholesterol levels and cardiovascular risk in patients with acute coronary syndrome	6

median of 24 months. At the end of the follow-up period, the median LDL cholesterol levels of the patients had decreased from 106 mg/dl at baseline to 95 mg/dl with pravastatin and to 62 mg/dl with atorvastatin. At 2 years, the Kaplan-Meier estimates of the rates of an endpoint combining death from any cause, myocardial infarction, unstable angina requiring hospitalization, revascularization and stroke were 26.3% with pravastatin and 22.4% with atorvastatin. Compared with pravastatin, atorvastatin was associated with a 14% reduction in the need for revascularization, a 29% reduction in the risk for unstable angina, and a 28% reduction in the risk of death from any cause. The greater benefits associated with atorvastatin were found after only 30 days of treatment, were maintained throughout the study and were consistent in men and women, patients with unstable angina, patients with myocardial infarction and patients with or without diabetes. The safety profiles of the two study treatments were similar, save for a significantly higher incidence of liver-related adverse events with atorvastatin. The authors concluded that patients with ACS may benefit from intensive lipid-lowering therapies that reduce LDL cholesterol levels to target values below those recommended in current guidelines (6).

1. *Lipitor approved to reduce risk of heart attacks.* DailyDrugNews.com (Daily Essentials) Aug 4, 2004.

2. *Canadian approval for Lipitor to lower risk of heart attack.* DailyDrugNews.com (Daily Essentials) Oct 13, 2004.

3. Kinlay, S., Schwartz, G.G., Olsson, A.G. et al. *Effect of atorvastatin on risk of recurrent cardiovascular events after an acute coronary syndrome associated with high soluble CD40 ligand in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study.* Circulation 2004, 110(4): 386.

4. Colhoun, H.M., Betteridge, D.J., Durrington, P.N. et al. *Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial.* Lancet 2004, 364(9435): 685.

5. Nissen, S.E., Tuzcu, E.M., Schoenhagen, P. et al. *Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. A randomized controlled trial.* JAMA - J Am Med Assoc 2004, 291(9): 1071.

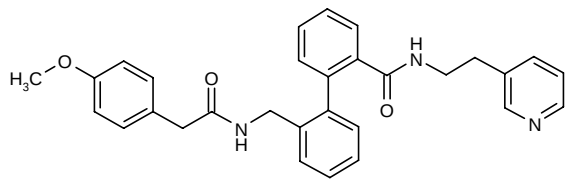
6. Cannon, C.P., Braunwald, E., McCabe, C.H. et al. *Intensive versus moderate lipid lowering with statins after acute coronary syndromes.* New Engl J Med 2004, 350(15): 1495.

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

Atorvastatin Calcium/ Torcetrapib

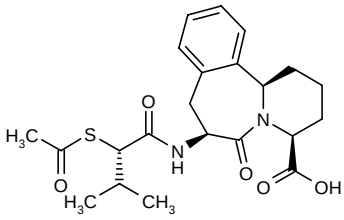
Atorvastatin calcium/torcetrapib, a combination of an HMG-CoA reductase inhibitor and a cholesteryl ester transfer protein (CETP) inhibitor, is in late-stage clinical development at Pfizer for atherosclerosis and other cholesterol disorders. For more information on torcetrapib, readers are referred to the monograph in this issue of the journal.

AVE-0118



AVE-0118 is an atrial potassium channel blocker in phase II development by Sanofi-Aventis for the treatment of atrial fibrillation. AVE-0118 blocks the ultra-rapid delayed rectifier current (I_{kur}) and the transient outward current (I_{to}), and prolongs atrial action potential without affecting ventricular repolarization.

AVE-7688



A dual angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP) inhibitor, AVE-7688 (Sanofi-Aventis) is in phase II development for the treatment of hypertension and diabetic nephropathy.

AVE-9488

AVE-9488 is an endothelial nitric oxide synthase (eNOS) expression enhancer in early clinical development by Sanofi-Aventis for the treatment of angina pectoris and congestive heart failure (CHF).

AVI-4126

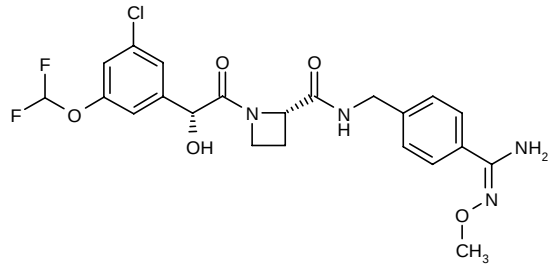
AVI BioPharma has reported that analysis of vessel lumen diameter and vessel wall thickness by intravascular ultrasound (IVUS) supports the angiographic data reported from the phase II trial of the company's Neugene® antisense drug AVI-4126 (Resten-NG®), which inhibits the expression of the *c-myc* gene. AVI previously reported a 75% reduction in the restenosis rate from angiographic analysis at 6 months. The multicenter AVAIL study evaluated the safety and efficacy of AVI-4126 in 57 patients at high risk of cardiovascular restenosis following angioplasty and stent placement. Patients were randomized to receive a control, a subtherapeutic dose (3 mg) of AVI-4126 or a therapeutic dose (10 mg) delivered via a coronary delivery catheter directly to the site of angioplasty and stent placement. The restenosis rate was 33.3% in both the control and subtherapeutic dose treatment arms, and 8.3% in the therapeutic dose treatment arm, representing a statistically significant 75% reduction in the rate of restenosis. The secondary endpoint of the study was late loss, which is the decrease in vessel lumen diameter at 6 months. The therapeutic dose treatment arm showed a significant reduction in late loss and lesion length compared with the control arm and the subtherapeutic treatment arm. The therapeutic dose treatment arm also experienced a lower rate of target lesion revascularization than the other arms. The IVUS data confirmed these results and suggested a dose-response benefit for increased lumen diameter and decreased vessel wall thickness (1). The company is also testing a microparticle formulation of AVI-4126 in phase Ib clinical studies delivered systemically after angioplasty (Resten-MP®), and clinical trials have been performed in polycystic kidney disease and breast cancer, with plans for a phase II bladder cancer study.

1. *Confirmatory data supports phase II Resten-NG data.* DailyDrugNews.com (Daily Essentials) Jan 7, 2004.

AZD-0837/AZD-6140/AZD-9684

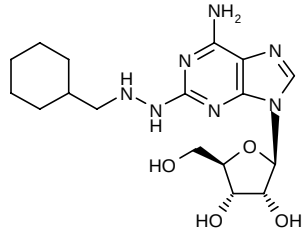
AstraZeneca has three phase II compounds for thrombosis with different mechanisms of action: the oral direct thrombin inhibitor AZD-0837, a follow-up compound to ximelagatran (see below), the oral ADP receptor ($P2Y_{12}$) antagonist AZD-6140 and the carboxypeptidase U inhibitor AZD-9684.

AZD-7009



Phase II clinical trials are in progress at AstraZeneca with AZD-7009, an atrial repolarization-delaying agent (ARDA), as an intravenous formulation for the conversion of atrial fibrillation and for the oral maintenance treatment of atrial fibrillation. The compound shows a unique mechanism of action, with separation of effects on the atrium and the ventricle of the heart.

Binodenoson



Binodenoson (MRE-0470), an adenosine A_{2A} receptor agonist developed by Aderis, is currently in phase III development for cardiac pharmacological stress SPECT (single photon emission computed tomography) imaging in the diagnosis of CAD. Unlike currently used drugs for CAD, binodenoson will be given as an intravenous bolus

Table VI: Clinical studies of binodenoson (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Coronary artery disease	Randomized Crossover Multicenter	Binodenoson, 0.5 μg/kg i.v. bolus Binodenoson, 1 μg/kg i.v. bolus Binodenoson, 1.5 μg/kg i.v. bolus Binodenoson, 1.5 μg/kg i.v. infusion over 3 min Adenosine	240	Binodenoson was as effective as adenosine in allowing the determination of the extent and severity of perfusion defects in patients with known or suspected coronary artery disease, and was better tolerated	2

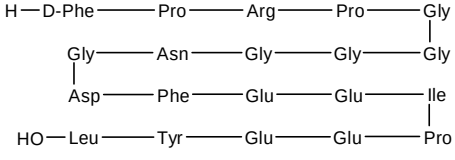
dose. Aderis has partnered with King Pharmaceuticals for the development and commercialization of binodenoson (1).

A multicenter, randomized, crossover phase II clinical trial examined the benefits of using binodenoson for pharmacological stress in myocardial perfusion imaging. A total of 240 patients with known CAD or a high pretest likelihood of CAD underwent two SPECT myocardial perfusion imaging studies: one with adenosine and another with binodenoson (0.5 μg/kg by i.v. bolus, 1 μg/kg by i.v. bolus, 1.5 μg/kg by i.v. bolus and 1.5 μg/kg i.v. for 3 min). The binodenoson studies showed good to excellent agreement with adenosine studies in determining the extent and severity of reversible perfusion defects, and the closest correlation (87%) was found with the 1.5 μg/kg i.v. bolus dose. The incidence of atrioventricular block was 3% with adenosine and 0% with binodenoson. Other side effects (*e.g.*, chest pain, dyspnea and flushing) were less frequent and less severe with binodenoson. No significant differences were found in the reduction of systolic or diastolic blood pressure induced by the study treatments (2) (Table VI).

1. *King Pharmaceuticals reports 2003 year-end R&D highlights.* King Pharmaceuticals Press Release 2004, Feb 19.

2. Udelson, J.E., Heller, G.V., Wackers, F.J.Th. et al. *Randomized, controlled dose-ranging study of the selective adenosine A_{2A} receptor agonist binodenoson for pharmacological stress as an adjunct to myocardial perfusion imaging.* Circulation 2004, 109(4): 457.

Bivalirudin



The thrombin-specific anticoagulant bivalirudin has been available in the U.S. as Angiomax® since 2001 for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). It was approved last year in the E.U. (Angiox™) for use as an anticoagulant in patients undergoing PCI. The direct thrombin inhibitor has a naturally reversible mechanism of action and has demonstrated reductions in both ischemic and bleeding complications compared to heparin, even in high-risk patients. The international REPLACE-2 (Randomized Evaluation in PCI Linking Bivalirudin to Reduced Clinical Events) trial in 6,010 patients undergoing urgent or elective PCI demonstrated that bivalirudin with provisional use of a gpIIb/IIIa inhibitor was noninferior to heparin plus gpIIb/IIIa inhibitors in terms of ischemic events, while significantly reducing the risk of major bleeding events by 41%. Bivalirudin was superior to heparin alone, reducing the risk of both ischemic and bleeding events. Developed by The Medicines Company, bivalirudin is licensed to Nycomed and Ferrer for marketing in the E.U. and Russia/CIS. Nycomed commenced the European roll-out of bivalirudin late last year, starting in Austria, Denmark, Finland, Germany and Sweden. The Medicines Company is also conducting phase III clinical programs for use in coronary artery bypass graft (CABG) surgery and in patients presenting to the emergency department with acute coronary syndrome (ACS). The FDA issued a not approvable letter last year relating to the company's application to amend the existing bivalirudin label to include use in patients undergoing coronary angioplasty with heparin-induced thrombocytopenia and thrombosis syndrome (HIT/TS) (1-6).

The Medicines Company has successfully completed the EVOLUTION (EValuation of patients during coronary artery bypass graft Operation: Linking Utilization of bivalirudin to Improved Outcomes and New anticoagulant strategies)-On phase III trial of bivalirudin, the second of two safety trials in the phase III cardiac surgery program. EVOLUTION-On evaluated the use of bivalirudin as an anticoagulant during cardiac surgeries conducted with the use of a cardiac pulmonary bypass machine. The primary objective of EVOLUTION-On was to demonstrate that bivalirudin is a safe alternative anticoagulant to heparin with protamine reversal in on-pump cardiac surgery. The primary endpoint results, a comparison of rates of acute procedural success, met the prespecified objectives. Patients treated with bivalirudin demonstrated a 95% success rate, compared to a 91.8% success rate in patients treated with heparin and protamine reversal. Acute procedural success was defined at 7 days postsurgery as absence of death, Q-wave myocardial infarction (heart attack), repeat operation or catheterization for coronary revascularization, or stroke. The Medicines Company is sponsoring the phase III study program investigating

bivalirudin as an anticoagulant in both on-pump and off-pump cardiac surgery to address a medical need among patients with or at risk for HIT/TS. The efficacy portion of the phase III program is comprised of the CHOOSE (CABG HIT/TS On and Off-pump Safety and Efficacy) studies, in which bivalirudin is being evaluated in patients with or at risk for HIT/TS who will be undergoing on-pump and off-pump cardiac surgery. In CHOOSE, HIT/TS is defined as a positive functional test for HIT antibodies, a platelet count decrease of 50% associated with heparin therapy, or the platelet count decrease plus any evidence of arterial or venous clotting. The safety portion of the phase III program comprises the EVOLUTION studies, which were conducted in the general cardiac surgery patient population. Primary results of EVOLUTION-Off, a 150-patient study in patients undergoing off-pump cardiac surgery, met the prespecified primary endpoint objectives. Both the EVOLUTION-On and EVOLUTION-Off trials were open-label, multicenter, randomized studies (7, 8).

1. *The Medicines Company reports 2003 year-end R&D highlights.* The Medicines Company Press Release 2004, Feb 10.

2. *Not approvable letter for proposed Angiomax label amendment.* DailyDrugNews.com (Daily Essentials) June 8, 2004.

3. *European CHMP hands down positive opinion for Angiox.* DailyDrugNews.com (Daily Essentials) June 30, 2004.

4. *The Medicines Company reports Q2 R&D highlights.* The Medicines Company Press Release 2004, July 20.

5. *European approval for Angiox for use in PCI. DailyDrugNews.com (Daily Essentials) Sept 28, 2004.*

6. *European launch for Angiox.* DailyDrugNews.com (Daily Essentials) Nov 2, 2004.

7. *The Medicines Company reports Q1 R&D highlights.* The Medicines Company Press Release 2004, April 20.

8. *Completion of EVOLUTION-On safety trial of Angiomax.* DailyDrugNews.com (Daily Essentials) Jan 3, 2005.

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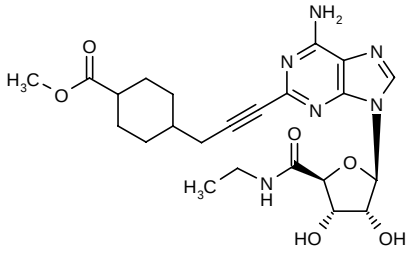
BMS-068645 (ATL-146e)



Phase II trials are under way for BMS-068645 (ATL-146e), a selective adenosine A_{2A} receptor agonist designed for use as a pharmacological stress agent in cardiac perfusion imaging studies. Adenosine Therapeutics granted a worldwide license to Bristol-Myers Squibb Medical Imaging in April 2000 covering the development and use of BMS-068645 for the diagnosis and prognosis of CAD. Bristol-Myers Squibb Medical Imaging is conducting and funding all clinical trials in cardiac imaging and licensing select data back to Adenosine Therapeutics for use outside the cardiac imaging field. Research to date suggests that BMS-068645 could potentially reduce or eliminate side effects associated with currently available pharmacological stress agents that are not selective for the A_{2A} receptor. Adenosine Therapeutics is studying ATL-146e for use in inflammatory bowel disease (IBD) due to the potent antiinflammatory and tissue-protective effects seen in rabbit models of ulcerative colitis (1, 2).

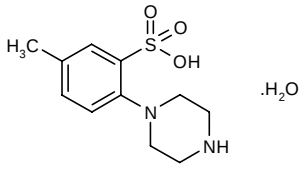
1. *BMS-068645 enters phase II trials.* DailyDrugNews.com (Daily Essentials) March 29, 2004.

2. *SBIR grant for IBD research at Adenosine Therapeutics and U. of Virginia.* DailyDrugNews.com (Daily Essentials) July 23, 2004.

C-1062/C-8834

C-1062 and C-8834 are in phase II clinical development at Merck & Co. for the treatment of atherosclerosis.

Caldaret Hydrate



Mitsubishi Pharma and Takeda have terminated their license agreement for an oral formulation of caldaret hydrate (MCC-135), a Ca^{2+} uptake enhancer currently in phase II development by Mitsubishi in the U.S. and the E.U. as an injectable formulation for myocardial infarction. Calderet demonstrates improvements in cardiac diastolic dysfunction and protective effects against cardiac necrosis by enhancing Ca^{2+} uptake by the sarcoplasmic reticulum and inhibiting sarcolemmal Na^{+}/Ca^{2+} exchange. The license agreement was concluded in July 2001, giving Takeda worldwide development and marketing rights, excluding Japan and several Asian countries, for the oral formulation of the compound. However, overall efficacy results of phase II studies conducted by Mitsubishi and Takeda in patients with chronic heart failure failed to meet Takeda's prespecified go/no go decision criteria for entry into phase III. Study results showed well-established safety, as well as efficacy, possibly related to pharmacological properties, observed for some endpoints. Mitsubishi may seek a new partner for the oral formulation (1, 2).

1. *Takeda Chemical Industries reports Q3 R&D highlights.* Takeda Chemical Industries Web Site 2004, Jan 27.

2. *Mitsubishi Pharma and Takeda terminate license agreement for oral MCC-135.* DailyDrugNews.com (Daily Essentials) Nov 8, 2004.

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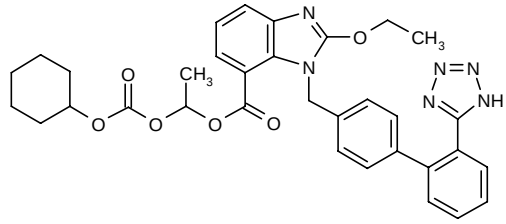
Candesartan Cilexetil



The angiotensin receptor blocker (ARB) candesartan cilexetil (TCV-116) is marketed worldwide under the brand names Blopress® and Amias® by Takeda and Atacand® and Ratacand® by AstraZeneca for the treatment of hypertension. Candesartan was submitted for Japanese approval for chronic heart failure in December

2001, as a fixed combination with a diuretic in December 2002, and is currently in phase III trials in Japan in a high-dose formulation. The product is also undergoing a phase III outcome study known as DIRECT (Diabetic Retinopathy Candesartan Trial) evaluating its potential in diabetic retinopathy. Earlier this year, the FDA approved AstraZeneca's supplemental NDA for the treatment of heart failure (New York Heart Association class II-IV and ejection fraction of 40% or less) to reduce the risk of death from cardiovascular causes and reduce hospitalizations from heart failure. Candesartan is the first ARB in the U.S. to receive an indication for reducing both cardiovascular mortality and hospitalizations for heart failure. Approval was primarily based on results from the CHARM-Alternative (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity Alternative) trial, which examined the effect of candesartan compared to placebo in 2,028 heart failure patients who were intolerant to ACE inhibitors, but were receiving other standard heart failure therapy. The trial demonstrated that the use of candesartan resulted in a 23% relative risk reduction in cardiovascular death or heart failure hospitalization (406 events in the placebo arm compared to 334 events in the patients receiving candesartan), with both components contributing to this effect. This finding was supported by a second study of 2,548 subjects—CHARM-Added— with NYHA class II-IV heart failure and ejection fraction of 40% or less, in which subjects were already on ACE inhibitors. Together, in these studies, patients on candesartan had a 15% lower risk of cardiovascular mortality. Symptoms of heart failure as assessed by NYHA functional class were also improved. In November 2004, AstraZeneca also announced that the European mutual recognition procedure evaluating the use of candesartan for the treatment of patients with heart failure and impaired left ventricular systolic function had been successfully completed. Furthermore, in August 2004, the companies received E.U. approval under the mutual recognition procedure for a higher dose 32-mg tablet for use in hypertension. The approval covers 14 E.U. countries, including the U.K., Germany, Austria, Italy, Spain, Portugal and Ireland (1-7).

1. *Randomization completed in candesartan diabetic retinopathy program.* DailyDrugNews.com (Daily Essentials) March 3, 2004.

2. *Takeda Chemical Industries reports Q3 R&D highlights.* Takeda Chemical Industries Web Site 2004, Jan 27.

3. *sNDA for Atacand in chronic heart failure.* DailyDrugNews.com (Daily Essentials) July 5, 2004.

4. *Atacand approved in Europe for treatment of chronic heart failure.* DailyDrugNews.com (Daily Essentials) Nov 30, 2004.

5. *Atacand approved for treatment of heart failure.* DailyDrugNews.com (Daily Essentials) Feb 24, 2005.

6. *European approval for higher dosage of candesartan cilexetil.* DailyDrugNews.com (Daily Essentials) Aug 18, 2004.

7. *European approval sought for candesartan cilexetil for chronic heart failure.* DailyDrugNews.com (Daily Essentials) April 14, 2004.

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Young, J.B. et al. *Mortality and morbidity reduction with candesartan in patients with chronic heart failure and left ventricular systolic dysfunction. Results of the CHARM low-left ventricular ejection fraction trials.* Circulation 2004, 110(17): 2618.

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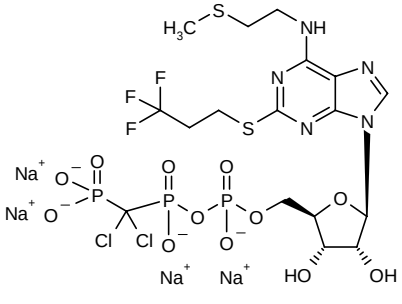
Cangrelor Sodium



The Medicines Company is developing cangrelor sodium, a short-acting, late-stage nonthienopyridine antiplatelet agent, following its acquisition in 2003 from AstraZeneca. Cangrelor is administered by injection and acts directly on the $P2Y_{12}$ platelet receptor to treat or prevent arterial thrombosis. The Medicines Company acquired rights to develop, market and sell cangrelor worldwide excluding Japan, China, Korea, Taiwan and Thailand. The company plans to develop cangrelor for use as an antiplatelet agent in patients undergoing PCI, such as angioplasty and stenting, and phase II trials are in progress in patients undergoing angioplasty. The initial focus of development will be to further study whether the short onset and offset of action at the platelet $P2Y_{12}$ receptor may provide important practical advantages over existing oral and parenteral agents in high-throughput cardiac catheterization centers. Cangrelor may also be developed for ACS and cardiovascular surgery. To date, cangrelor has been studied in approximately 500 patients and has shown inhibition of platelet activation and aggregation within seconds of initiation of drug administration, and recovery of platelet function within less than 60 min after stopping infusion, with a plasma half-life of approximately 10 min (1, 2).

1. *The Medicines Company reports 2003 year-end R&D highlights.* The Medicines Company Press Release 2004, Feb 10.

2. *The Medicines Company reports Q2 R&D highlights.* The Medicines Company Press Release 2004, July 20.

Celacade™

Vasogen was granted CE Mark regulatory approval in Europe last year for its immune modulation therapy Celacade™ (VAS-991) for the treatment of chronic heart failure. Vasogen plans to launch Celacade™ in Europe upon successful completion of its ongoing pivotal phase III ACCLAIM (Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy) trial in patients with advanced chronic heart failure. The 2,000-patient ACCLAIM trial, designed to support regulatory approvals in North America and Europe, is based on results from Vasogen's phase II trial, which demonstrated a significant reduction in the risk of death and hospitalization among advanced heart failure patients receiving Celacade™. ACCLAIM will further evaluate the impact of Celacade™ on reducing mortality and morbidity in this patient population. The primary outcome measure is the composite endpoint of all-cause mortality or hospitalization for cardiovascular causes (time to first event). Celacade™ is designed to activate the immune system's physiological antiinflammatory response to apoptotic cells. It upregulates the expression of cell-surface molecules that interact with specific receptors on antigen-presenting cells to modulate the production of cytokines. Celacade™ is also in phase III development for peripheral arterial disease (PAD). The pivotal phase III SIMPADI-

CO (Study of Immune Modulation Therapy in Peripheral Arterial Disease and Intermittent Claudication Outcomes) trial in 500 patients with PAD is designed to evaluate the impact of Celacade™ on maximal treadmill walking distance, the efficacy endpoint recognized by the FDA and other regulatory authorities for approving new PAD therapies. The company plans to launch Celacade™ in the U.S. for both cardiovascular indications simultaneously (1-5).

Patients with advanced heart failure (n=75) were randomized to placebo or immune modulation therapy in a 6-month double-blind phase II trial. Immune modulation therapy improved the NYHA functional classification of 15 patients and significantly reduced the risk of death and hospitalization compared with placebo (6).

1. *CE Mark for Celacade for chronic heart failure.* DailyDrugNews.com (Daily Essentials) Feb 4, 2004.

2. *Vasogen reports 2003 year-end R&D highlights.* Vasogen Press Release 2004, Feb 9.

3. *Vasogen updates Celacade phase III program.* DailyDrugNews.com (Daily Essentials) June 18, 2004.

4. *Full enrollment achieved in phase III study of Celacade for PAD.* DailyDrugNews.com (Daily Essentials) Nov 18, 2004.

5. *Vasogen reports Q2 R&D highlights.* Vasogen Press Release 2004, July 14.

6. Radovancevic, B., Young, J., Torre-Amione, G., Sestier, F. *Effects of a novel immune modulation therapy in patients with advanced chronic heart failure. Results of a randomized, controlled, phase II trial.* J Am Coll Cardiol 2004, 44(6): 1181.

CETP Vaccine

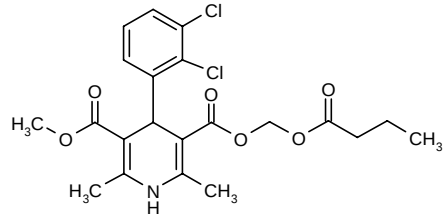
Avant Immunotherapeutics is considering various possibilities for the continued development of its CETi cholesteryl ester transfer protein (CETP) vaccine for cholesterol management, *i.e.*, the prevention or treatment of atherosclerosis, in patients with low levels of HDL cholesterol, including the use of new adjuvants to elicit a more robust antibody response. The company expects to have CETi back into the clinic towards the end of this year. In phase II trials the vaccine elevated HDL cholesterol levels by eliciting anti-CETP antibodies that block the transfer of cholesterol from HDL to LDL (1-3).

1. *Avant Immunotherapeutics reports Q1 R&D highlights.* Avant Immunotherapeutics Press Release 2004, April 21.

