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Annual Update 2004/2005 - Treatment of Respiratory Disorders

As in previous issues, the goal of this section is to present a balanced picture of the current status of therapies for respiratory disorders in the clinical stage, summarizing in a few pages the most important advances in this area over the last year or so. A table of oncolytic drugs for the treatment of respiratory/thoracic cancers (lung cancer, mesothelioma, thymoma) has been included at the end of this review.

J.R. Prous
Editor

Treatment of Respiratory Disorders by Condition

Condition	Phase	Drug	Source
ARDS	II	Lucinactant[2]	Discovery Laboratories/Esteve
	I	ALS-886	Advanced Life Sciences
Asthma	L-2005	Ciclesonide[2]	Altana/Sanofi-Aventis/Teijin
	Prereg. (EU)	Roflumilast[2]	Altana/Pfizer
	III	Levocetirizine[1]	UCB Pharma
	III	MCC-847	Mitsubishi Pharma
	II	274150	GlaxoSmithKline
	II	685698	GlaxoSmithKline
	II	766994	GlaxoSmithKline
	II	AER-001	Aerovance
	II	Andolast	Rotta
	II	AVT-01	Avontec
	II	Bimosiamose	Revotar Biopharmaceuticals
	II	CC-10004	Celgene
	II	CHF-4226 (TA-2005)	Chiesi/Tanabe Seiyaku
	II	Corus-1030	Corus Pharma
	II	CS-003	Sankyo
	II	CYT005-AllQbG10	Cytos Biotechnology
	II	Daclizumab[1]	Protein Design Labs/Roche
	II	EPI-12323	EpiGenesis
	II	Etanercept[1,2]	Wyeth
	II	Etiprednol dicloacetate	Ivax
	II	F-991	Fornix BioSciences
	II	GSK-159797 (TD-3327)	GlaxoSmithKline/Theravance
	II	GSK-597901	GlaxoSmithKline/Theravance
	II	GSK-678007	GlaxoSmithKline/Theravance
	II	Interferon gamma-1b[1]	Mondobiotech
	II	ISS-1018	Dynavax
	II	KCO-912	Novartis
	II	LAS-34273	Almirall Prodesfarma
	II	ME-3301	Meiji Seika
	II	Mepolizumab	GlaxoSmithKline
	II	MN-001	MediciNova
	II	NCX-1020	NicOx
	II	NS-126	Nippon Shinyaku/SSP Co.
	II	Ono-6126	Ono
	II	Pimecrolimus[1,2]	Novartis
	II	Pumactant	Britannia/AirPharma
	II	QAB-149	Novartis

Continuation

Treatment of Respiratory Disorders by Condition

Condition	Phase	Drug	Source
Asthma	II	R-411	Roche
	II	RBx-7796	Ranbaxy
	II (JP)	Roflumilast[2]	Tanabe Seiyaku
	II	S-5751	Shionogi
	II	SRP-299	SR Pharma/Sakai
	II	Tacrolimus[1,2], inhaled	Fujisawa
	II	Talactoferrin alfa	Agennix
	II	Tofimilast	Pfizer
	I/II	AVE-0309	Sanofi-Aventis
	I/II	AVE-5638	Sanofi-Aventis
	I/II	AVE-5883	Sanofi-Aventis
	I/II	AVE-7279	Sanofi-Aventis
	I/II	Ciclesonide/formoterol fumarate	Sanofi-Aventis
	I/II	Lumiliximab	Biogen Idec
	I/II	YS-TH2	Y's Therapeutics
	I	799943	GlaxoSmithKline
	I	ACZ-885	Novartis
	I	AI-128	Acusphere
	I	ASM-8	Topigen
	I	AVP-13358	Avanir
	I	AZD-3778	AstraZeneca
	I	CAT-354	Cambridge Antibody Technology
	I	CDP-323	UCB Pharma
	I	DSC-104	Discovery Laboratories
	I	DW-908e	Daiichi Pharmaceutical
	I	Efipladib	Wyeth
	I	GRC-3886	Glenmark Pharmaceuticals/Forest
	I	GSK-159802	GlaxoSmithKline/Theravance
	I	GSK-159802	GlaxoSmithKline/Theravance
	I	GSK-642444	GlaxoSmithKline/Theravance
	I	GSK-642444	GlaxoSmithKline/Theravance
	I	Hydroxychloroquine[1], aerosolized	APT Pharmaceuticals
	I	IL-4/IL-13 Trap	Regeneron
	I	KP-496	Kaken
	I	LAS-35201	Almirall Prodesfarma
	I	MEDI-528	MedImmune/Genaera
	I	MEN-91507	Menarini
	Discontinued	IPL-512602 (AVE-0547)	Inflazyme/Aventis
	Discontinued	IPL-550260	Inflazyme
	Discontinued	KW-4490	Kyowa Hakko
	Discontinued	NGD-2000-1	Neurogen
Bronchiectasis	II	Mannitol[1], inhaled	Pharmaxis
Bronchitis	II/III	Arofylline	Almirall Prodesfarma
	II	LAS-34273	Almirall Prodesfarma
	I	LAS-35201	Almirall Prodesfarma
Bronchitis, chronic	I	Mannitol[1], inhaled	Pharmaxis
Bronchitis, chronic, acute exacerbation	L-2004	Gemifloxacin mesilate[2]	Oscient Pharmaceuticals
COPD	Prereg.	Cilomilast[2]	GlaxoSmithKline
	Prereg. (EU)	Roflumilast[2]	Altana/Pfizer
	III	Arformoterol	Sepracor
	III	*N*-Acetylcysteine[1,2]	Zambon
	II	202405	GlaxoSmithKline
	II	274150	GlaxoSmithKline
	II	685698	GlaxoSmithKline
	II	AD-237	Arakis/Vectura
	II	AWD-12-281 (842470)[2]	elbion/GlaxoSmithKline
	II	CHF-4226 (TA-2005)	Chiesi/Tanabe Seiyaku
	II	CS-003	Sankyo
	II	GSK-159797 (TD-3327)	GlaxoSmithKline/Theravance
	II	GSK-597901	GlaxoSmithKline/Theravance
	II	GSK-678007	GlaxoSmithKline/Theravance

Continuation

Treatment of Respiratory Disorders by Condition

Condition	Phase	Drug	Source
COPD	II	IC-485	Icos
	II	Ono-6126	Ono
	II	Pranlukast hydrate[1,2]	Ono
	II	QAB-149	Novartis
	II	Tetomilast	Otsuka
	I	656933	GlaxoSmithKline
	I	681323	GlaxoSmithKline
	I	799943	GlaxoSmithKline
	I	AZD-8309	AstraZeneca
	I	AZD-9056	AstraZeneca
	I	CTX-100	CoTherix
	I	GRC-3886	Glenmark Pharmaceuticals/Forest
	I	GSK-159802	GlaxoSmithKline/Theravance
	I	GSK-159802	GlaxoSmithKline/Theravance
	I	GSK-642444	GlaxoSmithKline/Theravance
	I	GSK-642444	GlaxoSmithKline/Theravance
	I	NCX-1020	NicOx
	I (JP)	Roflumilast[2]	Tanabe Seiyaku
Cystic fibrosis	II	Amelubant	Boehringer Ingelheim
	II	Corus-1020	Corus Pharma
	II	DCF-987	BCY LifeSciences
	II	Denufosol tetrasodium	Inspire Pharmaceuticals
	II	DX-890	Debiopharm/Dyax
	II	Mannitol[1], inhaled	Pharmaxis
	II	Moli-1901	AOP Orphan/Lantibio
	II	PGN-0052	Pharmagene
	II	SPI-8811	Sucampo Pharmaceuticals
	II	Talniflumate[1,2]	Genaera
	II	tgAAVCF	Targeted Genetics
	I/II	PLAS*min*™ complex CFTR	Copernicus
	I	Curcumin	Seer Pharmaceuticals
	I	Doripenem[2]	Peninsula Pharmaceuticals
	I	HE-2000	Hollis-Eden
	I	PTC-124	PTC Therapeutics
	IND filed	Histatin P-113D	Demegen
	IND filed	MP-601205	Mpex Pharmaceuticals
Emphysema	II	R-667	Roche
Emphysema, hereditary	II	Recombinant α_1-antitrypsin	Arriva Pharmaceuticals/Baxter
	I	CTX-100	CoTherix
Idiopathic pulmonary fibrosis	III	Interferon gamma-1b[1]	InterMune
	III	*N*-Acetylcysteine[1,2]	Zambon
	III	Pirfenidone[2]	Shionogi/InterMune
	II/III	Bosentan[1,2]	Actelion
	II	Etanercept[1,2]	Wyeth
	I	FG-3019	FibroGen
	IND filed	GC-1008	Cambridge Antibody Technology/ Genzyme
Meconium aspiration syndrome	III	Lucinactant[2]	Discovery Laboratories/Esteve
Neonatal respiratory distress	Prereg.	Lucinactant[2]	Discovery Laboratories/Esteve
Pneumonia	L-2004	Gemifloxacin mesilate[2]	Oscient Pharmaceuticals
	III	Tifacogin	Chiron
	Discontinued	Iseganan hydrochloride[2]	IntraBiotics
Pulmonary hypertension	L-2004	Iloprost[1,2], solution for inhalation	Schering AG/Berlex/CoTherix
	Prereg.	Sildenafil citrate[1,2]	Pfizer
	III	Ambrisentan	Myogen
	III	Sitaxsentan sodium[2]	Encysive Pharmaceuticals
	II	Aviptadil[2]	Mondobiotech
	I	TBC-3711	Encysive Pharmaceuticals

Continuation

Treatment of Respiratory Disorders by Condition

Condition	Phase	Drug	Source
Respiratory disorders	II	C-3193	Merck & Co.
	II	C-3885	Merck & Co.
	I	AE-3763	Dainippon Pharmaceutical
Rhinitis, allergic	III	685698	GlaxoSmithKline
	III	Bilastine	Faes
	III	Efletirizine[2]	UCB Pharma
	III	Loteprednol etabonate[1,2]	Ivax
	III	Omalizumab[1,2]	Sankyo
	II/III	AIC	Dynavax/UCB Pharma
	II	R-112	Rigel
	II	274150	GlaxoSmithKline
	II	766994	GlaxoSmithKline
	II	Andolast	Rotta
	II	CS-712	Sankyo
	II	EV-131	Evolutec
	II	F-991	Fornix BioSciences
	II	MCC-847	Mitsubishi Pharma
	II	NCX-1510	Biolipox/NicOx
	II	NS-126	Nippon Shinyaku/SSP Co.
	II	RBx-7796	Ranbaxy
	II	S-5751	Shionogi
	II	TBN-15	Teijin
	I/II	AVE-7279	Sanofi-Aventis
	I/II	Bertilimumab	Cambridge Antibody Technology
	I/II	Lumiliximab	Biogen Idec
	I	799943	GlaxoSmithKline
	I	AVP-13358	Avanir
	I	AZD-3778	AstraZeneca
	I	Ciclesonide[1,2]	Altana
	I	Ono-4127.Na	Ono
	I	TAK-201	Takeda
Rhinitis, allergic seasonal	I	CRX-675	Corixa
	Clinical	L-888839	Merck Frosst
Rhinoconjunctivitis, allergic	II	CYT005-AllQbG10	Cytos Biotechnology
Sarcoidosis	I/II	Aviptadil[2]	Mondobiotech
SARS	I	SARS vaccine	Sinovac Biotech
Sinusitis	III	Gemifloxacin mesilate[1,2]	Oscient Pharmaceuticals
	II	Pranlukast hydrate[1,2]	Ono
	I	SPRC-AB01	SinusPharma
Upper respiratory tract disorders	Prereg.	Zaltoprofen[1,2]	Zeria/Nippon Chemiphar
	III	Ipratropium bromide/xylometazoline hydrochloride	Nycomed Pharma

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

Treatment of Respiratory Disorders by Source

Source	Condition	Drug	Phase
Actelion	Idiopathic pulmonary fibrosis	Bosentan[1,2]	II/III
Acusphere	Asthma	AI-128	I
Advanced Life Sciences	ARDS	ALS-886	I
Aerovance	Asthma	AER-001	II
Agennix	Asthma	Talactoferrin alfa	II
AirPharma	Asthma	Pumactant	II
Almirall Prodesfarma	Asthma	LAS-34273	II
		LAS-35201	I
	Bronchitis	Arofylline	II/III
		LAS-34273	II
		LAS-35201	I
Altana	Asthma	Ciclesonide[2]	L-2005
		Roflumilast[2]	Prereg. (EU)
	COPD	Roflumilast[2]	Prereg. (EU)
	Rhinitis, allergic	Ciclesonide[1,2]	I
AOP Orphan	Cystic fibrosis	Moli-1901	II
APT Pharmaceuticals	Asthma	Hydroxychloroquine[1], aerosolized	I
Arakis	COPD	AD-237	II
Arriva Pharmaceuticals	Emphysema, hereditary	Recombinant α_1-antitrypsin	II
AstraZeneca	Asthma	AZD-3778	I
	COPD	AZD-8309	I
		AZD-9056	I
	Rhinitis, allergic	AZD-3778	I
Avanir	Asthma	AVP-13358	I
	Rhinitis, allergic	AVP-13358	I
Aventis (now Sanofi-Aventis)	Asthma	IPL-512602 (AVE-0547)	Discontinued
Avontec	Asthma	AVT-01	II
Baxter	Emphysema, hereditary	Recombinant α_1-antitrypsin	II
BCY LifeSciences	Cystic fibrosis	DCF-987	II
Berlex	Pulmonary hypertension	Iloprost[1,2], solution for inhalation	L-2004
Biogen Idec	Asthma	Lumiliximab	I/II
Biogen Idec	Rhinitis, allergic	Lumiliximab	I/II
Biolipox	Rhinitis, allergic	NCX-1510	II
Boehringer Ingelheim	Cystic fibrosis	Amelubant	II
Britannia	Asthma	Pumactant	II
Cambridge Antibody Technology	Asthma	CAT-354	I
	Idiopathic pulmonary fibrosis	GC-1008	IND filed
	Rhinitis, allergic	Bertilimumab	I/II
Celgene	Asthma	CC-10004	II
Chiesi	Asthma	CHF-4226 (TA-2005)	II
	COPD	CHF-4226 (TA-2005)	II
Chiron	Pneumonia	Tifacogin	III
Copernicus	Cystic fibrosis	PLAS*min*™ complex CFTR	I/II
Corixa	Rhinitis, allergic seasonal	CRX-675	I
Corus Pharma	Asthma	Corus-1030	II
	Cystic fibrosis	Corus-1020	II
CoTherix	COPD	CTX-100	I
	Emphysema, hereditary	CTX-100	I
	Pulmonary hypertension	Iloprost[1,2], solution for inhalation	L-2004
Cytos Biotechnology	Asthma	CYT005-AllQbG10	II
	Rhinoconjunctivitis, allergic	CYT005-AllQbG10	II
Daiichi Pharmaceutical	Asthma	DW-908e	I
Dainippon Pharmaceutical	Respiratory disorders	AE-3763	I
Debiopharm	Cystic fibrosis	DX-890	II
Demegen	Cystic fibrosis	Histatin P-113D	IND filed
Discovery Laboratories	ARDS	Lucinactant[2]	II
	Asthma	DSC-104	I
	Meconium aspiration syndrome	Lucinactant[2]	III
	Neonatal respiratory distress	Lucinactant[2]	Prereg.
Dyax	Cystic fibrosis	DX-890	II
Dynavax	Asthma	ISS-1018	II
	Rhinitis, allergic	AIC	II/III
elbion	COPD	AWD-12-281 (842470)[2]	II

Continuation

Treatment of Respiratory Disorders by Source

Source	Condition	Drug	Phase
Encysive Pharmaceuticals	Pulmonary hypertension	Sitaxsentan sodium[2]	III
		TBC-3711	I
EpiGenesis	Asthma	EPI-12323	II
Esteve	ARDS	Lucinactant[2]	II
	Meconium aspiration syndrome	Lucinactant[2]	III
	Neonatal respiratory distress	Lucinactant[2]	Prereg.
Evolutec	Rhinitis, allergic	EV-131	II
Faes	Rhinitis, allergic	Bilastine	III
FibroGen	Idiopathic pulmonary fibrosis	FG-3019	I
Forest	Asthma	GRC-3886	I
	COPD	GRC-3886	I
Fornix BioSciences	Asthma	F-991	II
	Rhinitis, allergic	F-991	II
Fujisawa	Asthma	Tacrolimus[1,2], inhaled	II
Genaera	Asthma	MEDI-528	I
	Cystic fibrosis	Talniflumate[1,2]	II
Genzyme	Idiopathic pulmonary fibrosis	GC-1008	IND filed
GlaxoSmithKline	Asthma	274150	II
		685698	II
		766994	II
		799943	I
		GSK-159797 (TD-3327)	II
		GSK-159802	I
		GSK-597901	II
		GSK-642444	I
		GSK-678007	II
		Mepolizumab	II
	COPD	202405	II
		274150	II
		656933	I
		681323	I
		685698	II
		799943	I
		AWD-12-281 (842470)[2]	II
		Cilomilast[2]	Prereg.
		GSK-159797 (TD-3327)	II
		GSK-159802	I
		GSK-597901	II
		GSK-642444	I
		GSK-678007	II
	Rhinitis, allergic	274150	II
		685698	III
		766994	II
		799943	I
Glenmark Pharmaceuticals	Asthma	GRC-3886	I
	COPD	GRC-3886	I
Hollis-Eden	Cystic fibrosis	HE-2000	I
Icos	COPD	IC-485	II
Inflazyme	Asthma	IPL-512602 (AVE-0547)	Discontinued
		IPL-550260	Discontinued
Inspire Pharmaceuticals	Cystic fibrosis	Denufosol tetrasodium	II
InterMune	Idiopathic pulmonary fibrosis	Interferon gamma-1b[1]	III
		Pirfenidone[2]	III
IntraBiotics	Pneumonia	Iseganan hydrochloride[2]	Discontinued
Ivax	Asthma	Etiprednol dicloacetate	II
	Rhinitis, allergic	Loteprednol etabonate[1,2]	III
Kaken	Asthma	KP-496	I
Kyowa Hakko	Asthma	KW-4490	Discontinued
Lantibio	Cystic fibrosis	Moli-1901	II
MediciNova	Asthma	MN-001	II
MedImmune	Asthma	MEDI-528	I
Meiji Seika	Asthma	ME-3301	II
Menarini	Asthma	MEN-91507	I

Continuation

Treatment of Respiratory Disorders by Source

Source	Condition	Drug	Phase
Merck & Co.	Respiratory disorders	C-3193	II
		C-3885	II
Merck Frosst	Rhinitis, allergic seasonal	L-888839	Clinical
Mitsubishi Pharma	Asthma	MCC-847	III
	Rhinitis, allergic	MCC-847	II
Mondobiotech	Asthma	Interferon gamma-1b[1]	II
	Pulmonary hypertension	Aviptadil[2]	II
	Sarcoidosis	Aviptadil[2]	I/II
Mpex Pharmaceuticals	Cystic fibrosis	MP-601205	IND filed
Myogen	Pulmonary hypertension	Ambrisentan	III
Neurogen	Asthma	NGD-2000-1	Discontinued
NicOx	Asthma	NCX-1020	II
	COPD	NCX-1020	I
	Rhinitis, allergic	NCX-1510	II
Nippon Chemiphar	Upper respiratory tract disorders	Zaltoprofen[1,2]	Prereg.
Nippon Shinyaku	Asthma	NS-126	II
	Rhinitis, allergic	NS-126	II
Novartis	Asthma	ACZ-885	I
		KCO-912	II
		Pimecrolimus[1,2]	II
		QAB-149	II
	COPD	QAB-149	II
Nycomed Pharma	Upper respiratory tract disorders	Ipratropium bromide/xylometazoline hydrochloride	III
Ono	Asthma	Ono-6126	II
	COPD	Ono-6126	II
		Pranlukast hydrate[1,2]	II
	Rhinitis, allergic	Ono-4127.Na	I
	Sinusitis	Pranlukast hydrate[1,2]	II
Oscient Pharmaceuticals	Bronchitis, chronic, acute exacerbation	Gemifloxacin mesilate[2]	L-2004
	Pneumonia	Gemifloxacin mesilate[2]	L-2004
	Sinusitis	Gemifloxacin mesilate[1,2]	III
Otsuka	COPD	Tetomilast	II
Peninsula Pharmaceuticals	Cystic fibrosis	Doripenem[2]	I
Pfizer	Asthma	Roflumilast[2]	Prereg.
		Tofimilast	II
	COPD	Roflumilast[2]	Prereg.
	Pulmonary hypertension	Sildenafil citrate[1,2]	Prereg.
Pharmagene	Cystic fibrosis	PGN-0052	II
Pharmaxis	Bronchiectasis	Mannitol[1], inhaled	II
	Bronchitis, chronic	Mannitol[1], inhaled	I
	Cystic fibrosis	Mannitol[1], inhaled	II
Protein Design Labs	Asthma	Daclizumab[1]	II
PTC Therapeutics	Cystic fibrosis	PTC-124	I
Ranbaxy	Asthma	RBx-7796	II
	Rhinitis, allergic	RBx-7796	II
Regeneron	Asthma	IL-4/IL-13 Trap	I
Revotar Biopharmaceuticals	Asthma	Bimosiamose	II
Rigel	Rhinitis, allergic	R-112	II
Roche	Asthma	Daclizumab[1]	II
		R-411	II
	Emphysema	R-667	II
Rotta	Asthma	Andolast	II
	Rhinitis, allergic	Andolast	II
Sakai	Asthma	SRP-299	II
Sankyo	Asthma	CS-003	II
	COPD	CS-003	II
	Rhinitis, allergic	CS-712	II
		Omalizumab[1,2]	III
Sanofi-Aventis	Asthma	AVE-0309	I/II
		AVE-5638	I/II
		AVE-5883	I/II
		AVE-7279	I/II
		Ciclesonide[2]	L-2005
		Ciclesonide/formoterol fumarate	I/II
	Rhinitis, allergic	AVE-7279	I/II

Continuation

Treatment of Respiratory Disorders by Source

Source	Condition	Drug	Phase
Schering AG	Pulmonary hypertension	Iloprost[1,2], solution for inhalation	L-2004
Seer Pharmaceuticals	Cystic fibrosis	Curcumin	I
Sepracor	COPD	Arformoterol	III
Shionogi	Asthma	S-5751	II
	Idiopathic pulmonary fibrosis	Pirfenidone[2]	III
	Rhinitis, allergic	S-5751	II
Sinovac Biotech	SARS	SARS vaccine	I
SinusPharma	Sinusitis	SPRC-AB01	I
SR Pharma	Asthma	SRP-299	II
SSP Co.	Asthma	NS-126	II
	Rhinitis, allergic	NS-126	II
Sucampo Pharmaceuticals	Cystic fibrosis	SPI-8811	II
Takeda	Rhinitis, allergic	TAK-201	I
Tanabe Seiyaku	Asthma	CHF-4226 (TA-2005)	II
		Roflumilast[2]	II (JP)
	COPD	CHF-4226 (TA-2005)	II
		Roflumilast[2]	I (JP)
Targeted Genetics	Cystic fibrosis	tgAAVCF	II
Teijin	Asthma	Ciclesonide[2]	L-2005
	Rhinitis, allergic	TBN-15	II
Theravance	Asthma	GSK-159797 (TD-3327)	II
		GSK-159802	I
		GSK-597901	II
		GSK-642444	I
		GSK-678007	II
	COPD	GSK-159797 (TD-3327)	II
		GSK-159802	I
		GSK-597901	II
		GSK-642444	I
		GSK-678007	II
Topigen	Asthma	ASM-8	I
UCB Pharma	Asthma	CDP-323	I
		Levocetirizine[1]	III
	Rhinitis, allergic	AIC	II/III
		Efletirizine[2]	III
Vectura	COPD	AD-237	II
Wyeth	Asthma	Efipladib	I
		Etanercept[1,2]	II
	Idiopathic pulmonary fibrosis	Etanercept[1,2]	II
Y's Therapeutics	Asthma	YS-TH2	I/II
Zambon	COPD	N-Acetylcysteine[1,2]	III
	Idiopathic pulmonary fibrosis	N-Acetylcysteine[1,2]	III
Zeria	Upper respiratory tract disorders	Zaltoprofen[1,2]	Prereg.

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

Treatment of Respiratory Disorders

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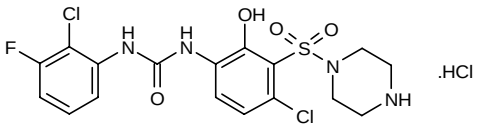
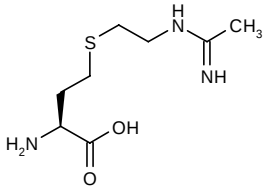
202405/656933/681323



656933

GlaxoSmithKline's respiratory pipeline includes several agents for chronic obstructive pulmonary disease (COPD) with different mechanisms of action. Among these are 202405, a muscarinic antagonist in phase II evaluation, 656933 (SB-656933), a selective chemokine CXCR2 (IL-8) receptor antagonist in phase I, and 681323, an orally active p38 protein kinase inhibitor in phase I trials for the treatment of COPD. 681323 is also in early clinical development for the treatment of atherosclerosis and rheumatoid arthritis.

274150



274150 (GW-274150) is a selective inhibitor of inducible nitric oxide synthase (iNOS) synthesized at GlaxoSmithKline and presently in phase II trials for the oral treatment of asthma, COPD and allergic rhinitis. The company is also evaluating 274150 in phase I and II trials for the treatment of migraine and rheumatoid arthritis, respectively.

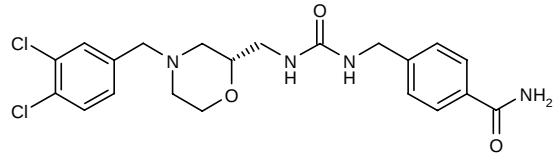
685698

685698 (GW-685698, Allermist), a once-daily glucocorticoid agonist for intranasal administration from GlaxoSmithKline, entered phase III clinical development for allergic rhinitis in the third quarter of 2004 based on positive phase II data. The compound is also in phase II clinical development, alone or in combination with a long-acting β_2-adrenoceptor agonist (LABA), for the treatment of asthma and COPD (1, 2).

1. *GlaxoSmithKline reports Q2 R&D highlights*. GlaxoSmithKline Press Release 2004, July 27.

2. *GlaxoSmithKline results announcement for the third quarter 2004*. GlaxoSmithKline Press Release 2004, Oct 28.

766994

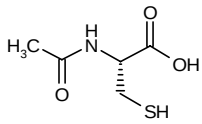


GlaxoSmithKline's oral chemokine CCR3 receptor antagonist 766994 (GW-766994) exerts antiinflammatory properties and has reached phase II trials for the treatment of asthma and allergic rhinitis.

799943

The glucocorticoid receptor agonist 799943 is undergoing phase I clinical evaluation at GlaxoSmithKline as a monotherapy for asthma and allergic rhinitis. The compound in combination with a LABA is also in early clinical development for asthma and COPD.

N-Acetylcysteine, New Indication



N-Acetylcysteine is an NF-κB activation inhibitor with antioxidant and mucolytic properties and known to stimulate intracellular glutathione production. Zambon, the originator of the drug, is evaluating *N*-acetylcysteine in phase III trials for the treatment of idiopathic pulmonary fibrosis (IPF) and COPD. In terms of nonrespiratory indications, Zambon is conducting phase II trials of *N*-acetylcysteine for renal failure and Adherex is carrying out phase I trials for the treatment of chemotherapy-induced thrombocytopenia. *N*-Acetylcysteine has been on the market for almost 35 years for the treatment of bronchial hypersecretion. In 1986, Dey launched the drug in the U.S. for the treatment of paracetamol overdose.

Results have been reported from Zambon's IFIGENIA (Idiopathic pulmonary Fibrosis International Group Exploring NACI Annual) study, showing that *N*-acetylcysteine substantially reduced the deterioration of lung function in patients with IPF. The multicenter, randomized, placebo-controlled trial enrolled 155 patients from 6 European countries between 2000 and 2003, after IPF diagnosis was confirmed by blinded, independent committees of histologists and radiologists. Patients were randomized to receive either 1800 mg/day of *N*-acetylcysteine (Fluimucil® 600, 3 x 600 mg/day) or placebo for 1 year, in addition to a standard treatment with corticosteroids and immunosuppressants (prednisone and azathioprine, respectively) as recommended by the ATS/ERS Consensus Statement. The primary endpoints of vital capacity (VC) and diffusing capacity (DL_{CO}) were found to be significantly better for *N*-acetylcysteine, both statistically and clinically, after 6 and 12 months of therapy. After 1 year, treatment with *N*-acetylcysteine significantly improved both VC and DL_{CO} by 9% and 24%, respectively, compared with placebo. Tolerability was excellent and similar for *N*-acetylcysteine and placebo, although signs of bone marrow toxicity were significantly reduced in the *N*-acetylcysteine group. The IFIGENIA study demonstrated that the *N*-acetylcysteine regimen substantially reduced the deterioration of lung function and is the first study to show positive results for a pharmacological therapy in IPF patients. The results confirm that the clinical benefits shown by *N*-acetylcysteine are most likely due to its antioxidant mechanism, which was demonstrated in earlier pivotal studies in patients with IPF. The finding could also be applicable to other respiratory conditions where oxidative stress plays a significant pathogenetic role, such as COPD (1).