2. *Avant Immunotherapeutics reports Q2 R&D highlights.* Avant Immunotherapeutics Press Release 2004, July 22.

3. *Avant reports fourth quarter and fiscal 2004 financial results – Provides 2005 financial guidance.* Avant Immunotherapeutics Press Release 2005, March 2.

Clevidipine



Clevidipine (Clevelox™), a short-acting intravenous calcium channel antagonist acquired by The Medicines Company from AstraZeneca in 2002, is being studied for the short-term control of high blood pressure in coronary surgery in phase III clinical trials (1-3).

Late in the year, The Medicines Company released preliminary results from the ESCAPE-1 (Efficacy Study of Clevidipine [Clevelox] Assessing its Preoperative Antihypertensive Effects in Cardiac Surgery) trial of clevidipine, which demonstrated that the trial met the prespecified objectives. Cardiac surgery patients with high blood pressure pretreated with clevidipine achieved treatment success 92.5% of the time *versus* 17.3% with placebo. Treatment success was measured by at least a 15% reduction in blood pressure. The efficacy portion of the clevidipine phase III program is now complete. In November 2004, similar primary results were reported from ESCAPE-2, a trial of clevidipine in patients after cardiac surgery. Both ESCAPE trials were placebo-controlled, double-blind, randomized studies. The phase III program is comprised of 5 clinical trials. Three trials, known as ECLIPSE (Evaluation of Clevelox in the Postoperative Treatment of Hypertension Assessing Safety Events), are evaluating clevidipine safety perioperatively in approximately 1,500 patients. All 3 ECLIPSE studies are currently enrolling patients, with completion expected toward the middle of 2005. If ECLIPSE results meet their objectives, The Medicines Company plans to file an NDA. Previous trials have demonstrated a fast-on, fast-off pressure response, highly selective arterial effect and clearance independent of the liver and kidneys (4).

1. *The Medicines Company reports 2003 year-end R&D highlights.* The Medicines Company Press Release 2004, Feb 10.

2. *The Medicines Company reports Q1 R&D highlights.* The Medicines Company Press Release 2004, April 20.

3. *The Medicines Company reports Q2 R&D highlights.* The Medicines Company Press Release 2004, July 20.

4. *Clevelox ESCAPE-1 study meets objectives.* DailyDrugNews.com (Daily Essentials) Dec 21, 2004.

Original monograph – Drugs Fut 2004, 29(2): 105.

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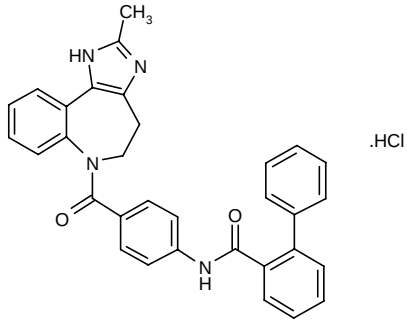
Conivaptan Hydrochloride



Prior to its merger with Fujisawa to form Astellas Pharma, Yamanouchi received an approvable letter from the FDA for conivaptan hydrochloride (YM-087, CI-1025) for the treatment of hyponatremia. Conditions for approval include the submission of additional safety data. Conivaptan is an injectable dual V_{1a}/V_2 vasopressin receptor antagonist which restores blood sodium levels in patients with euvolemic and hypervolemic hyponatremia by increasing the excretion of free water without increasing sodium output. If approved, conivaptan, potentially the world's first drug to treat this condition, will be marketed by Astellas (1, 2). The drug is also in phase II development in the E.U. and the U.S. for acute decompensated and chronic heart failure.

1. *NDA submission for YM-087 for hyponatremia.* DailyDrugNews.com (Daily Essentials) Feb 4, 2004.

2. *Approvable letter for hyponatremia drug YM-087.* DailyDrugNews.com (Daily Essentials) Dec 3, 2004.

Original monograph – Drugs Fut 2000, 25(11): 1121.

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CRD-5

Liponex's Charge Regulating Drug (CRD) CRD-5 is being positioned as a lipid-modifying therapeutic targeted at raising HDL levels for the treatment of atherosclerosis. Preclinical studies demonstrated its high efficacy as a lipid-lowering agent, as well as its good safety profile. The compound stimulates reverse cholesterol transport, promoting cholesterol excretion and thereby normalizing plasma lipid profiles in models of hypercholesterolemia. The company has completed phase I clinical trials with CRD-5 and phase II trials are expected to begin this year. In studies in healthy volunteers, preliminary efficacy data indicated that it can significantly increase the levels of HDL cholesterol while reducing levels of LDL cholesterol and triglycerides. No adverse events were observed (1).

1. *Liponex announces U.S. patent allowance and phase I trial results for drug that boosts good cholesterol.* Liponex Press Release 2004, Oct 19.

CYT006-AngQb

Cytos Biotechnology is conducting a combined phase I/II trial with the Immunodrug™ candidate CYT006-AngQb, a therapeutic vaccine for the treatment of hypertension. The study will include 16 normotensive and 72 hypertensive participants with mild to moderate hypertension and is designed to evaluate safety, tolerability and efficacy of the vaccine. The randomized, double-blind, placebo-controlled study will compare three different dose regimens of the vaccine against placebo. The treatment period of 4 months per individual will be followed by long-term monitoring of safety and efficacy over a further 8 months. Efficacy of the vaccine will be determined by measuring systolic and diastolic blood pressure, including 24-h ambulatory blood pressure monitoring. First results are expected in the second half of 2006. CYT006-AngQb is designed to instruct the patient's immune system to produce a specific antiangiotensin II antibody response. Vaccination with CYT006-AngQb is anticipated to induce antibodies that bind angiotensin II and thus inhibit or reduce binding to angiotensin II receptors. Consequently, blood pressure should be downregulated. Preclinical experiments have shown that vaccination of animals with CYT006-AngQb was effective and resulted in a statistically significant reduction in blood pressure. With CYT006-AngQb, Cytos Biotechnology aims to provide an antihypertensive vaccine that should allow for convenient dosing schedules and smooth control of blood pressure due to a sustained antibody response (1, 2).

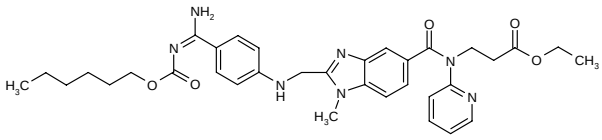
The company subsequently released the first phase I results for CYT006-AngQb from the pilot study in normotensive volunteers. CYT006-AngQb was shown to be safe, very well tolerated and immunogenic. Of the 16 healthy volunteers, 12 received 1 injection of the vaccine and 4 received placebo. All 12 participants receiving the vaccine mounted an angiotensin II-specific antibody response, whereas the 4 participants receiving placebo showed no detectable angiotensin II-specific antibodies. This corresponds to an immunological response rate of 100%. Furthermore, in all 12 responding participants, the angiotensin II-specific antibody levels peaked 2-3 weeks after injection and subsequently started to decline, as was anticipated from preclinical experiments. This reversible profile of the antibody response is a key safety feature of the Immunodrugs™. Based on these findings, Cytos will continue the combined phase I/II study with the planned 72 hypertensive subjects (3).

1. *Phase II/II trial for CYT006-AngQb for hypertension.* DailyDrugNews.com (Daily Essentials) Dec 16, 2004.

2. *Cytos Biotechnology reports 2004 achievements.* DailyDrugNews.com (Daily Essentials) March 2, 2005.

3. *Positive phase I findings for CYT006-AngQb for hypertension.* DailyDrugNews.com (Daily Essentials) March 2, 2005.

Dabigatran Etexilate



Dabigatran etexilate (BIBR-1048) is an orally available thrombin inhibitor synthesized at Boehringer Ingelheim and being developed for the prevention and treatment of thromboembolic disorders. Phase III trials were initiated late last year for the prevention of DVT following surgical intervention. A phase II trial was also completed in 2004 for the prevention of stroke in patients with atrial fibrillation, with phase III trials expected to begin soon.

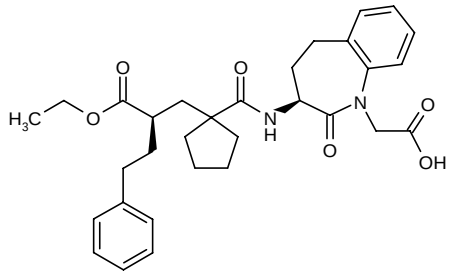
Pharmacokinetic/pharmacodynamic modeling and clinical trial simulation were used to analyze data from two multicenter clinical trials of dabigatran in the prevention of venous thromboembolism secondary to total hip or knee replacement. In an open-label trial, dabigatran (12.5, 25, 50, 100, 150, 200 and 300 mg b.i.d., or 150 and 300 mg once daily) was administered orally to 314 patients and in a double-blind trial, dabigatran (50, 150 and 225 mg b.i.d., or 300 mg once daily) or enoxaparin (40 mg) was given to 1,973 patients. In both studies, the patients received their allocated treatments for 6-10 days. The authors concluded that the dose-response relationship was best described by a 2-compartment model with first-order absorption and elimination (1).

1. Garnett, C., Liesenfeld, K.H., Tillmann, C., Troconiz, I., Lee, H., Schaefer, H.G., Stangier, J. *PK/PD-modeling (PK/PD) and clinical trial simulation (CTS) of early clinical data of a new oral direct thrombin inhibitor (dabigatran etexilate).* Pharm Sci World Congr (May 30-June 3, Kyoto) 2004, Abst P3E-X-027.

Additional References

Eriksson, B.I., Dahl, O.E., Buller, H.R. et al. *A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: The BISTRO II randomized trial.* J Thromb Haemost 2005, 3(1): 103.

Daglutril



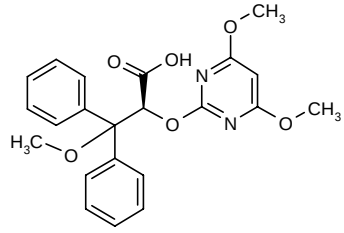
Solvay's daglutril (SLV-306) is a dual inhibitor of NEP and endothelin-converting enzyme (ECE) that is in phase II clinical studies for use in hypertension and CHF.

The use of NEP inhibitors for the treatment of CHF has been limited due to simultaneous increases in endothelin-1 (ET-1). The use of an agent that inhibits both NEP and ECE may be more effective. The efficacy of daglutril was therefore investigated in 75 patients with CHF who were undergoing right-sided heart catheterization. Patients were randomized to receive single oral doses of 200, 400 or 800 mg daglutril or placebo. Daglutril significantly reduced pulmonary and right atrial pressures at all concentrations, although the effect was not dose-dependent. There were no significant effects on heart rate, systemic blood pressure or cardiac output. Daglutril increased atrial and B-natriuretic peptides and big ET-1 levels in a dose-dependent manner. The drug was well tolerated (1).

1. Dickstein, K., De Voogd, H.J., Miric, M.P., Willenbrock, R., Mitrovic, V., Pacher, R., Koopman, P.A. *Effect of single doses of SLV306, an inhibitor of both neutral endopeptidase and endothelin-converting enzyme, on pulmonary pressures in congestive heart failure.* Am J Cardiol 2004, 94(2): 237.

Original monograph – Drugs Fut 2002, 27(1): 27.

Darusentan



Myogen has initiated a phase IIb trial to evaluate the safety and efficacy of oral darusentan in patients with resistant systolic hypertension. The primary objective of the randomized, double-blind, placebo-controlled trial is to determine if darusentan is effective in reducing SBP in patients with resistant systolic hypertension. Resistant hypertension is defined by The Seventh Report of the Joint National Committee on Prevention, Detection,

Evaluation and Treatment of High Blood Pressure sponsored by the National Institutes of Health (JNC7) as the failure to achieve goal blood pressure in patients who are adhering to full doses of an appropriate triple-drug regimen that includes a diuretic. Approximately 105 patients will be randomized to darusentan or placebo at some 30 sites. Patients will undergo forced titration every 2 weeks through 10, 50, 100 and 150 mg of darusentan or placebo until the target dose of 300 mg once a day is achieved. The treatment period is 10 weeks. Darusentan is a type A-selective endothelin (ET_A) receptor antagonist and potent inhibitor of endothelin-induced vasoconstriction and demonstrates a half-life that may be suitable for once-daily dosing. In 2000, the original sponsor (Abbott) of darusentan evaluated the safety and efficacy of the drug in 392 patients with moderate essential hypertension in a randomized, double-blind, placebo-controlled, dose-ranging phase II/III trial. Results demonstrated that darusentan produced statistically significant, clinically meaningful and dose-dependent reductions in DBP and SBP. The mean placebo-corrected change from baseline in SBP was –6.0 mmHg on 10 mg, –7.3 mmHg on 30 mg and –11.3 mmHg on 100 mg darusentan after 6 weeks of treatment. Significant reductions in DBP were also observed (–3.7, –4.9 and –8.3 mmHg, respectively). Heart rate remained unchanged in all groups. The study was conducted with a different patient population and protocol than in the new phase IIb trial (1, 2).

1. *New phase IIb study of darusentan for resistant systolic hypertension.* DailyDrugNews.com (Daily Essentials) July 20, 2004.

2. *Myogen reports Q2 R&D highlights.* Myogen Press Release 2004, Aug 5.

Original monograph – Drugs Fut 1999, 24(2): 141.

D-4F

Novartis licensed D-4F, a novel apoA-I (apolipoprotein A-I) mimetic, from BruinPharma during 2004. ApoA-I is a promising target for atherosclerosis therapy and phase I development of D-4F has been initiated (1).

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

DG-031

Enrollment is complete in deCODE Genetics' 10-week, information-rich phase IIa trial of DG-031, its developmental compound for the prevention of heart attack. The trial is designed to examine the effect of various doses of DG-031 on biomarkers such as CRP and myeloperoxidase, and on the production of leukotrienes. Data will be used in the design of a multicenter phase III registration trial for the prevention of a second heart attack. If successful for the prevention of second heart attacks, labeling extension will be sought for the prevention of heart attack in those who have never suffered one, as well as the prevention of stroke. deCODE has isolated common versions of genes within the leukotriene pathway that correlate with an increased risk of heart attack. This risk is the result of increased inflammation in atherosclerotic plaques, contributing to plaque rupture. DG-031 is designed to inhibit the activity of FLAP, or 5-lipoxygenase-activating protein, which modulates the activity of the leukotriene pathway (1, 2). The product was inlicensed from Bayer in 2003.

1. *Enrollment complete in phase IIa trial of DG-031 for heart attack prevention.* DailyDrugNews.com (Daily Essentials) June 22, 2004.

2. *deCODE provides update on key programs.* DailyDrugNews.com (Daily Essentials) June 30, 2004.

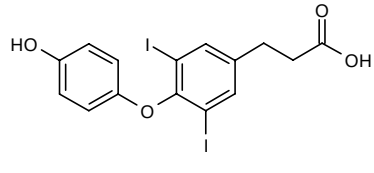
DG-041

deCODE Genetics has begun enrolling subjects in a phase I trial of DG-041 for peripheral arterial occlusive disease (PAOD). The single-blind, randomized, placebo-controlled, ascending-dose trial will evaluate the safety and the pharmacokinetic and pharmacodynamic profile of DG-041. DG-041 is a novel, first-in-class, orally administered small molecule which has been shown in preclinical studies to be a selective and potent antagonist of the EP_3 receptor for prostaglandin E_2 (PGE_2), inhibiting human platelet aggregation in a dose-dependent manner. In mice, DG-041 has been shown to protect against intravascular coagulation in a model based on prostanoid-induced platelet activation. DG-041 has also been shown to have minimal effect on bleeding time in animal studies. deCODE selected EP_3 as a target in PAOD through its population genetics research in Iceland, which linked variations in the gene encoding EP_3 (the *PTGER3* gene) to increased risk for the disease (1, 2).

1. *deCODE submits IND for novel antiatherosclerosis compound DG-041.* DailyDrugNews.com (Daily Essentials) Jan 18, 2005.

2. *deCODE opens phase I study for DG-041 for atherosclerosis.* DailyDrugNews.com (Daily Essentials) March 11, 2005.

DITPA



Titan has initiated a double-blind, randomized phase IIb study of DITPA (3,5-diiodothyropropionic acid), its

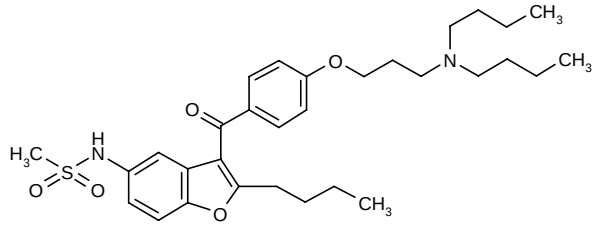
novel product in development for the treatment of CHF. The study will evaluate DITPA in the treatment of advanced CHF associated with low serum thyroid hormone levels. DITPA is a novel analogue of thyroid hormone with the potential to improve CHF while avoiding limitations inherent in the use of current thyroid hormone medications in patients with cardiovascular disease. The study will enroll 150 patients with NYHA class III-IV CHF and low serum T3 levels. Patients will receive either of two doses of DITPA or placebo for 6 months. The study will be performed at 35 U.S. sites. In addition to safety, the study will evaluate clinical and laboratory parameters related to the severity of CHF, including change in global clinical status, echocardiographic parameters, BNP levels, exercise testing and quality-of-life measurements. Approximately 30% of patients with advanced (NYHA class III and IV) CHF have abnormally low levels of T3, the active form of thyroid hormone needed by heart cells. These low levels are a strong independent predictor of increased mortality in CHF patients. The important role of thyroid hormone in maintaining heart and blood vessel function, and the association of low T3 and increased mortality in CHF, suggest a potential role for DITPA as a thyroid hormone replacement therapy in CHF. Currently available thyroid hormone medications are generally not suitable for chronic use in CHF because they are primarily T4 preparations, or have too short a half-life, and they have the potential to increase heart rate. In preclinical and preliminary placebo-controlled pilot clinical testing, DITPA demonstrated the ability to improve measures of diastolic function, reduce peripheral vascular resistance and improve systolic function, without increasing heart rate. Pilot clinical testing in CHF patients over 4 weeks also demonstrated no significant adverse effects. DITPA is also currently being evaluated in a second randomized, double-blind, placebo-controlled phase II study in 150 patients with NYHA class II-IV CHF, sponsored by the Department of Veterans Affairs Cooperative Studies Program and funded by a USD 3.8 million grant. Furthermore, DITPA may have potential utility in the treatment of diastolic dysfunction, and the treatment of patients with left ventricular dysfunction after myocardial infarction. Recent preclinical studies demonstrate that DITPA also stimulated coronary small blood vessel growth after myocardial infarction, and reduced infarct size by approximately 80%. In these studies, DITPA was also shown to reduce ventricular remodeling subsequent to myocardial infarction and improve heart function (1-3).

1. *New phase II study of Titan's DITPA for CHF.* DailyDrugNews.com (Daily Essentials) July 29, 2004.

2. *Titan Pharmaceuticals reports Q1 R&D highlights.* Titan Pharmaceuticals, Inc. Press Release 2004, May 6.

3. *Titan initiates phase IIb study of DITPA for congestive heart failure.* DailyDrugNews.com (Daily Essentials) Dec 16, 2004.

Dronedarone Hydrochloride



.HCl

The former Sanofi-Synthélabo, now Sanofi-Aventis, reported positive results from two pivotal studies of dronedarone hydrochloride (SR-33589), a class III antiarrhythmic agent, in the prevention of atrial fibrillation. The EURIDIS (EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maIntenance of Sinus rhythm) study was a multicenter, double-blind clinical trial conducted in 77 European centers that enrolled 612 patients in sinus rhythm with at least 1 documented event of atrial fibrillation during 1 month before inclusion. The patients were randomized to receive dronedarone (400 mg) or placebo twice daily for 12 months. The time to first recurrence of atrial fibrillation/atrial flutter (AF/AFL) was found to be 2.3 times longer with dronedarone compared to placebo; this difference was estimated to be equivalent to a 21.6% reduction in the risk of first recurrence of AF/AFL for dronedarone-treated patients. Similar results were derived from the ADONIS (American-Australian-African trial with DronedarONe In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm) study, a multicenter, double-blind, randomized, placebo-controlled clinical trial that enrolled 625 patients with the same baseline characteristics as above from 115 centers in the U.S., Canada, Argentina, Australia and South Africa. In this study, dronedarone (400 mg twice daily) given for 12 months extended the median time from randomization to first recurrence of AF/AFL by 2.7 times, and reduced the risk of first recurrence by 27.5% compared to placebo. No significant differences in the incidence of adverse events were found between treatments in each clinical trial. None of the patients who received dronedarone experienced proarrhythmia or torsades de pointes during the study periods (1-3) (see Table VII).

1. *Sanofi-Synthélabo reports 2003 year-end R&D highlights.* Sanofi-Synthélabo Press Release 2004, Feb 16.

2. *Sanofi-Synthélabo reports Q1 R&D highlights.* Sanofi-Synthelabo Press Release 2004, April 22.

3. *Hohnloser, S.H. EURIDIS and ADONIS: Maintenance of sinus rhythm with dronedarone in patients with atrial fibrillation or flutter.* ESC Congress (Aug 28-Sept 1, Munich) 2004, Present 716.

Additional References

Chevalier, P., Burri, H., Rivart, L., Durand-Dubief, A., Touboul, P. *Impact of myocardial ischaemia on ventricular defibrillation*

Table VII: Clinical studies of dronedarone hydrochloride (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Atrial fibrillation, Atrial flutter	Randomized Double-blind Multicenter Pooled/meta-analysis	Dronedarone, 400 mg b.i.d. x 12 mo (n=828) Placebo (n=409)	1237	Dronedarone was well tolerated and more effective than placebo in preventing the recurrence of atrial fibrillation or atrial flutter in patients with cardiac arrhythmia	3

threshold during chronic oral class III antiarrhythmic drugs therapy: Comparison between amiodarone, dronedarone and azimilide. Eur Heart J 2004, 25(Suppl.): Abst P1081.

Damy, T. et al. *Pharmacokinetic and pharmacodynamic interactions between metoprolol and dronedarone in extensive and poor CYP2D6 metabolizers healthy subjects.* Fundam Clin Pharmacol 2004, 18(1): 113.

Singh, B.N. et al. *The EURIDIS and ADONIS trials: Dronedarone for maintaining sinus rhythm in patients with atrial fibrillation/flutter.* Circulation 2004, 110(17, Suppl. 3): Abst 3429.

DS-992

AnGes is conducting two large multicenter, double-blind phase III clinical trials in Japan for its gene medicine to treat peripheral arterial disease (PAD). The HGF (hepatocyte growth factor) gene medicine DS-992 (TREAT-HGF) regenerates the blood vessels to improve the condition of patients with clogged capillaries due to arteriosclerosis or similar blood circulation disorders. It is being developed principally to treat PAD patients with progressive blood circulation disorders of the lower extremities, as well as those with progressive ischemic heart disease (IHD, also known as CAD) affecting the blood circulation in the heart. As the gene medicine operates in a different manner than conventional drugs, it is expected to be effective for people who do not respond to conventional drug therapy or who cannot undergo surgery. Phase II studies are under way in the U.S. for the HGF gene medicine for PAD. The FDA has also given the green light for the first clinical trial of the HGF plasmid in IHD, and a phase I study has been initiated. In the study, HGF plasmid will be administered directly to ischemic cardiac muscle using an endomyocardial catheter. The safety and preliminary efficacy of the treatment will be evaluated in approximately 10 subjects. AnGes is also making preparations for a phase I IHD trial in Japan. Marketing and distribution rights have been granted to Daiichi Pharmaceutical in Japan, Europe and the U.S. for both PAD and IHD (1-5).

A prospective, open-label clinical trial to evaluate the safety of intramuscular injection of DS-992 was performed in patients with PAD. Four weeks after plasmid injection, no elevation in serum HGF levels was detected. Various serious adverse effects were reported but they were not related to the administration of the HGF gene, indicating this gene therapy is well tolerated (6).

1. *Japanese trials of HGF genetic medicine cleared to begin.* DailyDrugNews.com (Daily Essentials) Jan 7, 2004.

2. *AnGes files IND for phase I trials of HGF.* DailyDrugNews.com (Daily Essentials) March 8, 2004.

3. *HGF enters clinic in Japan.* DailyDrugNews.com (Daily Essentials) March 22, 2004.

4. *Clinical study cleared to begin of HGF plasmid for ischemic heart disease.* DailyDrugNews.com (Daily Essentials) July 29, 2004.

5. *Phase I clinical trials of HGF plasmid for the treatment of ischemic heart disease underway in the United States.* AnGes MG, Inc. Press Release 2004, Nov 24.

6. Aoki, M., Makino, H., Hashiya, N., Yamasaki, K., Ogihara, T., Morishita, R., Kaneda, Y. *Results of safety from human clinical gene therapy using HGF (TREAT-HGF).* J Hypertens 2004, 22(Suppl. 1): Abst P 725.

Additional References

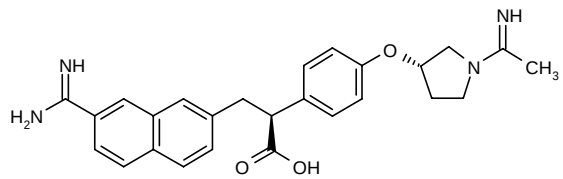
Hashiya, N., Morishita, R., Aoki, M., Yamasaki, K., Makino, H., Kaneda, Y., Ogihara, T. *Clinical results of treat-HGF (Japan trial to treat peripheral arterial disease by therapeutic angiogenesis using hepatocyte growth factor gene transfer).* J Hypertens 2004, 22(Suppl. 1): Abst P 531.

Morishita, R., Aoki, M., Hashiya, N. et al. *Safety evaluation of clinical gene therapy using hepatocyte growth factor to treat peripheral arterial disease.* Hypertension 2004, 44(2): 203.

DU-176b

Daiichi Pharmaceutical is conducting phase II clinical evaluation in the U.S. and Europe and phase I trials in Japan with DU-176b, a potent, orally active direct factor Xa inhibitor for arterial and venous thrombosis.

DX-9065a



$.5H_2O$ .HCl

DX-9065a is a selective, orally active factor Xa inhibitor in phase II studies at Daiichi Pharmaceutical for the treatment of unstable angina.

Table VIII: Clinical studies of DX-9065a (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Acute coronary syndrome	Randomized Double-blind	DX-9065a, 0.025 mg/kg i.v. bolus → 0.04 mg/kg infusion over 3 h → 0.012 mg/kg/h DX-9065a, 0.05 mg/kg i.v. bolus → 0.08 mg/kg infusion over 3 h → 0.024 mg/kg/h	405	Preliminary results suggested that DX-9065a may be an attractive option for inducing thrombolysis in patients with acute coronary syndrome	1

The XaNADU-ACS trial was a double-blind, randomized clinical trial that compared the antithrombotic efficacy and safety of unfractionated heparin and DX-9065a. Overall, 405 patients with non-S-T segment elevation ACS were included in the study, and DX-9065a was administered as a bolus injection of 0.025 or 0.05 mg/kg, followed respectively by a 3-h infusion of 0.04 or 0.08 mg/kg/h and a maintenance dose of 0.012 or 0.024 mg/kg/h. The preliminary results obtained from the first 339 patients included in the study suggested that DX-9065a may be an attractive therapeutic option to prevent thrombosis in patients with ACS (1) (Table VIII).

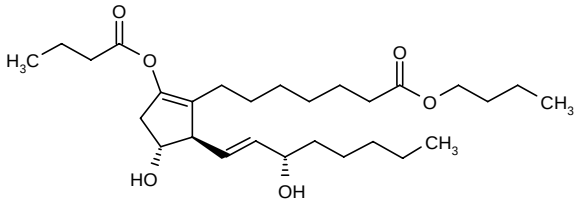
1. Alexander, J.H., Yang, H., Becker, R.C. et al. *Direct, selective, factor Xa inhibition in patients with non-ST elevation acute coronary syndromes from the United States, Canada, and Japan: Results of the XaNADU-ACS trial.* 53rd Annu Sci Sess Am Coll Cardiol (March 7-10, New Orleans) 2004, Abst 861-1.

Original monograph – Drugs Fut 1995, 20(6): 564.

Additional References

Alexander, J.H., Dyke, C.K., Yang, H. et al. *Initial experience with factor-Xa inhibition in percutaneous coronary intervention: The XaNADU-PCI Pilot.* J Thromb Haemost 2004, 2(2): 234.

Ecraprost



Ecraprost (AS-013) is a prostaglandin E_1 (PGE_1) prodrug incorporated into lipid microspheres presently undergoing phase III development in the U.S. and phase II trials in Japan by Mitsubishi Pharma in partnership with Asahi Glass for the treatment of PAOD.

Edifoligide Sodium

Following the disappointing results from the phase III PREVENT IV trial evaluating the use of Corgentech's E2F decoy edifoligide sodium (CGT-003) for the prevention of vein graft failure following CABG and peripheral artery bypass graft (PBG) surgery, the company and partner Bristol-Myers Squibb have decided to terminate development of the project. In this trial in over 3,000 patients, edifoligide was generally well tolerated but failed to meet the primary and secondary endpoints. The primary endpoint was the percent reduction in the incidence of graft failure compared to placebo; graft failure was defined as blockage of the graft of 75% or greater as measured by quantitative coronary angiography at 12 months. The phase I/II trial for the prevention of arteriovenous graft failure in patients with end-stage renal disease undergoing hemodialysis will also be terminated. Edifoligide, applied to the vein by the surgeon just prior to implanting the vein as a bypass, was designed to bind to E2F at its normal DNA binding site and block cell cycle progression (1-6).

Topline results from the first phase III trial of edifoligide —the randomized, double-blind, placebo-controlled PREVENT III trial— were reported late last year and also failed to show a benefit for edifoligide on the rate of vein graft failure during 12 months after surgery (7).

1. *Bristol-Myers Squibb reports 2003 year-end R&D highlights.* Bristol-Myers Squibb Press Release 2004, Feb 29.

2. *Patient enrollment commences in phase I/II trial of E2F decoy.* DailyDrugNews.com (Daily Essentials) May 20, 2004.

3. *Bristol-Myers Squibb highlights pipeline progress.* DailyDrugNews.com (Daily Essentials) Nov 19, 2004.

4. *Corgentech and Bristol-Myers Squibb announce results from edifoligide (E2F decoy) phase 3 trial for coronary artery bypass graft failure.* Corgentech Press Release 2005, March 30.

5. *Phase III PREVENT IV edifoligide study recommended to continue.* DailyDrugNews.com (Daily Essentials) July 1, 2004.

6. *Corgentech to discuss registration strategy for edifoligide with FDA.* DailyDrugNews.com (Daily Essentials) Feb 28, 2005.

7. *Topline results from phase III study of edifoligide for peripheral bypass graft.* DailyDrugNews.com (Daily Essentials) Dec 10, 2004.

EG-004

Ark Therapeutics' EG-004 (Trinam®), its novel therapy to prevent blockage of blood vessels after vascular graft access surgery, is a combination of a vascular endothelial growth factor (VEGF) gene in an adenoviral vector and Ark's biodegradable collagen collar local delivery device (EG-001). The initial target market for EG-004 is hemo-

dialysis access graft surgery, a treatment for kidney failure patients in which a plastic tube is grafted between blood vessels in the forearm to enable regular blood filtration. At the end of the access graft surgery procedure, the EG-001 delivery device is fitted around the outside of the vein where it has been joined to the access graft. The VEGF gene in solution is then injected into the reservoir formed between the delivery device and the blood vessel, from where it passes into the blood vessel wall, transfecting the smooth muscles cells in the wall. This allows EG-004 to be localized to the target tissue site where the therapy is needed. The efficacy and safety of EG-004 are being evaluated in a phase II ascending-dose study at Duke University in the U.S. in up to 20 patients undergoing hemodialysis access graft surgery. Phase II/III development was approved by the U.S. Recombinant DNA Advisory Committee in October 2001. Preclinical studies have demonstrated a significant effect in preventing intimal hyperplasia and successful adventitial gene transfer. The product has been granted orphan drug status in both the U.S. and the E.U. The company expects to file for E.U. marketing approval in 2007 (1-3).

1. *Ark to float on London SE; four lead products in pipeline.* DailyDrugNews.com (Daily Essentials) Feb 23, 2004.

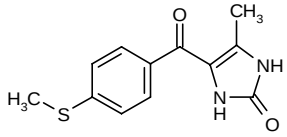
2. *Treatment commences in Trinam phase II study.* DailyDrugNews.com (Daily Essentials) May 13, 2004.

3. *Trinam receives orphan medicinal product status in Europe.* DailyDrugNews.com (Daily Essentials) June 21, 2004.

EMD-503982

The factor Xa inhibitor EMD-503982 is in early clinical development at Merck KGaA for the treatment of venous thromboembolism.

Enoximone, Oral



Enoximone is a highly selective phosphodiesterase type 3 (PDE3) inhibitor launched a number of years ago for intravenous injection or infusion in the treatment of acute decompensated heart failure. The drug is currently available as Perfan® IV in several European countries. At present, Myogen, which acquired worldwide rights from Aventis in 1998, is evaluating enoximone capsules in phase III trials for the long-term treatment of advanced chronic heart failure. In the event of regulatory approval of the capsule formulation, enoximone will be the first oral inhibitor of PDE3 to be commercialized for the treatment of chronic heart failure.

Original monograph – Drugs Fut 1983, 8(4): 343.

ETC-216

Pfizer completed its acquisition of Esperion Therapeutics last year and is continuing phase II clinical development of the HDL cholesterol-increasing compound ETC-216 (ApoA-I_{Milano}/phospholipid complex, AIM) for atherosclerosis in ACS (1, 2).

A clinical trial in healthy volunteers determined that ETC-216 was well tolerated and increased HDL levels. Based on these results, a multicenter, double-blind, randomized, pilot clinical trial evaluated the effects of ETC-216 in patients suffering from ACS, and found that the compound induced significant regression of atherosclerosis after 6 weeks. The authors suggested that the combination of functional HDL product candidates and traditional lipid regulation therapy may be effective for ACS (3, 4).

1. *Pfizer reports Q1 R&D highlights.* Pfizer Press Release 2004, April 20.

2. *Pfizer reports Q2 R&D highlights.* Pfizer Press Release 2004, July 21.

3. *Esperion Therapeutics reports 2003 year-end R&D highlights.* Esperion Therapeutics Press Release 2004, Jan 22.

4. Bisgaier, C. *New options in HDL therapy for acute and chronic treatment of atherosclerosis.* Atherosclerosis Suppl 2004, 5(1): Abst W06.162.

Original monograph – Drugs Fut 2004, 29(6): 566.

Additional References

Gratsiansky, N.A. *First clinical randomized controlled trial of recombinant ApoA-1(Milano) on coronary atherosclerosis in patients with acute coronary syndromes.* Kardiologiya 2004, 44(6): 82.

EW-A-401

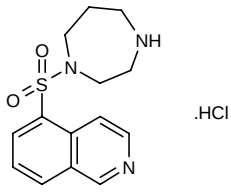
Edwards Lifesciences has initiated a phase I/II trial of EW-A-401, a new therapeutic compound designed to stimulate the natural growth of normal blood vessels for the treatment of intermittent claudication, a symptom of PAD. Following IND clearance in March, the AVENGE (Activating Vascular Endothelial Growth Factor) trial commenced in August 2004 with the treatment of the first patient at the Warren Grant Magnuson Clinical Center of the National Institutes of Health (NIH). The double-blind, placebo-controlled, dose-escalation study in 36 patients is designed primarily to measure EW-A-401's safety in

treating intermittent claudication, although preliminary data on the therapy's effectiveness in improving patients' blood flow, walking capacity and quality of life may also be obtained. The trial is expected to take approximately 12-18 months to screen and enroll patients, with an additional 6 months of safety follow-up. EW-A-401 was developed by Sangamo BioSciences and licensed to Edwards for use in the treatment and prevention of ischemic cardiovascular and vascular disease. The compound encodes a zinc finger DNA-binding protein transcription factor (ZFP TF) designed to uniquely activate all isoforms of the vascular endothelial growth factor A (VEGF-A) gene to stimulate angiogenesis. In preclinical studies, EW-A-401 was shown to be effective in stimulating the growth of functionally normal vessels and increasing blood flow in ischemic limbs. This approach may have distinct advantages over previous approaches that have attempted to stimulate blood vessel growth by using a single VEGF gene isoform. Preclinical studies suggested that the type of blood vessels produced when the natural VEGF gene is activated may be more normal and less leaky than those formed in response to alternative approaches. In the future, Edwards may pursue additional indications for the therapy, including critical limb ischemia and IHD (1, 2).

1. *IND filing for phase I/II AVENGE trial of EW-A-401.* DailyDrugNews.com (Daily Essentials) Feb 13, 2004.

2. *Phase I/II trial for EW-A-401.* DailyDrugNews.com (Daily Essentials) Sept 2, 2004.

Fasudil Hydrochloride

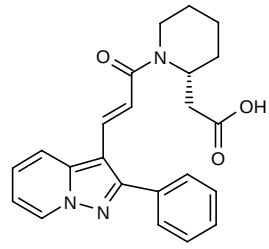


.HCl

Fasudil hydrochloride (AT-877), a rho kinase inhibitor and calcium channel blocker, was initially launched in 1995 by Asahi Kasei as Eril™ Injection for the treatment of vasospasm following surgery for subarachnoid hemorrhage. Currently, the same formulation of the compound is awaiting registration in Japan for the treatment of acute cerebral thrombosis. In addition, phase II trials of an oral formulation are under way in Japan and Europe for the treatment of stable angina pectoris by Asahi Kasei and U.S. and European licensee Schering AG, respectively.

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

FK-352B



The results of a multicenter, randomized, double-blind trial comparing the effects of FK-352B (Astellas Pharma), an adenosine A_1 receptor antagonist, and placebo in chronic hemodialysis patients with dialysis-induced hypotension were reported. The frequency of intradialysis hypotension was reduced by 12.3% when 50 mg of FK-352B was injected into the dialysis circuit 1 h after starting dialysis, but was not altered with placebo administration. Hemodialysis was not discontinued in patients receiving FK-352B, whereas 4.2% of patients in the placebo group discontinued. In addition, FK-352B produced significant reductions in symptoms associated with severe hypotension and was not associated with adverse effects (1).

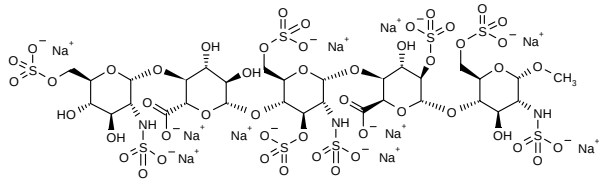
1. Imai, E., Fujii, M., Kono, Y., Kageyama, H., Nakahara, K., Tsubakihara, Y. *Adenosine A_1 antagonist improved intradialytic hypotension.* J Am Soc Nephrol 2004, 15: Abst SU-PO361.

Original monograph – Drugs Fut 1997, 22(4): 350.

Additional References

Fujii, M. et al. *Effect of an adenosine A_1 receptor antagonist (FK352) on intradialysis hypotension in chronic hemodialysis patients.* Nephrol Dial Transplant 2004, 19(5, Suppl.): Abst MP304.

Fondaparinux Sodium



Fondaparinux sodium (Org-31540/SR-90107A, Arixtra®, Quixidar®) is a selective inhibitor of activated factor X for the treatment and prophylaxis of thromboembolic diseases. Its structure is the copy of the heparin pentasaccharide sequence, the shortest chain required for antithrombin inhibition of activated factor X without antithrombin action. It was launched in the U.S. and Europe in 2002 by Organon and the former Sanofi-Synthélabo for use in the prophylaxis of DVT, which may lead to pulmonary embolism (PE) in patients undergoing surgery for hip fracture (including extended prophylaxis), knee replacement and hip replacement. Last year,

Table IX: Clinical studies of fondaparinux sodium (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Acute coronary syndrome	Randomized Double-blind	Fondaparinux, 2.5 mg s.c. o.d. x 3-7 d (n=229) Fondaparinux, 4 mg s.c. o.d. x 3-7 d (n=220) Fondaparinux, 8 mg s.c. o.d. x 3-7 d (n=225) Fondaparinux, 12 mg s.c. o.d. x 3-7 d (n=234) Enoxaparin, 1 mg/kg s.c. b.i.d. x 3-7 d (n=230)	1138	Fondaparinux and enoxaparin demonstrated similar efficacy in patients with non-S-T segment acute coronary syndrome	8

GlaxoSmithKline acquired, on a worldwide basis, fondaparinux and related assets from Sanofi-Aventis. The closing of the transaction followed Sanofi-Synthélabo's successful completion of its offer for Aventis. As part of the agreement, GlaxoSmithKline assumed responsibility for ongoing fondaparinux clinical trials. Prior to this agreement, Organon transferred its remaining rights and obligations related to fondaparinux to Sanofi-Synthélabo. Adolor and GSK subsequently signed a 2-year agreement to copromote the product in the U.S. (1-4). In addition to the new indiations discussed below, fondaparinux is in phase III evaluation for the treatment of ACS.

Fondaparinux recently received European Commission approval for use in the prevention of DVT in medical patients who are judged to be at high risk of thromboembolic complications. The new use extends to patients who are immobilized due to acute illness such as cardiac insufficiency, acute respiratory disorders, acute infectious disease and/or acute inflammatory disease. Also during last year, the product was approved in both the U.S. and the E.U. for the treatment of acute DVT and the treatment of acute PE. The file for the new indications was based on the findings of the MATISSE PE and MATISSE DVT studies which demonstrated that a new strength of fondaparinux (7.5 mg given as a once daily subcutaneous injection), when administered in conjunction with warfarin sodium, can effectively and safely treat the acute phases of both DVT and PE. The open-label MATISSE PE study involved 2,213 patients with symptomatic PE enrolled at 214 sites in 20 countries. The study showed that a fixed once-daily subcutaneous dose of 7.5 mg, without the need for coagulation monitoring, appears to be at least as effective and as safe as continuous intravenous and dose-adjusted unfractionated heparin (UFH). Moreover, 15% of patients received fondaparinux on an outpatient basis after receiving the first dose in the hospital, compared to none with UFH. The MATISSE DVT trial involved 2,205 patients with symptomatic DVT without symptomatic PE at 154 sites in 23 countries. The study showed that fondaparinux 7.5 mg, given once daily as a fixed subcutaneous dose, appears to be at least as effective and safe as dose-adjusted low-molecular-weight heparin (LMWH) administered subcutaneously twice a day (5-7).

Patients with ACS (n=1,138) were treated with fondaparinux (2.5, 4, 8 or 12 mg s.c. once daily) or enoxaparin (1 mg/kg b.i.d.) in a dose-finding study. Similar rates of the combined endpoint of death, myocardial infarction or recurrent ischemia were seen with the treatments through 9 days. No dose-response was seen with fondaparinux therapy (8) (Table IX).

1. *Akzo Nobel to transfer Arixtra to Sanofi-Synthelabo.* DailyDrugNews.com (Daily Essentials) Jan 13, 2004.

2. *GlaxoSmithKline to acquire Fraxiparine and Arixtra.* DailyDrugNews.com (Daily Essentials) April 19, 2004.

3. *Adolor to copromote Arixtra with GlaxoSmithKline.* DailyDrugNews.com (Daily Essentials) Jan 10, 2005.

4. *GlaxoSmithKline acquires Fraxiparine, Fraxodi and Arixtra. DailyDrugNews.com (Daily Essentials) Sept 3, 2004.*

5. *Extension of indication recommended for Arixtra, Quixidar.* DailyDrugNews.com (Daily Essentials) Aug 3, 2004.

6. *Arixtra receives new approval in Europe.* DailyDrugNews.com (Daily Essentials) Feb 10, 2005.

7. *Approval for new Arixtra indications.* DailyDrugNews.com (Daily Essentials) June 10, 2004.

8. Simoons, M.L., Bobbink, I.W.G., Boland, J. et al. *A dose-finding study of fondaparinux in patients with non-ST-segment elevation acute coronary syndromes. The Pentasaccharide in Unstable Angina (PENTUA) Study.* J Am Coll Cardiol 2004, 43(12): 2183.

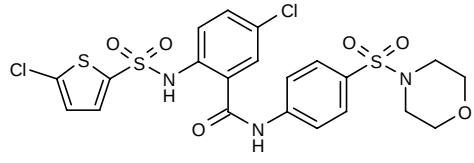
Original monograph – Drugs Fut 2002, 27(2): 122.

Additional References

Davidson, B., Turpie, A.G.G., Colwell, C., Kwong, L.M. *Early vs delayed initiation of fondaparinux prophylaxis to prevent postoperative pulmonary embolism: A clinical endpoint study.* Chest 2004, 126(4, Suppl.): 783S.

Piovella, F. *Initial outpatient treatment of pulmonary embolism with fondaparinux (Arixtra): The MATISSE-PE trial.* 9th Congr Eur Hematol Assoc (June 10-13, Geneva) 2004, Abst 154.

HMR-1069/HMR-1766



HMR-1766

HMR-1069 is a guanylate cyclase activator in early clinical development by Sanofi-Aventis for the treatment of chronic angina pectoris. Another guanylate cyclase activator, HMR-1766 (ataciguat), has reached phase II development for this indication.

Hydralazine Hydrochloride/ Isosorbide Dinitrate

NitroMed has completed the submission of an amendment to its NDA for hydralazine hydrochloride/isosorbide dinitrate (BiDil®) with the submission of the complete A-HeFT (African American Heart Failure Trial) study report. The A-HeFT (African American Heart Failure Trial) investigated BiDil® for its potential, when administered together with standard heart failure therapies, to reduce mortality and hospitalizations and improve the quality of life of African Americans diagnosed with heart failure. The FDA subsequently accepted the submission. The study's results demonstrated that African American patients with heart failure experienced a 43% improvement in survival, a 33% reduction in first hospitalization for heart failure and a significant improvement in overall quality of life after taking BiDil®. The trial was halted early in July 2004 due to the significant survival benefit seen in patients on BiDil®. If approved, a launch is expected to take place in 2005. BiDil® is an orally administered nitric oxide (NO)-enhancing drug candidate that combines isosorbide dinitrate, an NO donor, and hydralazine, an antioxidant and vasodilator. Neither drug separately is indicated for heart failure (1-5).

1. *A-HeFT trial of BiDil cleared to continue by DSMB.* DailyDrugNews.com (Daily Essentials) March 18, 2004.

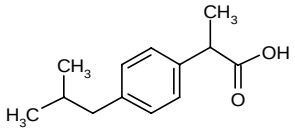
2. *Significant survival benefit in A-HeFT study of BiDil brings early conclusion.* DailyDrugNews.com (Daily Essentials) July 23, 2004.

3. *NitroMed submits BiDil NDA amendment.* DailyDrugNews.com (Daily Essentials) Dec 29, 2004.

4. *FDA accepts BiDil NDA resubmission.* DailyDrugNews.com (Daily Essentials) Feb 8, 2005.

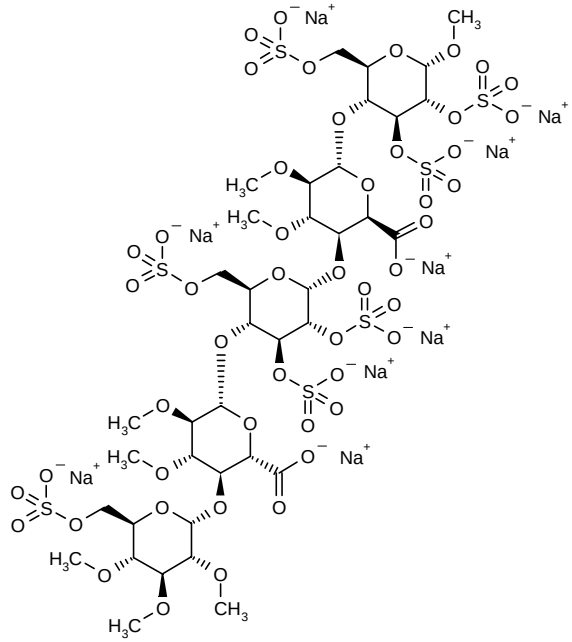
5. Taylor, A.L., Ziesche, S., Yancy, C. et al. *Combination of isosorbide dinitrate and hydralazine in blacks with heart failure.* New Engl J Med 2004, 351(20): 2049.

Ibuprofen, Injection



A known nonsteroidal antiinflammatory drug (NSAID), ibuprofen is currently available for a variety of inflammatory and painful conditions. In 2004, ibuprofen expanded its therapeutic range to include a cardiovascular application, following E.U. approval as a solution for injection (Pedea®; Orphan Europe) for the treatment of hemodynamically significant patent ductus arteriosus in preterm infants of less than 34 weeks' gestational age. The FDA granted orphan drug designation for the prevention and treatment of patent ductus arteriosus in 1996.

Idraparinux Sodium



Idraparinux is a long-acting pentasaccharide in phase III development for the long-term treatment of DVT/PE and atrial fibrillation.

The former Sanofi-Synthélabo (now Sanofi-Aventis) obtained all rights to the antithrombotic fondaparinux sodium and certain other oligosaccharides, such as idraparinux sodium, from partner Organon last year (1).

1. *Akzo Nobel to transfer Arixtra to Sanofi-Synthelabo.* DailyDrugNews.com (Daily Essentials) Jan 13, 2004.

Original monograph – Drugs Fut 2002, 27(7): 639

INO-1001

INO-1001 (Inotek) has been designated a fast track product by the FDA for the treatment of patients with S-T segment elevation myocardial infarction (STEMI) undergoing primary PCI. Following the agency's acceptance of the company's IND to study INO-1001 in clinical trials for the treatment of STEMI, a multicenter trial, conducted by Inotek in collaboration with the TIMI (Thrombolysis In Myocardial Infarction) Study Group, commenced enrollment and is evaluating its ability to prevent cardiac necrosis in patients undergoing emergent angioplasty after an acute myocardial infarction. The placebo-controlled, randomized, single-blind trial will enroll 40 patients and the primary endpoint is safety and pharmacokinetics, with secondary endpoints evaluating markers of poly(ADP-ribose) polymerase (PARP, NAD^+ ADP-ribosyltransferase) activation and myocyte injury. Enrollment is expected to be completed in the second or third quarter of 2005. A second INO-1001 phase II trial for this indication is expected to commence in the third or fourth quarter of 2005. This study will be a placebo-controlled, ran-

domized, double-blind trial in the same population of patients, those undergoing emergent angioplasty after an acute myocardial infarction. This trial will evaluate myocardial infarct size as well as safety in over 300 patients. INO-1001 is a potent inhibitor of the nuclear cell death enzyme PARP and already has fast track designation for the prevention of complications in patients undergoing thoracoabdominal aortic aneurysm (TAAA) repair surgery, for which a pivotal trial is expected to commence in the second half of this year. Inotek is studying INO-1001 in a variety of other scheduled procedures that have a high incidence of complications caused by ischemia and reperfusion injury, including high-risk cardiopulmonary bypass surgery and prostatectomy, and it is also under study for the treatment of certain late-stage cancers refractory to existing chemotherapy; phase Ib/IIa trials have commenced in glioblastoma multiforme and phase Ib/IIa trials in stage IV melanoma patients who have developed resistance to temozolomide are anticipated to begin this quarter (1-6).

1. *Fast track designation for INO-1001.* DailyDrugNews.com (Daily Essentials) May 27, 2004.

2. *Fast track status for INO-1001 for patients with STEMI.* DailyDrugNews.com (Daily Essentials) July 2, 2004.

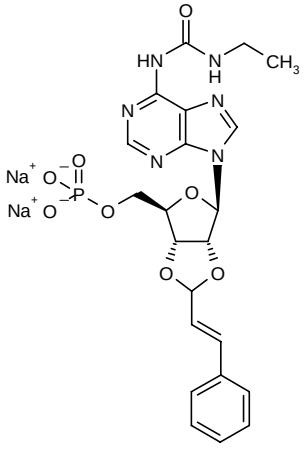
3. *Enrollment open in new phase II study of INO-1001.* DailyDrugNews.com (Daily Essentials) Dec 23, 2004.

4. *Orphan drug designation for INO-1001.* DailyDrugNews.com (Daily Essentials) Feb 17, 2005.