A method has been claimed for the treatment of respiratory infections and, in particular, the prevention or arrestment of biofilm formation associated with pathogens such as *Staphylococcus aureus*. The claim comprises the preparation and administration of pharmaceutical formulations containing the antioxidant NF-κB activation inhibitor *N*-acetylcysteine and further embodies the optional inclusion of the broad-spectrum antimicrobial agent thiamphenicol in order to augment the activity of *N*-acetylcysteine (2).

1. *IFIGENIA trial opens up new possibilities for treating an orphan disease: IPF*. Zambon Press Release 2004, Sept 20.

2. Ungheri, D. et al. (Zambon Group SpA) *Pharmaceutical compsns. for the treatment of infections of the respiratory system by pathogenic agents*. WO 0400298.

Original monograph – Drugs Fut 1995, 20(6): 559.

ACZ-885

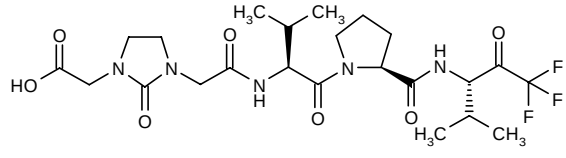
ACZ-885 is a monoclonal antibody specific for human IL-1β in phase I development by Novartis for the treatment of asthma.

AD-237

Arakis and Vectura's collaborative project AD-237, a novel inhaled bronchodilator treatment for COPD, has successfully completed a multicenter phase IIa clinical trial to study the safety and efficacy of a range of single doses in 45 COPD patients. The results of the phase IIa study showed that an optimized inhaled formulation of the drug offers a long-acting, once-daily profile. The formulation utilizes Vectura's patented PowderHale® technology to improve the efficiency of pulmonary delivery. Doses were administered using a commercially available dry powder capsule inhaler and FEV_1 was measured over a 32-h period. Results demonstrated clinically significant improvements in peak, average and trough FEV_1 *versus* placebo at all doses over the entire period studied. A clear dose-response relationship was seen and excellent tolerability was observed at all doses. The companies are now planning a phase IIb multiple-dose study under a U.S. IND regulatory authorization. AD-237 contains an antimuscarinic drug which is approved and marketed for different nonrespiratory indications (1).

1. *Phase IIa study of AD-237 in treatment of COPD shows positive results*. DailyDrugNews.com (Daily Essentials) May 19, 2004.

AE-3763



AE-3763 is a potent and selective leukocyte elastase inhibitor in phase I development by Dainippon

Pharmaceutical for the treatment of lung injury associated with systemic inflammatory response syndrome (SIRS). This compound is available for licensing.

AER-001

Aerovance, a new independent company dedicated exclusively to developing and commercializing biological products for respiratory diseases, was formed last year through the spin-out of Bayer Biotechnology respiratory projects. Bayer spun out the rights to two lead products to Aerovance: AER-001, an IL-4/IL-13 receptor antagonist for severe asthma entering phase II studies and bikunin (AER-002), a recombinant therapeutic protein for cystic fibrosis and COPD on track for IND filing (1).

1. *Apax Partners forms Aerovance*. DailyDrugNews.com (Daily Essentials) Aug 25, 2004.

AI-128

AI-128, a sustained-release powder formulation of a widely used asthma drug, is Acusphere's initial product candidate utilizing its PDDS™ (Pulmonary Drug Delivery System) technology. AI-128 offers the potential for improved safety and once-daily dosing in the treatment of asthma. A European phase I clinical trial has been completed and demonstrated that approximately 80% of inhaled AI-128 was delivered to the upper lung and that the microparticles remained in the lung for up to 24 h, releasing the drug in the lung over a 12-24-h period.

AIC

AIC is an immunotherapy antiallergy candidate in phase II/III clinical development by originator Dynavax and partner UCB Pharma for the treatment of allergic rhinitis, specifically ragweed allergy. The companies are also evaluating AIC in phase I trials for the treatment of children with ragweed allergy. In the future, Dynavax hopes to test AIC therapy to prevent the onset of severe allergic disease and sequelae such as chronic sinusitis and asthma. AIC consists of the major ragweed allergen Amb a 1 linked to Dynavax's ISS-1018 (see below), one of its unique short immunostimulatory sequences of single-stranded DNA. AIC targets the underlying cause of seasonal allergic rhinitis caused by ragweed and offers a convenient 6-week treatment regimen potentially capable of providing long-lasting therapeutic results. The linking of ISS to Amb a 1 ensures that both ISS and ragweed allergen are presented simultaneously to the same immune cells, producing a highly specific and potent inhibitory effect and suppressing the Th2 cells responsible for inflammation associated with ragweed allergy. Furthermore, this treatment reprograms the immune response away from the Th2 response and towards a Th1 memory response, so that, upon subsequent natural exposure to the ragweed allergen, long-term immunity is achieved.

A 1-year, multicenter phase II/III trial is under way to evaluate the safety and efficacy of AIC. The study has enrolled 462 subjects at 30 allergy clinics throughout the Midwest and eastern U.S. Prior to the 2004 ragweed season, subjects receive a 6-week regimen of escalating doses of up to 30 μg of AIC or placebo. Some subjects will receive 2 additional booster shots of AIC prior to the 2005 ragweed season. The primary endpoint is the change in nasal symptoms relative to placebo following the 2005 ragweed season, while secondary endpoints will be comparative medication use and quality-of-life parameters. The study is being conducted by Quintiles Transnational and managed in collaboration with UCB, which provides financial support under a February 2004 strategic partnering agreement with Dynavax (1, 2).

Dynavax successfully completed immunizations in a phase I pediatric trial of AIC. Only relatively minor and transient local reactions at the injection site were reported, and no dose adjustments were necessary. The pediatric trial is being conducted in 24 children aged 9-17 with known ragweed allergy, as documented by medical history and a strongly positive skin test to ragweed allergen. Subjects were subdivided into 3 cohorts, with each cohort receiving gradually increasing doses of AIC (3).

1. *New phase II/III trial for Dynavax ragweed allergy product*. DailyDrugNews.com (Daily Essentials) March 1, 2004.

2. *Phase II/III trial of AIC for treatment of ragweed allergy now fully enrolled*. DailyDrugNews.com (Daily Essentials) May 21, 2004.

3. *Immunization completed in phase I ragweed allergy immunotherapy study*. DailyDrugNews.com (Daily Essentials) July 1, 2004.

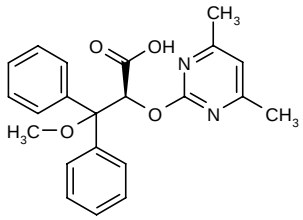
ALS-886

Phase I clinical trials are in progress at Advanced Life Sciences for ALS-886, a novel therapy for the treatment of acute respiratory distress syndrome (ARDS). It has proven effective in reducing the increase in microvascular permeability seen in acute lung injury and sepsis, and other potential indications include ischemia/reperfusion injury, including stroke, myocardial infarction, liver disease and transplant rejection, as well as other free radical-mediated conditions.

Table I: Clinical studies of ambrisentan (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hypertension, pulmonary	Randomized, Double-blind, Multicenter	Ambrisentan, 1 mg p.o. o.d. x 24 wks Ambrisentan, 2.5 mg p.o. o.d. x 24 wks Ambrisentan, 5 mg p.o. o.d. x 24 wks Ambrisentan, 10 mg p.o. o.d. x 24 wks	64	Ambrisentan was safe and dose-dependently increased the 6-min walking distance and improved hemodynamics in patients with pulmonary hypertension	3

Ambrisentan



Myogen is developing ambrisentan, a highly selective endothelin ET_A receptor antagonist that strongly inhibits vasoconstriction induced by endothelin, for the treatment of pulmonary arterial hypertension (PAH). The compound demonstrates high potency, high bioavailability and a half-life indicating the feasibility of once-daily dosing. The selectivity and potency of ambrisentan may offer significant advantages over nonselective endothelin receptor antagonists, including enhanced efficacy and a reduction in adverse effects.

The company announced early last year the beginning of ARIES I and II, 2 pivotal, double-blind, randomized, placebo-controlled phase III clinical trials that will assess the effects of ambrisentan given orally once daily for 12 weeks on exercise capacity, function and quality of life of PAH patients. The drug doses administered will be 5.0 and 10.0 mg/day in the ARIES I trial, and 2.5 and 5.0 mg/day in the ARIES II trial. Each study is expected to include a total of 186 patients. The product has received orphan drug designation from the FDA for this indication (1, 2).

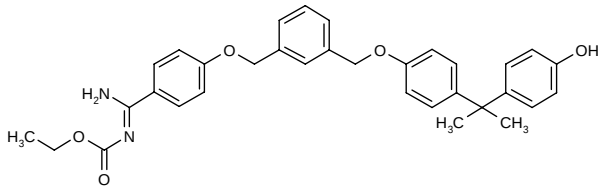
A total of 64 patients with moderate to severe PAH participated in a multicenter, double-blind, dose-finding clinical trial that evaluated the safety and effects of ambrisentan on exercise capacity. Patients were randomized to receive ambrisentan (1.0, 2.5, 5 and 10 mg p.o.) once daily for 12 weeks and then entered a 12-week open-label dose adjustment period. At 12 weeks, the 6-min walking distance of patients treated with 1.0, 2.5, 5 and 10 mg increased by 33.9, 37.1, 38.1 and 35.1 m, respectively. In patients with a baseline diagnosis of primary pulmonary hypertension, ambrisentan dose-dependently increased the 6-min walking distance by 31.2-54.1 m. These effects were associated with improvements in hemodynamics (mean pulmonary artery pressure, cardiac index and pulmonary vascular resistance) and WHO class of the patients. All ambrisentan doses were well tolerated throughout the 24-week study period. Four patients showed transient increases in serum transaminase levels, but only 1 subject had to discontinue the treatment (3) (Table I).

1. *Ambrisentan enters phase III clinical development*. DailyDrugNews.com (Daily Essentials) Jan 13, 2004.

2. *Orphan drug designation for ambrisentan for PAH*. DailyDrugNews.com (Daily Essentials) Aug 9, 2004.

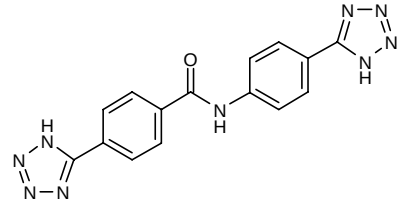
3. Rubin, L., Galie, N., Badesch, D. et al. *Ambrisentan improves exercise capacity and clinical measures in pulmonary arterial hypertension (PAH)*. Am J Respir Crit Care Med 2004, 169(7, Suppl.): A210.

Amelubant



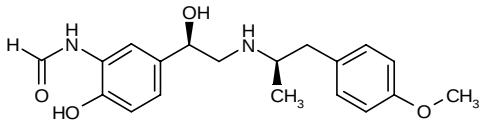
Amelubant is a potent, long-acting and orally active LTB_4 receptor antagonist in phase II development by Boehringer Ingelheim for the treatment of cystic fibrosis. In 2002, the EMEA granted orphan medicinal product designation to amelubant.

Andolast



Andolast is an inhibitor of IgE-mediated responses in phase II development by Rotta for the treatment of allergic rhinitis and asthma. According to the company, andolast is more potent than sodium cromoglycate in its antiallergic, cytoprotective and antisecretory properties.

Arformoterol



Arformoterol ([*R,R*]-formoterol) is a LABA that recently completed phase III trials at Sepracor for the treatment of bronchospasm in patients with COPD. The company has completed more than 100 preclinical studies, as well as 15 clinical studies with arformoterol inhalation solution for the treatment of bronchospasm in patients with COPD. In Sepracor's phase II program, arformoterol demonstrated a significant improvement in FEV_1 immediately after dosing and a duration of action of up to 24 h (1, 2).

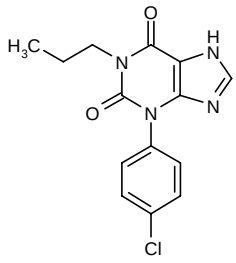
A method has been claimed for the prevention, amelioration or treatment of disorders of the respiratory tract, including bronchitis, asthma and COPD, and their respective symptoms. The claim embodies the combined daily administration of the phosphodiesterase type 4 (PDE4) inhibitor roflumilast with the β_2-adrenoceptor agonist arformoterol, or pharmaceutically acceptable salts thereof, in order to promote a synergistic therapeutic outcome. The claim further pertains to compositions permitting the concurrent, consecutive or independent administration of both active agents (3).

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

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

3. Beume, R. et al. (Altana Pharma Deutschland GmbH) *Synergistic combination comprising roflumilast and (R,R)-formoterol*. WO 0447828.

Arofylline



The selective PDE4 inhibitor arofylline is being evaluated in phase II/III trials for the treatment of bronchitis at Almirall Prodesfarma.

ASM-8

The FDA has cleared Topigen to conduct a phase I trial for ASM-8, a new inhalation antisense drug that is designed to treat asthma through a unique approach by attacking multiple mediators of the inflammatory mechanism rather than the single mediator approach of current therapies. The pilot study, set to begin by the end of January 2005, will investigate both the safety and tolerability of this new inhaled drug for the treatment of asthma. Healthy male and female volunteers will be randomized to receive a single inhaled dose of nebulized ASM-8. Standard and airways-specific assessments of safety parameters will be included in the study. The company had previously been cleared by the Canadian authorities to begin a phase I trial there, focusing on the safety and immunogenicity of the product in healthy volunteers. ASM-8 consists of two modified phosphorothioate antisense oligonucleotides (AS-ODNs). The AS-ODNs inhibit the expression and function of receptors that function in two distinct, but overlapping, pathways for inflammation. Each of the targeted inflammatory pathways has been shown to be important in allergic inflammation and asthma. Pharmacology studies conducted *in vitro* have shown that AS-ODNs inhibit these pathways in human cell lines and primary cell cultures, including eosinophils purified from the blood of asthmatic subjects (1, 2).

1. *Topigen to conduct pilot study of potential asthma treatment ASM-8*. DailyDrugNews.com (Daily Essentials) Dec 13, 2004.

2. *Topigen Pharmaceuticals Inc. to initiate phase I clinical trial of ASM8*. Topigen Pharmaceuticals Press Release 2004, April 15.

AVE-0309/AVE-5638/AVE-5883/AVE-7279

Prior to its merger with Sanofi-Synthélabo to form Sanofi-Aventis, Aventis Pharma had several compounds in early clinical development for the treatment of respiratory disorders. The status of these compounds at present has not been disclosed.

AVE-0309 is an IL-4 receptor antagonist in phase I/II evaluation for the treatment of asthma. AVE-7279 was last reported to be in phase I/II evaluation for the treatment of asthma and allergic rhinitis. AVE-5638, a tryptase inhibitor, was also in phase I/II trials for the treatment of asthma. Finally, the dual tachykinin NK_1/NK_2 receptor antagonist AVE-5883 was undergoing phase I/II trials for the treatment of asthma.

A double-blind, placebo-controlled, crossover trial evaluated the effects of a single dose of AVE-5883 (4.8 mg) administered using a metered-dose inhaler (MDI) in 20 asthmatics aged 19-47 years. All patients were challenged with serial dilutions (3.9-1000 μg/ml) of neurokinin A (NKA) inhaled 30 min after treatment with AVE-5883 or placebo. AVE-5883 provided significant protection

Table II: Clinical studies of AVE-5883 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Asthma	Randomized, Double-blind, Crossover	AVE-5883, 4.8 mg inhal. [30 min before challenge with neurokinin A] Placebo	20	AVE-5883 significantly protected asthmatic patients from bronchoconstriction and proinflammatory effects induced by challenge with neurokinin A	1

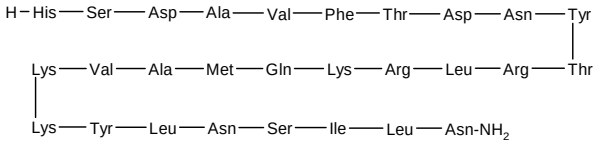
against inhaled NKA and was well tolerated in asthmatics (1) (Table II).

A randomized, double-blind study was conducted to determine the pharmacokinetics of inhaled AVE-5883 after single and multiple doses in healthy volunteers and patients with mild to moderate asthma. Subjects received single doses of 0.3-4.8 mg and multiple doses of 0.6-2.4 mg b.i.d. for 7 days, which led to dose-related increases in plasma concentrations. Systemic absorption occurred rapidly and plasma exposure was dose-proportional. With multiple dosing, steady state appeared to be reached by day 3 and accumulation was minimal. Pharmacokinetics were similar in healthy subjects and asthma patients after single doses of 4.8 mg and at steady state after multiple doses of 2.4 mg b.i.d. (2).

1. Diamant, Z., De Haas, S., Cohen, J. et al. *Effect of AVE5883, a dual NK_1/NK_2 receptor antagonist, on airway responsiveness to neurokinin A in asthma*. Eur Respir J 2004, 24(Suppl. 48): Abst P1384.

2. Zhang, J., Millet, S., Kirkesseli, S., Jensen, B.K., Wang, L., Krishna, R. *Single and multiple dose pharmacokinetics of inhaled AVE5883, a dual NK_1/NK_2 receptor antagonist, in healthy volunteers and in subjects with mild-to-moderate asthma*. 33rd Annu Meet Am Coll Clin Pharmacol (Oct 3-5, Phoenix) 2004, Abst 14.

Aviptadil

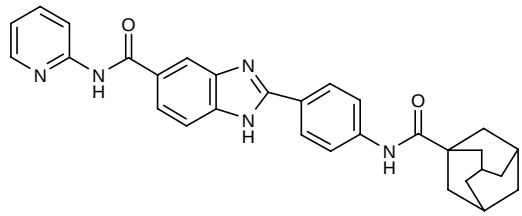


Aviptadil is a synthetic form of vasoactive intestinal polypeptide (VIP), a hormone that belongs to the glucagon/growth hormone-releasing factor/secretin superfamily and influences many aspects of pulmonary biology, as well as gastrointestinal secretion, relaxation of gastrointestinal vascular smooth muscle, lipolysis in adipocytes, pituitary hormone secretion, and excitation and hyperthermia after injection into the central nervous system. Aviptadil is Mondobiotech's lead compound and the company is conducting phase II trials for the inhalation treatment of PAH and phase I/II clinical trials in patients with lung sarcoidosis. The company is also carrying out preclinical studies of aviptadil for the treatment of autoimmune diseases, including pulmonary-associated scleroderma, systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Wegener's granulomatosis and Goodpasture syndrome. Mondobiotech has been granted orphan drug designation for aviptadil for the treatment of PAH and chronic thromboembolic pulmonary hypertension (an indication no longer developed by Mondobiotech) by the European Agency for the Evaluation of Medicinal Products (EMEA). In August 2004, Mondobiotech and Bachem signed a collaborative development and manufacturing agreement for aviptadil production. First approval of aviptadil for the indication of PAH is targeted for 2007 (1).

1. *mondoBIOTECH and Bachem sign aviptadil agreement*. DailyDrugNews.com (Daily Essentials) Aug 4, 2004.

Original monograph – Drugs Fut 1997, 12(10): 977.

AVP-13358



AVP-13358, an orally active, small-molecule IgE production inhibitor, is in phase I development by Avanir for the treatment of asthma and allergic rhinitis. AVP-13358 is designed to act early in the body's response to allergens by preempting the production or release of mediators involved in asthma and allergic rhinitis. The approach selectively targets both the production of the IgE antibody that is released by the immune system in response to allergen exposure, and a critical group of cytokines (Th2) thought to regulate the production of the antibody. The compound's mechanism of action is unique because, in addition to its effect on IgE, AVP-13358 demonstrated an ability to suppress antigen-stimulated IL-4 and IL-5 responses with a potency similar to that observed for IgE suppression. Avanir is currently seeking outlicensing opportunities on a worldwide basis for collaborative research, development and commercialization initiatives for AVP-13358.

Avanir has completed the initial phase I trial for AVP-13358. The study included 54 healthy volunteers and was designed to test safety, tolerability and pharmacokinetics following a single oral dose. AVP-13358 was well tolerated at all doses. Results indicate that AVP-13358 was detectable in the bloodstream at all doses administered and remains in the circulation long enough to allow once- or twice-daily dosing (1, 2).

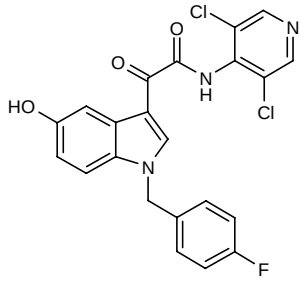
1. *Avanir completes initial phase I study of AVP-13358*. DailyDrugNews.com (Daily Essentials) May 5, 2004.

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

AVT-01

A decoy oligonucleotide (ODN)-based drug from Avontec, AVT-01 is in phase IIa clinical evaluation for the treatment of allergic asthma. The company's decoy ODNs target and neutralize transcription factors that play a role in pathological gene expression.

AWD-12-281 (842470)



AWD-12-281 (GW-842470, 842470), a phosphodiesterase type 4 (PDE4) inhibitor being codeveloped by elbion and GlaxoSmithKline, is currently in phase II clinical trials as an inhalation treatment for allergic and inflammatory airways diseases such as COPD. Under a 2002 collaborative agreement, GSK has exclusive worldwide development, registration, manufacturing and commercialization rights to the product. AWD-12-281 is also in preclinical development at elbion for the treatment of atopic dermatitis.

Pharmaceutical compositions comprising PDE4 inhibitors, such as AWD-12-281, have been claimed for the treatment of nonallergic rhinitis (1).

1. Rundfeldt, C. et al. (elbion AG) *Treatment of non-allergic rhinitis by means of selective phosphodiesterase-4 inhibitors*. WO 0422041, DE 10241407.

Original monograph – Drugs Fut 2002, 27(2): 111.

AZD-3778/AZD-8309

Two chemokine receptor antagonists are in early clinical testing at AstraZeneca for respiratory disorders: AZD-3778 in phase I for asthma/rhinitis and AZD-8309 in phase I for COPD. The latter compound is also in phase I clinical development as a potential treatment for rheumatoid arthritis.

AZD-9056

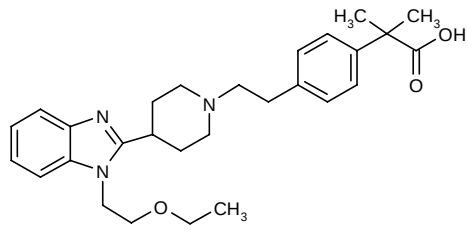
AZD-9056 is a new ion channel blocker from AstraZeneca in phase I clinical trials for COPD, as well as phase II clinical trials for rheumatoid arrhritis and osteoarthritis.

Bertilimumab

Bertilimumab (CAT-213) is a human IgG_4 monoclonal antibody that neutralizes eotaxin-1, thereby inhibiting the major stimulus that attracts eosinophils into tissues. The drug is in phase I/II trials at Cambridge Antibody Technology for the treatment of severe allergic rhinitis and the company is also evaluating bertilimumab in phase I/II for allergic conjunctivitis. The antibody may additionally be useful in the treatment of other conditions where raised levels of circulating eosinophils play a significant role in disease progression. Cambridge Antibody Technology has begun preliminary discussions with potential partners for the commercialization of the drug (1).

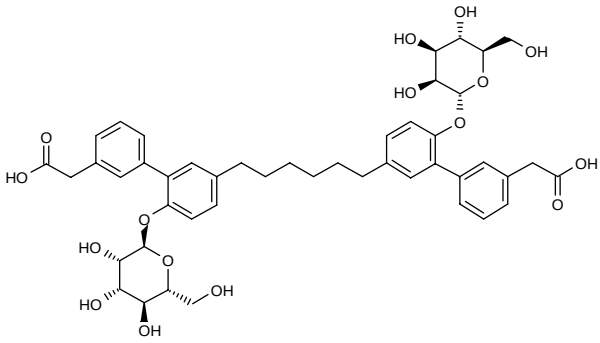
1. *Cambridge Antibody Technology reports Q2 R&D highlights*. Cambridge Antibody Technology Press Release 2004, March 17.

Bilastine



A potent histamine H_1 antagonist, bilastine, is in phase III development by Faes for the treatment of allergic rhinitis.

Bimosiamose

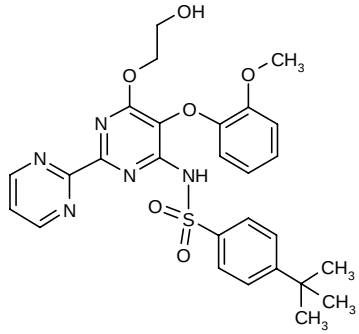


Bimosiamose (TBC-1269) is a small-molecule pan-selectin antagonist that blocks the initial slowing of leukocyte traffic, prevents leukocytes from migrating into the tissue and may alter cell activation and cell-cell signaling pathways. Phase II trials are under way with an inhalation formulation for the treatment of asthma, and phase II trials of a topical formulation are also in progress or planned for psoriasis and atopic dermatitis. A majority-owned affiliate of Encysive Pharmaceuticals (the former Texas Biotechnology), Revotar Biopharmaceuticals has exclusive worldwide rights to bimosiamose for the treatment of asthma and other inflammatory indications, as well as rights for topical indications outside North America. Encysive retains exclusive worldwide rights for its use in organ transplantation, as well as exclusive North American rights to all topical indications.

The effects of bimosiamose in allergic asthma were assessed in a double-blind, randomized, placebo-controlled, crossover phase II clinical trial. Twelve patients with mild allergic asthma were treated with placebo or bimosiamose (70 mg) inhaled twice daily for 4 days. The administration of bimosiamose attenuated by 49% the late airways response (LAR) induced by a standardized allergen challenge test after the last dose. Compared with placebo, bimosiamose significantly increased the levels of lymphocytes and decreased those of neutrophils in blood at 8 h after antigen challenge. No significant differences between treatments were found for early airways response (EAR), levels of exhaled nitric oxide and induced sputum cells. Additional studies are needed to confirm the potential of bimosiamose in asthma (1) (Table III).

1. Beeh, K.M., Beier, J., Buhl, R., Zahlten, R., Wolff, G. *Influence of inhaled bimosiamose (TBC 1269), a synthetic pan-selectin antagonist, on the allergen-induced late asthmatic response (LAR) in patients with mild allergic asthma*. Am J Respir Crit Care Med 2004, 169(7, Suppl.): A321.

Bosentan, New Indication



Following the successful development of bosentan (Tracleer®), an orally available dual endothelin receptor antagonist, for the treatment of PAH, Actelion is currently evaluating other potential indications for the drug in endothelin-related diseases. Clinical programs for bosentan are under way in idiopathic pulmonary fibrosis (IPF) and pulmonary fibrosis related to scleroderma (phase II/III BUILD program), digital ulcers associated with scleroderma (phase III) and metastatic melanoma (phase II). Bosentan is now available for the treatment of PAH in 18 countries, including the U.S., Canada, Switzerland and all E.U. markets with the exception of Denmark, Belgium and Luxembourg, and the company anticipates a potential launch in Japan this spring (1, 2).

A case study reported by clinicians at Queen Elizabeth Hospital in Birmingham (United Kingdom) indicated that bosentan may be used to successfully treat portopulmonary hypertension in liver transplant patients, possibly allowing more such patients to undergo liver transplantation. The case involved a 47-year-old woman who underwent orthotopic liver transplantation despite a

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

Indication	Design	Treatments	n	Conclusions	Ref.
Asthma	Randomized, Double-blind, Crossover	Bimosiamose, 70 mg inhal. b.i.d. x 4 d Placebo	12	Compared with placebo, bimosiamose attenuated the late airways response induced by a standardized allergen challenge test in patients with mild allergic asthma. No significant differences between treatments were found for early airways response, levels of exhaled nitric oxide or induced sputum cells	1

diagnosis of pulmonary hypertension. After an initial period of recovery, the patient experienced dyspnea and severe right heart failure. Epoprostenol treatment lowered elevated pulmonary artery pressure but did not increase the cardiac index. Both measures were improved 6 h after initiation of oral bosentan 62.5 mg b.i.d., however, and diuresis and resolution of peripheral edema were also observed. The bosentan dose was then increased to 125 mg b.i.d. and pulmonary artery pressure decreased to less than 50% systemic within 1 week. Liver function did not appear to be affected by bosentan treatment at day 154, and the drug was discontinued after 1 year. Pulmonary arterial pressure was normal upon subsequent investigation (3).

During recruitment for the BUILD 2 study of bosentan treatment in patients with interstitial lung disease secondary to systemic sclerosis, data concerning the use of the 6-min walk test as a possible outcome measure were gathered. Repeated testing showed that patients were able to complete the test with consistent results. Results were also correlated with the percent predicted DL_{CO}, but not with the Borg Dyspnea Index (4).