5. *SPA agreement for pivotal study of INO-1001.* DailyDrugNews.com (Daily Essentials) March 10, 2005.

6. *Enrollment open in phase Ib/IIa study of INO-1001 for glioblastoma multiforme.* DailyDrugNews.com (Daily Essentials) March 11, 2005.

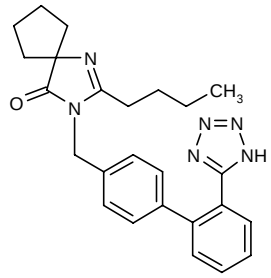
INS-50589



Inspire has initiated a phase I study for INS-50589 Cardiovascular. The double-blind, placebo-controlled study is designed to assess the safety and tolerability of an intravenous infusion of INS-50589 Cardiovascular in a minimum of 28 healthy volunteers. The study will also assess the pharmacokinetics and biological activity of the compound using various platelet function tests. Results are expected in mid-2005. INS-50589 Cardiovascular is a $P2Y_{12}$ receptor antagonist that blocks adenosine diphosphate, a clotting factor that activates platelet aggregation. INS-50589 Cardiovascular is highly selective for this receptor and has a rapid onset and offset of action, allowing for the ability to quickly modulate platelet function. The use of INS-50589 Cardiovascular may reduce post-surgical complications associated with cardiopulmonary bypass procedures. Unlike currently marketed products, INS-50589 Cardiovascular has been shown in preclinical studies to be a potent platelet aggregation inhibitor that is also fully and rapidly reversible. This unique profile could provide for platelet aggregation inhibition during bypass procedures and for restoration of normal platelet function following the procedure when intravenous administration of the drug is stopped (1).

1. INS-50589 Cardiovascular tested in new phase I study. DailyDrugNews.com (Daily Essentials) Dec 21, 2004

Irbesartan



Irbesartan (Aprovel®, Avapro®, Karvea®), an angiotensin AT_1 receptor antagonist, was initially launched in 1997 for the treatment of hypertension, followed by its introduction for the treatment of early- and late-stage renal disease in patients with high blood pressure and type 2 diabetes mellitus. Currently, irbesartan is in phase III development for the once-daily treatment of congestive heart failure (CHF). Discovered by Sanofi-Aventis, irbesartan has been codeveloped with Bristol-Myers Squibb since 1993 and is copromoted and marketed by the two companies in the U.S. Licensee Shionogi is awaiting approval in Japan for the treatment of hypertension.

Original monograph – Drugs Fut 1997, 22(5): 481.

Additional References

De Rosa, M.L., Viola, O., Polimeno, M., Chiariello, M. *Synergistic efficacy of irbesartan and benazepril on exercise performance and oxygen consumption at peak exercise in hypertensives with congestive heart failure.* Am J Hypertens 2004, 17(5, Part 2): Abst P-357.

ISIS-301012

ISIS-301012, a second-generation antisense inhibitor of apolipoprotein B-100 (apoB-100) for the treatment of high cholesterol (oral and subcutaneous forms) and one of Isis Pharmaceuticals' central programs, is currently completing phase I studies. Last year, preliminary data from a phase I trial showed the compound produced dose-dependent, rapid and prolonged reductions of its target, as well as LDL, VLDL and total cholesterol levels, in volunteers with borderline elevated cholesterol. An oral formulation of ISIS-301012 has also been shown to reduce cholesterol in animals and the company recently initiated clinical trials with this formulation (1-4).

1. *ISIS-301012 enters phase I study for treatment of cardiovascular disease*. DailyDrugNews.com (Daily Essentials) Jan 7, 2004.

2. *Isis Pharmaceuticals reports 2003 year-end R&D highlights*. Isis Pharmaceuticals Press Release 2004, Feb 10.

3. *Isis restructures*. DailyDrugNews.com (Daily Essentials) Jan 13, 2005.

4. *Isis Pharmaceuticals initiates phase 1 clinical trial of oral ISIS 301012 for cardiovascular disease.* Isis Pharmaceuticals Press Release 2005, March 15.

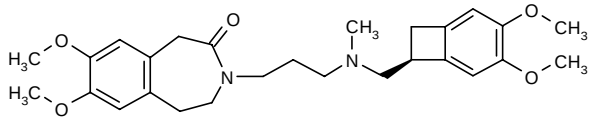
Isosorbide Mononitrate/ L-Arginine

Angiogenix is developing an oral fixed-dose combination of sustained-release isosorbide mononitrate and sustained-release L-arginine (Acclaim™) for the prevention of nitrate tolerance in chronic stable angina patients.

A total of 204 patients with chronic stable angina participated in a multicenter, double-blind, randomized, placebo-controlled phase II clinical trial that assessed the efficacy and safety of the combination in the prevention of nitrate tolerance. Compared to nitrate therapy alone, Acclaim™ had no significant effects on the treadmill walking time of the patients before moderate angina, but tended to increase the time to first onset of angina and the time to S-T segment depression. The company has announced that it intends to use these data to ensure that patients participating in future studies with Acclaim™ reach and maintain plasma L-arginine levels that are high enough to prevent nitrate tolerance (1).

1. *Phase II data on the benefits of Acclaim in chronic stable angina.* DailyDrugNews.com (Daily Essentials) Feb 2, 2005.

Ivabradine Hydrochloride



.HCl

Ivabradine hydrochloride (Procoralan®; Servier) is the first specific cardiac pacemaker I_f current inhibitor that selectively reduces heart rate by acting exclusively on the sinoatrial node. It is currently awaiting registration for the treatment of stable angina pectoris.

Original monograph – Drugs Fut 2003, 28(7): 652.

Additional References

Jondeau, G., Korewicki, J., Vasiliauskas, D. *Effect of ivabradine in patients with left ventricular systolic dysfunction and coronary artery disease.* Eur Heart J 2004, 25(Suppl.): Abst 2637.

Lopez-Bescos, L. et al. *Long-term safety and antianginal efficacy of the If current inhibitor ivabradine in patients with chronic stable angina. A one-year randomised, double-blind, multicentre trial.* Eur Heart J 2004, 25(Suppl.): Abst 876.

Ruzyllo, W. et al. *Antianginal and antiischaemic effects of the If current inhibitor ivabradine compared to amlodipine as monotherapies in patients with chronic stable angina. Randomised, controlled, double-blind trial*. Eur Heart J 2004, 25(Suppl.): Abst 878.

K-134/K-604

Kowa is conducting early clinical studies with the antiplatelet agent K-134 (E.U.) for the oral treatment of arteriosclerosis obliterans, as well as with the macrophage-selective ACAT inhibitor K-604 (U.S.) for the treatment of atherosclerosis.

KAI-9803

KAI Pharmaceuticals has initiated a phase I/II trial of KAI-9803, a protein kinase C (PKC) inhibitor designed to reduce reperfusion injury as an adjunct to current treatments of acute myocardial infarction. The DELTA-MI (Direct Inhibition of Delta Protein Kinase C Enzyme to Limit Total Infarct Size in Acute Myocardial Infarction) study will assess the safety and efficacy of KAI-9803 for injection in patients undergoing urgent angioplasty (with or without stent placement) for acute myocardial infarction. The randomized, double-blind, placebo-controlled study will evaluate increasing doses of KAI-9803. Outcome measures will include clinical endpoints such as heart failure and death, as well as surrogate measures of

infarct size, myocardial function and myocardial perfusion. Conducted in collaboration with the Duke Clinical Research Institute, the trial will enroll approximately 150 patients at 30 sites. KAI-9803, which has been granted fast track status for the study indication, is the first drug candidate designed to inhibit the specific PKC enzyme responsible for reperfusion injury. It targets the PKC isozyme δ-PKC, which has been found to activate a cascade of events causing cell injury and death during reperfusion injury. Selective inhibition of the δ-PKC isozyme by KAI-9803 prevents damage to the mitochondria and inhibits both necrosis and apoptosis during reperfusion injury. In preclinical studies, treatment with KAI-9803 resulted in a 70% reduction in infarct size, an improvement in heart function, restoration of intracellular energy generation, and protection of myocardial and endothelial cells. Specificity issues associated with modulating PKC isozymes were solved by a research team at Stanford, which has allowed the targeting of a specific isozyme without affecting biological processes regulated by other PKC isozymes (1).

1. *Phase I/II study for KAI-9803 in reperfusion injury.* DailyDrugNews.com (Daily Essentials) Oct 4, 2004.

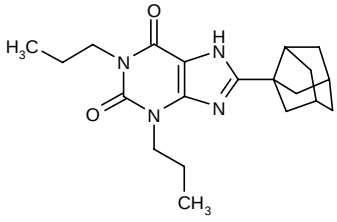
KFA-1982

The oral anticoagulant and factor Xa inhibitor KFA-1982 is being evaluated by Kissei in European phase I studies as a potential new drug for DVT.

KS-01-018

KS-01-018 is in early clinical development by Kos Pharmaceuticals for the treatment of PAD.

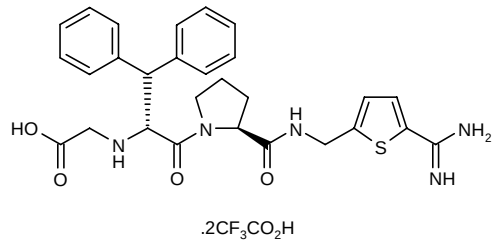
KW-3902



The adenosine A_1 receptor antagonist KW-3902 was developed at Kyowa Hakko and is currently in phase II development by NovaCardia for the i.v. treatment of CHF in patients undergoing diuresis. In 2003, Kyowa Hakko entered into an agreement granting NovaCardia an exclusive license to develop and market the compound outside Asia and Japan.

Original monograph – Drugs Fut 1992, 17(10): 876.

LB-30870



$.2CF_3CO_2H$

LB-30870 is a novel, low-molecular-weight, orally active direct thrombin inhibitor which LG Life Sciences is testing in early clinical trials as an anticoagulant for the prophylaxis and treatment of thrombotic disorders.

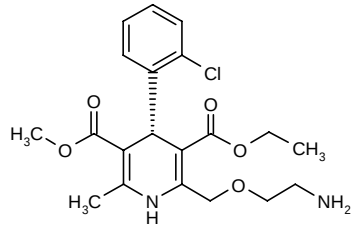
Lercanidipine Hydrochloride/ Enalapril Maleate

Recordati has submitted a new drug application for a fixed combination of lercanidipine hydrochloride, a calcium channel blocker, and enalapril maleate, an ACE inhibitor, known as Zanipress®, with the German medicines agency. Assuming approval is obtained, Germany will act as reference member state in the mutual recognition approval process for the rest of Europe. Recordati developed the new product in answer to the growing importance of fixed combination medications in the treatment of hypertension and as part of the life cycle management for lercanidipine (1, 2).

1. *Recordati seeks German approval of fixed combination product for hypertension.* DailyDrugNews.com (Daily Essentials) Dec 13, 2004.

2. *Recordati acquires Merckle's branded pharmaceutical business in Germany.* DailyDrugNews.com (Daily Essentials) Jan 20, 2005.

Levamlodipine



Since 2001, Sepracor has conducted phase I and phase II trials with the calcium channel blocker levamlodipine ([*S*]-amlodipine) as a potential treatment for hypertension and the company plans to expand its program to include the development of the drug in combina-

tion with other mechanistic approaches for the treatment of hypertension. Preclinical studies have suggested that levamlodipine may provide potential improvements over existing therapies (1-3).

1. *Progress and plans for Sepracor pipeline.* DailyDrugNews.com (Daily Essentials) Jan 14, 2004.

2. *Sepracor reports 2003 year-end R&D highlights.* Sepracor Press Release 2004, Jan 22.

3. *Sepracor reports Q1 R&D highlights.* Sepracor Press Release 2004, April 27.

Liprostin™

Endovasc has concluded its phase II Liprostin™ trial for patients with peripheral arterial occlusive disease (PAOD). The trial, which aimed to determine if Liprostin™ could postpone or eliminate the need for surgical intervention, had efficacy endpoints of maximum walking distance (MWD) and pain-free maximum walking distance (PFMWD) compared to baseline. Although it was designed to enroll up to 120 patients, enrollment was closed early due to initial response from investigators regarding patient improvement. Results from the 73 patients completing the trial showed significant improvements in both the MWD and PFMWD. The 3-month trial consisted of 10 patient visits over 12 weeks. Baseline was determined during visits 1 and 2. The MWD increased by more than 100% and the average PFMWD increased by almost 200%. Patient response to the trial PADWIQ standard questionnaire revealed significant day-to-day improvements in quality of life, as indicated by an increase in their overall walking distance and walking speed. Patients continued to improve during the third month of the trial, even though they were no longer receiving the drug. An extended trial may be necessary to evaluate the sustained improvement of these patients. Endovasc expects the trend to continue in further patient data. Liprostin™ is a liposome-encapsulated form of prostaglandin E_1 (PGE_1), a potent vasodilator and platelet inhibitor, as well as an antiinflammatory and antithrombotic agent. This encapsulated formulation has been shown to improve the therapeutic index of PGE_1, positively impacting many areas of treatment such as heart attack, occlusive disease, ischemic ulcers, critical limb salvage, claudication and arthritis. Endovasc is currently designing a phase III trial for initiation this year and recently transferred its intellectual property related to Liprostin™ to the newly created Liprostin subsidiary (1-9).

1. *Moscow sites open in phase II Liprostin trial.* DailyDrugNews.com (Daily Essentials) Jan 26, 2004.

2. *Enrollment completed in phase II trial of Liprostin for PVD.* DailyDrugNews.com (Daily Essentials) April 5, 2004.

3. *Preliminary results from phase II Liprostin trial in peripheral vascular disease.* DailyDrugNews.com (Daily Essentials) June 14, 2004.

4. *Conclusion of phase II study of Liprostin for PVD.* DailyDrugNews.com (Daily Essentials) July 22, 2004.

5. *Endovasc updates pipeline progress.* DailyDrugNews.com (Daily Essentials) July 30, 2004.

6. *Liprostin successfully completes phase II study in peripheral vascular disease.* DailyDrugNews.com (Daily Essentials) Aug 24, 2004.

7. *Positive new phase II results for Liprostin.* DailyDrugNews.com (Daily Essentials) Sept 1, 2004.

8. *Endovasc, Incorporated transfers promising drug technology into subsidiaries.* Endovasc Press Release 2004, Oct 8.

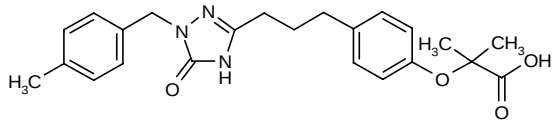
9. *Endovasc plans phase III trial for Liprostin in 2005.* DailyDrugNews.com (Daily Essentials) Dec 10, 2004.

LJP-1082

La Jolla Pharmaceutical's toleragen LJP-1082 targets β_2-glycoprotein I, a significant antigen in the antiphospholipid syndrome, also known as Hughes syndrome or antibody-mediated thrombosis. The agent was designed to crosslink surface immunoglobulin to inactivate pathological B-cells. Single 20-mg doses of the agent were well tolerated in a phase I study and higher doses were associated with reduced autoantibody levels. Promising results were obtained in a phase I/II trial in patients with a history of antibody-mediated thrombosis, but further study is required to elucidate the means by which optimal tolerance can be obtained, perhaps with toleragens, without complete negation of autoantibody production (1).

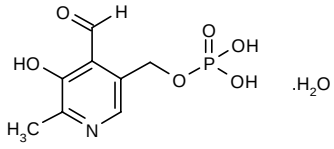
1. Merrill, J.T. *LJP 1082: A toleragen for Hughes syndrome.* Lupus 2004, 13(5): 335.

LY-674



Lilly and Ligand are collaborating on the development of LY-674 (LY-518674), a highly potent and selective peroxisome proliferator-activated receptor PPARα agonist currently in phase I clinical testing for preventing atherosclerosis.

MC-1/MC-4232



MC-1

MC-1 is a purinergic receptor antagonist in phase II/III clinical trials at Medicure as a cardioprotectant in patients undergoing CABG surgery. Phase II trials have been completed in patients undergoing angioplasty. MC-1 is also in early clinical development for stroke. As a purinergic antagonist, MC-1 inhibits the receptor-mediated activity of extracellular adenosine triphosphate (ATP). ATP, released in response to stress conditions, acts on purinergic receptors to cause an increase in intracellular calcium in heart cells and smooth muscle cells. By reducing this calcium influx, MC-1 may provide protection from cardiovascular disorders, such as hypertension, ischemic damage and ischemia-reperfusion injury. MC-4232 is a combination of MC-1 and an ACE inhibitor in phase II clinical trials for the treatment of hypertension in diabetic patients. In addition to cardioprotection, MC-4232 has the potential to lower blood pressure and reduce glycated hemoglobin (HbA1c), the primary measure of blood glucose control.

Enrollment is under way in Medicure's phase II/III MEND-CABG clinical trial evaluating the cardioprotective and neuroprotective effects of MC-1 in patients undergoing high-risk CABG surgery. The first patients were enrolled at the Montreal Heart Institute (MHI), which, along with Duke Clinical Research Institute (DCRI), will manage the trial. The phase II component of the phase II/III trial will enroll up to 900 patients at some 40 investigational sites in Canada and the U.S. Enrollment is expected to take up to 12 months to complete. The double-blind, placebo-controlled study is designed to evaluate the potential of MC-1 to reduce ischemic damage resulting from CABG procedures. The primary efficacy parameter is the reduction in the combined incidence of cardiovascular and cerebrovascular death, nonfatal myocardial infarction and nonfatal cerebral infarction, up to and including 30 days following CABG surgery. To this end, the incidence in each of two dose groups (250 and 750 mg/day) will be compared to the incidence in the placebo group. Secondary efficacy endpoints include evaluating the effect of MC-1 at 90 days following surgery on the same composite of events, measures of cardiac tissue damage as determined by CK-MB and neurological function. Safety will also be assessed (1, 2).

Promising results were also reported from a phase II clinical trial of MC-1 in 15 diabetic hypertensive patients. After 14 weeks of treatment with MC-1, the patients showed an average 4.9% reduction in the serum levels of HbA1c and the treatment was well tolerated. These findings led the company to evaluate the efficacy and safety of MC-4232 in the management of diabetic patients with hypertension (see below) (3).

Enrollment was subsequently completed in a new phase II trial to evaluate the effects of MC-4232 in the treatment of diabetic patients with hypertension. The MATCHED (MC-1 and ACE Therapeutic Combination for Hypertensive Diabetics) study, part of the expanded phase II/III development program for MC-4232, will evaluate MC-1 alone and in combination with an ACE inhibitor. The randomized, double-blind, placebo-controlled, crossover trial enrolled 120 patients with co-existing diabetes and hypertension. The crossover design will provide information on MC-1 alone and in combination with an ACE inhibitor for 8 weeks in each treatment regimen, for a total treatment period of 16 weeks per patient. MC-1 at doses of 100, 300 or 1000 mg or placebo will be given alone and in combination with an ACE inhibitor at a dose of 20 mg. Effects on blood pressure and metabolic function are among the parameters to be assessed, together with safety and tolerability. The primary blood pressure data will be provided by ambulatory blood pressure measurements, with standard blood pressure readings also being taken. Metabolic function measurements will include, among others, fasting serum glucose, HbA1c and triglycerides. The study, expected to be completed in the spring of 2005, will be followed by more extensive phase III evaluation in coexistent hypertension and diabetes mellitus (4, 5).

An intravenous formulation of Medicure's MC-1 has been developed and successfully completed a phase I clinical trial to assess its safety and tolerability in healthy volunteers. This new product presentation, which complements the existing oral dosage form, broadens MC-1's use as a cardioprotective agent in the management of cardiovascular emergencies. MC-1 has demonstrated cardioprotective properties when given orally to patients undergoing high-risk angioplasty. Medicure's proprietary i.v. formulation will now permit cardiovascular patients to receive MC-1 where oral administration is not viable, or where the rapid attainment of target drug levels in the blood is desirable. Hospitalized patients treated for stroke or ACS will benefit most from this product line extension (6).

1. *Medicure looks back at milestone developments.* DailyDrugNews.com (Daily Essentials) Jan 15, 2004.

2. *Enrollment commences in MEND-CABG trial of MC-1.* DailyDrugNews.com (Daily Essentials) April 7, 2004.

3. *Preliminary results from hypertension trial support expansion of MC-4232 program.* Medicure Press Release 2004, April 7.

4. *Enrollment begins in phase II trial of MC-4232.* DailyDrugNews.com (Daily Essentials) Aug 17, 2004.

5. *Full enrollment reached in phase II MATCHED study of MC-4232.* DailyDrugNews.com (Daily Essentials) Feb 3, 2005.

6. *New intravenous formulation of MC-1 gives positive phase I results.* DailyDrugNews.com (Daily Essentials) Sept 23, 2004.

MCC-977

Mitsubishi Pharma's MCC-977 is a highly selective thrombin inhibitor currently undergoing phase II trials in Europe for the treatment of DVT.

Microplasmin

ThromboGenics has prepared a stabilized recombinant form of microplasmin, a truncated form of the natural human protein plasmin. Phase IIa trials are under way in The Netherlands and Germany for intravitreal microplasmin in patients with vitreoretinal disease. The company holds FDA orphan drug designation for this indication. Also, phase I trials have been successfully completed, with phase IIa trials in preparation, for systemic microplasmin as a thrombolytic agent for stroke and peripheral arterial occlusive disease (PAOD).

MLN-2222

Millennium advanced MLN-2222 (formerly CAB-2), being developed in collaboration with Xoma, into phase I trials for CABG surgery in 2003. MLN-2222 is a novel, proprietary recombinant protein that blocks both C3 and C5 convertases, essential components of the complement pathway which is believed to contribute to harmful inflammatory responses in heart bypass surgery. It is being developed to reduce the incidence of postoperative death and heart attacks in patients undergoing cardiac surgeries. The companies subsequently restructured their agreement related to the collaboration for the development of MLN-2222. The new agreement supersedes the previous development and investment agreements, established in November 2001. Under the revised agreement, Xoma will be responsible for development work and expenses related to MLN-2222 through completion of the ongoing phase I trial. Millennium will assume responsibility for all subsequent development work and expenses for MLN-2222 at initiation of phase II testing. Under terms of the original agreement, Xoma was responsible for development work and expenses through phase II testing. Xoma will continue to provide quantities of bulk drug substance requested by Millennium at the expense of Millennium for phase II trials. Xoma will be entitled to receive an undisclosed royalty on future net sales of MLN-2222, as well as payments related to the achievement of clinical and regulatory milestones. Under the original agreement, Xoma had the option of either entering into a cost- and profit-sharing arrangement through phase III trials and commercialization or a milestone and royalty arrangement. The investment agreement between Millennium and Xoma is terminated and there will be no further issuance of Xoma common shares to Millennium (1, 2).

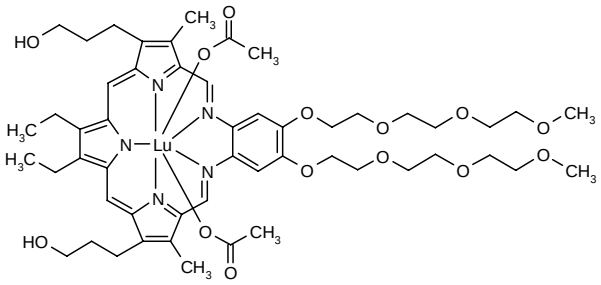
1. *Millenium Pharmaceuticals reports 2003 year-end R&D highlights.* Millennium Pharmaceuticals Press Release 2004, Jan 27.

2. *Millennium and Xoma announce restructuring of collaboration agreement for the development of MLN-2222.* Millennium Pharmaceuticals Press Release 2004, Oct 12.

Monteplase

Eisai submitted the thrombolytic agent monteplase (Cleactor®), a modified recombinant tissue plasminogen activator (t-PA), for approval in Japan last year for the additional indication of acute pulmonary embolism. Phase II trials are also in progress in Japan evaluating its use in cerebral embolism. Monteplase was first introduced in 1998 for use in the treatment of acute myocardial infarction.

Motexafin Lutetium



Motexafin lutetium (Antrin®) phototherapy, developed by Pharmacyclics, has completed phase I testing in CAD, with current and future work focusing on the ability of light-activated motexafin lutetium to reduce or eliminate vulnerable plaque. Phase I and II trials have also been completed in PAD. Preclinical studies in animal models of atherosclerosis have demonstrated the selective uptake and accumulation of the texaphyrin in vascular plaque. Motexafin lutetium targets macrophages that accumulate in vulnerable plaque and, following activation by far-red light, causes the macrophages to undergo apoptosis, thereby stabilizing vulnerable plaque or reducing inflammation. Normal regions of blood vessels appear not to be affected and the texaphyrin is readily cleared from the rest of the body.

The results of a multicenter, open-label, dose-escalating phase I clinical trial that evaluated the effects of motexafin lutetium phototherapy in CAD were presented last year. Seventy-nine patients scheduled to undergo balloon angioplasty and stent insertion were given intravenous doses of motexafin 18-24 h before the procedure. The compound was photoactivated using an optical fiber inserted into the coronary artery during balloon angioplasty. Intravascular ultrasound (IVUS) imaging studies conducted at the time of surgery and 6 months later

revealed that motexafin phototherapy prevented plaque build-up and induced no adverse effects on the vessel wall. The average atherosclerotic plaque area of the patients showed no changes at 6 months after receiving a dose of 2-4 mg/kg of motexafin combined with 100 J of light. Plaque area increased in patients who received motexafin doses below 2-4 mg/kg or greater light doses (200-600 J). Based on these favorable results, the company announced that it intended to continue evaluating the use of motexafin phototherapy in the diagnosis and treatment of vulnerable plaque (1, 2).

1. *Motexafin lutetium prevents atherosclerotic plaque increase after balloon angioplasty.* DailyDrugNews.com (Daily Essentials) Oct 8, 2004.

2. *Pharmacyclics reports Q4 R&D highlights.* Pharmacyclics, Inc. Press Release 2004, Aug 19.