Endothelial function was improved in bosentan-treated patients with systemic sclerosis enrolled in a prospective study. Endothelium-dependent flow-mediated dilatation in the brachial artery was normalized after 1 month of treatment with oral bosentan 125 mg/day. The 4-fold increase in this measure seen with bosentan was maintained throughout an additional month of treatment (5).

In an open, multicenter study, the quality of life of 177 patients with primary pulmonary hypertension or PAH related to systemic sclerosis or to systemic lupus erythematosus was assessed after treatment with bosentan. Bosentan was given at a dose of 62.5 mg b.i.d. for 1 month and then 125 mg b.i.d. for 5 months. Functional class improved or was stable in 81% and 100% of patients, respectively, with systemic sclerosis or systemic lupus erythematosus. SF-36 measures of quality of life were improved in patients with systemic sclerosis, with significant changes in the physical function, social function, vitality, role emotional and role physical domains. Similar trends were seen in patients with systemic lupus erythematosus (6).

1. *Actelion reports Q1 R&D highlights*. Actelion Press Release 2004, April 27.

2. *Tracleer progresses towards approval in Japan*. DailyDrugNews.com (Daily Essentials) Nov 16, 2004.

3. Clift, P.F., Bramhall, S., Isaac, J.L. *Successful treatment of severe portopulmonary hypertension after liver transplantation by bosentan*. Transplantation 2004, 77(11): 1774.

4. Seibold, J.R., Black, C.M., Denton, C.P. et al. *Utility of six minute walk test (6MWT) in fibrosing alveolitis (FA) secondary to systemic sclerosis (SSc): Preliminary results from a multicenter placebo controlled trial of bosentan*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1060.

5. Papamichael, C., Fragiadaki, K.G., Stamatelopoulos, K., Katsichti, V., Mavrikakis, M., Sfikakis, P.P. *Bosentan treatment results in sustained improvement of endothelial dysfunction in patients with systemic sclerosis: A controlled, two-month, prospective study*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1680.

6. Proudman, S. *Tracleer (bosentan), a dual endothelin receptor antagonist (ERA), for the treatment of pulmonary arterial hypertension (PAH) related to connective tissue diseases: Effect on quality of life (QoL)*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1853.

Original monograph – Drugs Fut 2001, 26(12): 1149.

C-3193/C-3885

Merck & Co. is developing at least two new compounds for the treatment of respiratory disorders: C-3193 and C-3885, both in phase II trials.

CAT-354

CAT-354 is a human anti-IL-13 monoclonal antibody which recently entered phase I trials at Cambridge Antibody Technology for the treatment of severe asthma following approval from the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA). The placebo-controlled, rising single intravenous dose study of CAT-354 is taking place in the U.K. at the Marix Drug Development Clinical Research Centre, Wales. The objectives of the trial will be to study the safety, tolerability and pharmacokinetics of CAT-354. Results are likely to be available during the second quarter of 2005 (1-3).

1. *Cambridge Antibody Technology reports Q2 R&D highlights*. Cambridge Antibody Technology Press Release 2004, March 17.

2. *CAT-354 to enter phase I study in U.K.* DailyDrugNews.com (Daily Essentials) Sept 10, 2004.

3. *Cambridge Antibody Technology announces preliminary results for the year ended 30 September 2004*. Cambridge Antibody Technology Press Release 2004, Nov 22.

CC-10004

CC-10004, Celgene's lead oral PDE4 inhibitor and anti-TNF-α agent, has entered phase II development for the treatment of asthma. The SelCID™ (Selective Cytokine Inhibitory Drug) compound successfully completed phase I testing, proving to be safe and well tolerated, with an excellent therapeutic index. Phase II trials are also planned in psoriasis (1, 2).

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

2. *Celgene reports record operating performance in second quarter with strong revenue and profit growth*. Celgene Press Release 2004, July 22.

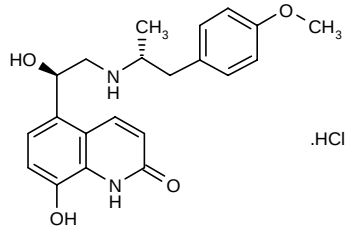
CDP-323

UCB Pharma (through its acquisition of Celltech Group) is evaluating CDP-323, an orally active small molecule targeting α_4 integrins, in phase I trials for the treatment of inflammatory diseases including allergic asthma, Crohn's disease, multiple sclerosis and rheumatoid arthritis (1, 2).

1. *Celltech reports 2003 year-end R&D highlights*. Celltech Group plc Press Release 2004, March 16.

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

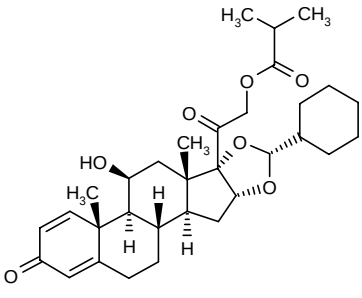
CHF-4226 (TA-2005)



CHF-4226 (TA-2005) is a once-daily LABA originally developed at Tanabe Seiyaku and licensed to Chiesi for development worldwide, excluding Japan, Korea and other Asian countries, for the treatment of asthma and COPD. It is in phase II trials in Europe. Chiesi and 3M Drug Delivery Systems signed an agreement last year for the development, scale-up and manufacture of Chiesi's Modulite® HFA products for the North American market. Chiesi will conduct clinical development for asthma and COPD and retains commercial rights for the products. The first product under the collaboration is CHF-4226 (1).

1. *Chiesi and 3M to develop Modulite HFA products for North America*. DailyDrugNews.com (Daily Essentials) Feb 13, 2004.

Ciclesonide



The ester prodrug ciclesonide (Alvesco®) is a new-generation, inhaled, nonhalogenated corticosteroid with potent local antiinflammatory properties developed by Altana Pharma and approved in 2004 in Australia, followed by the U.K. and the E.U., Brazil and Mexico, for the treatment of asthma in adults and adolescents aged 12 years and older. The inhaled corticosteroid was just introduced for the first time in the U.K., which acted as the reference member state for E.U.-wide approval, and is also expected to be launched in Germany in February. In October 2004, Altana and Aventis (now Sanofi-Aventis) received an approvable letter from the FDA regarding an NDA filed by the companies seeking approval of a metered-dose inhaler of ciclesonide for the treatment of persistent asthma (regardless of severity) in adults, adolescents and children aged 4 years and older. Altana has an additional marketing application for ciclesonide pending in Canada and licensee Teijin has submitted the drug for approval in Japan for the treatment of bronchial asthma. Altana is also evaluating the potential of ciclesonide in a phase I trial for the treatment of seasonal and allergic rhinitis and asthma. In 2001, Aventis and Altana signed an agreement to jointly develop and market ciclesonide in the U.S. In 1999, Teijin obtained rights to develop ciclesonide for asthma in Japan, Taiwan and Korea. The combination of the corticosteroid ciclesonide and the β_2-adrenoceptor blocker formoterol fumarate was in phase I/II evaluation by Aventis for the treatment of asthma prior to its recent merger with Sanofi-Synthélabo (now Sanofi-Aventis) (1-8).

The potential interaction between ciclesonide and erythromycin was evaluated in 18 healthy volunteers enrolled in an open-label, crossover trial. Each subject was randomized to receive a single dose of ciclesonide (640 μg by inhalation), a single dose of erythromycin (500 mg p.o.) or a single dose of both drugs combined. No significant differences were found among the pharmacokinetic profiles of the study treatments. A single inhaled dose of ciclesonide was well tolerated when administered alone or combined with erythromycin. The results suggested that the administration of erythromycin for respiratory infections would probably not reduce the effectiveness of asthma management with ciclesonide (9).

A clinical trial compared the pharmacokinetic profile of ciclesonide and its active metabolite desisobutyrylciclesonide in 12 asthma patients and 12 healthy volunteers after inhalation of a single dose of 1280 μg of ciclesonide administered using a metered-dose inhaler (MDI). The analysis of plasma levels of both compounds by high-performance liquid chromatography suggested similar pharmacokinetics in both asthma patients and healthy volunteers (10). The results from this and the following studies are described in Table IV.

An open-label, randomized, crossover clinical trial evaluated the pharmacokinetics of the active metabolite of ciclesonide when a dose of 320 μg of the drug was administered with or without a spacer to 30 patients with persistent asthma. Comparison of several parameters, such as AUC and peak concentration in serum, revealed that the use of a spacer had no significant effects on the

Table IV: Clinical studies of ciclesonide (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Asthma, Healthy volunteers	Open	Ciclesonide, 1280 μg inhal.	24	Ciclesonide was safe and well tolerated in patients with asthma and healthy volunteers	8
Asthma	Randomized, Open, Crossover	Ciclesonide, [with a spacer] 320 μg inhal. Ciclesonide, [without a spacer] 320 μg inhal.	30	No significant differences were found in the lung deposition of ciclesonide when administered with or without a spacer in patients with persistent asthma	9
Asthma	Randomized, Double-blind, Crossover	Ciclesonide, 800 μg b.i.d. x 4 wks Fluticasone propionate, 1000 μg b.i.d. x 4 wks	14	Ciclesonide and fluticasone propionate were effective in improving exhaled nitric oxide levels, lung function and asthma symptoms in patients with moderate persistent asthma. Fluticasone propionate also significantly inhibited the hypothalamic-pituitary-adrenal axis and reduced overnight 20-h urinary cortisol, suggesting that it may be associated with a lower therapeutic ratio compared to ciclesonide	10
Asthma	Randomized	Ciclesonide, 80 μg inhal. b.i.d. x 12 wks Fluticasone propionate, 88 μg inhal. b.i.d. x 12 wks	556	Inhaled ciclesonide was as effective as fluticasone propionate in improving the symptoms of mild to severe asthma	11
Asthma	Open	Ciclesonide, 320 μg inhal.	12	Administration of ciclesonide using a metered-dose inhaler resulted in most of the drug reaching the lungs (preferably the alveoli and small airways) in patients with asthma	12
Asthma	Randomized, Double-blind, Multicenter	Ciclesonide, 160 μg inhal. o.d. x 12 wks Fluticasone propionate, 88 μg inhal. b.i.d. x 12 wks	529	Once-daily ciclesonide was as effective as twice-daily fluticasone propionate in improving symptoms and reducing the need for rescue medication in patients with persistent asthma	13, 14
Asthma	Randomized, Double-blind, Multicenter, Pooled/meta-analysis	Ciclesonide, 80 μg inhal. o.d. x 12 wks Ciclesonide, 160 μg inhal. o.d. x 12 wks Ciclesonide, 320 μg inhal. o.d. x 12 wks Placebo	1015	Once-daily inhaled ciclesonide was associated with a low incidence of oropharyngeal adverse events and no significant effects on the hypothalamic-pituitary-adrenal axis in patients with mild to moderate asthma	15, 16
Asthma	Open	Ciclesonide, 640 μg inhal. o.d. x 4 wks → 160-1280 μg inhal. o.d. x 36 wks Ciclesonide, 640 μg inhal. b.i.d. x 4 wks → 160-1280 μg inhal. o.d. x 36 wks	283	Long-term administration of ciclesonide was well tolerated and induced no relevant systemic or oral adverse events	17
Asthma, Healthy volunteers	Crossover	Ciclsonide, 800 μg inhal. Budesonide, 800 μg inhal. Fluticasone propionate, 1000 μg inhal.	36	The oropharyngeal deposition of ciclesonide and its active metabolite desisobutyrylciclesonide was half of that found for budesonide and fluticasone propionate in both healthy volunteers and asthma patients	18
Asthma	Randomized, Double-blind	Ciclesonide, 80 μg inhal. o.d. x 12 wks (n=120) Ciclesonide, 320 μg inhal. o.d. x 12 wks (n=115) Placebo (n=125)	360	Inhaled ciclesonide was well tolerated and significantly more effective than placebo in improving the peak expiratory flow of patients with asthma	19

pharmacokinetic profile of the metabolite, although it may still be beneficial to some asthmatic patients (11).

A double-blind, randomized, crossover trial evaluated the effects of ciclesonide and fluticasone propionate on the plasma cortisol response to human corticotropin-releasing factor (hCRF) and methacholine. Fourteen patients with moderate persistent asthma and a mean FEV_1 of 67% were given ciclesonide (800 μg b.i.d.) or fluticasone (1000 μg b.i.d.) for 4 weeks. Both drugs were effective in improving exhaled nitric oxide levels, lung function and asthma symptoms, but fluticasone also significantly inhibited the hypothalamic-pituitary-adrenal (HPA) axis and reduced overnight 10-h urinary cortisol. The authors suggest that higher doses of ciclesonide may be associated with a better therapeutic ratio than fluticasone (12).

A randomized clinical trial found comparable efficacy for inhaled ciclesonide (80 μg b.i.d.) and inhaled fluticasone (88 μg b.i.d.) in 556 patients aged 6-15 years with mild to severe asthma (defined as a FEV_1 of 50-90% of predicted). After 12 weeks, the patients showed similar improvements in FEV_1 and both morning and evening peak expiratory flow (PEF). The median percentage of days with asthma control was 71.1% with ciclesonide and 73.5% with fluticasone. Both drugs significantly reduced the severity of asthma symptoms and the need for rescue medication (13).

Twelve adult patients with mild asthma participated in a clinical trial that evaluated the level of deposition of ciclesonide when administered using an MDI. Following administration of a single dose of 320 μg of radiolabeled ciclesonide, the analysis of 2-dimensional γ-scintigraphy images revealed that most of the drug was deposited in the lungs (52%) or in the oropharynx (32.9%). The amounts of ciclesonide found in the esophagus and the stomach were, respectively, 6.2% and 5.2% of the total dose. The largest deposition of ciclesonide within the lung was found in the small airways and the alveoli (14).

A total of 529 adult patients with persistent asthma participated in a double-blind, randomized trial that compared the efficacy of ciclesonide (160 μg once daily in the evening) and fluticasone propionate (88 μg twice daily), inhaled using an MDI for 12 weeks. Both treatments were equally effective in improving lung function, reducing asthma symptoms and decreasing the need for rescue medication (15, 16).

The safety profile and potential effects of ciclesonide on the HPA axis were assessed in 2 multicenter, double-blind phase III clinical trials that randomized 1,015 patients aged 12 years and older with mild to moderate persistent asthma and FEV_1 of 60-85% of predicted to receive placebo or ciclesonide (80, 160 or 320 μg) inhaled once daily in the morning for 12 weeks. At the end of the study, no significant differences compared to baseline were found in the peak serum cortisol levels (stimulated with 1 μg of cosyntropin) and the 24-h urinary cortisol levels corrected for creatinine of the patients. The authors concluded that once-daily ciclesonide had no significant effects on the HPA axis of patients with mild to moderate asthma. Patients treated with ciclesonide showed a similar incidence of treatment-related adverse events and oropharyngeal side effects as placebo-treated patients, although the percentage of patients who completed the study was higher with ciclesonide (85.2% *vs.* 66.7%) (17, 18).

A total of 283 persistent asthma patients who had received ciclesonide (160 and 640 μg once daily) or placebo for 12 weeks were included in an open-label extension study that determined the long-term safety of ciclesonide. These patients first received a dose of 640 μg of ciclesonide once or twice daily for 4 weeks, followed by an individualized dose ranging from 160 to 1280 μg/day for another 36 weeks. The incidence of oropharyngeal adverse events during the extension study was low and consisted mainly of pharyngitis (4%), voice alteration (2%) and oral candidiasis (1%). No relevant systemic or oral adverse events were reported, and most respiratory adverse events were considered to be unlikely to be or unrelated to ciclesonide. Long-term administration of ciclesonide was associated with a 28% increase in 24-h urine cortisol excretion (19).

The low frequency of oropharyngeal adverse effects found with ciclesonide may be associated with a low oropharyngeal deposition of the drug and its active metabolite desisobutyrylciclesonide. Eighteen healthy volunteers inhaled single doses of ciclesonide (800 μg) or budesonide (800 μg) and 18 asthma patients inhaled ciclesonide (800 μg) or fluticasone propionate (1000 μg) using an MDI. The analysis of rinsing 50% (v/v) ethanol solutions applied to the mouth within 60 min after inhalation revealed that the oropharyngeal deposition of ciclesonide and its active metabolite was approximately half of that found for budesonide or fluticasone propionate (20).

The efficacy and safety of ciclesonide were evaluated in a double-blind, randomized, placebo-controlled trial that enrolled 360 asthma patients with an FEV_1 of 60-90% of predicted and evidence of reversibility. The patients were first treated with beclomethasone dipropionate (400-800 μg) and after 2 weeks were randomized to inhale ciclesonide (80 and 320 μg) or placebo once daily in the morning for 12 weeks. The efficacy of the study regimens was estimated to be 62% for 80 μg ciclesonide, 77% for 320 μg ciclesonide and 45% for placebo. Compared to baseline, morning PEF increased by 129 and 192 ml with the low and high ciclesonide doses, respectively, whereas it decreased by 28 ml with placebo. No significant differences among treatments were found in the incidence of adverse events (21).

Combinations of a proton pump inhibitor, preferably soraprazan or pantoprazole, and an airways therapeutic, such as ciclesonide or roflumilast, for the treatment of airways disorders have been claimed. These combinations are particularly useful for the treatment of allergen- or inflammation-induced bronchial disorders (22, 23).

1. *Alvesco NDA submission for persistent asthma*. DailyDrugNews.com (Daily Essentials) Jan 7, 2004.

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

3. *Alvesco receives first approval in Australia*. DailyDrugNews.com (Daily Essentials) March 2, 2004.

4. *Aventis Pharma reports 2003 year-end R&D highlights*. Aventis Pharma Press Release 2004, Feb 5.

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17. Kerwin, E., Chervinsky, P., Fish, J., Kundu, S., Williams, J., Benerji, D., Hamedani, P. *Ciclesonide has no effect on hypothalamic-pituitary-adrenal (HPA)-axis at once-daily doses of 80 μg, 160 μg or 320 μg in the treatment of patients with mild-to-moderate asthma*. Am J Respir Crit Care Med 2004, 169(7, Suppl.): A90.

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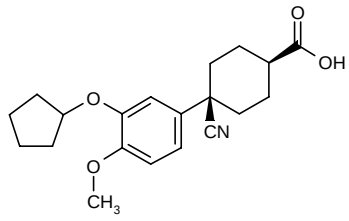
Cilomilast



GlaxoSmithKline's cilomilast (Ariflo®) is a selective PDE4 inhibitor in the preregistration stage in the U.S. for the maintenance of lung function in patients with COPD who are poorly responsive to albuterol. GlaxoSmithKline received an approvable letter from the FDA in 2003 and is presently working with the agency to clarify certain issues regarding the drug. Cilomilast is undergoing additional phase II and phase III development for COPD in Japan and Europe, respectively.

Combinations of a PDE4 inhibitor, such as cilomilast, and a histamine H_1 receptor antagonist, such as lorata-

dine, have been claimed for the treatment of pulmonary diseases such as COPD and asthma (1).

The administration of a PDE4 inhibitor, such as cilomilast, in combination with an anticholinergic agent, such as the muscarinic M_3 receptor antagonist tiotropium bromide, has been claimed for the prevention and treatment of pulmonary diseases such as COPD, asthma and allergic rhinitis (2).

PDE4 inhibitors have been reported to be useful for the treatment of exercise-induced asthma. Preferably useful are compounds which bind selectively to the low-affinity rolipram binding site of PDE4. These compounds, in particular cilomilast, demonstrated an increased therapeutic index and reduced side effects (3).

The combined, separate or sequential administration of a PDE4 inhibitor, such as cilomilast, a LABA, such as salmeterol xinafoate, and an antiinflammatory corticosteroid, such as fluticasone propionate, has been claimed for the prevention and/or treatment of respiratory diseases and the alleviation of exacerbations associated therewith. Targeted conditions include allergic and inflammatory diseases of the lungs and upper respiratory tract, such as allergic asthma, bronchial asthma, cough, COPD, bronchitic conditions and seasonal or perennial rhinitis (4).

1. Knowles, R.G. et al. (GlaxoSmithKline plc) *Compsn. comprising a PDE-4 inhibitor and H_1-receptor antagonist and the use thereof for the manufacture of a medicament for the treatment of respiratory diseases*. WO 0300289.

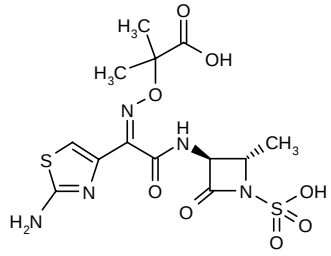
2. Knowles, R.G. and Ward, P. (GlaxoSmithKline plc) *Novel therapeutic method*. WO 0311274.

3. Nieman, R. et al. (GlaxoSmithKline Inc.) *Method for treating exercise induced asthma*. US 6555576, WO 0051599, EP 1156800, CA 2366041.

4. Rapeport, W.G. (GlaxoSmithKline plc) *Therapies for treating respiratory diseases*. WO 0330939.

Original monograph – Drugs Fut 1998, 23(6): 607.

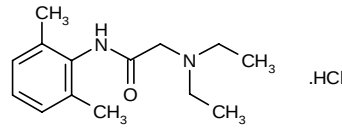
Corus-1020



Corus Pharma has announced positive phase II trial results for Corus-1020 (aztreonam lysinate for inhalation), a monobactam antibiotic intended to treat infections caused by a broad spectrum of Gram-negative bacteria, including *Pseudomonas aeruginosa,* in the respiratory tract of patients with cystic fibrosis. Inhaled delivery increases the concentration of the drug at the site of infection as compared to intravenous administration. Corus-1020 uses PARI Aerosol Research Institute's eFlow®, a portable electronic nebulizer platform that enables a very efficient aerosolization of liquid medications via a vibrating, perforated membrane. eFlow® can produce aerosols with a high density of active ingredients, a defined droplet size and a high proportion of respirable droplets in a shorter amount of time. PARI Aerosol Research Institute conducted most of the drug formulation work for Corus-1020 after Corus Pharma licensed PARI's eFlow® (1). Aztreonam is currently available for parenteral use in the treatment of Gram-negative infections. The FDA granted orphan drug status to Corus-1020 for cystic fibrosis in 2002.

1. *Positive phase II results for Corus-1020*. DailyDrugNews.com (Daily Essentials) Oct 25, 2004.

Corus-1030



Corus Pharma is evaluating lidocaine hydrochloride (Corus-1030), the well-known and widely used local anesthetic, as a topical solution in phase II clinical trials for the inhalation treatment of mild to moderate asthma and severe asthma. The company licensed this program in 2002 from the Mayo Clinic, where it was discovered to have similar effects to steroids on eosinophils, inducing apoptosis of these cells. Lidocaine is being administered using PARI's eFlow® inhalation technology.

Additional References

Hunt, L.W. et al. *Treatment of asthma with nebulized lidocaine: A randomized, placebo-controlled study*. J Allergy Clin Immunol 2004, 113(5): 853.

CRX-675

A phase I trial commenced last year to evaluate the safety and immune response activity of Corixa's CRX-675 for seasonal allergic rhinitis (SAR). The randomized, blinded, placebo-controlled, dose-escalation trial, to be conducted at Creighton University, will enroll 64 volunteers and will evaluate 4 different dose levels of CRX-675 given as a single intranasal dose to adults allergic to ragweed pollen. CRX-675 is a member of Corixa's family of proprietary compounds that interact with Toll-like receptor 4 (TLR4). As a TLR4 agonist, CRX-675 may influence innate immunity. TLR4 agonists can also affect the immune system's response to allergens. Preclinical test-

ing of CRX-675 has shown that allergic animals become nonresponsive to allergen challenge of the airways after 1 or 2 doses of CRX-675 administered as a nasal spray. CRX-675 may be administered via noninjectable routes such as intranasally, and potentially via oral administration (1).

1. *CRX-675 enters phase I trial for seasonal allergic rhinitis*. DailyDrugNews.com (Daily Essentials) April 28, 2004.

CS-003

CS-003 is a tachykinin NK_1, NK_2 and NK_3 receptor antagonist in phase II development at Sankyo for the treatment of asthma and COPD.

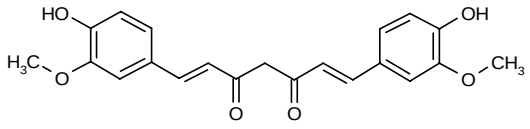
CS-712

A peptide composed of T-cell epitopes of two major cedar pollen allergens which are tandemly connected, CS-712 is in phase II development at Sankyo for the treatment of cedar pollen pollinosis. Sankyo has a technical collaboration with Hayashibara regarding CS-712.

CTX-100

CTX-100 is a proprietary aerosolized formulation of a hyaluronic acid solution that is delivered directly to the lungs via inhalation, in phase I development by CoTherix (formerly Exhale Therapeutics) for the treatment of hereditary emphysema associated with α_1-antitrypsin (AAT) deficiency. Additional phase I trials of CTX-100 are under way for smoking-related COPD. The company is seeking a partner to develop and commercialize CTX-100. Hyaluronic acid, a naturally occurring carbohydrate found throughout the body, is a safe, nontoxic agent currently approved for a variety of medical applications, including the treatment of arthritis, the prevention of surgical adhesions and as a vitreous humor substitute following ophthalmic surgical procedures. In 2002, the company received orphan drug designation from the FDA for CTX-100 for the treatment of patients with AAT deficiency.

Curcumin



Curcumin, a component of the spice turmeric, is in early clinical evaluation by Seer Pharmaceuticals in collaboration with Cystic Fibrosis Foundation Therapeutics for the treatment of cystic fibrosis. According to studies in mice, the compound may work by correcting the defect in the cystic fibrosis transmembrane regulator (CFTR) protein seen in these patients.

CYT005-AllQbG10

Cytos Biotechnology recently initiated a phase II trial with the Immunodrug™ candidate CYT005-AllQbG10, a therapeutic vaccine for the treatment of allergy. The study will include 20 patients with allergic rhinoconjunctivitis and asthma due to house dust mite allergy. The open-label, single-site study will evaluate safety, tolerability and efficacy of the vaccine. Efficacy of the vaccine will be determined by skin prick tests, conjunctival provocation tests and methacholine challenge. First results of the study are expected in the fourth quarter of 2005. CYT005-AllQbG10 consists of the Immunodrug™ carrier QbG10, an immunostimulatory adjuvant that consists of the virus-like particle Qβ loaded with an immunostimulatory DNA sequence called G10, mixed with the natural allergen extract of house dust mite. It aims at the induction of a nonallergic Th1-type immune response to balance an existing allergic Th2-type immune response. It is anticipated that the combination of classical desensitization therapy in conjunction with the carrier QbG10, which serves as an adjuvant, accelerates the establishment of an antiallergic Th1-type immune response against the allergen. In this way, the complete desensitization campaign could be shortened from up to 3 years to roughly 3 months when using CYT005-AllQbG10. In a phase I trial in healthy volunteers, QbG10 was shown to induce strong and specific T-cell responses, as measured by interferon gamma release (1-3).

1. *CYT005-AllQbG10 enters phase II house dust mite allergy trial.* DailyDrugNews.com (Daily Essentials) Dec 9, 2004.

2. *Cytos' second Immunodrug platform enters clinical development*. DailyDrugNews.com (Daily Essentials) April 15, 2004.

3. *Clinical trial advances Cytos Biotechnology's second Immunodrug™ platform.* Cytos Biotechnology Press Release 2004, Sept 16.

Daclizumab, New Indication

Daclizumab is a humanized monoclonal antibody that binds to the IL-2 receptor (α subunit, CD25) on activated T-cells and inhibits IL-2-mediated activation of lymphocytes, preventing the activation of the inflammatory cytokine response common in transplant rejection and autoimmune and inflammatory diseases. The antibody was originally created by Protein Design Labs, which licensed it to Roche for codevelopment and worldwide marketing. Daclizumab was first approved in December 1997 by the FDA as Zenapax® for use in combination with ciclosporin and corticosteroids to prevent acute organ

rejection in kidney transplant patients; it was subsequently approved in the E.U. and Canada. The antibody is in phase II evaluation by PDL and Roche for the treatment of asthma, and PDL is also conducting phase I/II clinical trials of daclizumab for the treatment of type 1 diabetes, multiple sclerosis and uveitis. In May 2004, the company discontinued its development for ulcerative colitis when the product did not meet the primary endpoint in a phase II clinical trial in patients with moderate or severe disease, and development of daclizumab for psoriasis has also been discontinued (1, 2).

PDL reported positive results from the initial clinical study of daclizumab in patients with chronic, persistent asthma whose disease was not well controlled with high doses of inhaled corticosteroids. The randomized, double-blind, placebo-controlled phase II clinical trial was conducted at 24 centers in the U.S. and treated a total of 114 patients. Treatment with daclizumab was generally well tolerated and the overall frequency and severity of adverse events did not differ between daclizumab and placebo groups. PDL currently expects that the next trial of daclizumab in asthma will be a phase II trial in which daclizumab is administered subcutaneously (3).

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

2. *Roche and PDL to codevelop Zenapax for asthma*. DailyDrugNews.com (Daily Essentials) Sept 20, 2004.

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

DCF-987

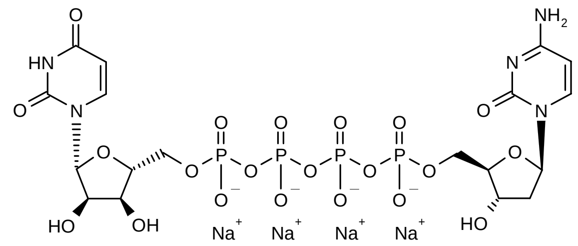
The low-molecular-weight dextran Usherdex-4, now called DCF-987, is a carbohydrate technology delivered by inhalation to the lungs intended to alleviate breathing difficulties in patients with diseases such as cystic fibrosis, COPD and other lung disorders. DCF-987 has been developed through preclinical and clinical trials by BCY LifeSciences pursuant to a licensing agreement with originator Polydex. In 2003, phase I and II trials were completed in adult cystic fibrosis patients in Canada. DCF-987 was well tolerated and showed a number of positive trends, including improved FEV_1 and a reduction in *P. aeruginosa* bacterial load in patient sputum. The company is seeking a partner to license the product for further clinical development in Europe and North America. According to the Clinical Summary Report from a phase II trial, at day 28 the primary outcome measurement, FEV_1-AUC, combined with absolute and relative differences in % predicted FEV_1 from baseline, suggested a slight trend towards clinical efficacy for DCF-987. At day 56, the CFU (colony-forming units) value decreased by 1 $\log_{10}$ unit for the high-dose group, a change considered clinically relevant. Based on the bacterial density data, BCY has signed an agreement to conduct additional animal studies to further evaluate the efficacy of DCF-987 on *P. aeruginosa* bacterial load. The major constituent of DCF-987, dextran-1, has been granted orphan drug designation by the FDA for the treatment of cystic fibrosis (1-3).

1. *BCY Lifesciences seeking partner or licensee for DCF-987*. DailyDrugNews.com (Daily Essentials) Jan 9, 2004.

2. *Update on Ushercell and Usherdex-4*. DailyDrugNews.com (Daily Essentials) Jan 26, 2004.

3. *BCY LifeSciences in discussions with potential partners for DCF-987*. DailyDrugNews.com (Daily Essentials) April 19, 2004.

Denufosol Tetrasodium



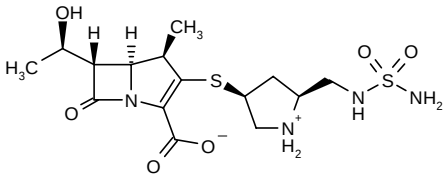
Denufosol tetrasodium (INS-37217 Respiratory) is a $P2Y_2$ receptor agonist from Inspire Pharmaceuticals with an extended duration of action, making it an attractive product candidate for cystic fibrosis. The molecule is designed to enhance the lung's innate mucosal hydration and mucociliary clearance mechanisms, which in cystic fibrosis patients are seriously impaired due to a genetic defect. By hydrating airways and stimulating mucociliary clearance through stimulation of the $P2Y_2$ receptor, denufosol is expected to help keep the lungs of cystic fibrosis patients clear of thickened mucus, reducing infections and the damage that result. These effects may also result in reduced frequency and length of hospitalizations, reduced need for antibiotics and other medications, reduced deterioration of lung function, and improved respiratory symptoms and health status. Denufosol (INS-37217 Ophthalmic) is also in phase II clinical evaluation for the treatment of retinal diseases associated with pathological subretinal or intraretinal accumulation of fluid.

Inspire has commenced an additional phase II trial to evaluate denufosol tetrasodium as a potential treatment for cystic fibrosis. The double-blind, randomized study will compare 2 doses of denufosol to placebo in 72 patients with cystic fibrosis at 17 U.S. sites. Denufosol or placebo will be administered 3 times daily for 28 days by standard jet nebulizer. This second phase II trial is being conducted to further assess the safety and tolerability of denufosol in a broader population of cystic fibrosis patients, which may allow expansion of the patient population for the upcoming phase III trial. This broader study population will include patients using antibiotics and other thera-

peutics currently used by cystic fibrosis patients, and the study will also include patients with reduced lung function (FEV_1 as low as 60%). Inspire also recently began 2 longer term inhalation toxicology studies in preparation for phase III trials. These required toxicology studies will be conducted in parallel with the new phase II trial. The company aims to complete ongoing studies and finalize plans with the FDA for a phase III program before the end of 2005 (1).

1. *Additional phase II trial of INS-37217 Respiratory in cystic fibrosis*. DailyDrugNews.com (Daily Essentials) Dec 27, 2004.

Doripenem



Doripenem (S-4661), discovered by Shionogi, is a broad-spectrum antibiotic and a new member of the carbapenem class of β-lactam antibiotics, preregistered in Japan for the treatment of bacterial infection. Licensee Peninsula Pharmaceuticals is conducting phase III trials with intravenous doripenem for the treatment of bacterial infections, including hospitalized patients with complicated urinary tract infections and complicated intraabdominal infections, hospital-acquired pneumonia and ventilator-associated pneumonia (VAP). The antibiotic is also in early clinical evaluation by Peninsula as an inhaled formulation for the treatment of *P. aeruginosa* or *Burkholderia cepacia* infections in cystic fibrosis patients. Peninsula licensed the exclusive rights to develop and commercialize doripenem in the U.S., Canada, Mexico, Puerto Rico and all countries in South America and Europe. The FDA has granted fast track designation for doripenem for the treatment of nosocomial pneumonia, including VAP (1-5).

1. *Phase I inhaled doripenem trial commences enrollment*. DailyDrugNews.com (Daily Essentials) Jan 19, 2004.

2. *Initiation of final pivotal phase III study of doripenem for VAP*. DailyDrugNews.com (Daily Essentials) July 15, 2004.

3. *Fast track status for doripenem for nosocomial pneumonia*. DailyDrugNews.com (Daily Essentials) Nov 4, 2004.

4. *Enrollment opens in pivotal trial of doripenem for hospital-acquired pneumonia*. DailyDrugNews.com (Daily Essentials) June 15, 2004.

5. *Enrollment commences in pivotal studies of doripenem for cIAI*. DailyDrugNews.com (Daily Essentials) April 6, 2004.

Original monograph - Drugs Fut 1995, 20(4): 367.

DSC-104

Discovery Laboratories has successfully completed a phase Ib trial evaluating the tolerability and lung deposition of DSC-104, its humanized lung surfactant delivered as an inhaled aerosol, in patients with asthma. The masked, placebo-controlled, randomized phase Ib dose-escalation study in the U.K. included 6 healthy subjects and 8 mild, persistent asthmatic patients. DSC-104 was safe and well tolerated, did not induce bronchospasm and was deposited to both the central and peripheral regions of the lungs in healthy volunteers and asthmatics. A phase II trial in the U.S. was planned for the second half of last year (1).

1. *Successful completion of phase Ib study for DSC-104 in asthma*. DailyDrugNews.com (Daily Essentials) March 12, 2004.

DW-908e

DW-908e is an integrin $\alpha_4\beta_1$ (VLA-4) antagonist in phase I development by Daiichi Pharmaceutical for the treatment of asthma.

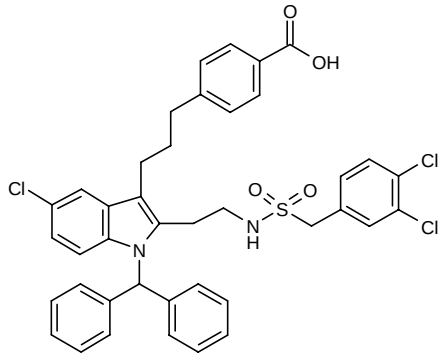
DX-890

A highly specific and potent recombinant protein inhibitor of human neutrophil elastase (HNE), DX-890 (EPI-hNE4) is a novel antiinflammatory agent targeting neutrophil-related inflammation with potential for the treatment of cystic fibrosis. DX-890 was discovered at Dyax and is being evaluated in the clinic for cystic fibrosis in collaboration with Debiopharm. The companies have an agreement whereby Debiopharm holds exclusive rights to commercialize the product in Europe, while Dyax retains rights to commercialize DX-890 in the rest of the world. The protein inhibitor may limit the damage caused by excessive inflammation in cystic fibrosis, thereby delaying disease progression and reducing mortality. The FDA and European authorities have granted DX-890 orphan drug designation/status for this indication. Phase IIa trials have been completed in cystic fibrosis patients in Europe and the companies are planning a larger multicenter phase IIb clinical trial for this indication. In an open-label, crossover phase II clinical trial in 34 children with cystic fibrosis, DX-890 (1, 2.5, 5 and 10 mg/ml inhaled over 10 min once daily for 1 week) was well tolerated and dose-dependently reduced the levels of HNE activity in the sputum of patients (1, 2).

1. *Dyax Corp. reports Q1 R&D highlights*. Dyax Corp. Press Release 2004, April 27.

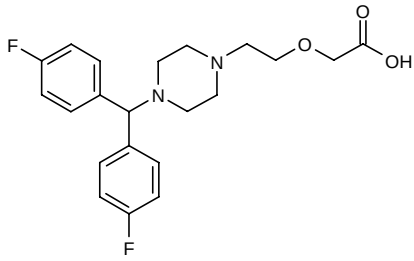
2. *Dyax Corp. and Debiopharm S.A. report positive results from Phase IIa clinical trial with DX-890 'EPI-hNE4' in children with cystic fibrosis*. Dyax Corp. Press Release 2004, Feb 24.

Efipladib



Phase I clinical studies are in progress at Wyeth for efipladib (PLA-902), a phospholipase A_2 (PLA_2) inhibitor with potential for the treatment of asthma, pain, rheumatoid arthritis and osteoarthritis.

Efletirizine



The histamine H_1 antagonist efletirizine (UCB-28754) is in phase III evaluation at UCB Pharma for the twice-daily treatment of allergic rhinitis. The company is also evaluating a once-daily formulation of efletirizine for the same indication in early clinical trials.

Original monograph – Drugs Fut 1997, 22(6): 626.

EPI-12323

EPI-12323 (Naturasone™) is a once-daily inhaled nonglucocorticoid steroid in phase II trials and preclinical development at EpiGenesis for the treatment of asthma and COPD, respectively. The agent, which targets the inflammatory and airways obstruction cascade in the irritated lung, has broad antiinflammatory and bronchodilating activities, with potentially fewer adverse effects compared to glucocorticoid steroids. EPI-12323 deletes adenosine pools believed to lead to asthma and exhibits a long duration of action and a pronounced effect on neutrophils.

Patients with mild allergic asthma who experienced an early and a late allergic reaction following allergen challenge during screening were randomized to receive placebo or EPI-12323 (25 mg) inhaled once daily for 5 days. A single-dose allergen challenge test conducted on day 5 revealed that, on average, the baseline FEV_1 of placebo-treated patients decreased by a maximum of 30.6% at 0-2 h and 21.1% at 3-8 h after challenge. In patients treated with EPI-12323, the mean maximum FEV_1 reductions were 27.4% at 0-2 h and 14.6% at 3-8 h compared to baseline. The authors concluded that EPI-12323 attenuated late allergic reactions in these patients but had no significant effect on early allergic reactions. EPI-12323 also tended to improve bronchial hyperresponsiveness, improved symptom score and reduced both nocturnal awakenings and the need for rescue β-agonists. The treatment was well tolerated, with no drug-related adverse events reported during the study (1, 2) (Table V).

1. Kanniess, F., Beier, J., Kleine-Tebbe, J., Magnussen, H. *Effects of inhaled EPI-12323 on allergen response in allergic asthmatics*. Am J Respir Crit Care Med 2004, 169(7, Suppl.): A322.

2. Kanniess, F., Beier, J., Jordan, R.J., Ball, H.A., Robinson, C.B. *The non-glucocorticosteroid EPI-12323 attenuates acute allergen LAR and improves symptomotology in mild asthmatics*. Eur Respir J 2004, 24(Suppl. 48): Abst P1392.

Etanercept, New Indication

Etanercept (Enbrel®) is a fully human TNF-α antagonist, a recombinant fusion protein comprising the soluble human p75 tumor necrosis factor (TNF) receptor linked to the Fc portion of human IgG_1, that acts by binding TNF and rendering the bound TNF biologically inactive, resulting in a significant reduction in inflammation. Jointly developed by Wyeth and Amgen, it is currently marketed

Table V: Clinical studies of EPI-12323 (from Prous Science Integrity®).

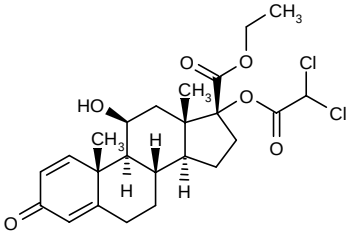
Indication	Design	Treatments	Conclusions	Ref.
Asthma	Randomized, Double-blind, Crossover	EPI-12323, 25 mg inhal. o.d. x 5 Placebo	Once-daily EPI-12323 was well tolerated and attenuated late allergic reactions following allergen challenge in patients with mild allergic asthma. No significant effects were seen on early allergic reactions	1, 2

for reducing the signs and symptoms, and inhibiting the progression of structural joint damage, in patients with moderately to severely active rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, as well as for the treatment of chronic, moderate to severe plaque psoriasis. The drug is also in phase II evaluation by Wyeth for the treatment of asthma and idiopathic pulmonary fibrosis (1).

1. *Wyeth reviews R&D pipeline*. DailyDrugNews.com (Daily Essentials) June 7, 2004.

Original monograph – Drugs Fut 1998, 23(9): 951.

Etiprednol Dicloacetate



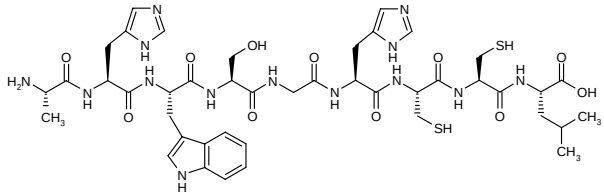
Ivax's etiprednol dicloacetate (BNP-166) is a soft corticosteroid that undergoes rapid conversion to well-characterized inactive metabolites when absorbed into the bloodstream, a process that reduces the likelihood of adverse effects caused by systemic exposure to corticosteroids. The compound is designed to locally deliver active drug to inflamed portions of the gastrointestinal tract in patients with Crohn's disease, as well as to bronchi in patients with asthma. Etiprednol dicloacetate recently entered phase II development at Ivax for the treatment of asthma (Respicort™) (1) and is also in phase II trials for Crohn's disease (Cronaze™).

1. *Ivax receives U.K. approval for QVAR in Easi-Breathe Inhaler*. Ivax Corp. Press Release 2004, Sept 30.

EV-131

Phase II trials are in progress at Evolutec for EV-131, a novel histamine-binding protein that prevents the activation of histamine receptors, including the H_4 receptor, for the treatment of allergic rhinitis, postoperative cataracts, allergic conjunctivitis and dry eye. Preclinical evaluation is under way for asthma and acute respiratory distress syndrome (ARDS). EV-131 is a major component of the saliva of feeding ticks that binds to histamine and blocks mast cell degranulation, thereby limiting the inflammatory reaction of the host. The protein, believed to be the only H_4 receptor antagonist in clinical development, shows activity against both early and late phases of inflammation, an advantage over widely prescribed antihistamines and corticosteroid therapies which show activity in early- and late-phase inflammation, respectively. Furthermore, EV-131 can be delivered by several different routes (injection, inhalation, topical), another advantage over existing therapies.

F-991



F-991 is a peptide that prevents the binding of immunoglobulin free light chains (Ig FLCs) to their receptors. It is in phase II development by Fornix BioSciences for the treatment of asthma, rhinitis and eczema resulting from exposure to dust mites and food allergens, and for skin allergy in patients with clinical symptoms indicative of contact oversensitivity to nickel. In the event that the ongoing clinical trials are successful, Fornix BioSciences intends to exploit separately the various indications for which F-991 may be pharmacologically active, including multiple sclerosis, Crohn's disease and contact allergy. The company is also seeking a partner for further development of this project (1).

1. *R&D programme status at Fornix BioSciences N.V.* Fornix BioSciences Press Release 2004, Dec 30.

FG-3019

A fully human monoclonal antibody directed against connective tissue growth factor (CTGF), FG-3019 is designed to bind, neutralize and clear CTGF from the body. Early clinical trials are under way at FibroGen in idiopathic pulmonary fibrosis (IPF). In animal models of lung, kidney and systemic fibrosis (including heart and liver fibrosis), treatment with FG-3019 reduced scar tissue formation and preserved organ structure and function. The presence of CTGF protein in lung tissue of IPF patients appears to be confined predominantly to those cell types believed to play a critical role in pulmonary fibrosis, specifically proliferating type II alveolar cells and activated fibroblasts. FibroGen has also filed an IND with the FDA seeking permission to begin clinical evaluation of FG-3019 for the treatment of pancreatic cancer. The company is also conducting phase I trials of FG-3019 for diabetic nephropathy, while Taisho is evaluating the antibody in preclinical studies for its potential in the treatment of renal disorders. The FG-3019 antibody was created using Medarex's UltiMAb Human Antibody Development

System®. Medarex may receive milestone payments and royalties on sales of products based on this antibody.

In the fall of last year, FibroGen announced promising results from its phase I trial of FG-3019 in patients with IPF. This open-label, dose-escalation study enrolled 21 patients to receive single doses of FG-3019 of 1, 3 or 10 mg/kg by 2-h infusion. The results indicated good safety and tolerability for the antibody, with no dose-limiting toxicities reported. The company plans to initiate a phase II study in patients with IPF this year (1).

1. *FibroGen announces FG-3019 found safe and well tolerated in patients with idiopathic pulmonary fibrosis*. FibroGen Press Release 2004, Oct 27.

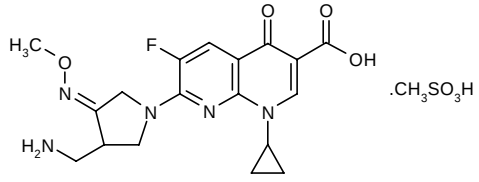
GC-1008

An IND application for a phase I trial in the U.S. of GC-1008, a pan-specific human anti-TGFβ monoclonal antibody being developed by Cambridge Antibody Technology and Genzyme for IPF, has been filed with the FDA. Following discussions with the FDA, a further preclinical safety study was undertaken and the results presented to the agency. A clinical trial in oncology is also scheduled for 2005 (1, 2).

1. *Cambridge Antibody Technology reports Q2 R&D highlights*. Cambridge Antibody Technology Press Release 2004, March 17.

2. *Cambridge Antibody Technology announces preliminary results for the year ended 30 September 2004*. Cambridge Antibody Technology Press Release 2004, Nov 22.

Gemifloxacin Mesilate



In the fall of 2004, Oscient Pharmaceuticals (the result of the merger of Genome Therapeutics and GeneSoft) launched once-daily gemifloxacin mesilate tablets 320 mg (Factive®), a potent new oral fluoroquinolone antibiotic, for the treatment of acute bacterial exacerbations of chronic bronchitis (ABECB) and mild to moderate community-acquired pneumonia (CAP). The antibiotic has also been approved in Canada for ABECB caused by *S. pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis* and *Staphylococcus aureus***.** Once-daily gemifloxacin offers short-course dosing (5 days for ABECB and 7 days for CAP) with no dosing adjustment requirements in the elderly, individuals with liver impairment or subjects with mild to moderate renal impairment. In its clinical development program in 6,775 patients, gemifloxacin demonstrated excellent clinical response rates at test-of-cure visit for CAP and ABECB, as good as comparators including clarithromycin, levofloxacin, amoxicillin/clavulanate, ceftriaxone and oral cefuroxime. Gemifloxacin was the first antibiotic approved for the treatment of multidrug-resistant *Streptococcus pneumoniae* and has the shortest course of therapy for this indication (7 days). The antibiotic targets both DNA gyrase and topoisomerase IV and covers a broad spectrum of strains that are resistant to other antibiotic classes. Oscient continues to develop gemifloxacin for the treatment of respiratory tract infections. Clinical trials for the treatment of acute bacterial sinusitis are complete and a regulatory submission for that indication is planned for 2005. A phase III trial is also under way for the potential treatment of CAP in 5 days. Furthermore, Oscient is developing an intravenous formulation for the potential treatment of patients hospitalized with severe CAP. Oscient is also recruiting investigators for its phase IV postmarketing FORCE (Factive Outpatient Respiratory infection Community Experience) study of gemifloxacin. The study is a postmarketing commitment required by the FDA and will examine the overall safety and efficacy of gemifloxacin in treating CAP *versus* clarithromycin and in treating ABECB *versus* amoxicillin/clavulanate. The U.S. multicenter study will enroll approximately 7,500 patients —5,000 in the gemifloxacin arm and 2,500 in the comparator arm. The study is scheduled to be completed during the next 3 years (1-6). GeneSoft licensed North American and European rights to the antibiotic from LG Life Sciences.

Data from phase III clinical trials were used in a 2,500-patient Monte Carlo simulation to evaluate the pharmacodynamics of gemifloxacin in patients infected with *S. pneumoniae*. The results suggested that gemifloxacin was more potent than other fluoroquinolones, including ciprofloxacin, ofloxacin and levofloxacin (7).

A total of 360 adult patients over 40 years of age participated in a multicenter, double-blind, randomized, placebo-controlled clinical trial that compared the efficacy and safety of gemifloxacin mesilate (320 mg once daily for 5 days) and levofloxacin (500 mg once daily for 7 days) in the treatment of ABECB. The percentage of patients who achieved clinical response was greater with gemifloxacin throughout the study: 97.5% *vs*. 93.5% at the end of therapy, 88.2% *vs*. 85.1% at days 14-21, and 83.7% *vs*. 78.4% at days 28-35. The bacteriological efficacy of the study treatments was similar. Most patients (93.1%) completed the study, although the percentage of discontinuations was significantly greater with levofloxacin. The most common adverse events causing discontinuation were diarrhea and vomiting (with gemifloxacin) and nausea (with levofloxacin). The overall incidence of adverse events was 39.6% with gemifloxacin and 33.7% with levofloxacin. The authors concluded that gemifloxacin was an effective alternative for ABECB patients (8). The results from this study and those that follow are depicted in Table VI.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Bronchitis	Randomized, Double-blind, Multicenter	Gemifloxacin, 320 mg o.d. x 5 d (n=182) Levofloxacin, 500 mg o.d. x 7 d (n=179)	360	A 5-day regimen with gemifloxacin was well tolerated and at least as effective as levofloxacin given for 7 days in the management of patients with acute exacerbation of chronic bronchitis	8
Pneumonia	Pooled/meta-analysis	Gemifloxacin, 320 mg o.d. x 7 d Gemifloxacin, 320 mg o.d. x 14 d Amoxicillin, 1 b t.i.d. + Clavulanate, 125 mg t.i.d. x 10 d Cefuroxime, 500 mg b.i.d. + Clarithromycin, 500 mg b.i.d. x 7 d Cefuroxime, 500 mg b.i.d. + Clarithromycin, 500 mg b.i.d. x 14 d Trovafloxacin, 200 mg o.d. x 7 d Trovafloxacin, 200 mg o.d. x 14 d Ceftriaxone, 2 g i.v. o.d. + Cefuroxime, 500 mg p.o. b.i.d. x 1-7 d → Ceftriaxone, 2 g i.v. o.d. + Cefuroxime, 500 mg p.o. b.i.d. x 1-13 d		Once-day gemifloxacin for 7 days was at least as effective as other therapies in patients with community-acquired pneumonia	9
Healthy Volunteers	Randomized	Gemifloxacin, 320 mg Gemifloxacin, 480 mg Gemifloxacin, 640 mg Placebo		A single dose of 320 mg of gemifloxacin had minimal effect on the Q-T_c interval of healthy volunteers	10
Infection, respiratory tract	Pooled/meta-analysis	Gemifloxacin	6775	Gender or race had little effect on the safety profile of gemifloxacin in the treatment of respiratory infections. The incidence of adverse events was greater in patients aged 18-40 years compared with patients older than 40 years	11
Pneumonia	Randomized, Double-blind, Multicenter	Gemifloxacin, 320 mg p.o. o.d. x 7 d Amoxicillin, 1 g p.o. t.i.d. + Clavulanate, 125 mg p.o. t.i.d. x 10 d	324	Once-daily gemifloxacin was as effective as three-times-daily amoxicillin plus clavulanate in inducing clinical, bacteriological and radiological responses in patients with community-acquired pneumonia	12
Rhinosinusitis	Pooled/meta-analysis	Gemifloxacin, 320 mg o.d. x 5 d (n=687) Gemifloxacin, 320 mg o.d. x 7 d (n=203)	890	Once-daily gemifloxacin given for 5 days was safe and effective in the treatment of acute bacterial rhinosinusitis	13
Bronchitis	Pooled/meta-analysis	Gemifloxacin, 320 mg o.d. x 5 d Gemifloxacin, 320 mg o.d. x 7 d Clarithromycin, 500 mg b.i.d. x 7 d Amoxicillin, 500 mg t.i.d. + Clavulanate, 125 mg t.i.d. x 7 d Trovafloxacin, 200 mg o.d. x 5 d		A daily dose of 320 mg of gemifloxacin given for 5 days showed efficacy in the treatment of acute exacerbations of chronic bronchitis	14

Six clinical trials established that gemifloxacin (320 mg once daily for 7 or 14 days) was at least as effective as other antibiotics in the treatment of adult patients suffering from CAP. The percentage of patients who achieved clinical resolution was 90.5% with gemifloxacin and 91.1% with one of the following regimens: amoxicillin/clavulanate, cefuroxime/clarithromycin, trovafloxacin or ceftriaxone/cefuroxime. Bacteriological response was detected in 88.9% of gemifloxacin-treated patients and 88.7% of patients treated with comparator therapies. Gemifloxacin showed high efficacy against *S. pneumoniae* infections, including those caused by strains resistant to macrolides, erythromycin and clarithromycin (9).

A meta-analysis that included data from 5 clinical trials found that, compared to placebo, single oral doses of 320, 400 and 640 mg of gemifloxacin tended to increase the Q-T_c interval of healthy subjects by 3-6 ms, although no dose-related effect was found. A greater effect on the duration of the Q-T_c interval was detected with repeated doses of gemifloxacin (320, 400 or 640 mg), which ranged between a reduction of 13 ms and an increase of 29 ms. The authors concluded that a dose of 320 mg of

gemifloxacin induces minimal effects on the Q-T_c interval (10).

Clinical data from 6,775 patients who participated in 20 phase II and III trials were used to determine the potential effects of race, age and gender on the safety profile of oral gemifloxacin. The overall incidence of adverse events was 44.7%, and the most common were rash, nausea, headache (especially in females) and diarrhea (especially in males). Adverse events were slightly more frequent in patients aged 18-40 years (45.8%). Race had no significant effect on the overall incidence of adverse events, although diarrhea and nausea were more common among black patients compared to white or oriental patients (11).

A multicenter, double-blind, randomized clinical trial compared the efficacy and safety of gemifloxacin (320 mg p.o. once daily for 7 days) and amoxicillin/clavulanate (1 g/125 mg p.o. t.i.d. for 10 days) in 324 patients with CAP. At the end of the treatment period, gemifloxacin achieved similar rates of clinical resolution (95.3% *vs*. 90.1%), bacteriological response (96.3% *vs.* 91.8%) and radiological response (89.1% *vs*. 87.6%) compared to the amoxicillin/clavulanate combination. The most common adverse events were diarrhea and rash with gemifloxacin, and diarrhea, fungal infection, vaginitis and vomiting with amoxicillin/clavulanate (12).

The efficacy of oral gemifloxacin in acute bacterial rhinosinusitis (ABRS) was evaluated in an open-label clinical trial and in a double-blind, randomized clinical trial. A total of 687 ABRS patients received gemifloxacin for 5 days, while another 203 patients were treated for 7 days. At the end of the treatment, clinical success was achieved by 95.0% and 96.2% of patients receiving gemifloxacin for 5 and 7 days, respectively. The analysis of samples obtained at end of therapy by sinus puncture and sinus aspiration showed an overall bacteriological success rate of 94.5% for gemifloxacin. The most common adverse events associated with gemifloxacin were nausea, diarrhea and headache, the incidence of which was similar in both treatment arms; however, rash was more frequent with the 7-day regimen (5.9% *vs*. 1.6%) (13).

Three controlled studies established that once-daily gemifloxacin given for 5 days was at least as effective as clarithromycin (500 mg b.i.d. for 7 days), amoxicillin/clavulanate (500/125 mg t.i.d. for 7 days) or trovafloxacin (200 mg once daily for 5 days) in the treatment of ABECB. The rates of eradication achieved with gemifloxacin in these trials were 91.8% for *H. influenzae*, 96.7% for *M. catarrhalis*, 75.0% for *S. pneumoniae*, 88.9% *for H. parainfluenzae* and 71.4% for *S. aureus*. An open-label study also revealed high rates of clinical and bacteriological success for a 7-day regimen of once-daily gemifloxacin in ABECB (14).