MRX-815

The first patient has been treated in a phase I/II trial evaluating the safety and efficacy of SonoLysis™ for the treatment of peripheral arterial obstructive disease (PAOD). SonoLysis™, which combines external ultrasound and ImaRx Therapeutics' proprietary nanobubbles (MRX-815), is designed to clear blood clots quickly and without the use of invasive surgery or potentially dangerous lytic drugs. In this 12-patient, multicenter trial, 6 patients will receive a 60-min treatment with SonoLysis™, while the remaining 6 will receive SonoLysis™ in conjunction with a small bolus of t-PA.This study followed a successful proof-of-concept trial in clotted dialysis grafts. SonoLysis™ trials are also ongoing in acute ischemic stroke (phase II) and deep venous thrombosis (DVT) (phase I/II) (1-3).

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

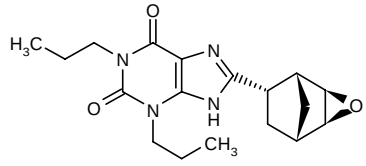
2. *ImaRx studies SonoLysis in phase II stroke study*. DailyDrugNews.com (Daily Essentials) April 8, 2005.

3. *ImaRx announces data from SonoLysis proof of concept trial*. ImaRx Therapeutics Press Release 2005, April 1.

MyoCell™

A tissue regeneration therapy product from BioHeart, MyoCell™ is currently undergoing phase I/II trials in Europe and phase I evaluation in the U.S. for the treatment of acute myocardial infarction and CHF. MyoCell™ is designed to work through the transplantation of autologous skeletal myoblasts.

Naxifylline



Originally developed at the University of Florida, naxifylline (CVT-124, BG-7919, Adentri™) is an adenosine A_1 receptor antagonist undergoing phase II evaluation at Biogen Idec for the treatment of CHF. Pursuant to a 1997 agreement, Biogen received exclusive worldwide rights from CV Therapeutics for the development, manufacture and commercialization of adenosine A_1 receptor antagonists for the treatment of acute and chronic CHF. In November of 2003, the former Biogen announced positive results of a phase II study of oral naxifylline in patients with stable heart failure (1).

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

NBI-69734

Neurocrine Biosciences has initiated a phase I trial to evaluate the safety, pharmacokinetics, and pharmacodynamics of NBI-69734 (urocortin-II, urocortin-2, UCN-2), a recently discovered endogenous peptide ligand of the corticotropin-releasing factor CRF2 receptor present in the cardiovascular system, in healthy volunteers. A pilot study has been completed to refine dosing. This is being followed by a single-blind, placebo-controlled, dose-escalation study in healthy subjects. The phase I study will transition into a phase II dose-escalating trial, which will be conducted in patients with mild to moderate CHF in early 2005. NBI-69734 has a novel mechanism of action. Based on preclinical efficacy and safety data, together with the known role of urocortin-II in human physiology, it is expected to have positive hemodynamic effects on cardiac output and blood pressure. Neurocrine licensed the the 38-amino-acid peptide from the Clayton Foundation for Research. It has demonstrated potent inotropic, vasodilating, cardioprotective and diuretic effects, and phase II trials in CHF are expected to commence in mid-2005 (1-3).

1. *Neuroscrine Biosciences reports 2003 year-end R&D highlights.* Neurocrine Biosciences Press Release 2004, Jan 29.

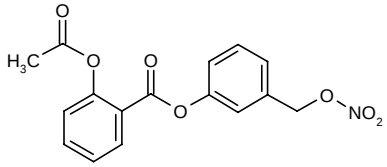
2. *Neurocrine Biosciences reports Q1 R&D highlights.* Neurocrine Biosciences Press Release 2004, May 3.

3. *Urocortin 2 evaluated in new phase I study.* DailyDrugNews.com (Daily Essentials) Oct 27, 2004.

Table X: Clinical studies of NCX-4016 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Single-blind	NCX-4016, 800 mg p.o. b.i.d. x 21 d (n=12) Aspirin, 325 mg p.o. o.d. x 21 d (n=12) NCX-4016, 800 mg p.o. b.i.d. + Aspirin, 325 mg p.o. o.d. x 21 d (n=12) Placebo (n=12)	48	NCX-4016 was as effective as aspirin in inhibiting cyclooxygenase activity, but caused less gastric damage and prevented monocyte activation	5

NCX-4016



NicOx's NCX-4016, a novel NO-donating derivative of aspirin, is being evaluated for its potential in endothelial dysfunction-related disorders, including peripheral arterial obstructive disease (PAOD) and for reducing the risk of cardiovascular complications in type 2 diabetes. Phase IIa trials have been performed in patients with both disorders. The primary efficacy endpoint was reached in a phase IIa study in patients with PAOD. The Italian study involved 44 PAOD patients diagnosed with Fontaine stage II, with limitations in walking capacity due to leg pain. For 1 month patients received either NCX-4016 (800 mg b.i.d.) or aspirin (100 mg once daily). At the end of the study, NCX-4016 showed statistical significance on the primary endpoint of reversing endothelial dysfunction induced by physical exercise, as measured by flow-mediated vasodilatation, whereas aspirin had no effect. Walking capacity, a secondary parameter defined by initial claudication distance (ICD) was evaluated by a standard treadmill exercise test and showed a clinically meaningful increase with NCX-4016 compared to aspirin. The safety and overall tolerability of NCX-4016 were excellent. The beneficial effects of NCX-4016 on vasculature are believed to be due to its ability to donate NO. PAOD will be the first indication to be pursued for marketing, with a regulatory submission anticipated in 2007. Preclinical and phase I data in more than 300 subjects showed that NCX-4016 has a broad range of vascular antiinflammatory and antithrombotic activity, acting on multiple targets in the ischemia-reperfusion pathway. An expanded phase II program will explore the drug's potential (1-3).

NicOx has completed full recruitment in a large phase II trial of NCX-4016 for the treatment of PAOD. A total of 34 European sites enrolled 450 patients with symptomatic PAOD and intermittent claudication (Leriche-Fontaine stage II). The trial was designed to evaluate the effects of NCX-4016 on clinical parameters in PAOD, with particular regard to walking distance. The primary endpoint is the change in maximum treadmill walking distance after 6 months. The study is expected to be completed in the second half of 2005 and results will be available following analysis of the data in the last quarter of 2005. This study follows the successful results of the first phase II pilot study in PAOD completed in 2004 (see above) (4).

The antiinflammatory activity and gastric tolerability of NCX-4016 were compared to aspirin in a study in which 48 healthy volunteers were given NCX-4016 800 mg b.i.d., NCX-4016 800 mg b.i.d. plus aspirin 325 mg, aspirin 325 mg or placebo for 21 days. Both NCX-4016 and aspirin inhibited platelet aggregation, reduced serum concentrations of thromboxane B_2 (TxB_2) and reduced urinary excretion of 11-dehydro-TxB_2. NCX-4016, however, also downregulated tissue factor, IL-6 and MCP-1 in *ex vivo* experiments and was not associated with gastric damage (5) (Table X).

1. *NCX-4016 reaches primary efficacy endpoint in phase IIa PAOD study.* DailyDrugNews.com (Daily Essentials) Jan 12, 2004.

2. *NicOx reports Q2 R&D highlights.* NicOx Press Release 2004, July 28.

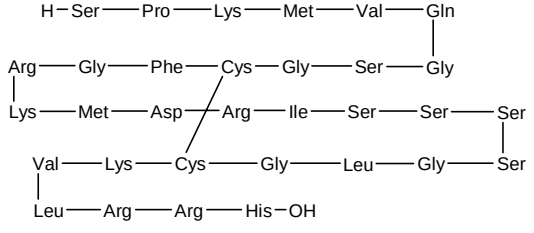
3. *NCX-4016 reported to decrease platelet activation in patients with type 2 diabetes.* DailyDrugNews.com (Daily Essentials) Feb 3, 2005.

4. *Enrollment completed in phase II PAOD trial of NCX-4016.* DailyDrugNews.com (Daily Essentials) Jan 24, 2005.

5. Fiorucci, S., Mencarelli, A., Meneguzzi, A., Lechi, A., Renga, B., Del Soldato, P., Morelli, A., Minuz, P. *Co-administration of nitric oxide-aspirin (NCX-4016) and aspirin prevents platelet and monocyte activation and protects against gastric damage induced by aspirin in humans.* J Am Coll Cardiol 2004, 44(3): 635.

Original monograph – Drugs Fut 1997, 22(11): 1231.

Nesiritide



Nesiritide is a recombinant form of B-type natriuretic peptide (BNP), a naturally occurring homrone secreted by

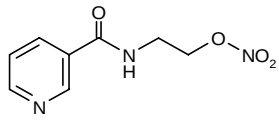
the heart in response to heart failure, launched in 2001 in the U.S. by Scios as Natrecor® for the intravenous treatment of CHF in acutely decompensated patients who have dyspnea at rest or with minimal activity. At present, the drug is in phase III trials in Europe by licensee GlaxoSmithKline (Noratak) for the treatment of acute heart failure. Scios is also conducting phase II trials to assess the effects of nesiritide in the perioperative setting for patients undergoing CABG surgery requiring cardiopulmonary bypass (CPB).

Additional References

Martin, C.A., Pickworth, K., Sun, B.S. *Evaluation of nesiritide in postoperative coronary artery bypass patients.* Pharmacotherapy 2004, 24(10): Abst 28.

Ota, L.T., Masters, P.L., Maroun-Monaco, C.A. *Perioperative use of nesiritide in cardiac surgery patients.* Pharmacotherapy 2004, 24(10): Abst 37.

Nicorandil

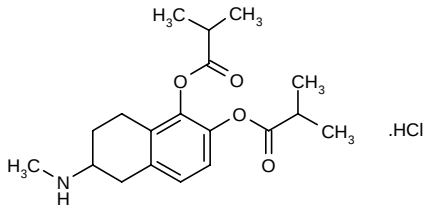


Nicorandil (SG-75, Sigmart®) is a K_{ATP} channel activator launched in 1983 in Japan for the oral treatment of angina pectoris, followed by its introduction in several other countries, including the U.K., France, Switzerland, Austria and Portugal. In June 2003, originator Chugai filed for regulatory approval of nicorandil injection in Japan for the treatment of acute heart failure and approval is pending (1).

1. *Chugai Pharmaceutical reports 2003 year-end R&D highlights.* Chugai Pharmaceutical Web Site 2004, Feb 13.

Original monograph – Drugs Fut 1979, 4(2): 134.

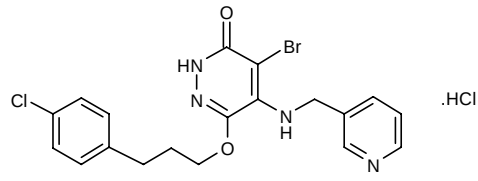
Nolomirole Hydrochloride



The dopamine D2 and α_2-adrenoceptor agonist nolomirole hydrochloride is in phase III development at Chiesi for the oral treatment of CHF.

Original monograph – Drugs Fut 2001, 26(11): 1046.

NT-702 (NM-702)



NT-702 (NM-702 in the U.S.) is an antiplatelet and vasodilating agent that potently inhibits phosphodiesterase (PDE) 3 and 4 and thromboxane A_2 (TxA_2) synthesis. Nissan Chemical and Taisho are collaborating on its development for the treatment of intermittent claudication, with phase II trials under way in Japan and the U.S.

NV-04

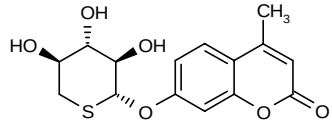
NV-04, Novogen's novel cardiovascular drug, is undergoing early clinical testing for its potential in the treatment of hypertension and atherosclerosis. The compound has demonstrated potent antioxidant, antihypertensive and antiatherosclerotic effects, and in preclinical studies it was shown to reduce cholesterol levels, LDL oxidation and vascular smooth muscle cell proliferation, as well as to improve vascular elasticity (1).

1. Novogen Annual Report 2004.

Octaparine

An indirect factor Xa and IIa inhibitor from Sanofi-Aventis, octaparine (AVE-5026) is in phase I clinical studies for the prophylaxis of DVT, DVT/PE and ACS.

Odiparcil



GlaxoSmithKline is conducting phase II clinical trials of odiparcil, an indirect thrombin inhibitor, for the prophylaxis of DVT and thrombotic complications of cardiovascular disease. Odiparcil was originally developed by Fournier and subsequently licensed to GlaxoSmithKline.

Olmesartan Medoxomil/ Azelnidipine

A combination of olmesartan medoxomil, an angiotensin AT_1 receptor antagonist, and azelnidipine, a calcium channel blocker, is in early clinical development in Japan by Sankyo for the treatment of hypertension.

Oral Heparin

Emisphere Technologies' lead product candidate is oral heparin (heparin/SNAC), an anticoagulant/antithrombotic for the prevention of DVT following surgery. The company selected a soft gelatin capsule formulation for further development last year following the evaluation of results from a clinical study comparing various oral formulations of heparin/SNAC to the previously tested liquid formulation. Following discussions with the FDA and based on the safety and proof-of-concept data from the earlier phase III PROTECT trial of the liquid formulation for thromboembolic complications following total hip replacement surgery, the company expects to initiate a pivotal phase III clinical trial of the new formulation in major surgery patients this year.

The soft gelatin capsule formulation of unfractionated heparin (UFH) was chosen after the evaluation of results from a randomized, open label, crossover, placebo-controlled, single-blind study in 15 healthy volunteers evaluating anticoagulant activity before and after the administration of four new oral dosage forms of UFH (tablets and soft gelatin capsules), as well as the company's liquid formulation and SNAC, the company's proprietary delivery agent alone, as a control arm. Following each dose, subjects were evaluated for anticoagulant activity, by measurement of anti-factor Xa and anti-factor IIa activity and activated partial thromboplastin time (aPTT). Three of the four new formulations delivered heparin as well or better than the liquid formulation. Subjects treated with SNAC alone showed no change from baseline in anticoagulant activity. Both soft gelatin capsule formulations contained less UFH and SNAC per dose than the previously tested liquid formulation, yet consistently demonstrated significant improvements over the liquid dose in delivering UFH (1-3).

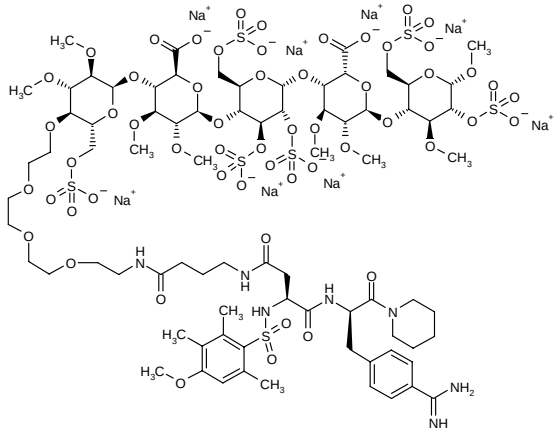
1. *Emisphere initiates new trial to select oral form of unfractionated heparin*. DailyDrugNews.com (Daily Essentials) June 18, 2004.

2. *Emisphere selects formulation of oral heparin*. DailyDrugNews.com (Daily Essentials) Aug 9, 2004.

3. *Emisphere Technologies reports Q1 R&D highlights*. Emisphere Technologies Press Release 2004, May 6.

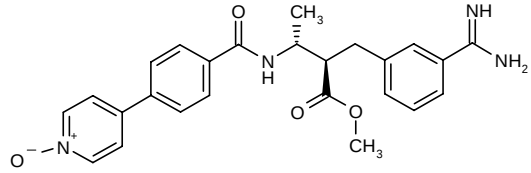
Original monograph – Drugs Fut 1997, 22: 885.

Org-42675



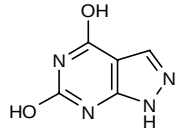
A dual inhibitor of factor Xa and factor IIa, Organon's Org-42675 is in phase II clinical testing as an antithrombotic.

Otamixaban



Phase II trials are under way at Sanofi-Aventis for otamixaban (XRP-0673), a direct factor Xa inhibitor with potential for the treatment of ACS (unstable angina pectoris).

Oxypurinol



Cardiome Pharma's oxypurinol is a xanthine oxidase inhibitor that is the active metabolite of allopurinol. By inhibiting the formation of uric acid, oxypurinol lowers uric acid levels in the blood and urine. Oxypurinol also sensitizes cardiac muscle cells to intracellular calcium, leading to increased cardiac oxygen use efficiency, which is expected to improve the clinical outcomes for CHF patients. Oxypurinol is currently being tested in a phase II clinical study for the treatment of CHF. The OPT-CHF trial enrolled 405 patients with moderate to severe symptomatic CHF to assess the safety and efficacy of orally administered oxypurinol (600 mg/day) as add-on treatment. This study is being conducted in 33 centers in U.S., with another 17 centers to be added in the next few months. The objective of this study is to define the efficacy of oxypurinol using surrogate measures of clinical efficacy, as well as clinical outcomes. The primary endpoint

is a composite that assigns all patients to one of three categories: improved, unchanged or worsened. Improvement consists of improvement in NYHA class or improvement in patient global heart failure assessment; worsening includes death, rehospitalization or emergency clinic visit, requirement for acute change in medication, and other factors. The company's independent DSMB has recommended that the OPT-CHF trial should continue as planned. The recommendation was based on the second of three planned safety analyses of data from patients who have completed the 24-week trial and a review of safety data from all patients currently enrolled. Results from this trial are anticipated for the third quarter of 2005. The open-label EXOTIC-EF (Evaluation of Xanthine Oxidase Inhibition to Improve Left Ventricular Function) trial enrolled 20 patients with CHF who were administered a single dose of 400 mg i.v. The objective of this study was to evaluate the effect of intravenous application of oxypurinol on left ventricular cardiac function in patients with CHD and a moderate- to high-grade reduction in left ventricular function. The results showed a 19.2% average relative increase in ejection fraction. A third study, the double-blind, randomized, placebo-controlled LaPlata trial, enrolled 60 patients with moderate to severe symptomatic heart failure and demonstrated a similar effect after 28 days of oral drug (600 mg/day). Oxypurinol increased the LVEF by 6.8%, decreased serum uric acid levels by 17.0 mg/l and increased cardiac output by 22.6% compared to placebo. The company submitted an NDA for oxypurinol in the treatment of allopurinol-intolerant hyperuricemia (gout) in 2003 and received an approvable letter from the FDA in June 2004. However, following discussions with the agency in September, Cardiome decided to stop pursuing this indication, at least for the time being (1-11).

1. *Cardiome submits oxypurinol NDA.* DailyDrugNews.com (Daily Essentials) Jan 5, 2004.

2. *Oxypurinol NDA accepted for review.* DailyDrugNews.com (Daily Essentials) March 16, 2004.

3. *Approvable letter for oxypurinol for allopurinol-intolerant hyperuricemia.* DailyDrugNews.com (Daily Essentials) July 1, 2004.

4. *OPT-CHF phase II study of oxypurinol recommended to continue.* DailyDrugNews.com (Daily Essentials) July 14, 2004.

5. *Cardiome Pharma reports Q1 R&D highlights.* Cardiome Pharma Press Release 2004, May 17.

6. *Cardiome congestive heart failure trial to continue.* Cardiome Pharma Press Release 2004, Dec 2.

7. *Enrollment completed in phase II congestive heart failure study of oxypurinol.* DailyDrugNews.com (Daily Essentials) Jan 4, 2005.

8. *Cardiome Pharma reports Q2 R&D highlights.* Cardiome Pharma Press Release 2004, Aug 12.

9. *Therapeutic benefits of oxypurinol in congestive heart failure.* DailyDrugNews.com (Daily Essentials) Feb 22, 2005.

10. *Cardiome reports third quarter results.* Cardiome Pharma Press Release 2004, Nov 15.

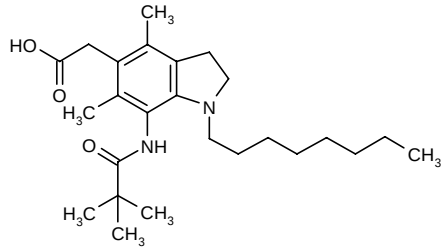
11. *Cardiome reports final oxypurinol clinical results.* Cardiome Pharma Press Release 2005, April 7.

Paclitaxel, Nanoparticles

American BioScience reported the results from the first clinical trial of systemic nanoparticle albumin-bound (nab™) paclitaxel (Coroxane™) for the treatment of in-stent restenosis at the recent Cardiovascular Revascularization Therapies Conference in Washington, D.C. The phase I SNAPIST-1 (Systemic Nanoparticle Paclitaxel for Treatment of In-Stent Restenosis) was designed to assess the safety and determine the effective dose and schedule of administration, and randomized 23 patients to doses of 10-100 mg/m^2 i.v. immediately before stenting. No significant adverse events were observed at doses below 70 mg/m^2 and a trend for efficacy by angiographic follow-up at 6 months was seen in patients receiving 30 and 70 mg/m^2. Further clinical trials assessing the effects of Coroxane™ in coronary restenosis are under way and American BioScience intends to seek a partner for global development (1). Another nanoparticle albumin-bound form of paclitaxel, Abraxane™, was launched in the U.S. earlier this year by the company's oncology division Abraxis Oncology for the treatment of breast cancer.

1. *American BioScience presents clinical trial results of the first human study of Coroxane™ for the treatment of restenosis at the Cardiovascular Revascularization Therapies (CRT) Conference.* American Pharmaceutical Partners, Inc. Press Release 2005, April 5.

Pactimibe



Pactimibe (CS-505), a dual ACAT and lipid peroxidation inhibitor originally developed by Kyoto Pharmaceutical, is currently undergoing phase II/III clinical trials in the E.U. and the U.S. by licensee Sankyo for the treatment of atherosclerosis; phase I trials are in preparation in Japan.

PAI-749

A first-in-class, orally active profibrinolytic agent, Wyeth's PAI-749 has potential for stroke prevention in patients with atrial fibrillation and may also prevent secondary cardiovascular complications of diabetes. Phase I trials are under way.

Pegmusirudin

A phase IIb clinical study is under way at Speedel with the long-acting anticoagulant pegmusirudin (SPP-200), a

recombinant protein that acts as a direct thrombin inhibitor, for reducing vascular graft occlusion in patients undergoing chronic hemodialysis for end-stage renal disease. Reducing clotting events in these patients is expected to extend the life of the grafts, as well as to reduce the frequency of heart attack and stroke. Speedel licensed the protein from Abbott, which retains an option to license it back at the end of the ongoing trial.

Pexelizumab

The FDA has confirmed its agreement with the protocols for two independent pivotal phase III trials of the investigational humanized anti-C5 monoclonal antibody fragment pexelizumab (h5G1.1-scFv), being jointly developed by Alexion and Procter & Gamble. Pexelizumab could become the first terminal complement inhibitor for patients undergoing CABG surgery and for patients undergoing PCI for acute myocardial infarction. One phase III protocol covers patients undergoing CABG surgery and the second covers a separate program in patients experiencing acute myocardial infarction (AMI) treated with primary PCI. The agreements for the protocols were reached under the FDA's Special Protocol Assessment (SPA) process. It is expected that, if successful, each trial will complete the filing package that will serve as the primary basis of review for the approval of BLAs for these indications. The first of the two pivotal trials, PRIMO-CABG-2 (Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery bypass Graft surgery), will examine the effects of pexelizumab on the composite endpoint of death or MI at 30 days after the procedure in moderate- to high-risk CABG surgery patients with or without concomitant valve surgery during cardiopulmonary bypass. Some 4,000 patients will be enrolled in the U.S. and Europe. Results of the first pivotal phase III study of pexelizumab in CABG surgery patients, PRIMO-CABG (see Table XI), showed that treatment was associated with a nonsignificant reduction in the primary endpoint, a composite of the incidence of death or myocardial infarction measured at 30 days after the procedure, in the subpopulation of patients undergoing CABG without concomitant valve surgery. In the 2,000-patient moderate- to high-risk study population from PRIMO-CABG with more than one prespecified risk factor, death/myocardial infarction at day 30 was reduced with statistical significance from 16.3% with placebo to 11.7% with pexelizumab. In the pexelizumab treatment arm, the incidence of death/myocardial infarction decreased by 49% in patients with previous CABG, by 37% in those with previous neurological events, by 35% in those with previous or recent myocardial infarction, and by 44% in those with three or more risk factors. Significant reductions were found with pexelizumab even in patients with more severe risk profiles. Among all patients, including those undergoing valve surgery, the incidence of death or myocardial infarction at 30 days was significantly reduced in the pexelizumab group (11.5% *versus* 14%). The benefit of pexelizumab was also maintained for 6 months. In the total study group, the relative reduction in the incidence of death or myocardial infarction was 17% in the pexelizumab group. The second newly approved pivotal phase III trial, APEX-AMI (Assessment of PEXelizumab in Acute Myocardial Infarction), will examine the effects of pexelizumab on death at 90 days after procedure in patients undergoing PCI for AMI. The study is expected to enroll approximately 8,500 patients in the U.S., Europe, Australia and New Zealand. It follows the phase II COMMA (COMplement inhibition in Myocardial infarction treated with Angioplasty) study, which examined the effects of pexelizumab in AMI patients treated with PCI. The primary analysis showed that treatment with a bolus of pexelizumab followed by an infusion continuing to 24 h did not significantly reduce infarct size (the primary endpoint) but was associated with a significant 70% reduction in 90-day mortality (1-4).

Data from the PRIMO-CABG trial were used to determine the benefits of pexelizumab in patients simultaneously undergoing an aortic valve (AV) procedure and CABG surgery. A total of 218 of the 3,099 patients with cardiovascular risk factors who participated in the trial underwent both AV and CABG surgery; 106 were treated with pexelizumab and 112 were given placebo. The percentage of patients who died was significantly lower with pexelizumab compared to placebo, both at 30 days (3.8% *vs.* 9.9%) and at 180 days after surgery (5.7% *vs.* 14.4%). No significant difference between groups was found for the incidence of MI during the first 30 days after surgery (5). The results from this and the following studies are illustrated in Table XI.

The plasma levels of high-sensitivity C-reactive protein (hsCRP), TNF-α and IL-6 were evaluated in 350 patients with AMI participating in the COMMA trial at baseline (*i.e.*, before study treatment and primary PCI), at the end of a 24-h infusion with pexelizumab or placebo, and at 72 h from baseline. The levels of all three inflammatory markers increased with time, although IL-6 peaked at the end of the 24-h infusion and the other two markers peaked at 72 h. The plasma levels of IL-6 and hsCRP were higher in high-risk patients who were older than 65 years or had high levels of CK-MB. Pexelizumab reduced the increase in the levels of IL-6 and hsCRP and had greater effects in high-risk patients (6).

A double-blind, placebo-controlled clinical trial compared the effects of placebo and pexelizumab in 3,681 CABG surgery patients and 1,274 AMI patients receiving reperfusion therapy. A bolus injection and 20-24-h infusion of pexelizumab significantly reduced 30-day mortality in both patient groups (7).

1. *FDA agrees to two pivotal protocols for pexelizumab.* DailyDrugNews.com (Daily Essentials) June 16, 2004.

2. *Enrollment underway in PRIMO-CABG-2 study of pexelizumab.* DailyDrugNews.com (Daily Essentials) July 22, 2004.

Table XI: Clinical studies of pexelizumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Coronary artery disease, Cardiac surgery	Randomized Double-blind Multicenter	Pexelizumab, 2 mg bolus [10 min before CABG] → 0.05 mg/kg/h x 24 h (n=1553) Placebo (n=1546)	3099	Compared with placebo, pexelizumab reduced the incidence of mortality and myocardial infarction in patients with cardiovascular risk factors scheduled to undergo CABG	3, 4
Coronary artery disease, Cardiac surgery	Randomized Double-blind Multicenter	Pexelizumab (n=106) Placebo (n=112)	218	Compared with placebo, pexelizumab significantly decreased the incidence of death within 30 and 180 days after simultaneous aortic valve and CABG surgery	5
Myocardial infarction	Randomized Double-blind	Pexelizumab i.v. bolus → over 24 h Placebo	350	Pexelizumab was more effective than placebo in reducing the plasma levels of hsCRP, TNF-α and IL-6 in patients with acute myocardial infarction	6
Myocardial infarction, Cardiac surgery	Randomized Double-blind	Pexelizumab, i.v. bolus → over 20-24 h (n=2460) Placebo (n=2442)	4955	Pexelizumab was significantly more effective than placebo in reducing the 30-day death rate in patients with acute myocardial infarction receiving reperfusion therapy or CABG surgery	7

3. Haverich, A., Taylor, K.M., Carrier, M. et al. *Inhibition of complement activation by pexelizumab reduces death and myocardial infarction in cardiac surgical patients with selected risk profiles: Results from the international multi-center PRIMO-CABG study.* Circulation 2004, 110(17, Suppl. 3): Abst 1985.

4. Verrier, E.D., Shernan, S.K., Taylor, K.M. et al. *Terminal complement blockade with pexelizumab during coronary artery bypass graft surgery requiring cardiopulmonary bypass. A randomized trial.* JAMA - J Am Med Assoc 2004, 291(19): 2319.

5. Carrier, M., Taylor, K.M., Haverich, A. et al. *Inhibition of complement activation by pexelizumab reduces death in patients undergoing combined aortic valve procedure and coronary artery bypass surgery.* Circulation 2004, 110(17, Suppl. 3): Abst 3116.

6. Theroux, P., Armstrong, P.W., Mahaffey, K.W. et al. *Markers of inflammation predict mortality and are reduced by pexelizumab in patients with acute myocardial infarction: Insights from the Complement Inhibition in Myocardial Infarction Treated with Angioplasty (COMMA) trial.* 53rd Annu Sci Sess Am Coll Cardiol (March 7-10, New Orleans) 2004, Abst 833-5.

7. Van de Werf, F., Armstrong, P.W., Levy, J. et al. *Pexelizumab, a C5 complement inhibitor, reduces 30-day mortality in patients undergoing coronary artery bypass surgery or receiving reperfusion therapy for acute myocardial infarction.* 53rd Annu Sci Sess Am Coll Cardiol (March 7-10, New Orleans) 2004, Abst 810-4.

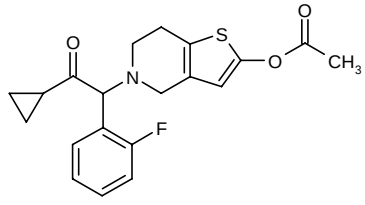
Original monograph – Drugs Fut 2003, 28(5): 435.

Additional References

Mathew, J.P. et al. *Preliminary report of the effects of complement suppression with pexelizumab on neurocognitive decline after coronary artery bypass graft surgery.* Stroke 2004, 35(10): 2335.

Shernan, S.K., Fitch, J.C., Nussmeier, N.A. et al. *Impact of pexelizumab, an anti-C5 complement antibody, on total mortality and adverse cardiovascular outcomes in cardiac surgical patients undergoing cardiopulmonary bypass.* Ann Thorac Surg 2004, 77(3): 942.

Prasugrel



Lilly and Sankyo have initiated a phase III trial to compare the effects of prasugrel (CS-747, LY-640315), an investigational antiplatelet agent and $P2Y_{12}$ antagonist, with clopidogrel in patients undergoing PCI. The study, TRITON-TIMI 38, will include 13,000 patients worldwide with ACS who are to undergo PCI. The study will be conducted by Lilly and Sankyo in conjunction with the TIMI Study Group at Harvard Medical School and Brigham & Women's Hospital. Approximately 850 hospitals in 25 countries are targeted for participation in this study. The primary focus of the study is to compare the agents' ability to prevent heart attack, stroke and death in patients who undergo PCI. The secondary focus will be to look at the impact on bleeding, recurrent heart-related chest pain or the need for additional procedures to restore blood flow. Prasugrel, discovered by Sankyo and Ube Industries, is being codeveloped by Lilly and Sankyo for

Table XII: Clinical studies of prasugrel (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Coronary artery disease	Randomized Double-blind	Prasugrel, 40 mg p.o. → 7.5 mg p.o. x 30 d Prasugrel, 60 mg p.o. → 10 mg p.o. x 30 d Prasugrel, 60 mg p.o. → 15 mg p.o. x 30 d Clopidogrel, 300 mg p.o. → 75 mg p.o. x 30 d	908	Prasugrel was at least as well tolerated as clopidogrel in patients undergoing percutaneous coronary intervention. Patients treated with prasugrel showed a lower incidence of major adverse cardiac events, myocardial infarction and target vessel thrombosis during the treatment period	2

the treatment of patients who have suffered a heart attack or heart-related chest pain. The investigational oral antiplatelet agent is designed to prevent platelet activation by blocking adenosine diphosphate receptors on the platelet surface (1).

The JUMBO (Joint Utilization of Medications to Block platelets Optimally)-TIMI 26 Study was a double-blind, randomized, dose-finding phase II clinical trial that compared the effects of prasugrel (loading dose of 40, 60 and 60 mg and maintenance doses of 7.5, 10 and 15 mg, respectively) or clopidogrel (loading dose of 300 mg plus a maintenance dose of 75 mg) in 908 adult patients undergoing elective or urgent PCI. No significant differences between groups were found in the percentage of patients who experienced significant non-CABG bleeding during a follow-up period of 30 days (1.2% with clopidogrel and 1.7% with the pooled prasugrel regimens). Patients treated with prasugrel showed a lower incidence of major adverse cardiac events (7.2% *vs.* 9.4%), myocardial infarction (5.7% *vs.* 7.9%) and target vessel thrombosis (0.6% *vs.* 2.4%) (2, 3) (Table XII).

1. *Prasugrel to be studied in PCI patients in phase III trial.* DailyDrugNews.com (Daily Essentials) Oct 28, 2004.

2. Wiviott, S.D., Antman, E.M., Winters, K.J., Weerakkody, G., Behounek, B.D., McCabe, C.H., Braunwald, E. *Joint Utilization of Medications to Block Platelets Optimally (JUMBO) - TIMI 26: Primary 30-day results with CS-747 (LY640315), a novel thienopyridine P2Y12 antagonist, compared to clopidogrel in PCI.* Eur Heart J 2004, 25(Suppl.): Abst 3705.

3. Wiviott, S.D. *JUMBO-TIMI 26: Joint Utilisation of Medications to Block platelets Optimally.* ESC Congress (Aug 28-Sept 1, Munich) 2004, Present 714.

Original monograph – Drugs Fut 2001, 26(9): 835.

Additional References

Asai, F. et al. *A comparison of prasugrel (CS-747, LY640315) with clopidogrel on platelet function in healthy male volunteers.* 54th Annu Sci Sess Am Coll Cardiol (March 6-9, Orlando) 2005, Abst 868-8.

Brandt, J.T. et al. *Superior responder rate for inhibition of platelet aggregation with a 60 mg loading dose of prasugrel (CS-747, LY640315) compared with a 300 mg loading dose of clopidogrel.* 54th Annu Sci Sess Am Coll Cardiol (March 6-9, Orlando) 2005, Abst 868-5.

Wallentin, L. et al. *Inhibition of platelet aggregation with prasugrel (CS-747, LY640315), a novel thienopyridine $P2Y_{12}$ receptor antagonist, compared with clopidogrel in aspirin-treated patients with atherosclerotic vascular disease.* 54th Annu Sci Sess Am Coll Cardiol (March 6-9, Orlando) 2005, Abst 1126-136.

PW-2101

A pivotal efficacy study for PW-2101, Penwest's β-blocker product for the treatment of hypertension, met the primary endpoints, concluding the clinical development program. PW-2101 is a reformulation of a known branded product using the company's TIMERx® oral controlled-release delivery technology. The randomized, double-blind, parallel-group study compared PW-2101 to placebo. A total of 163 subjects in the intent-to-treat population were evaluated for efficacy compared to placebo based on the primary endpoint. Results for all strengths were statistically significant. A total of 164 subjects received at least one dose of study medication and were evaluated for safety. Adverse events were mild and transient, with the exception of one moderate adverse event. The FDA recently accepted for review Penwest's NDA for the three higher strengths of PW-2101. The company is seeking a marketing partner for PW-2101 in the U.S. Penwest is also developing a low-dose strength of PW-2101, which failed to meet the primary endpoint in a pivotal efficacy trial reported at the end of last year. Although the results were positive, they were not statistically significant. However, the low-dose strength did meet some of the trial's key secondary endpoints, including the measurement of the change in 24-h mean ambulatory diastolic blood pressure from baseline to week 6. The randomized, double-blind, parallel-group study in 110 hypertensive patients compared PW-2101 to placebo. The primary endpoint was a change in the mean seated office cuff diastolic blood pressure from baseline to week 6. In the first pivotal trial conducted on this low-dose strength of PW-2101, the drug demonstrated a statistically significant reduction in exercise-induced heart rate in volunteers, meeting the primary endpoint. Penwest intends to submit the data to the FDA in the first quarter of 2005 and hopes to discuss approvability and labeling for the low dose of PW-2101 with the agency (1-3).

1. *Pivotal study for PW-2102 meets primary endpoint.* DailyDrugNews.com (Daily Essentials) March 29, 2004.

2. *Penwest Pharmaceuticals reports Q1 R&D highlights.* Penwest Pharmaceuticals Press Release 2004, April 29.

3. *Low-dose PW-2101 fails to meet primary endpoint in pivotal hypertension study.* DailyDrugNews.com (Daily Essentials) Dec 7, 2004.

PW-2132

PW-2132 is in phase II clinical trials at Penwest for the oral treatment of CHF.

Pyridoxalated Hemoglobin Polyoxyethylene

Curacyte is developing the NO scavenger pyridoxalated hemoglobin polyoxyethylene (PHP), a chemically modified human hemoglobin, for the treatment of distributive shock, a type of shock that involves peripheral vasodilatation, hypotension and tissue ischemia mediated by an excessive production of NO that may result in multiple organ failure and death. A multicenter phase IIc clinical trial evaluated the efficacy and safety of PHP in 62 patients with systemic inflammatory response syndrome (SIRS) and dependent on catecholamines after fluid resuscitation, who were randomized to receive a conventional therapy of catecholamines and placebo, or catecholamines plus PHP. PHP increased systemic blood pressure and was also associated with a series of effects suggestive of an improved outcome (*e.g.*, lower 28-day mortality rate, reduced need for pressors and ventilation, shorter stays at ICUs and hospitals). PHP was well tolerated and did not increase morbidity. Following these encouraging results, the company is in discussions with potential development and marketing partners. The same study design will be used in a future pivotal phase III clinical trial with PHP in this indication. PHP is also in phase I development as a concomitant treatment for IL-2-treated patients with renal cell carcinoma and metastatic melanoma. NO-related hypotension is a dose-limiting side effect of high-dose IL-2 treatment in these cancers and shock is a frequent adverse event, preventing patients from receiving a full dose of IL-2. PHP may decrease the incidence of dose-limiting hypotension and shock and could therefore improve the outcome of IL-2 therapy (1-4) (see Table XIII).

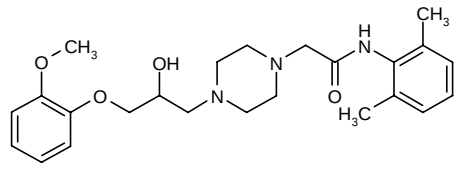
1. *Successful completion of a phase II clinical trial with PHP in distributive shock.* DailyDrugNews.com (Daily Essentials) Jan 23, 2004.

2. *Curacyte to merge with IBFB Pharma.* DailyDrugNews.com (Daily Essentials) March 1, 2005.

3. *Curacyte announces successful completion of phase II study for PHP in distributive shock, its lead product.* Curacyte Press Release 2004, Jan 21.

4. Kinasewitz, G., Malcynski, J., Steingrub, J., Balk, R., De Angelo, J. *Pyridoxalated hemoglobin polyoxyethylene (PHP) in distributive shock.* Crit Care Med 2004, 32(12, Suppl.): Abst 42.

Ranolazine



Ranolazine (Ranexa™) is a partial fatty acid oxidation (pFOX) inhibitor and sodium channel blocker currently awaiting approval in the E.U. and the U.S. for the oral treatment of chronic stable angina pectoris. CV Therapeutics is also conducting phase III trials with ranolazine for the treatment of ACS, *i.e.*, unstable angina pectoris (1).

CV Therapeutics has initiated enrollment in the MERLIN (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes) TIMI-36 study of ranolazine. MERLIN TIMI-36 is being conducted by the TIMI Study Group under the FDA's SPA process. The multinational, double-blind, randomized, placebo-controlled, parallel-group trial is designed to evaluate the efficacy and safety of ranolazine during acute and long-term treatment in approximately 5,500 patients with non-S-T segment elevation ACS treated with standard therapy. The primary efficacy endpoint is time to first occurrence of any element of the composite of cardiovascular death, myocardial infarction or recurrent ischemia in patients with non-S-T segment elevation ACS receiving standard therapy. The study also evaluates the safety of long-term treatment with ranolazine compared to placebo. Within 48 h of the onset of angina due to ACS,

Table XIII: Clinical studies of pyridoxalated hemoglobin polyoxyethylene (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Shock	Randomized Double-blind Multicenter	PHP, 20 mg/kg/h i.v. infusion over 100 h + Catecholamines (n=33) Placebo + Catecholamines (n=29)	62	PHP increased systemic blood pressure, reduced 28-day mortality and decreased the need for pressors and ventilation in patients with distributive shock	3, 4

eligible hospitalized patients are enrolled in the study and randomized to receive intravenous ranolazine or placebo, followed by long-term outpatient treatment with oral ranolazine or placebo. All patients also receive standard therapy during both hospital-based and outpatient treatment. The oral doses of ranolazine used in MERLIN TIMI-36 have been studied in previous phase III trials. Under the SPA agreement, if statistical significance on the primary endpoint is achieved, ranolazine could gain approval for hospital-based treatment of ACS and for long-term prevention of ACS in patients who present at the hospital with ACS and are treated and discharged. If treatment with ranolazine is not associated with an adverse trend in death or arrhythmia compared to placebo, the large safety database could support potential approval as first-line chronic angina therapy, even if statistical significance on the primary endpoint is not achieved. As part of this SPA agreement, CV Therapeutics will also perform a separate clinical evaluation of higher doses of ranolazine to support potential use as first-line therapy for chronic angina. The study's duration will be event-driven. Some 600 study sites worldwide are expected to enroll patients. Preliminary data could be available by the end of 2006 (2, 3).

CV Therapeutics is enrolling angina patients into the ERICA (Evaluation of Ranolazine In Chronic Angina) study of ranolazine ahead of schedule. At the current rate of enrollment, the trial should be fully enrolled by the end of the first quarter of 2005 and data should be available late in the second quarter or early in the third quarter of 2005. Prior to the initiation of the study, the company had expected to complete enrollment by the end of 2005. Since it began in August 2004, the study has enrolled 372 of the anticipated 500 patients. The study is being conducted under an SPA, which would support the approval of ranolazine for the treatment of chronic angina in a restricted patient population should the trial be successful. The multinational, double-blind, randomized, placebo-controlled, parallel-group study is designed to evaluate the effectiveness of ranolazine (1000 mg twice daily) in approximately 500 patients with chronic angina who remain symptomatic despite daily treatment with the maximum labeled dose of the approved calcium channel blocker amlodipine (10 mg daily). Patients are randomized to receive ranolazine 1000 mg or placebo twice daily in addition to a daily dose of 10 mg of amlodipine during a 6-week assessment period. The primary efficacy endpoint is angina frequency. Based on the reduction in angina frequency observed in the phase III CARISA (Combination Assessment of Ranolazine in Stable Angina) study (see below), ERICA is calculated to be 95% powered to detect a statistically significant reduction in angina frequency due to ranolazine. In CARISA, ranolazine (1000 mg) reduced the frequency of angina by an average of 1.2 attacks per week compared to placebo. Other objectives of ERICA are to gather additional data on the safety and tolerability of ranolazine and to learn more about its effect on nitroglycerin consumption during angina attacks and quality of life. Prior to entering the study, patients are required to have had at least 2 weeks of treatment with amlodipine (10 mg daily), with the discontinuation of other antianginal therapy for at least 5 days. Physicians are able to add long-acting nitrates as background therapy at the start of the study (4-6).

The CARISA study was a multicenter, randomized, double-blind, placebo-controlled clinical trial that evaluated the potential use of ranolazine in enhancing the effects of other antianginal drugs. A total of 823 patients with CAD and stable angina who were receiving antianginals (50 mg of atenolol, 180 mg of diltiazem or 5 mg of amlodipine) once daily were randomized to supplement their baseline treatments with placebo or sustained-release ranolazine (750 or 1000 mg b.i.d.) for 12 weeks. Compared to placebo, both ranolazine doses increased the treadmill exercise duration, times to angina and times to electrocardiogram ischemia, and reduced the mean number of angina attacks and nitroglycerin uses per week. The specific antianginal drug each patient was receiving at baseline had no effect on the response to ranolazine. Adverse events were slightly more common with ranolazine (31.2% and 32.7% for the 750- and 1000-mg doses, respectively, compared to 26.4% with placebo). Ranolazine was associated with a dose-dependent reduction in the mortality rate (0.7% and 0.4%, respectively, *vs.* 1.1% with placebo) and an increase in the incidence of constipation, dizziness, nausea and asthenia. Analysis of the electrocardiograms of the patients showed that ranolazine induced small dose-related increases in Bazett's Q-T_c interval but had no effects on Q-T dispersion or the induction of torsades de pointes. An associated long-term follow-up study that included 750 patients receiving ranolazine showed survival rates of 98.4% and 95.6% after 1 and 2 years, respectively (7) (Table XIV).

1. *CV Therapeutics seeks European approval of ranolazine for chronic angina.* DailyDrugNews.com (Daily Essentials) April 1, 2004.

2. *CV Therapeutics and FDA agree to SPA for Ranexa.* DailyDrugNews.com (Daily Essentials) Aug 4, 2004.

3. *Initiation of MERLIN TIMI-36 study of Ranexa.* DailyDrugNews.com (Daily Essentials) Oct 14, 2004.

4. *Enrollment progressing ahead of schedule in Ranexa angina study.* DailyDrugNews.com (Daily Essentials) Oct 29, 2004.

5. *CV Therapeutics initiates approval-enabling study of Ranexa.* DailyDrugNews.com (Daily Essentials) Aug 5, 2004.

6. *CV Therapeutics and FDA agree on Ranexa study protocol.* DailyDrugNews.com (Daily Essentials) June 7, 2004.

7. Chaitman, B.R., Pepine, C.J., Parker, J.O. et al. *Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina. A randomized controlled trial.* JAMA - J Am Med Assoc 2004, 291(3): 309.

Original monograph – Drugs Fut 1988, 13(9): 837.

Table XIV: Clinical studies of ranolazine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Angina pectoris, Coronary artery disease	Randomized Double-blind Multicenter	Ranolazine, 750 mg o.d. + Background antianginals (n=279) Ranolazine, 1000 mg o.d. + Background antianginals (n=275) Placebo + Background antianginals (n=269)	823	Ranolazine administered to stable angina patients already treated with antianginals further reduced the mean number of angina attacks per week and the weekly use of nitroglycerin. It also increased treadmill exercise duration, time to angina and time to electrocardiogram ischemia, and dose-dependently reduced the mortality rate	7

Additional References

Berger, P. *Ranolazine and other antianginal therapies in the era of the drug-eluting stent.* JAMA - J Am Med Assoc 2004, 291(3): 365.

Chaitman, B.R. et al. *Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina.* J Am Coll Cardiol 2004, 43(8): 1375.

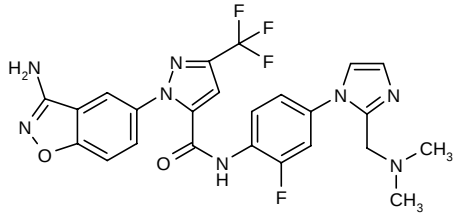
Lüscher, T. *Future directions in the management of chronic angina and ACS - The MERLIN-TIMI 36 trial.* Eur Heart J - Suppl 2004, 6(Suppl. I): I17.

Lyakishev, A.A. *Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina. Results of CARISA.* Kardiologiya 2004, 44(3): 78.

Rousseau, M.F., Pouleur, H., Cocco, G., Wolff, A.A. *Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris.* Am J Cardiol 2005, 95(3): 311.

Tavazzi, L. *The ranolazine clinical experience.* Eur Heart J - Suppl 2004, 6(Suppl. I): I13.

Razaxaban Hydrochloride



.HCl

A clinical trial evaluated the antithrombotic effects of razaxaban hydrochloride (formerly DPC-906), a direct-acting thrombin inhibitor designed by Bristol-Myers Squibb and currently in phase II clinical development for DVT, in 20 healthy male volunteers. A single dose of razaxaban (25 or 100 mg p.o.) dose-dependently inhibited thrombus formation, reducing both the low shear and the high shear rates using the Badimon perfusion chamber (which mimics venous and arterial flow), and increasing the aPTT of the subjects. These findings suggest that razaxaban may be effective in reducing the thrombotic complications of cardiovascular disease (1).

A method has been claimed for the treatment of thromboembolic conditions, including but not restricted to unstable angina, initial or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack and stroke. The claim embodies the preparation and administration of pharmaceutical compositions capable of facilitating the simultaneous or sequential administration of a coagulation factor Xa inhibitor, such as razaxaban, with the $P2Y_{12}$ (P2T) receptor antagonist clopidogrel, or a pharmaceutically acceptable salt or prodrug thereof. The claim pertains in particular to the application of subtherapeutic doses of both agents and also allows for the coadministration of additional therapeutic agents, such as aspirin or pravastatin (2).

1. Zafar, M.U., Viles-Gonzalez, J., Valdviezo, C. et al. *Tissue factor pathway inhibition, a new antithrombotic strategy: Phase-II study of a novel, oral factor Xa inhibitor.* 53rd Annu Sci Sess Am Coll Cardiol (March 7-10, New Orleans) 2004, Abst 1007-173.

2. Wong, P. and Knabb, R. (Bristol-Myers Squibb Co.) *Novel combination of a factor Xa inhibitor and clopidogrel.* WO 0431143, US 2004067995.

Additional References

Swaminathan, A. et al. *Pharmacokinetic and pharmacodynamic characteristics in healthy volunteers of razaxaban, an orally-active, potent, selective inhibitor of factor XA.* Clin Pharmacol Ther 2004, 75(2): Abst PI-12.

Recombinant Human Antithrombin III

GTC Biotherapeutics expects to receive a list of outstanding issues with additional questions from the European Medicines Evaluation Agency (EMEA) as part of the review of its market authorization application (MAA) for recombinant human antithrombin III (ATryn®). GTC is seeking approval of ATryn® for the treatment of patients with a hereditary deficiency of antithrombin who are undergoing high-risk procedures such as surgery or child-

birth. The time required to respond to the EMEA's anticipated questions will delay the previously forecasted timelines for market launch. The U.S. FDA also recently informed the company that it will allow it to begin a clinical study for this indication in the U.S., with a view to submitting a BLA. The company is continuing its partnering negotiations for ATryn®. GTC expresses antithrombin, a plasma protein with anticoagulant and antiinflammatory properties, in the milk of goats that have the human antithrombin gene linked to a milk protein promoter (1-4).

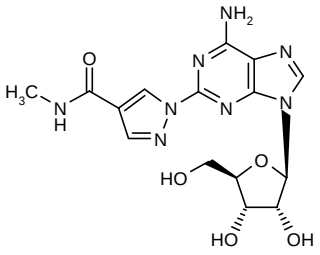
1. *GTC restructures*. DailyDrugNews.com (Daily Essentials) Feb 11, 2004.

2. *GTC submits responses regarding ATryn MAA*. DailyDrugNews.com (Daily Essentials) Dec 23, 2004.

3. *GTC Biotherapeutics awaits EMEA comments regarding ATryn MAA*. DailyDrugNews.com (Daily Essentials) March 22, 2005.

4. *GTC Biotherapeutics to begin ATryn® US clinical study*. GTC Biotherapeutics Press Release 2005, April 6.

Regadenoson



CV Therapeutics has initiated a second phase III trial of regadenoson (CVT-3146), a selective, short-acting adenosine A_{2A} receptor agonist being jointly developed with Astellas Pharma for potential use as a pharmacological stress agent in cardiac perfusion imaging studies. The first international, double-blind phase III trial, also in patients undergoing a cardiac stress test, was initiated in October 2003. Regadenoson has been designed to be delivered rapidly as a bolus and to selectively stimulate the A_{2A} receptor. In an open-label phase II trial, regadenoson produced a dose-dependent increase in coronary blood flow velocity in patients undergoing cardiac catheterization. Under their collaboration agreement, CV Therapeutics is managing the clinical development program of regadenoson, with Astellas taking responsibility for manufacturing, selling and marketing the drug in North America (1).