1. *Shareholder approval of Genome Therapeutics/Genesoft merger*. DailyDrugNews.com (Daily Essentials) Feb 5, 2004.

2. *Canadian approval for Factive*. DailyDrugNews.com (Daily Essentials) March 16, 2004.

3. *Oscient updates status of leading programs*. DailyDrugNews.com (Daily Essentials) July 22, 2004.

4. *Oscient launches Factive for lower respiratory tract infections*. DailyDrugNews.com (Daily Essentials) Sept 14, 2004.

5. *Genome Therapeutics completes merger with Genesoft*. DailyDrugNews.com (Daily Essentials) Feb 12, 2004.

6. *Genome Therapeutics and Amgen conclude research agreement*. DailyDrugNews.com (Daily Essentials) Jan 15, 2004.

7. Bhavnani, S.M., Ambrose, P.G., Owens, R.C. *Pharmacodynamic evaluation of gemifloxacin (GEM) against Streptococcus pneumoniae (SP) using Monte Carlo simulation and population pharmacokinetics*. 42nd Annu Meet Infect Dis Soc Am (Sept 30-Oct 3, Boston) 2004, Abst 312.

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9. Mandell, L., Tillotson, G., Carlin, B. *An overview of the efficacy of gemifloxacin for the treatment of community-acquired pneumonia (CAP)*. 42nd Annu Meet Infect Dis Soc Am (Sept 30-Oct 3, Boston) 2004, Abst 422.

10. File, T., Patou, G., Tillotson, G., Iannini, P. *Influence of oral gemifloxacin on the QTc interval of healthy volunteers*. 42nd Annu Meet Infect Dis Soc Am (Sept 30-Oct 3, Boston) 2004, Abst 436.

11. Iannini, P., Tillotson, G., Mandell, L. *Influence of patient age, race, and gender on the tolerability of gemifloxacin*. 42nd Annu Meet Infect Dis Soc Am (Sept 30-Oct 3, Boston) 2004, Abst 435.

12. Mandell, L., Tillotson, G., File, T. *Safety and efficacy of gemifloxacin compared to high dose amoxicillin/clavulanate for the treatment of community-acquired pneumonia (CAP) of suspected pneumococcal origin*. 42nd Annu Meet Infect Dis Soc Am (Sept 30-Oct 3, Boston) 2004, Abst 418.

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14. San Pedro, G., Mandell, L., Tillotson, G., Campbell, D. *The efficacy of 5-day gemifloxacin once daily for the treatment of acute exacerbations of chronic bronchitis (AECB)*. 42nd Annu Meet Infect Dis Soc Am (Sept 30-Oct 3, Boston) 2004, Abst 417.

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GRC-3886

Glenmark Pharmaceuticals' PDE4 inhibitor GRC-3886 is entering phase I clinical trials in the U.K. as a potential new treatment for asthma and COPD. The trial will evaluate the safety and bioavailability of single and multiple oral doses in healthy volunteers, and pharmacodynamics will also be assessed in whole blood using a surrogate marker (lipopolysaccharide-induced TNF-α inhibition). The company has conducted extensive preclinical animal studies in rodents, dogs, primates and ferrets, demonstrating GRC-3886 to be a potent (IC_{50} = 1.4 nM), bioavailable (> 50% across species), safe and nonemetic PDE4 inhibitor, with a significantly larger therapeutic window than other PDE4 inhibitors in development. Glenmark has established a collaborative agreement with Forest pursuant to which Forest will develop, register and commercialize GRC-3886 in North America, while Glenmark will retain commercialization rights for the rest of the world. GRC-3886 is currently claimed by U.S. patent applications which, if issued, will expire in 2024 (1-3).

1. *Glenmark files to advance GRC-3886 into phase I studies in U.K.* DailyDrugNews.com (Daily Essentials) Sept 10, 2004.

2. *Glenmark's GRC-3886 to enter phase I clinical trials in U.K., the compound moves ahead of its previous PDE4 inhibitor compound, GRC-3015*. Glenmark Pharmaceuticals Press Release 2004, April 20.

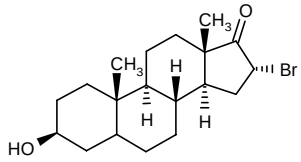
3. *Glenmark and Forest collaborate on GRC-3886*. DailyDrugNews.com (Daily Essentials) Sept 29, 2004.

GSK-159797 (TD-3327)/ GSK-597901/GSK-678007/ GSK-159802/GSK-642444

In 2003, Theravance and GlaxoSmithKline established a collaboration for the development and commercialization of LABAs for the treatment of asthma and COPD. The collaboration involves 8 LABA product candidates that have demonstrated efficacy in relevant preclinical models. The most advanced compounds in the series are GSK-159797 (159797, TD-3327), GSK-597901 (597901) and GSK-678007 (678007), which have reached phase IIa clinical development as monotherapies for COPD and in combination with a glucocorticoid agonist for asthma and COPD. In a study in 38 patients with mild asthma, single-dose inhalation of GSK-159797 achieved the target increase in FEV_1 throughout the 25-h evaluation period, without increasing heart rate.

In earlier clinical development for these indications are GSK-159802 (159802) and GSK-642444 (642444).

HE-2000



HE-2000 (Immunitin™) is an investigational immunoregulating hormone from Hollis-Eden with antioxidant and antiinflammatory activities which is being studied in phase I clinical trials for the treatment of cystic fibrosis. The company believes that HE-2000 may decrease the chronic inflammation in lungs which can lead to the damage associated with cystic fibrosis. By stimulating the immune system, HE-2000 may also limit and prevent pulmonary infections in these patients. If the hormone is able to correct immune dysfunction in this setting, it may also have utility in pulmonary disorders such as chronic bronchitis, asthma and COPD. Phase II trials have also been performed in HIV/AIDS patients and malaria, as well as phase I trials in tuberculosis.

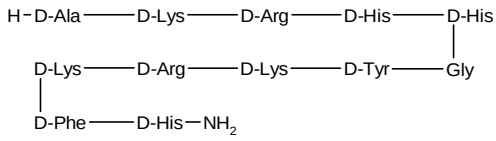
New data relating to the molecular mechanism of action by which HE-2000 may regulate the immune system back towards homeostasis in the treatment of a variety of disease conditions were presented early last year. HE-2000 has been shown to upregulate antioxidant response genes and downregulate inflammatory mediators. Controlling oxidative stress and inflammation, two conditions that dysregulate innate and adaptive immunity, allows recovery of innate and adaptive immune function. Molecular analysis indicates that HE-2000 upregulates antioxidant response genes, including the glutamate-cysteine ligase modifier subunit gene (GCLM) and gluta-

mate-cysteine ligase catalytic subunit gene (GCLC), which together regulate glutathione homeostasis. In addition, the cystine/glutamate exchange transport protein gene (xCT), which is important in maintaining intracellular glutathione levels, heme oxygenase-1 gene (HO-1), important in upregulating manganese superoxide dismutase antioxidant enzyme, and NAD(P)H:quinone oxidoreductase gene (NQO1) that protects cells against damage by free radicals and reactive oxygen species, were also upregulated in these studies. Further molecular analyses demonstrated that HE-2000 downregulates inflammatory mediator genes, including the IL-1β gene, the IL-6 gene, the macrophage chemotactic protein-1 (MCP-1) gene, the inducible nitric oxide synthase (iNOS) gene responsible for the generation of nitric oxide (NO), and the matrix metalloprotease 9 (MMP9) gene involved in tissue destruction and bone remodeling. The CD36 gene, an antiinflammatory pathway shifting macrophages to phagocytosis, was also upregulated. *In vitro* and *in vivo* assays in preclinical models support these findings, showing for example that HE-2000 inhibits inflammation in the carrageenan-induced pleurisy model in mice. Examples in clinical studies include a phase II study in HIV patients, in which they had dramatically elevated levels of a variety of inflammatory mediators before receiving treatment with HE-2000. After receiving HE-2000 these inflammatory mediators, including IL-6, IL-1β and TNF-α, were downregulated in the peripheral blood cells to near normal levels. There was also a decrease in MCP-1, improvement in HIV-gag peptide-specific CD8 responses and a subsequent statistically significant drop in HIV viral load. Improved immunity was also apparent in a separate study in late-stage AIDS patients treated with HE-2000, shown by a statistically significant decrease in opportunistic infections. In phase I studies, volunteers treated with HE-2000 showed upregulation of monocyte CD36 compared to placebo-treated volunteers. One mechanism of parasite removal is by CD36 on the surface of macrophages. Phase II studies in malaria showed rapid clearance of malaria parasites in HE-2000 patients. Immune function improvement was shown in a murine tuberculosis (TB) chronic infection model. This study demonstrated increased interferon gamma and IL-2, with decreased IL-4 in the lungs of the mice treated with HE-2000. Increasing Th1 cytokines such as interferon gamma and IL-2, and decreasing Th2 cytokines such as IL-4, is believed to be important in allowing the host immune system to control TB infection. In preclinical studies in TB, animals cleared TB from chronic infection, and when combined with triple-antibiotic treatment, HE-2000 provided more rapid clearance of the disease (1, 2).

1. *New data indicate mechanism of action of Immunitin*. DailyDrugNews.com (Daily Essentials) March 23, 2004.

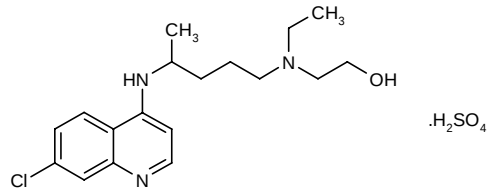
2. Stickney, D., Reading, C., Garsd, A., Ahlem, C., Onizuka-Handa, N., Frincke, J. *HE2000 decreases inflammatory cytokines and viral load in HIV patients and opportunistic infections in late stage AIDS patients*. Clin Microbiol Infect 2004, 10(Suppl. 3): Abst O128.

Histatin P-113D



Histatin P-113D is a novel, synthetic 12-amino-acid antimicrobial peptide for delivery via a pulmonary spray for the treatment of lung infection in patients with cystic fibrosis. Demegen has submitted an IND seeking approval to begin clinical trials of histatin P-113D for this indication. In 2002, the FDA granted P-113D orphan drug status for the treatment of cystic fibrosis. P-113D was originally developed by Periodontix and became part of Demegen's product pipeline upon the acquisition of Periodontix by Demegen in 2001. P-113D is based on histatins, naturally occurring antimicrobial proteins found in human saliva active in the body's natural defense against disease in the oral cavity. This peptide has demonstrated a high level of *in vitro* activity against *P. aeruginosa*, including drug-resistant patient isolates. Because of its unique mechanism of action, it is expected that P-113D will not result in drug resistance to classical antibiotics.

Hydroxychloroquine, Aerosolized



APT Pharmaceuticals, founded by Research Corporation Technologies, has completed a phase I study in Australia in healthy volunteers to determine the safety, pharmacokinetics and taste tolerability of aerosolized hydroxychloroquine (AHCQ). The results showed a favorable safety profile, excellent pharmacokinetics and tolerable taste. Plasma concentrations of hydroxychloroquine following aerosol administration were well below those seen after oral dosing of hydroxychloroquine to treat lupus and rheumatoid arthritis. The study was conducted using the advanced AERx® pulmonary delivery system from Aradigm. Aerosolized hydroxychloroquine is being developed as a new class of antiinflammatory drug for treating asthma, COPD, severe acute respiratory syndrome (SARS), allergic rhinitis and nasal polyposis. Hydroxychloroquine is a treatment for malaria and is also classified as a slow-onset disease-modifying antirheumatic drug (DMARD) administered in tablet form as a first-line therapy for systemic lupus erythematosus, rheumatoid arthritis and sarcoidosis. APT's proprietary

aerosolized dosage forms and routes of administration may achieve a faster onset of action and greater therapeutic effect than conventional oral therapy at substantially lower systemic doses. APT is now focused on closing financing to support phase II asthma studies and accelerating development of the rhinitis product. The company is seeking corporate collaborators or venture investors to participate in the next round of financing. APT has collaborated with researchers from leading academic centers in the U.S. and Canada to investigate the benefit of AHCQ on viral respiratory infections. Laboratory studies have demonstrated that hydroxychloroquine inhibits both the transmission and the inflammatory responses of human airways cells to the common cold virus. Initial laboratory studies funded by the National Institute of Allergy and Infectious Diseases (NIAID) showed that hydroxychloroquine inhibits SARS-associated coronavirus at similar low concentrations. These results were corroborated recently at the Rega Institute for Medical Research in Belgium, where the closely related drug chloroquine was also found to be effective at inhibiting SARS coronavirus *in vitro*. The NIAID is supporting further studies of hydroxychloroquine in an animal model (1, 2).

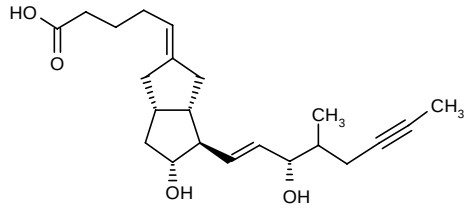
1. *Aerosolized hydroxychloroquine enters clinical testing for respiratory diseases*. DailyDrugNews.com (Daily Essentials) Sept 16, 2004.

2. *Phase I studies completed for aerosolized hydroxychloroquine*. DailyDrugNews.com (Daily Essentials) Nov 23, 2004.

IC-485

Icos is conducting a phase II clinical trial with IC-485, an orally administered, small-molecule inhibitor of PDE4, in patients with COPD, which is scheduled for completion in 2005.

Iloprost, Solution for Inhalation



Iloprost solution for inhalation (Ventavis®) is a synthetic prostacyclin analogue developed by Berlex and Schering AG and available in several European countries and Australia since last year for the treatment of PAH. The U.S. licensee CoTherix recently received FDA approval for the product. Iloprost in combination with the endothelin receptor antagonist bosentan is also in phase II evaluation by CoTherix for the treatment of PAH. The STEP (iloprost inhalation solution safety and pilot efficacy trial in combination with bosentan for evaluation in pulmonary arterial hypertension) study will evaluate the combination of iloprost with bosentan in 60 patients. The product has been available for over 10 years for the treatment of obstructive peripheral vascular disease, including Raynaud's phenomenon and Buerger's disease. The drug's effects include direct vasodilatation of the pulmonary arterial bed, with subsequent significant improvement in pulmonary artery pressure, pulmonary vascular resistance and cardiac output, as well as mixed venous oxygen saturation. Iloprost holds orphan drug desgination in both the U.S. and the E.U. for this new indication (1-4).

1. *CoTherix submits NDA for Ventavis*. DailyDrugNews.com (Daily Essentials) July 6, 2004.

2. *Ventavis NDA accepted for priority review*. DailyDrugNews.com (Daily Essentials) Sept 13, 2004.

3. *CoTherix Inc. initiates phase II trial of Ventavis® in combination with Tracleer® in patients with pulmonary arterial hypertension*. CoTherix Press Release 2004, June 15.

4. *FDA approves Ventavis™ for the treatment of pulmonary arterial hypertension (PAH).* CoTherix Press Release 2004, Dec 29.

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IL-4/IL-13 Trap

IL-4/IL-13 Trap is a dual high-affinity antagonist of IL-4 and IL-13 designed using Regeneron's proprietary Trap technology. The Trap proteins consist of a fusion between two distinct receptor components and a portion of an antibody molecule called the Fc region, resulting in the generation of blockers that bind a cytokine or growth factor very tightly. IL-4/IL-13 Trap is in early clinical development for the treatment of mild to moderate asthma. The company recognizes the potential of IL-4/IL-13 Trap for the treatment of allergy and related conditions as well.

Table VII: Clinical studies of IL-4/IL-13 Trap (from Prous Science Integrity®).

Indication	Treatments	n	Conclusions	Ref.
Healthy volunteers	IL-4/IL-13 Trap, 50 µg/kg s.c. (n=4) IL-4/IL-13 Trap, 100 µg/kg s.c. (n=4) IL-4/IL-13 Trap, 200 µg/kg s.c. (n=4) IL-4/IL-13 Trap, 400 µg/kg s.c. (n=4) IL-4/IL-13 Trap, 800 µg/kg s.c. (n=4)	20	IL-4/IL-13 Trap was well tolerated when administered s.c. to healthy volunteers	3

IL-4/IL-13 Trap completed a phase I trial for asthma in 2004, where it proved to be generally safe and well tolerated at the doses tested, with no indications that a maximum tolerated dose had been reached (1, 2).

The pharmacokinetic profile of a single dose of IL-4/IL-13 Trap (50, 100, 200, 400 and 800 µg/kg s.c.) was evaluated in 20 healthy volunteers. The average peak concentration in plasma increased dose-dependently from 377 ng/ml to 5837 ng/ml. Dose-dependent increases were also found for the average AUC from 0 to 30 days (from 141 to 2465 µg·h/ml) and the average half-life (from 10 to 18 days). No significant differences were found between the incidence of adverse events in patients treated with IL-4/IL-13 Trap and those receiving placebo (3) (Table VII).

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

2. Parsey, M. et al. *A phase I study of IL-4/13 Trap in patients with clinically stable, mild to moderate asthma*. Am J Respir Crit Care Med 2004, 169(7, Suppl.): A859.

3. Parsey, M., Fauci, G., Dunn, J., Marks, C., Skop, E., Stahl, N., Furfine, E. *Human pharmacokinetic evaluation of the IL-4/13 Trap: A novel immunomodulatory agent for the treatment of HIV disease*. 11th Conf Retroviruses Opportunistic Infect (Feb 8-11, San Francisco) 2004, Abst 522.

Interferon Gamma-1b, New Indication

Interferon gamma-1b, a bioengineered form of interferon gamma, acts as a biological response modifier and stimulates the immune system. Its effects include the induction of major histocompatibility complex (MHC) class II antigens, macrophage activation, increased immunoglobulin production from B-lymphocytes and enhanced NK cell activity. Originally introduced in the U.S. in 1991 for chronic granulomatous disease, interferon gamma-1b was launched in 2000 in the U.S. by InterMune as Actimmune® solution for injection to delay the progression of severe, malignant osteopetrosis. The drug reached its second market in 2000 for this indication when InterMune launched Actimmune® in Canada. Boehringer Ingelheim, which holds development and marketing rights outside the U.S., Canada and Japan, is awaiting approval in the E.U., where the drug will be marketed as Imukin®. InterMune is also developing the product in phase III for the treatment of idiopathic pulmonary fibrosis (IPF) and as first-line therapy for the treatment of ovarian cancer, and additional phase II trials are under way with interferon gamma-1b in combination with interferon alfacon-1 for the treatment of patients chronically infected with hepatitis C virus who have failed to respond to therapy with pegylated interferon alfa-1 plus ribavirin. Under a research collaboration with InterMune dating from 2002, Mondobiotech is evaluating interferon gamma-1b injections in phase II trials for the treatment of asthma associated with severe bronchial disease (1-4).

1. *Disappointing results for interferon gamma-1b trial in advanced liver fibrosis*. DailyDrugNews.com (Daily Essentials) Jan 23, 2004.

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

3. *Early completion of enrollment in pivotal Actimmune trial for ovarian cancer*. DailyDrugNews.com (Daily Essentials) April 19, 2004.

4. *InterMune reports Q1 R&D highlights*. InterMune Press Release 2004, April 29.

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Antoniou, K.M., Alexandrakis, M., Sfiridaki, K., Tzortzaki, E.G., Tzanakis, N., Dimadi, M., Siafakas, N.M., Bouros, D. *Randomized, colchicine-controlled study of interferon gamma-1b (IFN-gamma 1b) treatment on cytokine profile (IL-12 and IL-18) in patients with idiopathic pulmonary fibrosis (IPF)*. Am J Respir Crit Care Med 2004, 169(7, Suppl.): A108.

Lynch, D. et al. *HRCT diagnosis of IPF and relationship between HRCT characteristics and histology and clinical findings in patients in a phase 3, randomized, double-blind, placebo-controlled trial of interferon gamma-1b (IFN-gamma 1b)*. Chest 2004, 126(4, Suppl.): 773s.

Lynch, D., Godwin, J.D., Webb, W.R., Bradford, W.Z., Starko, K. *HRCT findings at baseline and follow-up in patients with idiopathic pulmonary fibrosis (IPF) in a phase 3, randomized, double-blind, placebo-controlled trial of interferon gamma-1b (IFN-gamma 1b)*. Am J Respir Crit Care Med 2004, 169(7, Suppl.): A706.

Strieter, R.M. et al. *Effects of interferon gamma-1b on biomarker expression in idiopathic pulmonary fibrosis patients*. Am J Respir Crit Care Med 2004, 170(2): 133.

Zisman, D.A. et al. *Rates and characteristics of serious adverse events (SAES) in 210 patients with idiopathic pulmonary fibrosis (IPF) treated with interferon-gamma 1b (IFN-gamma 1b) in an open-label study*. Chest 2004, 126(4, Suppl.): 772S.

IPL-512602 (AVE-0547)/ IPL-550260

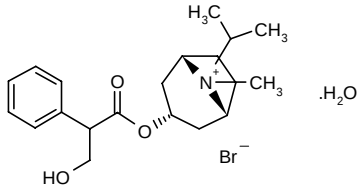
Using its proprietary small-molecule LSAIDs™ (Leukocye Selective Anti-Inflammatory Drugs) technology, Inflazyme Pharmaceuticals has generated several orally active compounds which were demonstrated to be safe and well tolerated in phase I clinical trials. Two compounds had progressed to phase II for the treatment of asthma, one of which was IPL-512602 (AVE-0547), developed in collaboration with Aventis (now Sanofi-Aventis). Although this compound showed some activity, the primary endpoint of improvement in FEV_1 was not achieved and the company does not expect to develop it further for this indication. Another LSAID –IPL-550260– had reached phase I clinical evaluation. However, Inflazyme does not plan to dedicate further resources to the LSAID series at this time and is seeking strategic collaborations for a broad range of inflammatory indications (1-3).

1. *Financial results for quarter ended September 30, 2004 and shareholder update*. Inflazyme Pharmaceuticals Press Release 2004, Nov 4.

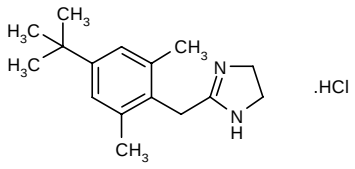
2. *Inflazyme reports negative outcome of phase IIa asthma trial; company to focus on recently acquired technologies.* Inflazyme Pharmaceuticals Press Release 2004, June 18.

3. *Inflazyme Pharmaceuticals announces re-aligned R&D strategy undertaking restructuring to focus resources*. Inflazyme Pharmaceuticals Press Release 2004, July 27.

Ipratropium Bromide/ Xylometazoline Hydrochloride



Ipratropium Bromide

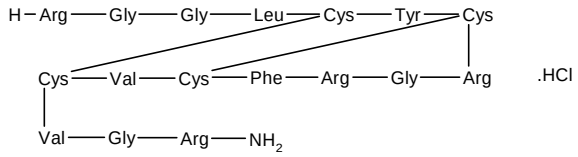


Xylometazoline Hydrochloride

The combination of ipratropium bromide, a muscarinic antagonist, and the decongestant xylometazoline hydrochloride (ZyComb™) is in phase III development by Nycomed Pharma as a nasal spray for the simultaneous treatment of the two major symptoms of the common cold: nasal congestion and runny nose. Nycomed is considering partial or complete outlicensing of the combination. Data from a multinational, double-blind phase III study confirmed the efficacy and safety of the combination. The study in almost 800 adult patients with the common cold randomized in parallel groups was designed to confirm the efficacy and safety of the combination in comparison with the individual substances and placebo. Results showed that ipratropium/xylometazoline is significantly more effective than current treatments. The first patents covering the combination are expected to be granted within the next year (1).

1. *ZyComb shows efficacy and safety in phase III study.* DailyDrugNews.com (Daily Essentials) July 14, 2004.

Iseganan Hydrochloride



IntraBiotics terminated its iseganan hydrochloride development program last summer following the recommendation of an independent data monitoring committee that the company discontinue its clinical trial of iseganan for the prevention of ventilator-associated pneumonia (VAP) based on interim data analysis. A higher rate of both VAP and mortality was observed in the active treatment group compared to placebo (1-3).

1. *Iseganan study in VAP stopped for safety reasons*. DailyDrugNews.com (Daily Essentials) June 30, 2004.

2. *IntraBiotics reports third quarter 2004 financial and operating results*. IntraBiotics Pharmaceuticals Press Release 2004, Nov 10.

3. *IntraBiotics reports second quarter 2004 financial and operating results*. IntraBiotics Pharmaceuticals Press Release 2004, Aug 10.

Original monograph – Drugs Fut 2002, 27(3): 234.

ISS-1018

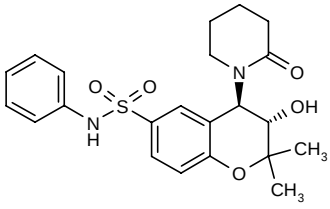
ISS-1018 is an immunostimulatory sequence (ISS), a 22-base synthetic DNA molecule designed by Dynavax Technologies to enhance the ability of the immune system to fight disease and control chronic inflammation. ISS-1018 alone is being evaluated in phase II trials in asthma. ISS-1018 inked or combined with hepatitis B virus (HBV) surface antigen is in phase II/III development for the prevention and immunotherapy of HBV infection and the company is also evaluating ISS-1018 linked with

allergens responsible for major allergies. AIC (see above) is one such product in phase II/III clinical development with UCB Pharma for allergic rhinitis due to ragweed allergy. Dynavax is conducting phase I trials of ISS-1018 in combination with rituximab (Rituxan) for the treatment of B-cell non-Hodgkin's lymphoma.

A phase IIa asthma challenge study confirmed the safety of inhaled ISS-1018 in asthmatic patients, and showed substantial and statistically significant pharmacological activity, based upon the induction of genes associated with a reprogrammed immune response. The study was designed to achieve three objectives: to determine the safety of ISS-1018 at the highest dose tested in man; to determine whether ISS-1018 was pharmacologically active in the lungs of mild asthmatics exposed to allergen; and to determine whether ISS-1018 could inhibit changes in lung function caused by inhaled allergen challenge. The study enrolled 39 patients, 21 of whom received ISS-1018 while 18 patients received saline. Study drug and placebo were administered by inhalation on 4 consecutive weeks. Pulmonary function was measured after the second and fourth treatments to provide information on the early and late airways response and airways hyperresponsiveness. Safety results of the trial showed no differences in treatment-emergent or drug-related adverse events or in serious adverse events. Common side effects included symptoms frequently associated with asthma, such as headache, chest tightness and wheezing. There were no differences in vital signs or hematology or chemistry values between those receiving study drug and those receiving saline. ISS-1018 produced statistically significant elevations in both peripheral blood and induced sputum of genes induced by interferon alfa, the main agent in the biological cascade triggered by ISS-1018. No induction of these genes was observed in the placebo-treated patients. After allergen challenges at weeks 2 and 4, no significant changes in pulmonary function were observed between placebo and treated groups (1).

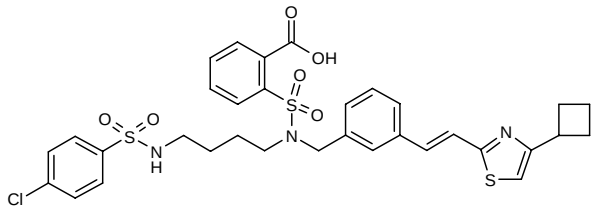
1. *Positive outcome of Dynavax phase IIa asthma challenge study*. DailyDrugNews.com (Daily Essentials) Aug 2, 2004.

KCO-912



A potent and selective K_{ATP} channel activator from Novartis, KCO-912 has reached phase IIa clinical development as a potential treatment for asthma and is currently available for licensing.

KP-496

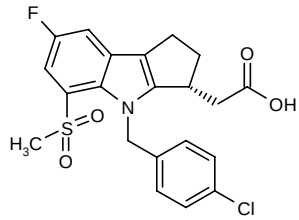


Kaken's KP-496 (S-36496) is a dual leukotriene LTD_4 and thromboxane A_2 (TxA_2) receptor antagonist in early clinical development for the treatment of asthma.

KW-4490

Kyowa Hakko has stopped the development of the antiasthmatic agent KW-4490 due to insufficient efficacy in phase IIa clinical trials.

L-888839

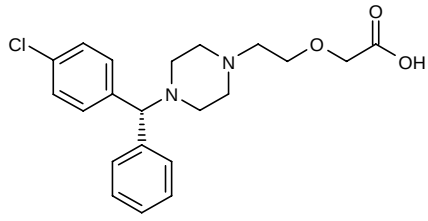


L-888839 is a potent and selective prostanoid DP receptor antagonist last reported to be in in clinical evaluation by Merck Frosst for the treatment of seasonal allergic rhinitis.

LAS-34273/LAS-35201

Two muscarinic M_3 receptor antagonists –LAS-34273 and LAS-35201– are in phase II and phase I clinical development, respectively, at Almirall Prodesfarma as potential new agents for bronchitis and asthma.