The efficacy and safety of regadenoson (400 and 500 μg by i.v. bolus) were determined in 36 subjects included in a pharmacological stress SPECT myocardial perfusion imaging protocol. Regadenoson was associated with acceptable hemodynamic effects: a peak average increase of 21.9 beats/min in heart rate and a peak average reduction of 5.9 mmHg in systolic blood pressure within 2 and 4 min, respectively. The differences between doses were minimal and no subjects reached systolic blood pressure values below 90 mmHg. Overall, 72% of the patients showed adverse events, most of which were mild or moderate and resolved within 15 min after administration. The incidence of chest discomfort (33%), headache (25%) and abdominal pain (11%) was similar in both dose groups, whereas that of flushing, dyspnea and dizziness increased with dose (2) (Table XV).

The administration of at least one selective adenosine A_{2A} receptor agonist, such as regadenoson, together with a radionuclide has been claimed for use in myocardial perfusion imaging for the detection and characterization of CAD (3).

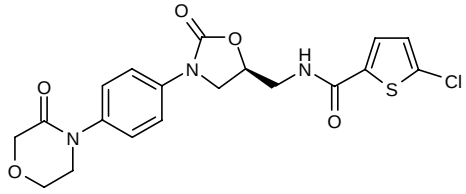
1. *Second phase III trial for regadenoson.* DailyDrugNews.com (Daily Essentials) April 29, 2004.

2. Cerqueira, M.D., Iskandrian, A.E., Jerling, M., Abdallah, H.Y., Leppo, J.A., Hendel, R.C., Mahmarian, J.J., Bateman, T.M. *Initial results regarding the safety, tolerability, and hemodynamic effects of CVT-3146, a selective adenosine A_{2A} agonist, in patients undergoing stress SPECT myocardial perfusion imaging.* 53rd Annu Sci Sess Am Coll Cardiol (March 7-10, New Orleans) 2004, Abst 1170-141.

3. Belardinelli, L. (CV Therapeutics, Inc.) *Myocardial perfusion imaging using A_{2A} receptor agonists.* WO 0411010.

Original monograph – Drugs Fut 2004, 29(10): 998.

Rivaroxaban



The structure of Bayer's novel antithrombotic agent rivaroxaban (Bay-59-7939) was recently revealed. Rivaroxaban, an oxazolidinone derivative, is a potent and

Table XV: Clinical studies of regadenoson (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Coronary artery disease	Randomized Double-blind	Regadenoson, 400 μg i.v. bolus (n=18) Regadenoson, 500 μg i.v. bolus (n=18)	36	Regadenoson was well tolerated and induced acceptable hemodynamic effects in patients undergoing pharmacological stress SPECT myocardial perfusion imaging	2

selective, orally active direct factor Xa inhibitor previously reported to have excellent antithrombotic activity and currently undergoing phase II clinical development for the prevention and treatment of thromboembolic diseases (1).

1. Roehrig, S., Straub, A., Pohlmann, J., Lampe, T., Pernerstorfer, J., Schlemmer, K.H., Perzborn, E. *Discovery of the novel antithrombotic agent BAY 59-7939, an orally active, direct factor Xa inhibitor.* 228th ACS Natl Meet (Aug 22-26, Philadelphia) 2004, Abst MEDI 156.

rNAPc2

Nuvelo reinitiated a phase IIa trial with rNAPc2 (recombinant nematode anticoagulant protein c2) for the treatment of patients with ACS last year after licensing the molecule from Dendreon in February 2004. Prior to reinitiation, 77 patients had been enrolled in the trial. An additional 98 patients will be enrolled in this phase of the trial for a total of 175 patients in centers across the U.S. and Canada. The multicenter, randomized, double-blind, placebo-controlled, dose-ranging study, known as ANTHEM (Anticoagulation with NAPc2 To Help Eliminate MACE)/TIMI 32 and being conducted with the TIMI Study Group, will evaluate the safety and efficacy of rNAPc2 in patients with non-S-T segment elevation ACS. During the dose-ranging phase, seven ascending doses of rNAPc2 will be compared, one at a time, to matching placebo doses in a 4:1 randomization. The primary focus of this phase will be to identify the highest safe and effective dose measured by major or minor hemorrhage occurring in the period from randomization to 7 days after the last dose of study drug, and the presence of ischemia measured by a Holter monitor. In the dose confirmation phase, the highest safe and effective dose will be compared to placebo in a 1:1 randomization. Furthermore, all patients will receive low-molecular-weight heparin or unfractionated heparin and aspirin, and clopidogrel use will be strongly encouraged. The anticoagulant effect of rNAPc2 results from its apparent ability to block the factor VIIa/tissue factor protease complex. rNAPc2 blocks the first step in the clotting cascade, inhibiting coagulation before it starts. A phase II study for the prevention of DVT also showed that rNAPc2 appears to reduce the risk of developing DVT and related complications by over 50% compared to the current standard therapy for patients undergoing total knee replacement surgery, without compromising safety. A second phase IIa study demonstrated that rNAPc2 was well tolerated when added to standard therapy with unfractionated heparin, aspirin and clopidogrel in patients undergoing elective PCI. rNAPc2 suppressed the formation of thrombin for at least 36 h following a single administration compared to standard therapy alone, after which thrombin generation continued unabated. Other potential indications under evaluation include orthopedic and vascular surgery, Ebola and cancer (1-4).

1. *Nuvelo licenses rNAPc from Dendreon.* DailyDrugNews.com (Daily Essentials) Feb 9, 2004.

2. *Nuvelo reports 2003 year-end R&D highlights.* Nuvelo Press Release 2004, Feb 5.

3. *Nuvelo restarts phase IIa trial with rNAPc2.* DailyDrugNews.com (Daily Essentials) May 17, 2004.

4. *Nuvelo reports Q1 R&D highlights.* Nuvelo Press Release 2004, May 6.

RSD-1235

Cardiome Pharma has three phase III clinical trials under way related to the RSD-1235 intravenous project. The first, ACT 1 (Atrial arrhythmia Conversion Trial), will enroll approximately 420 patients and will provide data on the level of safety and effectiveness of RSD-1235, a mixed sodium and potassium channel blocker, in the acute treatment of atrial fibrillation and atrial flutter. This study seeks to confirm the findings of the successful phase II proof-of-concept CRAFT trial. This study is being carried out at more than 40 centers in North America and Europe. The primary efficacy endpoint will be acute conversion of atrial arrhythmia to normal heart rhythm. The ACT 2 study will enroll approximately 210 patients and will evaluate the efficacy and safety of intravenous RSD-1235 for the treatment of patients who have developed transient atrial fibrillation following cardiac surgery. This study is being carried out at 25 centers in North America and Europe. The primary endpoint of this clinical trial will be acute conversion of atrial arrhythmia to normal heart rhythm. A third phase III efficacy study of RSD-1235 is under way for the acute treatment of atrial fibrillation. The ACT 3 study is being conducted by Cardiome's codevelopment partner Astellas Pharma. The placebo-controlled study at more than 50 sites worldwide will measure the safety and efficacy of RSD-1235 in recent-onset atrial arrhythmia patients. Under their agreement, signed in October 2003, Cardiome granted the former Fujisawa an exclusive license to develop and commercialize intravenous RSD-1235 in North America. The companies will codevelop i.v. RSD-1235 to NDA, with Astellas Pharma responsible for 75% of development costs. Cardiome has retained all rights to the intravenous formulations outside Canada, the U.S. and Mexico, and has also retained worldwide rights to oral RSD-1235 for the prevention of atrial fibrillation (1-5).

Earlier this year, Cardiome disclosed new results from the ACT-1 study in 416 patients with atrial arrhythmia. The first results of the study, which were presented in December 2004, revealed that intravenous RSD-1235 was well tolerated and effective in converting 52% of patients with recent-onset atrial arrhythmia to normal heart rhythm. According to the new results, the median time to conversion was 11 min from the beginning of administration, and only 1 of 75 patients with recent-onset arrhythmia who converted to normal heart rhythm

relapsed within 24 h. RSD-1235 showed little efficacy in converting patients with atrial flutter. The drug was well tolerated, only 1.4% of patients treated with RSD-1235 experiencing potentially drug-related serious adverse events during the first 30 days after administration, and no cases of drug-related torsades de pointes were reported (6, 7).

Dosing has commenced in Cardiome's phase I study of a controlled-release formulation of oral RSD-1235. The open-label, crossover evaluation of two controlled-release formulations of RSD-1235 compared to an immediate-release formulation will enable the selection of a formulation for further clinical trials. The controlled-release oral formulation of RSD-1235 is being developed as a chronic treatment for atrial fibrillation. Oral RSD-1235 is expected to prevent or slow the recurrence of atrial fibrillation, and is designed to be used as a follow-on therapy to intravenous RSD-1235. The controlled-release formulations have provided targeted plasma levels in preclinical studies for periods of time in excess of 10 h, and RSD-1235 has previously been reported to have bioavailability of greater than 70% in healthy volunteers (8).

Based on the successful completion of the above trial, Cardiome has selected a controlled-release formulation of oral RSD-1235 to advance into further clinical development, and has initiated a phase Ib study with the formulation. The formulation is designed to enable twice-daily dosing for the selected atrial fibrillation patient population. The pharmacokinetic results of the phase Ia study were consistent with that objective. The chosen formulation will be assessed in a series of phase I studies in order to determine the dosing regimen to be used in a phase II efficacy study planned for the second half of 2005. The new phase Ib study will examine the effect of food on the absorption of RSD-1235 using a crossover design. In this study, subjects will be dosed with a single controlled-release tablet in the fasted state or following a meal. A multiple-dose study is then planned to assess the pharmacokinetics and safety of repeated daily doses of controlled-release RSD-1235 tablets (9).

1. *Second phase III study of RSD-1235 in atrial fibrillation commences.* DailyDrugNews.com (Daily Essentials) April 1, 2004.

2. *New phase III study for RSD-1235.* DailyDrugNews.com (Daily Essentials) July 12, 2004.

3. *Cardiome Pharma reports Q1 R&D highlights.* Cardiome Pharma Press Release 2004, May 17.

4. *Cardiome completes ACT 1 enrollment.* Cardiome Pharma Press Release 2004, Oct 12.

5. *Cardiome Pharma reports Q2 R&D highlights.* Cardiome Pharma Press Release 2004, Aug 12.

6. *A phase III trial confirms the therapeutic benefits of RSD-1235 in AF.* DailyDrugNews.com (Daily Essentials) Dec 29, 2004.

7. *New phase III data on the efficacy of RSD-1235 in atrial arrhythmia.* DailyDrugNews.com (Daily Essentials) Feb 10, 2005.

8. *Dosing commences in study of controlled-release oral RSD-1235.* DailyDrugNews.com (Daily Essentials) Sept 29, 2004.

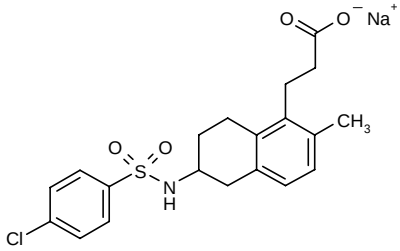
9. *Cardiome selects oral controlled-release formulation of RSD-1235.* DailyDrugNews.com (Daily Essentials) Dec 1, 2004.

RUS-3108

Dr. Reddy's Laboratories has initiated phase I trials of its cardiovascular drug candidate RUS-3108. The trials are being conducted in Belfast and will explore the safety and pharmacokinetic profiles of this drug candidate in humans. RUS-3108 is being developed for, and represents a new approach to, the treatment of atherosclerosis. The first-in-class drug candidate works by affecting multiple pathways involved in the disease, such as inflammation, proliferation and thrombosis, by inducing the protein perlecan (1).

1. *Cardiovascular drug candidate RUS-3108 enters phase I in Ireland.* DailyDrugNews.com (Daily Essentials) Feb 9, 2005.

S-18886

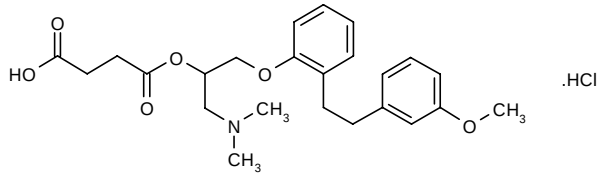


An orally active thromboxane A_2 (TP) receptor antagonist, S-18886 is in late-stage clinical development at Servier for atherothrombosis.

Additional References

Fiessinger, J.N. *S 18886, a new specific TP-receptor antagonist, is safe and as effective as aspirin in inhibiting platelet aggregation in patients with peripheral arterial disease*. Eur Heart J 2004, 25(Suppl.): Abst P573.

Sarprogrelate Hydrochloride

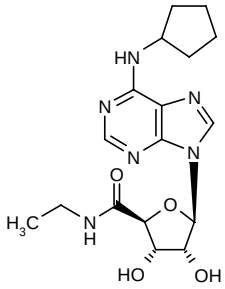


Sarpogrelate hydrochloride is a selective oral 5-HT_{2A} antagonist first launched in 1993 as Anplag by Mitsubishi Pharma for the treatment of ischemic symptoms, including pain, ulcers and cold sensation, due to chronic arterial obstruction. The company is also evaluating its poten-

tial for the prevention of the recurrence of stroke in phase III trials and for the treatment of intermittent claudication and chronic pain in phase II studies.

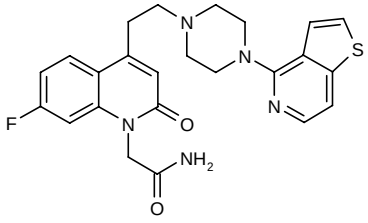
Original monograph – Drugs Fut 1992, 17(12): 1093.

Selodenoson



Aderis is evaluating selodenoson (DTI-0009), an adenosine A_{1A} receptor agonist, in phase II trials for the intravenous treatment of atrial fibrillation. The compound has been found to be much longer acting, more selective and more potent than currently available treatments. Aderis is also developing an oral formulation of selodenoson for the chronic treatment of atrial fibrillation, which has completed a phase I clinical trial. Aderis reacquired U.S. and Canadian rights to the i.v. formulation from the former Fujisawa Healthcare (now Astellas Pharma) last year.

SL-65.0472



A dual 5-HT_{1B}/5-HT_{2A} receptor antagonist synthesized at Sanofi-Aventis, SL-65.0472 is undergoing early clinical testing for use in PAOD.

SLV-320

SLV-320 is an adenosine A_1 receptor antagonist currently in phase II development at Solvay for use in congestive heart failure (CHF) and renal failure.

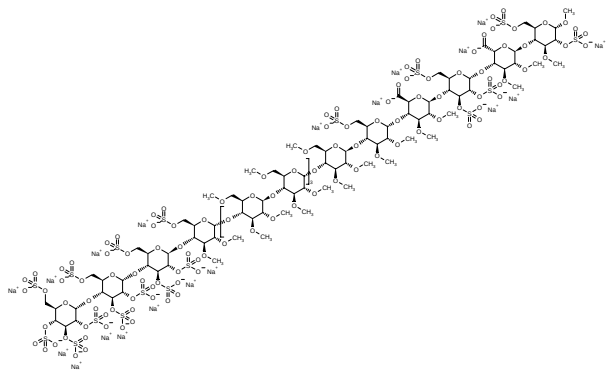
SMP-797

Sumitomo's ACAT inhiitor SMP-797 is in early clinical development in Europe as a potential new treatment for atherosclerosis and hypercholesterolemia.

Two clinical trials determined the pharmacokinetics and safety of SMP-797 in healthy male Caucasian volunteers. Oral SMP-797 had an average half-life of 6 h, showed a slightly nonlinear pharmacokinetic profile and was well tolerated at doses up to 5 mg. Both drug exposure and peak plasma drug concentration decreased when it was coadministered with food. In a placebo-controlled trial, SMP-797 (1 or 3 mg/kg p.o.) given once daily for 28 days to 24 healthy volunteers also exhibited a good safety profile and potential for once-daily dosing (1).

1. Cain, D., Clinch, B., Taylor, M., Tamura, N., Fujiwara, F. *SMP-797 a novel lipid lowering compound: Safety, tolerability and pharmacokinetics in healthy volunteers.* 15th Int Symp Drugs Affect Lipid Metab (Oct 24-27, Venice) 2004, 131.

SR-123781

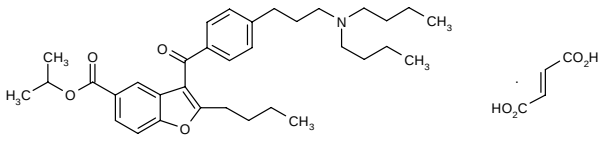


Sanofi-Aventis is conducting phase IIb clinical trials with SR-123781, a short-acting hexadecasaccharide with both anti-factor Xa and anti-factor IIa activity, assessing its potential for preventing major cardiovascular events in ACS.

SSR-126517

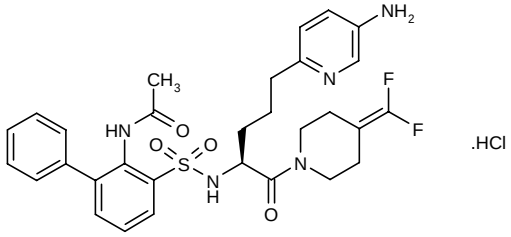
SSR-126517 is a back-up compound to idraparinux (see above) in phase I clinical evaluation at Sanofi-Aventis for the treatment of thromboembolic diseases.

SSR-149744



A potential new agent for the treatment of atrial fibrillation, SSR-149744, is in phase II clinical testing at Sanofi-Aventis as a back-up compound to dronedarone (see above).

SSR-182289

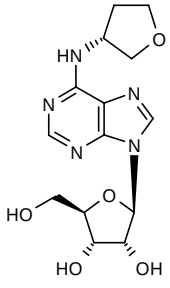


SSR-182289 (Sanofi-Aventis) is an orally active direct thrombin inhibitor which is undergoing phase IIa clinical trials for thromboembolic diseases.

Staphylokinase

Recombinant staphylokinase, a thrombolytic protein, is one of ThromboGenics' lead development programs, with phase II trials under way for the i.v. treatment of acute myocardial infarction. The company is also evaluating a polyethylene glycol-derivatized (PEGylated) recombinant staphylokinase variant SY161 (PEG-Sak) in phase II for this indication. ThromboGenics is actively seeking a codevelopment partner for further clinical development of staphylokinase.

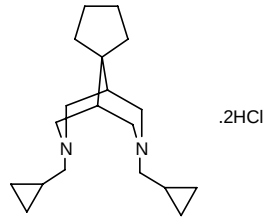
Tecadenoson



The adenosine A_1 receptor agonist tecadenoson (CVT-510) is undergoing phase III clinical evaluation by CV Therapeutics for the i.v. treatment of paroxysmal supraventricular tachycardia (PSVT). The company is also conducting phase II clinical trials for the treatment of atrial fibrillation. Based on its ability to selectively stimulate the A_1 receptor and slow electrical impulses in the heart without significantly stimulating the A_2 receptor, the i.v. administration of tecadenoson may hold potential for rapid intervention in the control of atrial arrhythmias, without lowering blood pressure.

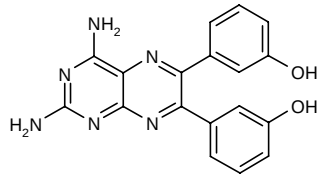
Original monograph – Drugs Fut 2002, 27(9): 846.

Tedisamil Hydrochloride



Solvay is developing tedisamil hydrochloride (KC-8857, Pulzium®) as a novel class III antiarrhythmic agent with additional bradycardic and antiischemic properties and which acts via potassium channel blockade. Originally targeted for the treatment of angina pectoris, for which phase III trials have been completed, the product is now being developed for the treatment of atrial fibrillation. An intravenous formulation is in phase III clinical trials and an oral formulation is in phase I.

TG-100115



TargeGen has initiated a 100-patient phase I/II trial of TG-100115, a potent and selective phosphatidylinositol 3-kinase (PI3-kinase) inhibitor that has demonstrated the ability to suppress vascular leakage and significantly reduce infarct size in preclinical models of acute myocardial infarction. TG-100115, when administered intravenously, is designed to block vascular leakage and inflammation following an ischemic event, thereby preserving heart muscle tissue (1, 2).

1. *IND active for phase I/II study of TG-100-115.* DailyDrugNews.com (Daily Essentials) July 22, 2004.

2. *Phase I/II trial for TG-100-115 in heart attack patients.* DailyDrugNews.com (Daily Essentials) Jan 11, 2005.

TGN-167/TGN-255

Trigen has two clinical-stage direct thrombin inhibitors: the orally active TGN-167, being developed as a safe, effective, predictable and convenient anticoagulant for chronic outpatient use in the prevention and treatment of thrombosis, and TGN-255, an intravenous anticoagulant for use in the hospital setting.

Eurand and Trigen recently established a collaboration to develop controlled-release formulations of TGN-167. Eurand will apply its proprietary drug delivery expertise and technologies to the project. The collaboration aims to develop tablet forms of TGN-167, which already has a broad window of absorption along the gastrointestinal tract, with optimal kinetic and dynamic profiles. Trigen will retain all commercialization and development rights to TGN-167. Commercial discussions are ongoing with Trigen's potential partners. Trigen previously announced the successful completion of a phase I dose-escalation study on TGN-167 using a classical rapid-release tablet formulation (1).

In a phase I study in 16 healthy male volunteers, subjects were randomized to placebo or infusions of TGN-255 25 or 40 mg/h for 24 h. The drug was rapidly absorbed and demonstrated a systemic half-life of about 2.3 h. Dose-related increases in thrombin clotting time of a mean 4.5-6.8 times the baseline values were seen. Thrombin clotting time decreased to 3 times the baseline values within 30 min posttreatment. The effect on aPTT was less marked and of shorter duration, and no clinical adverse events were observed (2, 3).

A phase I ascending-dose trial of TGN-255 examined the following doses: a 7-mg bolus with an infusion of 25 mg/h for 3 h, a 10-mg bolus with an infusion of 40 mg/h for 3 h and an infusion of 40 mg/h given for 3 h. Dose-proportional pharmacokinetics were measured, and plasma drug concentrations increased rapidly upon bolus administration. A systemic half-life of 1.7 h was determined. Thrombin clotting time increased quickly and in a dose-related manner and was greatest at 2-3 h after infusion was begun. The increase in thrombin clotting time over baseline declined rapidly after the end of drug administration. The effects on aPTT were less pronounced and no adverse events were observed (4).

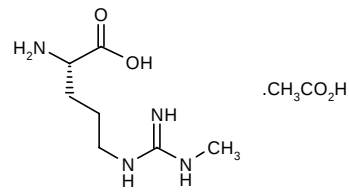
1. *Trigen and Eurand to develop controlled-release TGN-167*. DailyDrugNews.com (Daily Essentials) Nov 26, 2004.

2. Combe, S., Allen, G., Kennedy, T., Patrick, G.M. *A phase I double-blind 24 hour intravenous dosing study of a synthetic direct thrombin inhibitor, TGN255*. J Am Soc Nephrol 2004, 15: Abst F-PO523.

3. Combe, S., Allen, G., Kennedy, T. *A phase 1 double-blind 24-hour intravenous infusion study with TGN255, a direct thrombin inhibitor*. Am J Cardiol 2004, 94(6A, Suppl.): Abst TCT-417.

4. Combe, S., Allen, G., Kennedy, T., Patrick, G. *A phase I double-blind, intravenous ascending dose study of a synthetic direct thrombin inhibitor, TGN255*. J Am Soc Nephrol 2004, 15: Abst F-PO524.

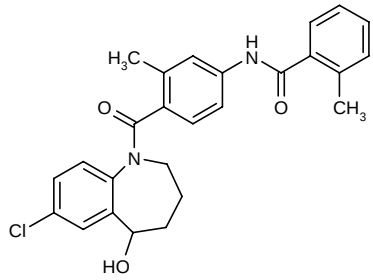
Tilarginine Acetate



An NOS inhibitor, tilarginine acetate is currently in late-stage development at Arginox Pharmaceuticals for its potential in the treatment of heart attack-related cardiogenic shock. Following positive survival results from a phase II dose-ranging study, the company has received FDA approval to proceed with a pivotal phase III trial, called TRIUMPH (Tilarginine Acetate Injection in a Randomized International Study in Unstable AMI patients with Cardiogenic Shock) (1).

1. *Arginox completes $25 million Series C financing.* Arginox Pharmaceuticals Press Release 2005, March 1.

Tolvaptan



Otsuka's tolvaptan (OPC-41061) is a vasopressin V_2 antagonist in phase III clinical development for the oral treatment of congestive heart failure (CHF) and hyponatremia. The agent is also in early clinical development for polycystic kidney disease.

Original monograph – Drugs Fut 2002, 27(4): 350.

Additional References

Costello-Boerrigter, L.C., Burnett, J.C. Jr., Smith, W.B., Ouyang, J., Zimmer, C.A., Orlandi, C. *Tolvaptan (OPC-41061), a V2 vasopressin receptor antagonist, enhances aquaresis and renal hemodynamics compared to furosemide in mild to moderate heart failure.* Eur Heart J 2004, 25(Suppl.): Abst 2636.

Gheorghiade, M. et al. *Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure. A randomized controlled trial.* JAMA - J Am Med Assoc 2004, 291(16): 1963.

Shoaf, S.E. et al. *Lack of clinically significant interaction between steady state tolvaptan and digoxin in healthy volunteers.* Clin Pharmacol Ther 2004, 75(2): bst PI-129.

TP-10

TP-10, a novel inhibitor of complement-mediated inflammation designed by Avant Immunotherapeutics, is being assessed in a double-blind, placebo-controlled phase IIb trial in approximately 300 female patients undergoing cardiac surgery utilizing cardiopulmonary bypass (CPB). The study is examining the effect of a 30-min infusion of TP-10 *versus* placebo and the ability of TP-10 to reduce the incidence of death and heart attack that occurs in cardiac surgery patients on CPB. Results from a previous phase II adult cardiac surgery study of TP-10 showed, in men, a statistically significant 36% reduction in the primary endpoint, as well as a significant 43% reduction in the combined endpoint of death or myocardial infarction. However, a similar effect was not seen in the female population, possibly due to the small numbers of women enrolled in the study. With partner Lonza Biologics, Avant is working to complete process development and scale-up efforts in preparation for the production of phase III clinical materials and the start of that trial by the end of 2005 (1-3).