Levocetirizine, New Indication



A nonsedating histamine H_1 antagonist and inhibitor of IL-8 and TNF expression, levocetirizine was first

launched in 2001 in Germany by UCB Pharma as Xusal® tablets for two separate indications: the treatment of seasonal and perennial allergic rhinitis and the treatment of chronic idiopathic urticaria. Later that year, UCB received approval for levocetirizine in the E.U. as Xyzal® for both the treatment of allergic rhinitis and the treatment of idiopathic urticaria in adults and children aged 6 years and older. At present, the company is evaluating levocetirizine in phase III trials for the early prevention of asthma in atopic children. The product is characterized by a fast onset of action, outstanding efficacy and an excellent safety profile. Developed by Sepracor, levocetirizine was exclusively licensed in 1999 to UCB Farchim, an affiliate of UCB, in all countries except the U.S. and Japan.

Levocetirizine is the active *R*-enantiomer of cetirizine and represents a new second-generation histamine H_1 antagonist with high affinity and selectivity for H_1 receptors. Comparative studies have shown evidence of superior H_1 receptor binding affinity over its racemate, cetirizine. Levocetirizine has a favorable pharmacokinetic profile; it is rapidly and extensively absorbed, minimally metabolized, and has a lower volume of distribution than some other second-generation antihistamines. A number of studies using the histamine-induced wheal and flare model have repeatedly demonstrated marked suppressive effects for levocetirizine. Levocetirizine has also been found to be effective in relieving symptoms of seasonal and perennial allergic rhinitis, including nasal congestion, and its side effects are minor (1).

1. Day, J.H., Ellis, A.K., Rafeiro, E. *Levocetirizine: A new selective H1 receptor antagonist for use in allergic disorders*. Drugs Today 2004, 40(5): 415.

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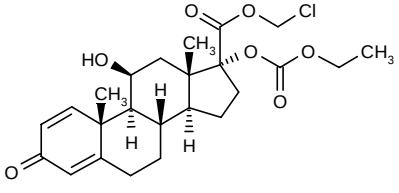
Lee, D.K.C., Gray, R.D., Wilson, A.M., Robb, F.M., Soutar, P.C., Lipworth, B.J. *Single and short-term dosing effects of levocetirizine on adenosine monophosphate bronchoprovocation in atopic asthma*. Br J Clin Pharmacol 2004, 58(1): 34.

Lee, D.K.C., Lipworth, B.J. *The bronchoprotective effects of levocetirizine on adenosine monophosphate challenge in patients with atopic asthma*. Eur Respir J 2004, 24(Suppl. 48): Abst P1393.

Loteprednol Etabonate, New Indication



Loteprednol etabonate is a soft corticosteroid that is rapidly deactivated after reaching the general circulation. The compound has good local activity and a high therapeutic index, being devoid of systemic side effects. Loteprednol was codeveloped by Bausch & Lomb and Pharmos and launched in 1998 (Alrex®, Lotemax®) as an ophthalmic suspension for the treatment of allergic conjunctivitis and postoperative ocular inflammation following ocular surgery. Currently, Ivax is testing loteprednol in phase III clinical studies for the treatment of allergic rhinitis and in phase II clinical trials for the treatment of dermatitis.

Original monograph – Drugs Fut 1997, 22(10): 1086.

Lucinactant

Lucinactant (KL4-surfactant, Surfaxin®) is an engineered version of natural human lung surfactant based on the 21-amino-acid peptide KL4 (sinapultide) and designed to closely mimic the essential human lung surfactant protein B (SP-B). Unlike animal-derived surfactants, lucinactant can be produced in virtually unlimited quantities, in consistent pharmaceutical-grade quality, and has no risk of potential transmission of animal-associated diseases. Discovery Laboratories, which has a licensing agreement with Esteve for certain European countries, has filed for approval of lucinactant in the U.S. and the E.U. for the prevention of respiratory distress syndrome (RDS) in premature infants. In the U.S., the NDA has a target review date of February 13, 2005. The filings include data from 2 phase III RDS trials. The first, a landmark 1,294-patient pivotal study, demonstrated lucinactant's superiority over Exosurf®, a non-protein-containing synthetic surfactant; the second trial, a supportive study in 252 patients, demonstrated the noninferiority of lucinactant compared to Curosurf® (poractant alfa), a pig-derived surfactant (see results below). The product has received a positive opinion in Europe recommending the granting of orphan medicinal product designation for the prevention and treatment of RDS in premature infants. Although satisfactory methods of prevention and treatment of RDS have been approved in Europe, lucinactant was deemed to potentially offer significant benefit to those at risk of developing or affected by the condition. Lucinactant already has orphan drug designation for the prevention of RDS in premature infants in the U.S. Discovery and Esteve are also evaluating the drug in phase III trials for the treatment of full-term infants with meconium aspiration syndrome (MAS) and in phase II trials for the treatment of acute respiratory distress syndrome in adults (ARDS). Discovery also just recently began a phase II clinical trial of lucinactant for the prevention of bronchopulmonary dysplasia in premature infants (1-7).

The FDA has selected lucinactant for the treatment of ARDS as the only applicant with the Division of Pulmonary and Allergy Drug Products to be included in the Continuous Marketing Application (CMA) Pilot 2 Program. The Pilot 2 program is designed to evaluate the

Table VIII: Clinical studies of lucinactant (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Respiratory distress, neonatal	Randomized, Double-blind	Lucinactant x 28 d (n=119) Poractant alfa x 28 d (n=124)	243	Lucinactant was safe and as effective as poractant alfa in preventing the appearance of respiratory distress syndrome in premature infants	9

costs and benefits of enhanced sponsor access to guidance and feedback from the FDA during the IND phase of new drug development of fast track products and determine whether such activity can improve the efficiency of the drug development and review process (8).

A multicenter, double-blind, randomized clinical trial compared the efficacy and safety of two surfactants in preventing RDS in very preterm babies. A total of 243 babies with a gestational age of 24-29 weeks and a birthweight of 600-1250 g who were successfully intubated at birth were randomized to receive either the novel compound lucinactant or the animal-derived surfactant poractant alfa for 28 days. At the end of the treatment period, 37.8% of children given lucinactant and 33.1% of those given poractant alfa were alive without any signs of bronchopulmonary dysplasia. No significant differences between study groups were found in the frequency of oxygen desaturation, bradycardia or apnea, the mortality rate and the incidence of air leaks and pulmonary hemorrhage. Both drugs were safe and showed similar efficacy (9) (Table VIII).

1. *FDA accepts for filing Surfaxin NDA*. DailyDrugNews.com (Daily Essentials) June 18, 2004.

2. *European approval sought for Surfaxin*. DailyDrugNews.com (Daily Essentials) Oct 13, 2004.

3. *European orphan drug designation recommended for Surfaxin*. DailyDrugNews.com (Daily Essentials) July 6, 2004.

4. *NDA filing for Surfaxin for RDS in premature infants*. DailyDrugNews.com (Daily Essentials) April 19, 2004.

5. *Encouraging preliminary phase II data with Surfaxin in the management of ARDS.* DailyDrugNews.com (Daily Essentials) Dec 16, 2004.

6. *Discovery and Esteve restructure strategic alliance.* DailyDrugNews.com (Daily Essentials) Dec 16.

7. *Discovery Labs initiates two phase 2 clinical trials – Surfaxin® for bronchopulmonary dysplasia and aerosolized SRT to treat neonatal respiratory failures.* Discovery Laboratories Press Release 2005, Jan 6.

8. *Surfaxin selected for CMA Pilot 2 Program*. DailyDrugNews.com (Daily Essentials) Feb 24, 2004.

9. Sinha, S., Soler, A.V.I., Lacaze-Masmonteil, T. et al. *Randomised controlled trial of a new surfactant, Surfaxin(R) (lucinactant) v Curosurf(R) (poractant alfa) for the prevention of RDS in very preterm babies*. Arch Dis Child 2004, 89(Suppl. 1): Abst G5.

Original monograph – Drugs Fut 2004, 29(6): 570.

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Moya, F., Gadzinowski, J., Bancalari, E., Salinas, V., Kopelman, B., Bancalari, A., Kornacka, M., Segal, R., Schaber, C., Tsai, H. *Superiority of a novel surfactant, Surfaxin (lucinactant), over Exosurf in preventing respiratory distress syndrome in very preterm infants: A pivotal, multinational, randomized trial*. Annu Meet Pediatr Acad Soc (May 1-4, San Francisco) 2004, Abst 2643.

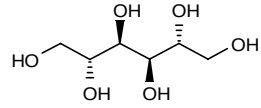
Nutt, M., Patel, N., Rairkar, M., Niven, R. *Comparison of the novel lung surfactant Surfaxin (lucinactant) with currently available commercial products*. Annu Meet Pediatr Acad Soc (May 1-4, San Francisco) 2004, Abst 2912.

Sinha, S., Lacaze-Masmonteil, T., Valls Soler, A., Gadzinowski, J., Sanchez-Luna, M., Hajdu, J., Bernstein, G., Segal, R., D'Agostino, R., Wiswell, T. *Randomized, controlled trial of a new generation surfactant, Surfaxin (lucinactant), versus Curosurf (poractant alfa) for the prevention and treatment of RDS in very preterm infants*. Annu Meet Pediatr Acad Soc (May 1-4, San Francisco) 2004, Abst 2644.

Lumiliximab

Lumiliximab (formerly IDEC-152) is an anti-CD23 monoclonal antibody in development at Biogen Idec that has reached phase I/II trials for the treatment of allergic asthma and allergic rhinitis. It is also in phase I clinical evaluation for chronic lymphocytic leukemia (CLL). Seikagaku has withdrawn from the project.

Mannitol, Inhaled



Pharmaxis is assessing a dry powder inhaler system of the nonionic osmolyte mannitol (Bronchitol™) in phase I trials for the treatment of chronic bronchitis and in phase II trials for the treatment of bronchiectasis and cystic fibrosis. Bronchitol™ was licensed to Pharmaxis from the Central Sydney Area Health Service. Mannitol is widely used as a food additive and sweetener, and an injection formulation was launched as Osmitrol in the U.S. over 40 years ago by Baxter for the treatment of cerebrovascular disorders, glaucoma and renal disorders. Pharmaxis also

has a lung function test known as Aridol™ comprising an inhalable dry powder mannitol formulation, administered using a hand-held device, in late-stage (phase III) clinical development.

MCC-847

MCC-847 is a leukotriene $CysLT_1$ (LTD_4) antagonist with the ability to inhibit bronchoconstriction and the allergic response, licensed by Mitsubishi Pharma from AstraZeneca in 2001. Phase III clinical trials for the treatment of asthma and phase II trials for allergic rhinitis are under way.

ME-3301

Phase II clinical studies are in progress at Meiji Seika for ME-3301, a new antiasthmatic/antiallergic agent. ME-3301 inhibits the release of inflammatory mediators such as histamine and PGD_2 from mast cells.

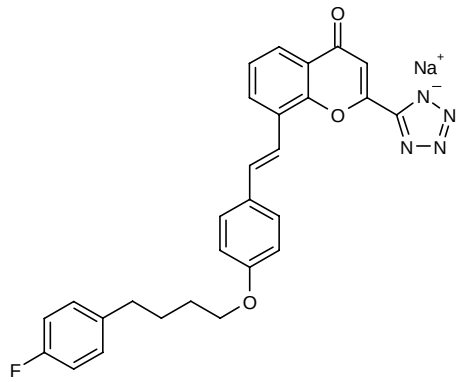
MEDI-528

MedImmune has commenced dosing in a phase I trial of MEDI-528, an anti-IL-9 monoclonal antibody. The open-label, dose-escalation study in 24 healthy adult volunteers is designed to evaluate safety and tolerability and to gather pharmacokinetic and immunogenicity data. Volunteers will receive 0.3, 1.0, 3.0 or 9.0 mg/kg of the antibody. The IL-9-neutralizing antibody is the culmination of intensive genetic, immunological and developmental research at Genaera, the Ludwig Institute of Cancer Research and other academic institutions. Data from preclinical studies in models of asthma suggest that IL-9-neutralizing monoclonal antibodies may help reduce airways hyperreactivity, mucus production and inflammation. The molecule is therefore being studied as a potential new treatment for symptomatic, moderate to severe, persistent asthma. Initiation of the new phase I study triggers a USD 500,000 milestone payment to Genaera. MedImmune and Genaera entered into a collaboration and licensing agreement in April 2001 to codevelop an IL-9-based treatment for asthma. The alliance provided Genaera with a significant equity investment by MedImmune and collaborative research funding for 2 years. Genaera could also receive future royalties and up to USD 55 million in milestone payments. MedImmune conducts all development, manufacturing, marketing and sales for any product. Genaera retains rights to certain IL-9-based vaccines and diagnostics (1, 2).

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

2. *MedImmune advances IL-9 monoclonal antibody into new phase I study*. DailyDrugNews.com (Daily Essentials) Aug 23, 2004.

MEN-91507



MEN-91507 (LM-1507.Na) is a potent and selective leukotriene $CysLT_1$ (LTD_4) antagonist discovered and developed by Menarini and currently in early clinical development for the treatment of mild to moderate asthma.

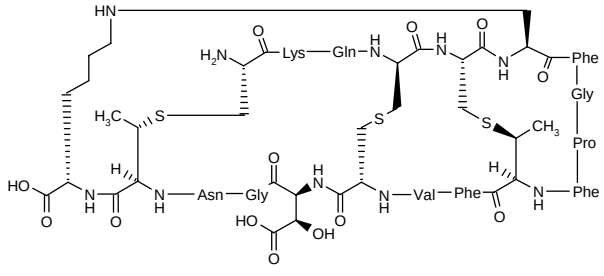
Mepolizumab

GlaxoSmithKline's mepolizumab, a chimeric monoclonal antibody with anti-IL-5 activity, is in phase II trials for the treatment of steroid-sparing asthma and hypereosinophilic syndrome therapy.

MN-001

MN-001 is an orally bioavailable leukotriene $CysLT_{1/2}$ (LTD_4/C_4) antagonist and PDE4 inhibitor entering phase II development at MediciNova for the treatment of asthma and interstitial cystitis. The drug was licensed from Kyorin.

Moli-1901



AOP Orphan and Lantibio (formerly MoliChem Medicines) have entered into a licensing and commercialization agreement for the development of Moli-1901

Table IX: Clinical studies of Moli-1901 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Fibrosis, cystic, Healthy volunteers	Randomized, Single-blind	Moli-1901, 0.01 μmol/l i.n. Moli-1901, 0.03 μmol/l i.n. Moli-1901, 0.1 μmol/l i.n. Moli-1901, 0.3 μmol/l i.n. Moli-1901, 1 μmol/l i.n. Moli-1901, 3 μmol/l i.n. Moli-1901, 10 μmol/l i.n. Placebo	8	Intranasal Moli-1901 induced hyperpolarization and significantly increased chloride transport in healthy volunteers and patients with cystic fibrosis. Response resolved more quickly in patients with cystic fibrosis, and the greatest response was found at a dose of 3 μmol/l. No drug-related adverse events were observed	2

(PA-48009, duramycin) for the treatment of cystic fibrosis in European territories. AOP will assume full responsibility for the clinical and nonclinical development of the Lantibio proprietary technology in Europe. Lantibio will be responsible for technical development activities to support regulatory filings in the E.U. and will have access to AOP's European data to support regulatory filings in the U.S. AOP will shortly initiate phase II trials in Germany (1). Lantibio (as MoliChem Medicines) obtained rights to the use of duramycin for the treatment of respiratory indications from the former Glaxo (now GlaxoSmithKline) and the University of North Carolina at Chapel Hill in 1997. The product was developed in the U.S. for cystic fibrosis up to phase II clinical trials, but the company refocused its development efforts for Moli-1901 towards dry eye syndrome in 2003.

The potential use of Moli-1901 to restore chloride transport in cystic fibrosis was evaluated in a randomized, single-blind, placebo-controlled phase I clinical trial in 4 adult cystic fibrosis patients and 4 healthy volunteers. Up to 10 μmol/l of Moli-1901 and vehicle were administered intranasally to the subjects, and the nasal potential difference was measured using a high-impedance voltimeter both at baseline and after each dose. At baseline, the nasal epithelia of cystic fibrosis patients showed a different behavior to several stimuli compared to the epithelia of healthy subjects. Intranasal Moli-1901 induced hyperpolarization and significantly increased chloride transport compared with vehicle in both cystic fibrosis patients and healthy volunteers, although the response resolved more quickly in the patients. The greatest chloride secretion response was found with the dose of 3 μmol/l. Evidence suggesting a dose-response relationship was found, but the great variability of the results in cystic fibrosis patients prevented the estimation of the half-life of the chloride response. No drug-related adverse events were reported; the mild to moderate edema, erythema and bleeding found in the nasal epithelium of some patients were determined to be associated with the study design (2) (Table IX).

1. *AOP and Lantibio enter licensing agreement for Moli-1901*. DailyDrugNews.com (Daily Essentials) June 2, 2004.

2. Zeitlin, P.L., Boyle, M.P., Guggino, W.B., Molina, L. *A phase I trial of intranasal Moli1901 for cystic fibrosis*. Chest 2004, 125(1): 143.

MP-601205

An IND was filed late last summer by Mpex Pharmaceuticals for a phase Ib clinical trial studying its aerosol drug candidate MP-601205 in cystic fibrosis patients. MP-601205 is a bacterial efflux pump inhibitor that may significantly increase the efficacy of antibiotics in the treatment of acute and chronic bacterial infections in cystic fibrosis, hospital-acquired pneumonia and certain chronic obstructive pulmonary diseases. The study will evaluate the safety of a dose expected to be effective. If this endpoint is achieved, the company will begin a phase II trial evaluating the efficacy of MP-601205 in combination with ciprofloxacin in the treatment of pulmonary exacerbations in cystic fibrosis patients (1).

1. *Mpex Pharmaceuticals announces IND filing for aerosol candidate to treat respiratory infections associated with cystic fibrosis*. Mpex Pharmaceuticals Press Release 2004, Aug 9.

NCX-1020

Clinical development of NCX-1020, NicOx's patented NO-donating derivative of budesonide, is in progress for chronic asthma (phase II) and COPD (phase I). NCX-1020 is the first in a new class of inhaled nitrosteroids aimed at the treatment of severe respiratory diseases such as asthma and COPD. Data from several animal models have shown that NCX-1020 has a broad pharmacological profile and considerably more potent antiinflammatory activity than budesonide. Unlike budesonide, it exhibited marked bronchodilating activity in several acute and chronic animal models.

NCX-1510

NCX-1510 is a nitric oxide (NO)-donating histamine receptor antagonist in phase II testing by Biolipox and NicOx for the treatment of allergic rhinitis. NCX-1510 is the first compound to be selected from the ongoing research and codevelopment agreement signed in 2001

between the companies for the discovery and development of novel compounds in the respiratory field. The nasal spray is being developed for the treatment of both allergic and nonallergic rhinitis. Biolipox was granted an exclusive worldwide license to NCX-1510.

NCX-1510 reached its primary efficacy endpoint in a phase IIa study for the treatment of allergic rhinitis last summer. This phase IIa clinical study took place at Lund University and involved 36 patients. NCX-1510 treatment produced a statistically significant reduction in symptoms measured as a lower total nasal symptom score compared with placebo. Furthermore, NCX-1510 demonstrated equivalent efficacy to the standard systemic treatment (1, 2).

1. *First compound from Biolipox/NicOx collaboration enters phase II*. DailyDrugNews.com (Daily Essentials) Jan 23, 2004.

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

NGD-2000-1

Neurogen has discontinued its C5a receptor antagonist program for inflammation. The lead compound in the series, NGD-2000-1 had reached phase II clinical trials for both asthma and rheumatoid arthritis, but did not reach clinical endpoints (1, 2).

1. *New phase II results described for NGD-2000-1 in asthma*. DailyDrugNews.com (Daily Essentials) Jan 20, 2004.

2. *Neurogen reports phase IIa clinical trial results for oral RA drug*. Neurogen Corp. Press Release 2004, June 14.

NS-126

Nippon Shinyaku has synthesized a novel steroid, NS-126, which is being codeveloped with SSP Co. and has reached phase II trials for the treatment of bronchial asthma and allergic rhinitis.

Omalizumab, New Indication

Omalizumab (olizumab, rhuMAb E25, Xolair®) is a recombinant humanized anti-IgE monoclonal antibody that binds to free IgE and prevents its binding to specific receptors on the surface of cells, thus preventing the release of immune mediators. Reducing IgE levels also helps to improve inflammation of the airways, making omalizumab the first nonsteroidal therapy that is proven to have a major antiinflammatory effect in allergic asthma. Omalizumab has a good safety profile, with only mild to intermediate drug-related adverse events, and is conveniently administered by subcutaneous injection every 2 or 4 weeks. Developed jointly by Novartis, Genentech and Tanox, omalizumab was approved by the FDA in June 2003 and subsequently launched in the U.S. for the treatment of allergic asthma. Novartis has also introduced the antibody in Australia and has submitted its application for the European approval of omalizumab as a novel therapy for the prevention of asthma exacerbations and the control of symptoms in adults and adolescents with severe persistent allergic asthma who remain inadequately controlled despite use of inhaled corticosteroids and LABAs. The European submission is based on clinical trial experience in around 5,500 patients demonstrating omalizumab's efficacy in controlling symptoms and reducing asthma exacerbations, even in patients with severe allergic asthma that is uncontrolled by existing medication. A multicenter, randomized, open-label, parallel-group study in 312 patients with poorly controlled moderate to severe allergic asthma was designed to investigate omalizumab's efficacy and tolerability in a real-life clinical setting. Data showed that the number of asthma exacerbations was significantly lower with omalizumab than with best standard care alone, equivalent to a reduction of 60.8%. More patients treated with omalizumab remained exacerbation-free than those on best standard care alone (49.5% *vs*. 26.4%). The antiinflammatory properties of omalizumab were highlighted in a further study involving 43 patients with mild to moderate disease, whose airways had not been modified by treatment with corticosteroids. The 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study showed that omalizumab led to a reduction in many types of cells involved in airways inflammation, especially eosinophils. The mean sputum eosinophil count decreased significantly from 6.6% to 1.7% in the omalizumab group, a reduction significantly greater than with placebo. Submitted data also include findings from a recently completed 28-week randomized, double-blind, placebo-controlled study in 419 adults and adolescents with inadequately controlled severe allergic asthma. Phase III development is under way by licensee Sankyo for the treatment of both bronchial asthma and allergic rhinitis. Additional phase III trials are being conducted by Genentech, Novartis ant Tanox in pediatric patients with moderate to severe, persistent and inadequately controlled allergic asthma. Tanox and Genentech are evaluating the drug in phase II studies for the treatment of peanut allergy (1-7).

Subcutaneous omalizumab (total dose = 0.016 mg/kg/IgE) or placebo was administered every 2 or 4 weeks to 23 patients with allergic rhinitis in a randomized, double-blind trial. After 16 weeks, nasal symptom scores after allergen challenge were significantly reduced by omalizumab. Human serum albumin and TNF-α were also decreased in nasal lavage fluid of omalizumab-treated patients (8).

Combinations of an anti-IgE antibody and an antiallergic compound for the treatment or prevention of

allergic conditions such as allergic asthma, allergic rhinitis and atopic dermatitis have been claimed. Preferably the antibody is omalizumab, which is used in combination with pimecrolimus (9).

1. *Omalizumab: An effective anti-IgE treatment for allergic asthma and rhinitis*. Drugs Today 2004, 40(4): 367.

2. *Novartis seeks European approval of Xolair for severe allergic asthma*. DailyDrugNews.com (Daily Essentials) July 7, 2004.

3. *Enrollment open in phase II Xolair peanut allergy study*. DailyDrugNews.com (Daily Essentials) July 9, 2004.

4. *Phase III trial of Xolair begins in pediatric allergic asthma patients*. DailyDrugNews.com (Daily Essentials) May 20, 2004.

5. *Novartis reports Q2 R&D highlights*. Novartis Press Release 2004, July 20.

6. *Genentech, Novartis and Tanox settle disputes surrounding Xolair and TNX-901*. Genentech Press Release 2004, Feb 26.

7. *Genentech reports Q2 R&D highlights*. Genentech Web Site 2004, July 7.

8. Hanf, G., Noga, O., O'Connor, A., Kunkel, G. *Omalizumab inhibits allergen challenge-induced nasal response*. Eur Respir J 2004, 23(3): 414.

9. Owen, C.E. et al. (Novartis AG) *Combination treatments for allergic disease comprising administering an anti-IgE antibody and antiallergic cpd.* WO 0357249.

Original monograph – Drugs Fut 2002, 27(6): 537.

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Holgate, S.T. et al. *Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma*. Clin Exp Allergy 2004, 34(4): 632.

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Vignola, A.M. et al. *Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR*. Allergy 2004, 59(7): 709.

Ono-6126

The PDE4 inhibitor Ono-6126 is being developed by Ono Pharmaceutical for the oral treatment of bronchial asthma and COPD. In Japan and Europe, a phase II clinical study of the drug is under way as a treatment for bronchial asthma. In North America, a phase II clinical study is ongoing for the treatment of COPD (1).

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

Ono-4127.Na

The potent prostanoid DP receptor antagonist Ono-4127.Na is in early clinical testing by Ono Pharmaceutical for the treatment of allergic rhinitis.

PGN-0052

Enzon and Pharmagene have signed an agreement for the development of a long-acting version of Pharmagene's drug candidate PGN-0052. PGN-0052, a synthetic version of human secretin, has successfully completed 3 phase I studies, and is in a phase IIa proof-of-concept trial in cystic fibrosis patients designed to assess the impact of the drug on mucociliary clearance. If the study confirms the therapeutic principle, the development program will continue with a version of PGN-0052 with an optimized pharmacokinetic profile. In clinical studies to date, PGN-0052 has demonstrated a favorable safety and tolerability profile and has proven effective in improving airways function following intravenous administration. The disease-modifying drug acts by promoting airways smooth muscle relaxation, as well as hydrating lung secretion. Extending the duration of action of PGN-0052 may provide greater overall effectiveness and improve its potential as a therapeutic. In addition to cystic fibrosis, the drug may have further applications for other respiratory disorders such as COPD and asthma. Under the agreement, Enzon will apply its proprietary PEGylation technology to engineer a molecule with optimized pharmacokinetic properties and an extended duration of action. Enzon will receive an initial fee upon signing and a milestone payment upon certain predetermined criteria. Subject to achievement of such criteria, the companies have the option to enter into a worldwide joint development and commercialization agreement for the product. Should the companies exercise this option, they would share equally in development costs and profits and Pharmagene would be eligible to receive future licensing and milestone payments, which could reach approximately GBP 26.5 million. Should the companies not elect to enter into a joint development and commercialization agreement, Pharmagene will be entitled to use the PEGylated molecule for development and commercialization purposes and Enzon will receive certain comarketing rights and royalties on worldwide sales for all indications (1, 2).

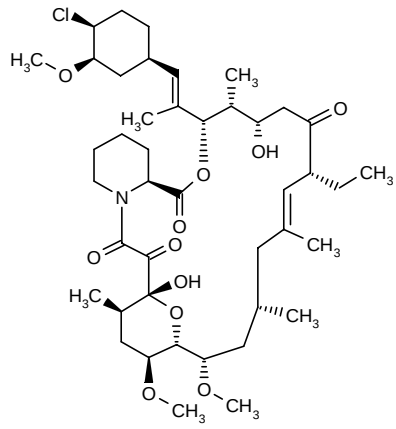
A single-blind, randomized, crossover clinical trial was conducted in order to evaluate the potential effects of PGN-0052 in asthmatics. Ten otherwise healthy male patients with mild to moderate asthma were given single doses of placebo or PGN-0052 (1, 10 or 100 μg/h i.v.). The cumulative dose of inhaled histamine needed to reduce the baseline FEV_1 of the patients by 20% increased from 0.618 μmol with placebo to 0.647 μmol with 1 μg/h of PGN-0052, to 1.31 μmol with 10 μg/h and to 1.43 μmol with 100 μg/h. PGN-0052 was well tolerated and induced only a slight increase in heart rate. The authors concluded that bronchodilatation induced by PGN-0052 may be a secondary benefit for patients with cystic fibrosis (3) (Table X).

1. *PGN-0052 advances to phase II*. DailyDrugNews.com (Daily Essentials) Jan 5, 2004.

2. *Enzon and Pharmagene to develop PEGylated secretin for cystic fibrosis*. DailyDrugNews.com (Daily Essentials) Sept 20, 2004.

3. Pawsey, S.D., Coleman, R.A., Spencer, L. *Effects of PGN0052 on histamine-induced brochoconstriction in asthmatic subjects*. Am J Respir Crit Care Med 2004, 169(7, Suppl.): A325.

Pimecrolimus, New Indication



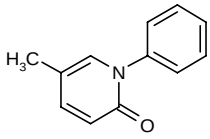
First introduced in 2002 in Denmark by originator Novartis as Elidel® topical cream, pimecrolimus is a cytokine production inhibitor for the treatment of atopic dermatitis. Subsequent launches of Elidel® took place in the U.S., the U.K., Canada and Germany, while regulatory approval in the E.U. is pending. At present, pimecrolimus is in phase II development by Novartis for the oral treatment of asthma. Novartis is also evaluating the product in phase II studies as eye drops for the treatment of eye disorders and as ointment and oral formulations for skin inflammation.

Original monograph – Drugs Fut 1998, 23(5): 508.

Table X: Clinical studies of PGN-0052 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Asthma	Randomized, Single-blind, Crossover	PGN-0052, 1 μg/h i.v. PGN-0052, 10 μg/h i.v. PGN-0052, 100 μg/h i.v. Placebo	10	PGN-0052 was well tolerated and dose-dependently increased the cumulative dose of inhaled histamine needed to reduce the baseline FEV_1 of asthmatic patients by 20%	3

Pirfenidone



Pirfenidone is an orally active small-molecule TNF-α production inhibitor originated by Marnac and currently in phase III development by Shionogi (S-7701) for the treatment of idiopathic pulmonary fibrosis (IPF). InterMune is conducting phase II trials of pirfenidone for the same indication, as well as for Hermansky-Pudlak syndrome, with phase III studies planned for this year. Pirfenidone may inhibit collagen synthesis, downregulate the production of multiple cytokines and block fibroblast proliferation and stimulation in response to cytokines. Marnac licensed worldwide rights to develop and commercialize pirfenidone for all fibrotic diseases to InterMune, excluding Japan, Korea and Taiwan, where the drug is licensed to Shionogi. In March 2004, pirfenidone was granted orphan drug designation by the FDA for the treatment of IPF (1-3).

1. *Orphan drug designation for pirfenidone for IPF*. DailyDrugNews.com (Daily Essentials) March 29, 2004.

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

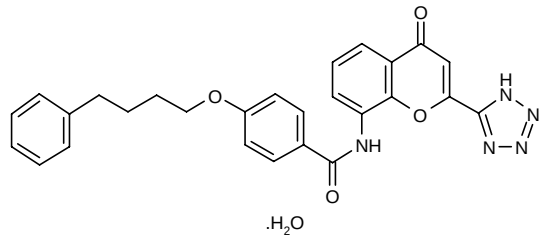
3. *Early access program for pirfenidone in IPF*. DailyDrugNews.com (Daily Essentials) Feb 10, 2004.

Original monograph – Drugs Fut 1977, 2(6): 396.

PLAS*min*™ Complex CFTR

Copernicus Therapeutics' lead candidate is a novel nonviral gene therapy for cystic fibrosis using a new compacted DNA technology known as PLAS*min*™ complexes. The PLAS*min*™ complexes are highly compacted DNA structures that are small enough to fit through the nuclear pores, resulting in efficient gene expression in nondividing cells. The company is working on an inhaled PLAS*min*™ complex delivering a functional CFTR gene directly to the lungs of patients with cystic fibrosis. Encouraging results were obtained in a preliminary phase I trial in 12 patients, with indications that gene transfer had occurred and good tolerance.

Pranlukast Hydrate, New Indication



Pranlukast hydrate (Onon®) is a leukotriene $CysLT_1$ (LTD_4) and $CysLT_2$ (LTC_4) antagonist first launched in Japan in 1995 for the oral treatment of bronchial asthma and allergic rhinitis. Currently, Ono Pharmaceutical is evaluating the drug in phase II for the oral treatment of COPD and sinusitis. A dry syrup formulation of pranlukast is in phase II/III for the treatment of allergic rhinitis in pediatric patients. Ono has a license agreement with Schering-Plough for the development and marketing of pranlukast in Latin America.

Original monograph – Drugs Fut 1988, 13(4): 317.

PTC-124

A phase I trial is evaluating the safety, tolerability and pharmacokinetic profile of PTC Therapeutics' PTC-124, a small-molecule drug being investigated initially as a treatment for cystic fibrosis and Duchenne muscular dystrophy. The phase I program will evaluate escalating doses of PTC-124 in healthy volunteers. Preliminary results from the first trial have confirmed that PTC-124 is orally bioavailable and well tolerated in the initial subjects. Final results of the phase I studies are expected to form the basis for initiation of phase II studies in early 2005. PTC-124 is a novel, orally administered drug that targets nonsense mutations. The agent allows the cellular machinery to bypass the nonsense mutation and continue the translation process, thereby restoring the production of full-length functional protein in genetic disease models harboring nonsense mutations. Approximately 15% of the cases of Duchenne muscular dystrophy and 10% of the cases of cystic fibrosis are due to nonsense mutations. PTC has catalogued over 1,800 distinct genetic disorders where nonsense mutations are the cause of the disease in an appreciable percentage of patients. The concept of reading through nonsense mutations as a treatment for cystic fibrosis was previously studied with the antibiotic gentamicin. However, for systemic use gentamicin must be given intravenously and can have severe side effects. PTC-124 shows significant activity in preclinical models of cystic fibrosis, but unlike gentamicin, is an oral drug with a good preclinical safety profile. PTC plans to conduct initial patient studies in children and young

adults with cystic fibrosis and Duchenne muscular dystrophy, eventually extending to patients with various different genetic disorders. Other potential indications under consideration for PTC-124 include hemophilia, neurofibromatosis, retinitis pigmentosa, bullous skin diseases and lysosomal storage diseases. In preclinical studies, PTC-124 exhibited substantial oral bioavailability, demonstrated significant activity, and was well tolerated at dose levels much higher than those required to show activity (1-3).

1. *PTC Therapeutics raises funds to support development of PTC-124*. DailyDrugNews.com (Daily Essentials) Jan 20, 2004.

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

3. *PTC Therapeutics awarded grant for Duchenne muscular dystrophy research*. DailyDrugNews.com (Daily Essentials) Sept 6, 2004.

Pumactant, New Indication

AirPharma and Britannia Pharmaceuticals have signed a global licensing agreement under which AirPharma will develop AP-0016, a dry powder formulation of Britannia's synthetic surfactant pumactant. AirPharma will initiate a clinical program to study the drug's efficacy for seasonal allergic asthma, followed by additional respiratory indications such as perennial allergic asthma and COPD. AirPharma will also assume control of regulatory and marketing initiatives for AP-0016, as well as activities related to the eventual commercialization of the product worldwide, except for the U.K. and Ireland, which will remain under Britannia's management. A phase II trial conducted at the University of Southampton School of Medicine showed that all asthma patients who received AP-0016 before exposure to inhaled allergens were able to completely eliminate early asthmatic responses. The drug's effect on late asthmatic responses, which occur 3-10 h after exposure to the allergens, was less dramatic but still promising. There were no significant side effects. AP-0016 is a protein-free synthetic surfactant made from the naturally occurring phospholipids dipalmitoylphosphatidycholine (DPPC) and phosphatidylglycerol (PG). When inhaled by patients, the AP-0016 powder enhances the body's surfactant system, helping to protect the lungs from inhaled allergens, dust particulates and other environmental insults. Because AP-0016 is made without proteins, it can be inhaled by patients without risk of infection or allergic reaction (1). Pumactant was originally developed by Britannia as a lung surfactant for infant respiratory distress syndrome (RDS) and launched in the U.K. as Alec®, although it was subsequently withdrawn in 2000. The company has also developed a dry powder aerosol formulation for the prevention of surgical adhesions, known as AdSurf®, which is in phase III clinical development.

1. *AirPharma and Britannia sign licensing agreement for asthma drug AP-0016*. DailyDrugNews.com (Daily Essentials) Nov 16, 2004.

QAB-149

Novartis's novel long-acting inhaled β_2-adrenoceptor agonist QAB-149 is in phase II trials for asthma and COPD. SkyePharma and Novartis are jointly developing a new product for the treatment of asthma and COPD that combines the drug with SkyePharma's SkyeHaler™, a breath-activated multidose dry powder inhaler (MDDPI) device, to be marketed by Novartis as the Certihaler™. SkyeProtect®, a powder formulation that protects the drug from atmospheric moisture to ensure product stability and dose-to-dose reproducibility, will also be used.

R-112

R-112 (Rigel) is an inhibitor of Syk kinase in phase II development for the treatment of chronic allergic rhinitis. Rigel is also evaluating R-112 in preclinical studies for the treatment of asthma. R-112 enters mast cells, binds to an intracellular target and interrupts the signal from the IgE receptor, thus preventing downstream signaling and subsequent chemical mediator release. The drug is designed to block all of the major pathways that are triggered in an allergic attack, with a rapid onset of action. It is delivered intranasally and no systemic exposure to R-112 has been detected in any intranasal administration in clinical trials to date.

Rigel has reported successful outcomes from a phase II study of R-112 for the treatment of the symptoms of allergic rhinitis. The day 1 data indicated that R-112 reduced the Global Nasal Allergy Symptom Score by 7.0 points (38%) *versus* 5.4 points (29%) for placebo, an absolute difference of 9%, and a relative improvement over placebo of 24%. Results on day 2 were of similar magnitude. The randomized, placebo-controlled study enrolled 319 patients who were verified to suffer from allergic rhinitis. The primary objective was to measure safety and efficacy of R-112 as an intranasal treatment for allergic rhinitis. The Global Nasal Allergy Symptom Score used in the study showed a greater than 20% relative improvement for R-112 over placebo and up to 38% improvement for R-112 from baseline measurements. There were no significant drug-related adverse events. As early as the 30-min time interval after dosing, R-112 showed a statistically significant improvement in symptom scores over placebo, demonstrating a rapid onset of action in symptom improvement. These beneficial effects lasted throughout the entire measurement period until the end of the park day. Symptoms most closely associated with chronic nasal congestion were dramatically improved with R-112 over placebo (1-3).

The efficacy and safety of a single dose of R-112 were investigated in a double-blind, randomized, crossover trial in 20 out-of-season volunteers with grass or ragweed pollen-induced allergic rhinitis. After screening subjects by nasal allergen challenge to establish extract dose (Bousquet dose of 5), 1 dose of R-112 or vehicle was given intranasally and followed by nasal allergen challenge 15 min later. Histamine, PGD_2 and tryptase content were evaluated at baseline, 5 and 10 min after allergen challenge. R-112 administration decreased PGD_2 (1.7-fold) and tryptase (1.8-fold) concentrations, but no changes in histamine concentration could be detected. Although R-211 improved rhinorrhea, symptom scores were not significantly different between treated and control groups. R-112 was well tolerated and may be useful for reducing mediator release in allergic rhinitis patients (4).

1. *Phase II trial under way for R-112 in allergic rhinitis*. DailyDrugNews.com (Daily Essentials) April 22, 2004.

2. *Rigel Pharmaceuticals reports Q1 R&D highlights*. Rigel Pharmaceuticals Press Release 2004, May 4.

3. *R-112 reduces symptoms of allergic rhinitis in phase II study*. DailyDrugNews.com (Daily Essentials) Aug 4, 2004.

4. Guyer, B., Shimamoto, S., Bradhurst, A., Grossbard, E., Dreskin, S., Nelson, H. *The effect of a novel inhibitor of mast cell activation on mediators, symptoms and nasal patency in allergic rhinitis*. J Allergy Clin Immunol 2004, 113(2, Suppl.): Abst 17.

R-411

R-411 is a dual $\alpha_4\beta_1/\alpha_4\beta_7$ integrin (VLA-4/LPAM-1) antagonist developed at Roche and in phase II clinical development as a potential new treatment for allergic asthma. The orally active nonsteroidal compound targets the inflammatory process underlying asthma and has shown better efficacy than leukotriene antagonists and single integrin antagonists in animal studies, without the adverse effects of inhaled steroids.

The safety, tolerability and pharmacokinetics of R-411 after oral administration as single ascending doses (10, 50, 150, 300, 600, 900 and 1200 mg) were evaluated in 7 groups of 10 subjects under fasting conditions. The C_{max} of the active metabolite Ro-0270608 ranged from 35 µg/l (10 mg) to 2021 µg/l (1200 mg), with a t_{max} of 1-2 h and a terminal $t_{1/2}$ of 7-9 h. The exposure increased proportionally with dose and was linear in the 150-1200 mg interval. No significant adverse effects were observed compared to placebo (1).

A 3-part phase I study was conducted in 132 healthy volunteers to assess the pharmacokinetics and safety of R-411 and its active metabolite Ro-0270608 after oral administration of R-411. Absolute bioavailability was determined in an open-label, single-dose, crossover study in which 12 subjects were given oral R-411 200 mg followed 7 days later by i.v. administration of Ro-0270608 100 mg and then R-411 200 mg p.o. again on day 15. The absolute bioavailability of the metabolite after oral R-411 administration was 27 ± 4% and the half-life was approximately 7-9 h. Single-dose pharmacokinetics were assessed in a randomized, double-blind, placebo-controlled study of oral R-411 10, 50, 150, 300, 600, 900 and 1200 mg. Exposure of Ro-0270608 rose proportionally with doses of 150-1200 mg. A randomized, double-blind, placebo-controlled study evaluated administration of R-411 50, 150, 300, 600 and 900 on day 1 followed by repeated daily doses on days 3-10. No accumulation was seen with this schedule, and pharmacokinetic parameters did not change after 8 days of drug administration. R-411 was also well tolerated after single-dose administration of doses up to 1200 mg and with repeated administration of doses up to 900 mg for 3 weeks. No serious adverse events were noted (2).

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R-667

Phase II clinical evaluation is in progress at Roche for R-667, a selective retinoic acid receptor RARγ agonist, for the treatment of pulmonary emphysema. In animal studies, R-667 has been shown to regenerate lung tissue and restore lung function, and may address the underlying pathology of emphysema.

RBx-7796

RBx-7796 is an integrin $\alpha_4\beta_1$ (VLA-4) antagonist synthesized at Ranbaxy and undergoing phase II proof-of-concept trials for the treatment of both bronchial asthma and allergic rhinitis (1, 2).

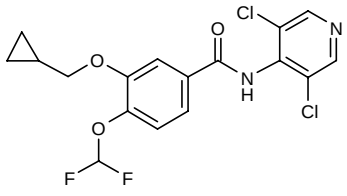
Recombinant α_1-Antitrypsin

Recombinant α_1-antitrypsin (α_1-proteinase inhibitor, rAAT) produced in genetically modified yeast cells is a leukocyte elastase inhibitor in phase II development by Arriva-ProMetic, a joint venture between Arriva Pharmaceuticals and ProMetic formed in 1999, as a topical gel for the treatment of atopic dermatitis and other dermatological disorders, including psoriasis. Arriva and partner Baxter are conducting phase II trials of an inhaled formulation of rAAT for the treatment of emphysema in patients with congenital AAT deficiency. Arriva is also conducting preclinical studies of inhaled rAAT for the treatment of cystic fibrosis, asthma, COPD and otitis media. An inhaled formulation of rAAT would provide patients more immediate control in managing disease symptoms than does the current infusion method. α_1-Antitrypsin is a glycoprotein primarily produced by hepatocytes and immune system cells that belongs to a family of structurally related proteins classified as serine protease inhibitors (serpins), which inhibit several proteases, including trypsin, cathepsin G, thrombin, tissue kallikrein, as well as neutrophil elastase. Orphan drug designation for rATT has been granted in the U.S. for both cystic fibrosis and hereditary emphysema. A human plasma-derived α_1-proteinase inhibitor was previously developed by Alpha Therapeutics, a U.S. subsidiary of Mitsubishi Pharma, and launched in the U.S. in 2003 as Aralast™ by licensee Baxter for the treatment of hereditary emphysema in patients with congenital AAT deficiency. Baxter subsequently obtained all rights to the product from Alpha Therapeutics and signed a copromotion agreement for the U.S. with InterMune.

Baxter and Arriva reported the successful completion of a phase I trial of rAAT administered to the lungs by nebulization. The trial was conducted at 4 U.S. centers and evaluated the safety, immunogenicity and tolerability of the jointly developed rAAT therapy. Results showed that all doses were well tolerated, including the maximum amount administered (1).

1. *Successful completion of first phase I trial for nebulized rAAT*. DailyDrugNews.com (Daily Essentials) March 3, 2004.

Roflumilast



Altana has submitted its respiratory drug roflumilast (Daxas®) for European approval. Roflumilast is being developed as an oral, once-daily, selective PDE4 inhibitor for the treatment of COPD and asthma together with Pfizer in the U.S. and other markets, while a cooperation agreement has been signed with Tanabe Seiyaku (APTA-2217) in Japan, where it is in phase II for asthma and in preparation for phase II trials for COPD. Altana reported that enrollment in its extensive clinical program for roflumilast in the U.S. is taking longer than previously anticipated, delaying the planned submission to seek approval of the drug. An application for the approval of roflumilast was originally scheduled for the first half of 2005, but this will now take place later. Roflumilast has been evaluated in 16 clinical studies involving more than 4,400 patients with asthma and COPD, and an additional 10 phase III trials in 4,100 patients will increase the data generated to date (1-5).

An open-label, randomized, crossover clinical trial compared the pharmacokinetics of roflumilast and its primary metabolite roflumilast *N*-oxide in 19 healthy male volunteers. Once-daily administration of roflumilast (250 or 500 μg p.o.) on day 1 and then on days 5-12 was associated with dose-dependent increases in the drug exposure levels and peak plasma concentrations of both roflumilast and roflumilast *N*-oxide. Most adverse events were mild or moderate and transient (6).

An open-label, crossover clinical trial assessed the potential pharmacokinetic interaction between roflumilast and erythromycin, a drug that may be given to treat airways infections. Eighteen healthy male volunteers successively received erythromycin alone (single dose of 500 mg p.o.), roflumilast alone (500 μg p.o. once daily for 10 days) and a single dose of roflumilast (500 μg p.o.) combined with erythromycin (500 mg p.o.). Analysis of blood samples collected during the study revealed that both the area under the curve and the peak plasma concentration of roflumilast and its active metabolite roflumilast *N*-oxide did not change significantly with concomitant erythromycin. Roflumilast slightly reduced the values of both parameters for erythromycin, although the absence of clinically relevant changes in electrocardiograms or vital signs led researchers to suggest that no dose adjustments would be necessary when roflumilast was coadministered with erythromycin (7).

Two open-label, randomized, crossover clinical trials evaluated the pharmacokinetics of a single dose of roflumilast (500 μg p.o.) given to 28 healthy volunteers under different fasting and timing conditions. No significant differences were found in the extent of absorption when the drug was given while fasting, after a fat-rich breakfast, in the morning or in the evening after a standardized meal. Food reduced the rate of absorption and almost doubled the time to peak plasma levels, but had no effects on the area under the curve or the peak plasma levels of the pharmacologically active *N*-oxide metabolite of roflumilast. No significant pharmacokinetic effects were associated with administration timing (8).

The results of 2 open-label, randomized, crossover clinical trials that enrolled 24 healthy male volunteers revealed that the pharmacokinetics of roflumilast (500 μg p.o. once daily) were not affected when combined with

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

Indication	Design	Treatments	n	Conclusions	Ref.
Chronic obstructive pulmonary disease	Randomized, Double-blind, Multicenter	Roflumilast, 250 μg p.o. o.d. x 24 wks (n=576) Roflumilast, 500 μg p.o. o.d. x 24 wks (n=555) Placebo (n=280)	1411	Roflumilast significantly improved FEV_1 and reduced the number of exacerbations in patients with moderate to severe chronic obstructive pulmonary disease	10
Asthma	Randomized, Double-blind, Crossover	Roflumilast, 500 μg p.o. o.d. x 28 d Placebo	16	Roflumilast was effective in improving lung function in patients with exercise-induced asthma. The drug also inhibited *ex vivo* endotoxin-induced TNF-α formation in blood	12
Asthma	Randomized, Double-blind, Multicenter	Roflumilast, 100 μg p.o. o.d. x 12 wks Roflumilast, 250 μg p.o. o.d. x 12 wks Roflumilast, 500 μg p.o. o.d. x 12 wks	690	Daily doses of roflumilast of 100, 250 and 500 μg for 12 weeks dose-dependently increased FEV_1 in patients with chronic stable asthma. The drug was well tolerated and was not associated with relevant changes in vital signs, ECG or laboratory parameters	13
Asthma	Open	Roflumilast, 100 μg p.o. o.d. x 52 wks Roflumilast, 250 μg p.o. o.d. x 52 wks Roflumilast, 500 μg p.o. o.d. x 52 wks	456	Roflumilast administered for up to 1 year was well tolerated and significantly improved lung function in patients with chronic stable asthma	14
Asthma	Randomized, Double-blind, Crossover	Roflumilast, 250 μg p.o. o.d. x 7-10 d Roflumilast, 500 μg p.o. o.d. x 7-10 d Placebo	23	Roflumilast dose-dependently inhibited the early and late allergic response induced by allergen exposure in patients with mild allergic asthma	16
Asthma	Randomized, Double-blind	Roflumilast, 500 μg p.o. o.d. x 12 wks (n=207) Beclomethasone dipropionate, 200 μg inhal. b.i.d. x 12 wks (n=214)	421	Roflumilast and beclomethasone dipropionate were well tolerated and effective in improving the FEV_1 and FVC in patients with bronchial asthma	17

budesonide (400 μg by inhalation b.i.d.) or salbutamol (200 μg by inhalation t.i.d.) for 7 days, therefore suggesting that no dose adjustment would be needed for roflumilast if given simultaneously with these drugs (9).

A total of 1,411 patients participated in a multicenter, double-blind, randomized, placebo-controlled clinical trial that determined the efficacy and safety of roflumilast in the treatment of moderate to severe COPD. Once-daily roflumilast (250 or 500 μg p.o.) given for 24 weeks significantly and dose-dependently improved the lung function of the patients. The increase in the average FEV_1 achieved with 250 and 500 μg of roflumilast was, respectively, 74 and 97 ml greater than that found in placebo-treated patients. The number of exacerbations also decreased significantly with roflumilast and it significantly and dose-dependently improved the health-related quality of life of the patients (10, 11). The results from this and several of the studies reported below are described in Table XI.

Sixteen patients with exercise-induced asthma were included in a double-blind, randomized, crossover clinical trial and received placebo or roflumilast (500 μg p.o. once daily). Exercise challenge tests conducted at different times during the trial showed that roflumilast improved the lung function of the patients. The strong antiinflammatory effects of roflumilast were confirmed by the finding that it also reduced lipopolysaccharide-stimulated TNF-α formation *ex vivo* in whole blood, which is a surrogate marker for inflammation (12).

A multicenter, randomized, double-blind clinical trial enrolled a total of 690 patients with stable asthma to receive roflumilast (100, 250 or 500 μg p.o. once daily) for 12 weeks. The FEV_1 of the patients increased dose-dependently by 260, 320 and 400 ml, respectively, compared to baseline. Roflumilast was well tolerated and was not associated with relevant changes in vital signs, electrocardiogram parameters or laboratory parameters (13).

A total of 456 patients who had completed this study participated in an open-label follow-up study where they continued receiving the drug for another 40 weeks. The results confirmed that roflumilast was well tolerated and effective in providing long-term control of asthma symptoms and improving lung function (14).

The long-term safety profile of roflumilast was assessed in a clinical trial that consisted of a 26-week double-blind period during which placebo or roflumilast (250 or 500 μg p.o. once daily) was administered, followed by a 26-week open-label extension period during which roflumilast (500 μg p.o. once daily) was administered to 397 COPD patients. The overall incidence of

adverse events was 49% in the double-blind period and 41% in the extension period. Most adverse events were mild to moderate and transient. Only 2.5% of patients experienced drug-related adverse events, and only 3 patients withdrew from the study because of them (15).

In a double-blind, randomized, placebo-controlled, crossover clinical trial that included 23 patients with mild allergic asthma, roflumilast (250 or 500 μg p.o. once daily) was significantly more effective than placebo in inhibiting the early and late asthmatic responses induced by allergen exposure (16).

A double-blind, randomized, placebo-controlled clinical trial compared the efficacy and safety of roflumilast (500 μg p.o. once daily) and beclomethasone dipropionate (200 μg by inhalation b.i.d.) given for 12 weeks to 421 asthma patients with FEV_1 of 50-85% of that predicted. At the end of the treatment, the FEV_1 of the patients increased by 0.3 l with roflumilast and by 0.37 l with beclomethasone. Both study medications also significantly improved forced vital capacity (FVC) and reduced asthma symptoms and the need for rescue medication. Roflumilast was well tolerated and mostly associated with mild to moderate and transient adverse events (17).

A treatment for respiratory tract disorders has been claimed comprising the administration of a PDE4 or PDE3/4 inhibitor, such as roflumilast, in simultaneous, sequential or separate combination with a leukotriene $CysLT_1$ (LTD_4) receptor antagonist, such as montelukast sodium (18).

Pharmaceutical formulations comprising a selective PDE4 or PDE3/4 inhibitor, such as roflumilast or pumafentrine, in combination with a histamine receptor antagonist, such as the selective H_1 receptor antagonist loratadine, or pharmaceutically acceptable derivatives of either, have been claimed for the treatment of respiratory diseases including asthma (19).

Combinations of a proton pump inhibitor, preferably soraprazan or pantoprazole, and an airways therapeutic, such as ciclesonide or roflumilast, have been claimed for the treatment of airways disorders. These combinations are particularly useful for the treatment of allergen- or inflammation-induced bronchial disorders (20, 21).

Topical pharmaceutical compositions comprising a moderately soluble formulation of the PDE4 inhibitor roflumilast, or certain pharmaceutically acceptable salts or derivatives thereof, have been claimed for the treatment of conditions affecting the skin, eyes and airways, such as dermatoses (*e.g.,* psoriasis) and eczema, conjunctivitis, keratitis and uveitis, and bronchitis, bronchial asthma and COPD (22).

A medicament suitable for daily use which permits the concurrent, consecutive or independent administration of the PDE4 inhibitor roflumilast with a β_2-adrenoceptor agonist, such as formoterol or arformoterol (see above), or pharmaceutically acceptable salts thereof, has been claimed for the synergistic prevention and/or treatment of diseases of the respiratory tract. Targeted conditions include bronchitis, asthma and COPD and their respective symptoms (23, 24).

Formulations comprising a combination of the PDE4 inhibitor roflumilast and an anticholinergic agent such as ipratropium bromide, oxitropium bromide or tiotropium bromide, or revatropate, have been patented. These synergistic combinations are expected to be particularly useful for the prophylaxis and/or treatment of respiratory diseases, in particular COPD. These compositions inhibited methacholine-induced bronchoconstriction in anesthetized, mechanically ventilated guinea pigs (25-27).

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23. Beume, R. et al. (Altana Pharma Deutschland GmbH) *New synergistic combination comprising roflumilast and formoterol*. WO 0447829.

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25. Bundschuh, D. et al. (Altana Pharma Deutschland GmbH) *Synergistic combination comprising roflumilast and an anticholinergic agent selected from ipratropium, oxitropium and tiotropium salts for the treatment of respiratory diseases*. WO 0484896.

26. Bundschuh, D. et al. (Altana Pharma Deutschland GmbH) *Synergistic combination comprising roflumilast and an anticholinergic agent selected from ipratropium, oxitropium and tiotropium salts for the treatment of respiratory diseases*. WO 0484897.

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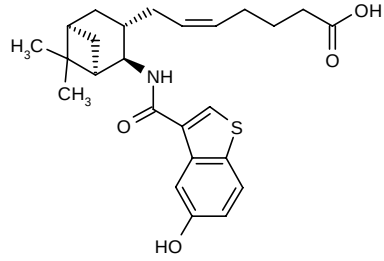
S-5751



A potent and selective prostaglandin DP receptor antagonist developed by Shionogi, S-5751 is in phase II trials in the U.S. and phase I studies in Japan as a new therapy for asthma and allergic rhinitis.

SARS Vaccine

A SARS (severe acute respiratory syndrome) vaccine is in early clinical development by Sinovac Biotech. The Chinese State Drug Administration (SFDA) is fast-tracking the drug approval process for this potential SARS vaccine. Sinovac is currently the only company in the world to have commenced human clinical trials for a vaccine to prevent SARS.

All 36 subjects in Sinovac Biotech's phase I trial of its inactivated SARS vaccine have now been vaccinated with either the SARS vaccine or placebo. The final 12 subjects in the second group of 18 volunteers have received the vaccination. The first 6 of this second group of 18 volunteers were injected in July 2004. These

subjects together comprise the second group of 18 volunteers who have been injected with either the high-dose (32 su/ml antigen) SARS vaccine or a placebo. The first group of 18 people who have been inoculated with low-dose (16 su/ml antigen) SARS vaccine and the second group of 18 who have been inoculated with high-dose (32 su/ml antigen) vaccine have not experienced any adverse reactions and are all in good health. The 2-dose immunization schedule has been completed for the initial group of 18 volunteers who received low-dose SARS vaccine or placebo. The second group of 18 volunteers receiving the high-dose SARS vaccine have received their first inoculation. Each subgroup of 6 volunteers is scheduled to receive the second inoculation 28 days after the first inoculation dates. The volunteers enrolled in the study are 21-40 years of age. Each subject will be observed until day 210, the completion date of the phase I trial. The ultimate aim of the vaccine will be to provoke the body's immune system into action, so that it can destroy the SARS virus if infected. In addition to safety, antibody levels induced by the vaccine are also being tested for the duration of the phase I trial. However, the ability of these antibodies to prevent infection from SARS will not be tested in this trial. Preclinical trials in rhesus and macaque monkeys showed that Sinovac's vaccine was effective in preventing infection. Monkeys inoculated with the vaccine experienced no serious side effects after they were exposed to the virus. Immune responses were evoked in all animal models. No immune enhancement was observed in any of the preclinical studies (1-6).