1. *Phase IIb trial to assess TP-10 in women undergoing cardiac surgery with CBP.* DailyDrugNews.com (Daily Essentials) Feb 19, 2004.

2. *Avant Immunotherapeutics reports Q1 R&D highlights.* Avant Immunotherapeutics Press Release 2004, April 21.

3. *Avant Immunotherapeutics reports Q2 R&D highlights.* Avant Immunotherapeutics Press Release 2004, July 22.

Additional References

Lazar, H.L. et al. *Soluble human complement receptor 1 limits ischemic damage in cardiac surgery patients at high risk requiring cardiopulmonary bypass.* Circulation 2004, 110(Suppl. 1): II-274.

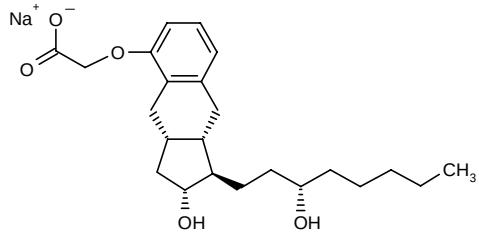
Li, J.S., Sanders, S.P., Perry, A.E., Stinnett, S.S., Jaggers, J., Bokesch, P., Reynolds, L., Nassar, R., Anderson, P.A.W. *Pharmacokinetics and safety of TP10, soluble complement receptor 1, in infants undergoing cardiopulmonary bypass.* Am Heart J 2004, 147(1): 173.

trans-NV-04

Novogen is commencing a second clinical trial to evaluate its cardiovascular drug *trans*-NV-04. The trial, to be conducted at the Baker Heart Research Institute, Melbourne, will study *trans*-NV-04 in subjects who are at risk of cardiovascular disease, but are otherwise healthy. Safety and tolerability will be evaluated initially in a dose-ranging study, which will be followed by a double-blind, randomized, placebo-controlled, crossover study in subjects receiving either *trans*-NV-04 or placebo. Effects on cardiovascular risk factors, including arterial stiffness, blood pressure, plasma lipids, circulating adhesion and inflammatory molecules, insulin sensitivity and plasma cortisol, will be compared between groups. The study will also help establish a dosing regimen for potential use in healthy subjects to reduce cardiovascular risk factors and in people suffering from atherosclerosis to reduce the damage in diseased arteries and to hasten the recovery from surgical interventions used to manage the disease, such as bypass surgery and angioplasty. *trans*-NV-04 is an advanced version of Novogen's experimental NV-04 (see above) compound. A *trans*-NV-04 analogue was tested in volunteers in a pre-phase I study, in which direct infusion of the drug into the brachial artery induced elasticity in blood vessels and increased forearm blood flow. In the initial human trial, all 6 subjects responded favorably following direct infusion of the compound into the bloodstream, with significant increases in blood flow in a particular artery. Follow-up laboratory studies have identified *trans*-NV-04 as potentially even more effective than the parent compound while retaining its good safety profile. Previous laboratory studies conducted by the Baker team have demonstrated that *trans*-NV-04 also acts as an antioxidant and inhibits smooth muscle cell growth in blood vessels. The NV-04 research effort has been assisted by an award of AUD 3.7 million through the Australian government's R&D START program (1).

1. *Second clinical trial evaluates trans-NV-04.* DailyDrugNews.com (Daily Essentials) July 8, 2004.

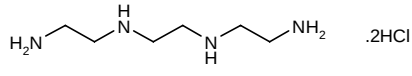
Treprostinil Sodium



United Therapeutics' prostacyclin analogue treprostinil sodium (Remodulin®, UT-15) was first approved by the U.S. FDA in 2002, followed by regulatory authorities in Canada and Israel, for the treatment of pulmonary arterial hypertension. The company is also developing the drug for late-stage peripheral vascular disease (PVD), also known as critical limb ischemia. Following the successful completion of a phase II trial in 1998, treprostinil entered prepivotal trials for this indication. Sustained-release oral formulations are also in the early stage of development.

Original monograph – Drugs Fut 2001, 26(4): 364.

Trientine Hydrochloride



Trientine hydrochloride is a therapeutic copper-binding molecule first launched in 1986 in the U.S. as

Syprine® by Merck Sharp & Dohme for the oral treatment of Wilson's disease in patients with penicillamine intolerance. Phase II trials are presently under way at Protemix (Laszarin™) for the treatment of diabetic cardiopathy, with phase III trials expected to begin this year. In patients with type 2 diabetes treated for 6 months, a significant reduction in elevated left ventricular mass was seen. In preclinical studies, the drug significantly alleviated heart failure without lowering blood glucose following 7 weeks of treatment. In addition, cardiomyocyte structure improved substantially and the increase in left ventricular collagen and β_1 integrin levels was reversed.

Original monograph – Drugs Fut 1983, 8(8): 697.

TTP-889

Phase I trials have been successfully completed for TransTech Pharma's first drug candidate TTP-889. The orally bioavailable, selective inhibitor of the intrinsic coagulation pathway is being developed as an anticoagulant for the treatment of thromboembolic disorders. TTP-889 is the only known selective, small-molecule inhibitor of factor IX/IXa, a key enzyme in the intrinsic pathway of the blood coagulation system. TTP-889 has limited effects on the extrinsic pathway, but by targeting the intrinsic pathway it is expected to provide protection from thromboembolism with reduced bleeding complications compared to existing anticoagulants. Initial results suggest that TTP-889 can be administered as a pill or capsule. The drug is expected to avoid some or all of the complications associated with warfarin, including slow onset of action, multiple drug interactions and the requirement for frequent monitoring of its anticoagulant effect. TTP-889 has proven effective in preventing clot formation in several animal models of human disease, including stroke and pulmonary embolism. When tested in healthy subjects, TTP-889 was found to be safe at all doses, single and multiple, in both young and elderly populations, at blood levels well above the predicted therapeutic range, with no drug-related adverse events observed. TTP-889 demonstrated an oral half-life of approximately 20 h, making it ideal for once-daily dosing. It also showed a predictable pharmacokinetic profile. There were no bleeding events reported during the phase I study (1).

1. *TTP-889 successfully completes phase I*. DailyDrugNews.com (Daily Essentials) May 13, 2004.

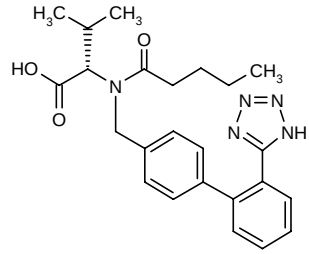
V-10153

Vernalis reported positive results from an initial phase II proof-of-concept study of V-10153 (formerly BB-10153, TAPgen) in acute myocardial infarction patients. V-10153 is a recombinant form of the thrombolytic protein thrombin-activatable plasminogen targeted at thrombotic disorders. Further development will continue, with a phase II study in stroke beginning in the first quarter of 2005 (1, 2).

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.

Valsartan



Valsartan (Diovan®), an angiotensin AT_1 receptor antagonist from Novartis, is currently available in over 80 countries for the first-line treatment of hypertension and in more than 50 countries for use in heart failure. In 2004, it was approved in Turkey, the U.K. and Sweden for improving survival and reducing cardiovascular events in patients at high risk after surviving a heart attack. It is now available in the U.K. for this indication. Further filings for use in heart failure patients have been submitted in the U.S., Switzerland, Australia and other European and certain Asian and Latin American countries.

In the VALIANT (VALsartan In Acute myocardial infarctioN Trial) in 14,703 post-heart attack patients, valsartan prolonged survival after heart attack as effectively as the ACE inhibitor captopril, and was at least as effective as the ACE inhibitor in reducing recurrent heart attacks and hospitalizations for heart failure in these patients. The effects of valsartan in combination with captopril were also studied and showed similar overall results, adding no additional mortality benefit above monotherapy. Valsartan is the only cardiovascular agent ever demonstrated by a head-to-head trial to have matched the proven benefits of an ACE inhibitor in these patients. The valsartan clinical research program involves more than 50,000 patients. The next trial to report will be VALUE (Valsartan Antihypertensive Long-Term Use Evaluation), a study of 15,314 hypertensive patients with at least 1 additional risk factor for cardiovascular events. The NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial is also ongoing in 9,150 prediabetes patients at risk for cardiovascular events. VAL-MARC continues to study the effects of valsartan on CRP in 5,610 high blood pressure patients (1-4).

1. *Novartis files sNDA for new indication for Diovan.* DailyDrugNews.com (Daily Essentials) Jan 5, 2004.

2. *Novartis files global applications for new Diovan indication.* DailyDrugNews.com (Daily Essentials) Feb 4, 2004.

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

4. *Diovan approved in Sweden to treat high-risk heart attack patients.* DailyDrugNews.com (Daily Essentials) Dec 3, 2004.

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Lyakishev, A.A. *Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. Results of VALIANT.* Kardiologiya 2004, 44(1): 73.

Mirza, A.A., Kober, L., Velazquez, E.J., White, H., Aylward, P.E., Kenchaiah, S., Wright, R.S., Solomon, S.D. *Influence of body mass index on mortality following high-risk myocardial infarction: The VALIANT experience.* 8th Annu Sci Meet Heart Fail Soc Am (Sept 12-15, Toronto) 2004, Abst 321.

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Solomon, S.D., Skali, H., Anavekar, N.S., Van de Werf, F., Barvik, S., Ghali, J.K., Bourgoun, M., Pfeffer, M.A. *The effect of valsartan, captopril, or both on left ventricular size and function following high-risk myocardial infarction: The VALIANT Echo study.* 8th Annu Sci Meet Heart Fail Soc Am (Sept 12-15, Toronto) 2004, Abst 029.

Solomon, S.D., Velazquez, E.J., White, H., Zelenkofske, S., Dalby, A.J., Leimberger, J.D., Myers, M., McMurray, J.J.V. *Hypertension and the risk of adverse cardiovascular outcomes following myocardial infarction: The VALIANT experience.* 8th Annu Sci Meet Heart Fail Soc Am (Sept 12-15, Toronto) 2004, Abst 334.

VEGF-2 Gene Therapy

Corautus Genetics has opened a phase IIb trial to evaluate the safety and efficacy of vascular endothelial growth factor-2 (VEGF-2) gene therapy for the treatment of severe cardiovascular disease. The randomized, double-blind, dose-ranging, placebo-controlled GENASIS (GENnetic Angiogenic Stimulation Investigational Study) trial will enroll up to 404 patients with class III or IV angina at around 20 U.S. sites. The trial will evaluate the efficacy and safety of defined doses of VEGF-2 delivered percutaneously via the Boston Scientific Stiletto™ endocardial direct injection catheter system, pursuant to their 2003 strategic alliance for the joint development of the VEGF-2 gene therapy. VEGF-2 is a growth factor believed to promote therapeutic angiogenesis. In the new study, VEGF-2 is delivered to the ischemic tissue in the heart muscle in the form of a naked DNA plasmid. Once administered, the DNA plasmid appears to be taken up and expressed by myocardium near the injection site. Inside the cell, the DNA plasmid then enters the nucleus of the cell without requiring incorporation into the genomic DNA. The phase IIb trial expects to see the effect of the expression of DNA-encoded VEGF-2, which in turn stimulates the growth of new blood vessels by promoting the migration and proliferation of endothelial cells in the heart (1).

1. *Phase IIb study evaluates VEGF-2 for severe cardiovascular disease.* DailyDrugNews.com (Daily Essentials) Sept 13, 2004.

VLTS-934/VLTS-589

A phase IIb trial of VLTS-934 (PINC™ polymer) was recently initiated at Valentis in patients with PAD, specifically intermittent claudication. This double-blind, randomized, placebo-controlled study in approximately 148 patients will examine the efficacy and safety of the nonionic block copolymer, or poloxamer, compared to placebo, with a primary endpoint of improvement in exercise tolerance. This trial follows a previously completed phase IIa trial in 105 patients that investigated the company's Deltavasc™ product (VLTS-589) combining VLTS-934 with the angiogenesis gene *Del-1* (developmental endothelial locus-1). In that trial, both products similarly increased exercise tolerance and the ankle-brachial index. The company intends to assess the potential benefits of Deltavasc™ in noncardiovascular conditions (1-4).

1. *Enrollment completed in phase II study of Deltavasc for PAD.* DailyDrugNews.com (Daily Essentials) April 1, 2004.

2. Rajagopalan, S., Snell, J., Young, S.W., Schaer, G.L. *Deltavasc™ - Phase I study of intramuscular administration of plasmid Del-1 (developmentally regulated endothelial cell locus-1) in humans with peripheral arterial disease (PAD).* 7th Annu Meet Am Soc Gene Ther (June 2-6, Minneapolis) 2004, Abst 194.

3. *Phase II results on the efficacy of Deltavasc in peripheral artery disease.* DailyDrugNews.com (Daily Essentials) Oct 4, 2004.

4. *Valentis announces initiation of phase IIb clinical trial of VLTS-934 for the treatment of peripheral arterial disease.* Valentis Press Release 2005, March 31.

Additional References

Rajagopalan, S. et al. *A phase II multicenter, randomized, double-blind, placebo-controlled trial of plasmid Del-1 (developmen-*

tally regulated endothelial locus 1) in subjects with intermittent claudication secondary to peripheral arterial disease: Δ1-PAD. Circulation 2004, 110(17, Suppl. 3): Abst 2439.

Rajagopalan, S., Olin, J.W., Young, S. et al. *Design of the Del-1 for therapeutic angiogenesis trial (Δ-1), a phase II multicenter, double-blind, placebo-controlled trial of VLTS-589 in subjects with intermittent claudication secondary to peripheral arterial disease.* Hum Gene Ther 2004, 15(6): 619.

Rajagopalan, S., Snell, J., Litt, M., Schaer, G.L., Karisberg, R., Dohad, S., Young, S.W. *A phase I study of intramuscular administration of plasmid, developmentally regulated endothelial cell locus-1 gene, in humans with peripheral arterial disease.* 53rd Annu Sci Sess Am Coll Cardiol (March 7-10, New Orleans) 2004, Abst 1066-191.

VMDA-3601

VMDA-3601, which combines ViroMed's proprietary naked DNA vector with the gene for vascular endothelial growth factor 165 (VEGF165), is in phase II development at Dong-A and ViroMed as a new treatment for PAD. According to ViroMed, VMDA-3601 promotes angiogenesis and therefore compensates for degeneration resulting from PAD.

VT-111

A spin-off from Roberts Research Institute, Viron Therapeutics reported last year that it was ready to advance its lead drug candidate VT-111 to phase II clinical trials. An antiinflammatory protein, VT-111 may have potential for preventing acute inflammation by blocking the migration of immune cells (macrophages and monocytes) into unstable coronary plaque, thereby preventing heart attacks. It may also reduce inflammation related to transplant surgery. The company completed a phase I trial in 2003 assessing the tolerability, safety and pharmacokinetics of the protein (1, 2).

1. *Strong endorsement from industry leaders.* Viron Therapeutics Press Release 2004, Jan 28.

2. *Viron Therapeutics announces appointment of new President & CEO.* Viron Therapeutics Press Release 2004, July 26.

VX-702

In mid-2004, Vertex announced topline results from the pilot phase IIa study of VX-702, a novel, orally active inhibitor of p38 mitogen-activated protein (MAP) kinase. The study was designed to evaluate the safety and tolerability of VX-702 in patients with ACS undergoing PCI. Preliminary results indicated that VX-702 met its primary endpoint of safety and tolerability. Treatment with VX-702 also resulted in dose-dependent inhibition of CRP. As part of its development program for VX-702, Vertex also plans to begin a phase IIa study in patients with rheumatoid arthritis (1-3). Kissei is Vertex's licensee for the Far East.

1. *Vertex Pharmaceuticals reports Q1 R&D highlights.* Vertex Pharmaceuticals Press Release 2004, April 26.

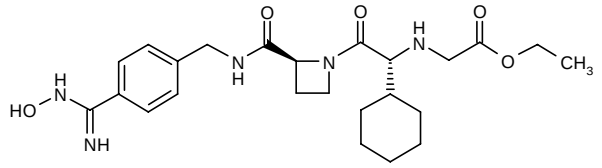
2. *Vertex Pharmaceuticals reports Q2 R&D highlights.* Vertex Pharmaceuticals Press Release 2004, July 26.

3. *Preliminary phase IIa data for VX-702 demonstrate tolerability and reduction in C-reactive protein in cardiovascular patients.* Vertex Pharmaceuticals Press Release 2004, Oct 18.

Additional References

Godfrey, C. et al. *The pharmacokinetics (PK) and pharmacodynamics (PD) of VX-702, a novel, oral p38MAP kinase inhibitor, in healthy volunteers.* Clin Pharmacol Ther 2004, 75(2): Abst PII-1.

Ximelagatran



Following the first approval by French authorities in late 2003 of AstraZeneca's anticoagulant compound ximelagatran (Exanta®) for the prevention of venous thromboembolic events (VTE) in patients undergoing major elective orthopedic surgery, *i.e.*, hip or knee replacement, the E.U. mutual recognition procedure was successfully completed and the first launch took place in Germany, followed by Portugal, Sweden, Finland, Norway, Iceland, Austria, Denmark and Switzerland, as well as Argentina. The E.U. approvals were based on the METHRO (Melegatran for Thrombin inhibition in Orthopedic surgery) study program, which compared injectable low-molecular-weight heparin, initiated in the evening before surgery, with preoperative (METHRO II) or postoperative (METHRO III) initiation of melagatran, followed by oral ximelagatran, in 4,688 patients undergoing total hip or knee replacement. Filings were also made in the U.S. for three indications: the prevention of VTE in patients undergoing knee replacement surgery; the prevention of stroke and other thromboembolic complications associated with atrial fibrillation; and long-term secondary prevention of VTE after standard treatment for an episode of acute VTE. The FDA subsequently decided not to grant approval of the drug for these indications. Additional filings were also made in France for two new indications in that and other E.U. markets: the prevention of stroke and other thromboembolic complications associated with atrial fibrillation; and the treatment of VTE. However, the French regulatory authorities subsequently

Table XVI: Clinical studies of ximelagatran (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Atrial fibrillation	Double-blind Open Pooled/meta-analysis	Ximelagatran, 36 mg p.o. b.i.d. x 19 [mean] mo Warfarin, adjusted to target INR of 2.0-3.0 x 19 [mean] mo	7332	Compared with dose-adjusted warfarin, ximelagatran was as effective in preventing thromboembolism and was associated with a lower incidence of hemorrhage in patients with atrial fibrillation	12
Surgery, Venous thrombosis prophylaxis	Open Multicenter	Ximelagatran, 24 mg b.i.d. x 7-12 d Ximelagatran, 36 mg b.i.d. x 7-12 d Warfarin, INR 1.8-3.0 x 7-12 d	2301	Ximelagatran provided more effective venous thromboembolism prophylaxis than warfarin in patients undergoing total knee replacement	14

requested further information confirming the efficacy and demonstrating safety of ximelagatran in atrial fibrillation to allow a definitive benefit/risk assessment to be made. For VTE treatment, the authority does not believe the data presented in the single THRIVE (Thrombin Inhibitor in Venous Thromboembolism) Treatment study provide adequate support for this use of ximelagatran and is proposing a rejection of this indication. Ximelagatran is a small-molecule double prodrug of the noncovalent peptide thrombin inhibitor melagatran, which exhibits poor bioavailability and absorption upon oral dosing. Following oral administration, the prodrug ximelagatran —itself inactive as an anticoagulant— is rapidly hydrolyzed and reduced to the active thrombin inhibitor melagatran. Ximelagatran is the first oral anticoagulant to reach late-stage clinical trials since the development of warfarin more than 50 years ago (1-7).

Alcohol did not alter the pharmacokinetics, pharmacodynamics, tolerability or safety of ximelagatran in healthy male and female volunteers. The potential interaction was assessed in a randomized, open, crossover study in which single doses of ximelagatran 36 mg were given with and without a single oral dose of alcohol (8).

Two clinical trials compared the efficacy of ximelagatran (36 mg p.o. b.i.d.) and a carefully adjusted warfarin dose in the prevention of stroke and systemic embolic events associated with persistent or paroxysmal nonvalvular atrial fibrillation. The SPORTIF (Stroke Prevention by ORal Thrombin Inhibitor in atrial Fibrillation) III study was a multicenter, randomized clinical trial that enrolled 3,407 European and Australian patients and concluded that ximelagatran was better tolerated and at least as effective as a well-controlled warfarin regimen. The same study design was used in the double-blind, randomized SPORTIF V trial that included 3,922 patients in the U.S. This study compared the first occurrence of strokes or systemic embolic events in both study groups, together with other parameters such as major and minor bleeding, treatment discontinuation, death and myocardial infarction (9). A pooled analysis of these studies indicated that ximelagatran therapy resulted in fewer minor and major bleeding events and was as effective as the comparator in preventing stroke and systemic embolic events. 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. 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) (10-12) (see Table XVI).

In the double-blind, randomized THRIVE Treatment study, 2,489 patients with DVT with or without PE were assigned to ximelagatran (36 mg p.o. b.i.d.) for 6 months or enoxaparin (1 mg/kg s.c. b.i.d.) for a minimum of 5 days followed by warfarin (targeted international normalized ratio [INR] of 2-3) for 6 months. Both regimens were equally effective in preventing venous thromboembolism (13).

Venous thromboembolism prophylaxis with ximelagatran (24 or 36 mg b.i.d.) was compared to that with warfarin (target INR = 2.5) in a multicenter trial in 2,301 patients who underwent total knee replacement. With no increase in bleeding, ximelagatran 36 mg was associated with a lower incidence of venous thromboembolism than warfarin through 12 days (20.3% *vs.* 27.6%) (14) (Table XVI).

1. *France is first country to approve oral thrombin inhibitor.* DailyDrugNews.com (Daily Essentials) Dec 30, 2003.

2. *AstraZeneca reports 2003 year-end R&D highlights.* AstraZeneca Press Release 2004, Jan 29.

3. *Exanta completes E.U. mutual recognition procedure.* DailyDrugNews.com (Daily Essentials) May 12, 2004.

4. *FDA advisory committee recommends further data for Exanta approval.* DailyDrugNews.com (Daily Essentials) Sept 14, 2004.

5. *France requests further information on Exanta for AF.* DailyDrugNews.com (Daily Essentials) Jan 26, 2005.

6. *No FDA approval for Exanta.* DailyDrugNews.com (Daily Essentials) Oct 14, 2004.

7. *Exanta launched in Germany.* DailyDrugNews.com (Daily Essentials) June 25, 2004.

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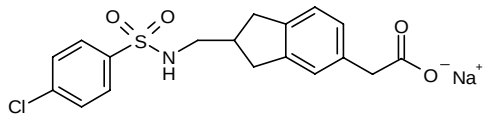
XRP-0038

XRP-0038, a nonviral vector for the delivery of the gene encoding for fibroblast growth factor-1 (FGF-1), an angiogenic growth factor, is currently in phase II development for the treatment of PVD in the U.S. and Europe by the former Gencell, a wholly owned subsidiary of Sanofi-Aventis renamed Centelion in October. Gencell established an agreement in 2000 with Vical for the use of Vical's naked DNA technology to deliver the FGF gene.

YM-150

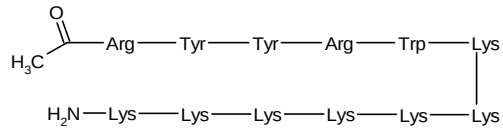
The orally active factor Xa inhibitor YM-150 is in phase II clinical evaluation by Astellas Pharma in Europe as a potential new drug for the prevention of DVT and the prevention of thromboembolism in atrial fibrillation.

Z-335



The thromboxane A_2 (TxA_2) receptor antagonist Z-335 (Zeria) is currently in phase II development in Japan for the treatment of chronic arterial occlusive disorders (PAD).

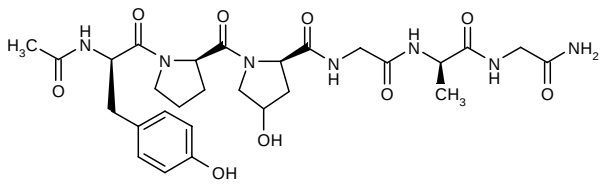
ZP-120



ZP-120 is a first-in-class peripherally acting ORL-1 receptor agonist which has advanced to phase II clinical testing at Zealand Pharma for heart failure. The compound produces a rapid and significant increase in the urinary excretion of water (aquaretic effect), while preventing excessive electrolyte loss, and may offer faster and more effective relief of fluid overload in patients with acute CHF compared to conventional diuretics. Due to its additional vasodilating effect, it also has the potential to reduce lung congestion in heart failure patients. Proof of principle was demonstrated in a phase I trial of s.c. ZP-120 in healthy volunteers and a phase IIa trial in patients with stable heart failure was then conducted using a continuous i.v. infusion. Results demonstrated that it was well tolerated and another phase II trial in patients with more severe disease is planned (1).

1. Zealand Pharma Annual Report 2004.

ZP-123 (GAP-486)



A novel small peptide that modulates protein channels in the heart known as gap junctions and a drug candidate

for the treatment of arrhythmias, ZP-123 (GAP-486) is being codeveloped by Zealand Pharma and Wyeth under a 2003 licensing agreement. Gap junctions are responsible for conducting electrical impulses between cells to maintain the heart's normal rhythm and modulation of these channels is therefore considered a promising approach to the treatment of cardiovascular disorders. Preclinical toxicological evaluation was completed last year, followed by the initiation of phase I studies for the prevention of ventricular tachyarrhythmias in patients with myocardial ischemia. Phase II trials in patients with a history of heart disease and acute myocardial ischemia are anticipated to commence by mid-2005 (1, 2).

1. Zealand Pharma Annual Report 2004.

2. *Zealand Pharma enters into expanded collaboration agreement with Wyeth Pharmaceutical.* Zealand Pharma Press Release 2005, March 4.