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3. *Sinovac SARS vaccine candidates to enter clinic in China*. DailyDrugNews.com (Daily Essentials) April 27, 2004.

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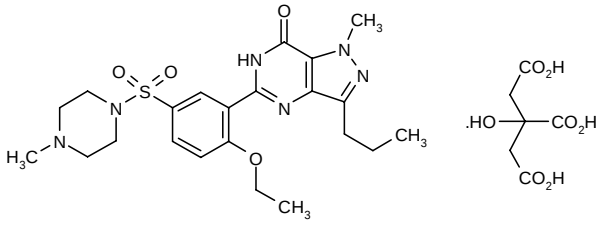
Sildenafil Citrate, New Indication –



Sildenafil citrate is a PDE5A inhibitor first introduced in 1998 in the U.S. as Viagra® for the treatment of erectile dysfunction and now available for this indication in several countries. In February 2004, Pfizer discontinued the development of sildenafil for the treatment of female sexual dysfunction.

The company recently submitted regulatory filings in the U.S. and Europe for sildenafil citrate (Revatio™) as a treatment for PAH. In the E.U., the company filed its dossier to regulatory authorities in The Netherlands and Spain, the rapporteur and corapporteur, respectively, and the European Medicines Evaluation Agency (EMEA). Clinical studies conducted throughout the world have shown sildenafil 20 mg taken 3 times daily to be effective in treating PAH. Patients treated with sildenafil had improved physical functioning, as demonstrated by increased walking distance over a 6-min time interval. Patients on sildenafil also had both a reduction in blood pressure in arteries of the lungs and an increase in cardiac output, which is critical in the treatment of this disease (1).

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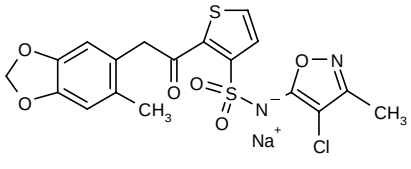
Sitaxsentan Sodium



Sitaxsentan sodium (TBC-11251, Thelin™) is a highly selective small-molecule endothelin ET_A receptor antagonist presently undergoing phase III trials at Encysive Pharmaceuticals (formerly Texas Biotechnology) for the treatment of PAH. In November 2004, sitaxsentan was granted orphan drug designation by the FDA for this disorder. Encysive plans to retain all marketing rights to the drug although it had previously planned to license marketing rights outside North America while keeping U.S. and Canadian rights for itself. An NDA submission is anticipated around the end of the first quarter of this year (1, 2).

Analysis of the pivotal STRIDE-1 (Sitaxsentan To Relieve ImpaireD Exercise) trial facilitated the design of a comprehensive clinical program evaluating sitaxsentan in the broadest patient population ever studied in this drug class. The STRIDE-1 study was a multicenter, double-blind, randomized, placebo-controlled clinical trial that evaluated the efficacy and safety of sitaxsentan sodium in the treatment of PAH. A total of 178 patients aged 16-75 years with symptomatic PAH unresponsive to previous treatments received placebo or sitaxsentan (100 or 300 mg p.o. once daily) for 12 weeks. Compared with placebo, both sitaxsentan doses induced similar and significant improvements in the 6-min walk distance, NYHA functional class, cardiac index and pulmonary vascular resistance. The higher sitaxsentan dose also significantly improved the percentage of predicted peak oxygen uptake (VO_2), measured during cycle ergometry, whereas no such improvement was found with the lower dose. No significant differences between study groups were found in the incidence of adverse events. The most frequent events with sitaxsentan were headache, peripheral edema, nausea, nasal congestion and dizziness. Liver abnormalities, which are commonly associated with endothelin receptor antagonists, were found in 3% of placebo-treated patients and in 0% and 10% of those treated with 100 mg and 300 mg of sitaxsentan, respectively (see Table XII). Encysive is concurrently running 5 separate protocols for sitaxsentan in the treatment of PAH. STRIDE-2 is a randomized, double-blind, placebo-controlled phase III safety and efficacy study of sitaxsentan with an open-label bosentan arm in patients with PAH. Patients are randomized to receive 1 of 4 treatments: sitaxsentan 50 mg once daily, sitaxsentan 100 mg once daily, placebo once daily or bosentan twice daily according to the package insert. The duration of the trial is 18 weeks. STRIDE-2X is an open-label extension study to evaluate the long-term safety of sitaxsentan in patients with PAH. Patients receive sitaxsentan 100 mg once daily or bosentan twice daily for an additional 36 weeks dependent on randomization after completion of STRIDE-2. STRIDE-3 is an open-label study to evaluate the long-term safety of sitaxsentan in a broad range of patients with PAH. Patients receive sitaxsentan 100 mg once daily. STRIDE-4 is another randomized, double-blind, placebo-controlled phase III safety and efficacy study of sitaxsentan in patients with PAH. Patients are randomized to receive 1 of 3 treatments: sitaxsentan 50 mg once daily, sitaxsentan 100 mg once daily or placebo. The duration of the trial is 18 weeks. STRIDE-6 is a randomized, double-blind safety and efficacy study of sitaxsentan in patients with PAH who have failed bosentan therapy. Patients receive sitaxsentan 50 or 100 mg once daily for up to 12 weeks. Upon

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

Indication	Design	Treatments	n	Conclusions	Ref.
Hypertension, pulmonary	Randomized, Double-blind,	Sitaxsentan, 100 mg p.o. o.d. x 12 wks (n=55) Sitaxsentan, 300 mg p.o. o.d. x 12 wks (n=63) Placebo (n=60)	178	Both sitaxsentan doses were more effective than placebo in improving the 6-min walking distance, functional class, cardiac index and pulmonary vascular resistance in patients with pulmonary arterial hypertension. The higher dose also improved the precentage of predicted peak oxygen uptake during cycle ergometry, but was associated with a worse safety profile than the lower dose	5
Hypertension, pulmonary	Randomized, Double-blind, Multicenter	Sitaxsentan, 100 mg p.o. o.d. x 26 [median] wks (n=79) Sitaxsentan, 300 mg p.o. o.d. x 26 [median] wks (n=91)	170	Once-daily staxsentan was well tolerated and effective in improving the condition of patients with pulmonary arterial hypertension	7
Hypertension, pulmonary	Open	Sitaxsentan p.o. x 12 wks	13	Patients with pulmonary arterial hypertension who discontinued bosentan due to clinical deterioration improved their 6-min walking distance by an average of 26 m with sitaxsentan compared to baseline. Patients who stopped receving bosentan due to liver toxicity also improved their functional capacity and showed no signs of liver toxicity with sitaxsentan	13

successful completion of STRIDE-4 or STRIDE-6, patients are eligible for enrollment in STRIDE-3. In addition to these, at least 14 clinical pharmacology studies are completed, under way or planned to evaluate sitaxsentan (3-5).

A total of 170 patients who had completed the STRIDE-1 study participated in a blinded extension study and received sitaxsentan (100 or 300 mg once daily) for a median of 26 weeks. The percentage of patients who improved at least 1 functional class during the extension study was 53% and 44%, respectively, on 100 and 300 mg of sitaxsentan. Most of the patients who improved did so during the first 12 weeks of drug administration. Both doses were well tolerated, although the rate of liver function abnormalities increased with dose (5% with 100 mg and 21% with 300 mg) (6, 7) (see Table XII).

The latest results of the STRIDE-6 clinical trial suggest that sitaxsentan may be effective in the treatment of PAH following discontinuation of bosentan therapy. Forty-eight PAH patients who had stopped receiving bosentan due to lack of efficacy (n=35) or safety issues (n=13; mostly liver function abnormalities) were randomized to receive sitaxsentan (50 or 100 mg) once daily for 12 weeks. The 6-min walk test results improved in 10% and 33%, respectively, of patients who discontinued bosentan due to lack of efficacy after receiving 50 and 100 mg of sitaxsentan for 12 weeks. The most common adverse events were nausea, fatigue, edema, headache and upper respiratory tract infections. Only 1 of the patients who stopped receiving bosentan due to safety issues discontinued sitaxsentan therapy because of liver function abnormalities. Overall, 45 of the patients included in the STRIDE-6 study were enrolled in the long-term extension trial STRIDE-3 (8).

Encysive has reported that results from a 24-subject drug interaction study of sitaxsentan sodium and sildenafil citrate (Viagra®; Pfizer) demonstrated only a minor pharmacokinetic drug-drug interaction. A group of 24 normal healthy volunteers participated in 2 treatment periods to receive sitaxsentan (100 mg) for 7 days and a single dose of sildenafil (100 mg) on the seventh day, and 7 days of placebo and 100 mg of sildenafil on the seventh day. Subjects were randomized to which treatment they received first. Blood was drawn to determine plasma levels of sitaxsentan, sildenafil and sildenafil's active metabolite *N*-desmethylsildenafil. Results showed that sildenafil administration did not appear to alter sitaxsentan levels. In the presence of sitaxsentan, the C_{max} of sildenafil increased by 18% and the AUC increased by 28%. No effects on the levels of the sildenafil metabolite were observed. The minor effect of sitaxsentan on overall sildenafil pharmacokinetics was presumed to be based on the expected weak cytochrome P-450 3A4 inhibition seen in cultured hepatocytes. The findings suggest that administration of a combination of sitaxsentan and sildenafil should not require dose adjustment of either drug, both of which are under active investigation for PAH (9).

Subgroup analysis of 42 patients with connective tissue diseases revealed an increase in the 6-min walk test of 20 m with sitaxsentan treatment. Test results worsened

in the placebo group by 38 m. The percentage of patients who achieved an improvement of at least 1 NYHA functional class was also greater with sitaxsentan (24% *vs.* 11%). Sitaxsentan was well tolerated, and no evidence of liver function abnormalities was found (10, 11).

An open-label clinical trial assessed the benefits of using sitaxsentan sodium in patients with PAH who were not successfully treated with bosentan. Eleven patients with PAH who discontinued bosentan therapy due to liver toxicity or deteriorating functional capacity were given sitaxsentan for up to 12 weeks. An interim analysis conducted after an average follow-up period of 93 days found that patients who discontinued bosentan due to clinical deterioration improved their 6-min walk test results by an average of 26 m with sitaxsentan compared to baseline. Patients who stopped receiving bosentan due to liver toxicity also improved their functional capacity and showed no signs of liver toxicity with sitaxsentan (12, 13) (see Table XII).

1. *Thelin receives orphan drug designation*. DailyDrugNews.com (Daily Essentials) Nov 15, 2004.

2. *Encysive to retain Thelin marketing rights*. DailyDrugNews.com (Daily Essentials) June 8, 2004.

3. *Encysive Pharmaceuticals reports Q1 R&D highlights*. Encysive Pharmaceuticals Press Release 2004, April 29.

4. *Enrollment target reached in STRIDE-2 study of Thelin*. DailyDrugNews.com (Daily Essentials) Sept 13, 2004.

5. Barst, R.J., Langleben, D., Frost, A. et al. *Sitaxsentan therapy for pulmonary arterial hypertension*. Am J Respir Crit Care Med 2004, 169(4): 441.

6. Horn, E., Langleben, D., Frost, A., Oudiz, R., Barst, R.J. *Long-term sitaxsentan therapy in PAH*. Eur Respir J 2004, 24(Suppl. 48): Abst 4334.

7. Horn, E., Langleben, D., Frost, A. et al. *Long-term sitaxsentan therapy in pulmonary arterial hypertension (PAH)*. Eur Heart J 2004, 25(Suppl.): Abst P2831.

8. *Therapeutic benefits of sitaxsentan in PAH patients failing bosentan*. DailyDrugNews.com (Daily Essentials) Oct 8, 2004.

9. *Results from Thelin and Viagra drug-drug interaction study*. DailyDrugNews.com (Daily Essentials) Sept 1, 2004.

10. McLaughlin, V.V., Hill, N., Tapson, V., Frost, A., Langleben, D., Oudiz, R., Shapiro, S., Robbins, I., Barst, R.J. *Sitaxsentan improves 6MW in patients with pulmonary arterial hypertension (PAH) related to connective-tissue diseases (CTD)*. Chest 2004, 126(4, Suppl.): 759S.

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12. Frost, A.E., Purl, H. *Sitaxsentan sodium for the treatment of pulmonary hypertension (PAH) in patients failing bosentan: Preliminary single center data*. Chest 2004, 126(4, Suppl.): 885S.

13. Frost, A., Purl, H. *Sitaxsentan sodium for the treatment of pulmonary hypertension (PAH) in patients failing bosentan: Preliminary single center data*. Eur Respir J 2004, 24(Suppl. 48): Abst 4333.

Original monograph – Drugs Fut 2000, 25(2): 159.

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Frost, A.E., Purl, H. *Sitaxsentan sodium for the treatment of pulmonary hypertension (PAH) in patients failing bosentan: Preliminary single center data*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1694.

Horn, E. et al. *Chronic sitaxsentan in pulmonary arterial hypertension*. Am J Respir Crit Care Med 2004, 169(7, Suppl.): A210.

Langleben, D. et al. *Sustained clinical and functional benefit in patients with pulmonary arterial hypertension after one year of therapy with the selective orally-active endothelin-A receptor antagonist, sitaxsentan*. Am J Respir Crit Care Med 2004, 169(7, Suppl.): A174.

Langleben, D. et al. *Sustained hemodynamic benefit in patients with pulmonary arterial hypertension after one-year of therapy with the selective orally-active endothelin-A receptor antagonist, sitaxsentan*. 53rd Annu Sci Sess Am Coll Cardiol (March 7-10, New Orleans) 2004, Abst 1123-183.

McLaughlin, V.V. et al. *Sitaxsentan improves 6MW and hemodynamics in patients with pulmonary arterial hypertension (PAH) related to connective tissue disease (CTD)*. Circulation 2004, 110(17, Suppl. 3): Abst 2602.

SPI-8811

Sucampo Pharmaceuticals' SPI-8811 (RU-8811) is an ion transport modulator that facilitates the transport of chloride ions across cell membranes. It has been granted orphan drug status by the FDA for the treatment of cystic fibrosis and is in phase II trials for this indication. It is also in phase II trials for portal hypertension/nonalcoholic fatty liver.

SPRC-AB01

SinusPharma has initiated a phase I trial of SPRC-AB01, a proprietary formulation of an antibiotic for nasal inhalation. The trial in healthy volunteers will test the safety of various doses of SPRC-AB01 prior to clinical trials in chronic rhinosinusitis (CRS) patients (1).

1. *Phase I study for SPRC-AB01*. DailyDrugNews.com (Daily Essentials) Oct 7, 2004.

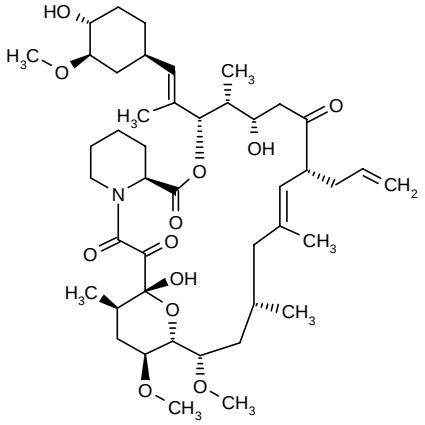
SRP-299

SRP-299 (heat-killed *M. vaccae*) is an immunomodulator in phase II development by SR Pharma for the treatment of allergic asthma in collaboration with Sakai. SRP-

299's unique mode of action stops the immune system from overreacting to nonthreatening agents such as cat dander or house dust mites, and prevents asthma attacks and allergic reactions rather than treating allergic symptoms or blocking reactions to specific allergens as do currently marketed agents. The immunomodulator was also in development for atopic dermatitis with Genesis Research and Development**.** However, based on results from a 166-patient trial of SRP-299 in moderate to severe atopic dermatitis in children, it was concluded that, at the dose levels studied, SRP-299 had no efficacy of clinical significance in this particular indication. SR Pharma has decided that it will not invest further in advancing the product in this indication (1).

1. *SRP-299 discontinued for moderate to severe pediatric atopic dermatitis.* DailyDrugNews.com (Daily Essentials) Nov 25, 2004.

Tacrolimus, Inhaled



A naturally occurring macrolide isolated from the fermentation broth of *Streptomyces tsukubaensis* by Fujisawa in 1984, tacrolimus (FK-506, Prograf®) is widely used as an immunosuppressant for the treatment of organ transplant rejection and an ointment formulation (Protopic®) is available in a number of markets for the treatment of atopic dermatitis. It has also been introduced in Japan for myasthenia gravis. The agent is in various stages of clinical development for a range of other disorders, including rheumatoid arthritis, lupus nephritis, ulcerative colitis, vernal conjunctivitis, dry eye syndrome and psoriasis, and new formulations are also being tested. Phase II trials are in progress in Europe for the inhalation treatment of asthma.

Original monograph – Drugs Fut 1989, 14(8): 746.

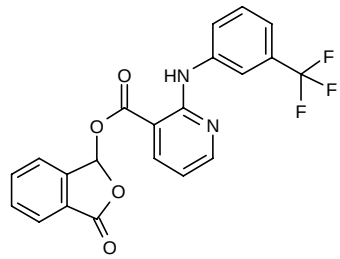
TAK-201

TAK-201 (MT-201), originally discovered by the former Meiji Milk Products (now Meiji Dairies), is in early clinical development at Takeda for *Cryptomeria* pollinosis. TAK-201 acts directly on T-cells to prevent allergic responses.

Talactoferrin Alfa

Talactoferrin alfa (recombinant human lactoferrin) is a natural antiinflammatory and immunomodulatory protein in development by Agennix for different indications. The company currently has several phase II clinical trials in progress for the treatment of asthma, cancer and diabetic foot ulcers. Talactoferrin alfa has demonstrated the ability to protect against early and late asthmatic responses, as well as against allergen-induced delayed hypersensitivity and cellular infiltration in animal models. Results from early clinical trials indicate that it is safe and well tolerated following oral administration. A randomized, placebo-controlled phase II trial is under way to assess its efficacy in asthma patients.

Talniflumate, New Indication



Genaera's oral calcium-activated chloride channel (hCLCA1) antagonist talniflumate (Lomucin™) entered a European phase II trial in October 2002 to evaluate its effects on respiratory symptoms and pulmonary function in patients with cystic fibrosis. The drug was originally discovered, developed and marketed as a nonsteroidal antiinflammatory by Laboratorios Bago and has been on the market for almost 20 years in Argentina and other countries, excluding the U.S., Europe and Japan. Although Genaera has evaluated talniflumate for other respiratory indications, including asthma, the company expects to focus future clinical development efforts on the treatment of cystic fibrosis. Genaera has an exclusive agreement with Laboratorios Bago to develop and commercialize talniflumate as a new chemical entity and mucoregulatory drug in all major pharmaceutical markets, including the U.S., Europe and Japan. The company is working with Cystic Fibrosis Foundation Therapeutics on the development of talniflumate for cystic fibrosis.

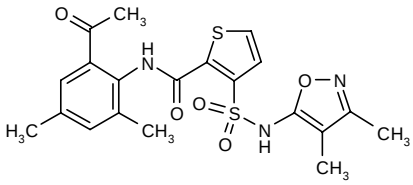
A method has been claimed for the administration of pharmaceutical compositions comprising regulators of mucin synthesis, such as the nonsteroidal antiinflammatory drug talniflumate, for the treatment of diseases in

which its overproduction is implicated, such as COPD, asthma, chronic bronchitis, inflammatory lung diseases, cystic fibrosis and acute or chronic respiratory infectious diseases (1).

1. Zhou, Y. et al. (Genaera Corp.) *Mucin synthesis inhibitors*. WO 0311294, US 2002147216, US 2002165244.

Original monograph – Drugs Fut 1979, 4(6): 448.

TBC-3711

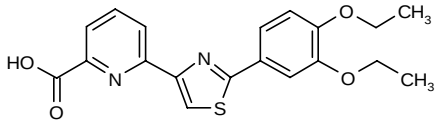


The next-generation oral endothelin ET_A receptor antagonist TBC-3711 is in phase I development at Encysive Pharmaceuticals (formerly Texas Biotechnology) for its potential in the treatment of hypertension, pulmonary hypertension and heart failure.

TBN-15

TBN-15 (Teijin) is a nasally delivered steroid in phase II trials for the treatment of allergic rhinitis.

Tetomilast



Otsuka Maryland Research Institute is developing the PDE4 inhibitor and superoxide production inhibitor tetomilast (OPC-6535). Phase III trials are under way as a once-daily oral treatment for ulcerative colitis and phase II clinical trials for the treatment of COPD.

A safe medicament comprising one or more thiazole derivatives, such as the antioxidant tetomilast, or pharmaceutically acceptable salts thereof, has been claimed for the treatment of COPD (1).

1. Sekiguchi, K. et al. (Otsuka Pharmaceutical Co., Ltd.) *Use of thiazole derivs. for the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease*. WO 0309844, JP 2003104890.

Original monograph – Drugs Fut 2004, 29(10): 1003.

tgAAVCF

Targeted Genetics' tgAAVCF (tgAAV-CF, tgAAV-CFTR) uses an adeno-associated virus (AAV) vector to deliver functional copies of the cystic fibrosis transmembrane regulator (CFTR) gene directly into the lungs for the treatment of cystic fibrosis. The gene therapy is in phase II clinical evaluation.

An independent data monitoring committee recommended the continuation of the phase IIb trial of tgAAVCF to treat patients with cystic fibrosis based on an analysis of the possibility that upon full enrollment the study could show a statistically significant positive impact on lung function measurements in patients treated with tgAAVCF compared to placebo. The analysis was conducted after 53 patients were dosed with either the product candidate or placebo. The double-blind, randomized, placebo-controlled study is partially funded by Cystic Fibrosis Foundation Therapeutics (CFFT), the drug discovery and development affiliate of the Cystic Fibrosis Foundation, and is being conducted through CFFT's Therapeutics Development Network. The trial includes bimonthly evaluation of lung function after repeated dosing with tgAAVCF. The impact of tgAAVCF on inflammation and biological markers is being assessed over time compared to placebo. Safety and tolerability are also being monitored. A total of 100 patients, aged 12 years and older, are divided equally into treatment and placebo groups. Participants receive 2 doses of 1 x 10^{13} DNAse-resistant particles (DRP) of tgAAVCF or placebo, delivered via nebulizer on day 0 and day 30 of the study. They are evaluated for efficacy every 2 weeks over 90 days. Participants are monitored for safety for 7 months (1).

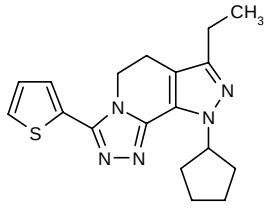
1. *Phase IIb trial of tgAAVCF for cystic fibrosis cleared to continue*. DailyDrugNews.com (Daily Essentials) June 29, 2004.

Tifacogin

Tifacogin is a recombinant form of tissue factor pathway inhibitor (TFPI) currently in phase III clinical evaluation at Chiron for the treatment of severe community-acquired pneumonia (CAP). The CAPTIVE study is an international, randomized, placebo-controlled trial which is expected to enroll over 2,000 patients, with a primary endpoint of reduction in 28-day mortality (1). Increased expression of tissue factor in the lungs of pneumonia patients is believed to contribute to the activation of coagulation and inflammation. Tifacogin restores the balance between tissue factor and TFPI and interferes with these activities of tissue factor.

1. *Phase III trial begins with tifacogin as treatment for severe community-acquired pneumonia*. DailyDrugNews.com (Daily Essentials) May 20, 2004.

Tofimilast



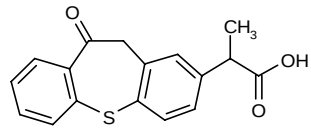
Pfizer is evaluating tofimilast (CP-325366), a PDE4 inhibitor, in phase II clinical trials as a potential new treatment for asthma.

YS-TH2

Y's Therapeutics has submitted applications to the Ethics Committee and Ministry of Health (BfArM) in Germany to begin phase II trials of one of its most advanced projects: YS-TH2 for asthma. YS-TH2 is a small-molecule drug in development for the treatment of asthma and other diseases in which a Th2-type cytokine imbalance is suspected. It works by inhibiting T-cell proliferation and migration, and by inhibiting Th2-type and proinflammatory cytokine production, while exerting no effect on Th1-type cytokine production. The company plans to establish a subsidiary company in Germany to manage clinical studies in European countries and another in the U.S (1).

1. *Y's Therapeutics files to begin European phase II studies of YS-IL6 and YS-TH2*. DailyDrugNews.com (Daily Essentials) July 29, 2004.

Zaltoprofen, New Indication



Zaltoprofen (Peon, Soleton) is a nonsteroidal antiinflammatory drug preregistered in Japan by Nippon Chemiphar and Zeria for the treatment of acute upper respiratory tract inflammation. Originated by Nippon Chemiphar and jointly developed with Zeria, zaltoprofen has been on the market in Japan since 1993 for the relief of pain and inflammation resulting from arthritis deformans, periarthritis of the shoulder and neck-shoulder-arm syndrome, rheumatoid arthritis, lumbago, surgery, trauma and tooth extraction.

Original monograph – Drugs Fut 1988, 13(4): 302.

Annual Update 2004/2005 - Treatment of Respiratory/ Thoracic Cancers

The respiratory/thoracic cancer group includes lung cancer, mesothelioma and thymoma. The two most common forms of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC, the more frequent form of lung cancer (accounting for approximately 80% of all cases), typically grows and spreads more slowly. SCLC, in contrast, is more aggressive and more likely to metastasize to other parts of the body. Without treatment, the median survival from diagnosis of SCLC is just 2-4 months. In spite of significant advances in the treatment of lung cancer, this disease continues to be the leading cause of cancer death among both men and women worldwide.

The annual incidence of NSCLC worldwide is over 1 million. In the U.S. alone, new cases of lung and bronchial cancer accounted for 13% of cancer diagnoses for the year 2003. While lung cancer mortality has decreased among U.S. males, it has continued to increase among women.

Mesothelioma is derived from mesothelial tissues of the peritoneum, pleura and pericardium, and is often associated with exposure to asbestos. Thymoma is a tumor of the thymus, an organ that is part of the lymphatic system and is located in the chest, behind the breastbone. Both mesothelioma and thymoma are rare cancers.

In the table that follows, drugs under active development for these types of cancer are shown (*Source: Prous Science Integrity®*).

References

1. NCI website (www.cancer.gov)

2. Prous Science Backgrounders (Lung Cancer)

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Treatment of Respiratory/Thoracic Cancers

Condition	Phase	Drug	Target	Source
Non-small cell lung cancer	I/II	Doxorubicin hydrochloride[1]	DNA topoisomerase II	Zivena
	II	Dexosome vaccine (lung cancer)	MAGE peptides	Anosys
	III	Thalidomide[1]	TNF-α	National Cancer Institute
	III	Carboxyamidotriazole	Calcium	National Cancer Institute
	I	Decitabine	DNA methyltransferase	National Cancer Institute/ SuperGen
	III	Carboplatin[1]	DNA	National Cancer Institute
	II	Trabectedin		PharmaMar
	III	Topotecan hydrochloride[1]	DNA topoisomerase I	GlaxoSmithKline
	I/II	Efaproxiral sodium		Allos
	L- 2004	Pemetrexed disodium[1]	Thymidylate synthase	Lilly
	I/II	Satraplatin	DNA	GPC Biotech
	II	ABT-751	Tubulin	Abbott/National Cancer Insitute
	II	Glufosfamide	DNA	Baxter Oncology
	II	Etalocib sodium	LTB_4; PPARγ; 5-lipoxygenase	Lilly
	II	Pralatrexate	DHFR	Sloan-Kettering Institute
	II	SGN-15	CD174 (Lewis y)	Seattle Genetics
	II	Squalamine	VEGF	Genaera

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Treatment of Respiratory/Thoracic Cancers

Condition	Phase	Drug	Target	Source
Non-small cell lung cancer	Prereg.	Tegafur/gimeracil/oxonic acid		Taiho
	II	Dofequidar fumarate	P-glycoprotein (MDR-1)	Schering AG
	II	Denileukin diftitox[1]	IL-2 receptor	Ligand
	II	3-AP	Ribonucleoside-diphosphate reductase	Vion/National Cancer Institute
	II	Perifosine	PKB	Keryx
	III	Bexarotene[1]	RXR	Ligand
	II	Talactoferrin alfa	Heparin	Agennix
	III	Canfosfamide hydrochloride	DNA	Telik
	III	Vinflunine	Tubulin	Pierre Fabre/Bristol-Myers Squibb
	I/II	Cantuzumab mertansine	C242 antigen	ImmunoGen
	II	Becatecarin	DNA topoisomerase I	Exelixis
	II	Bevacizumab[1]	VEGF	National Cancer Institute
	III	Aprinocarsen sodium	PKCα	Lilly
	II	Kahalalide F		PharmaMar
	I/II	Combretastatin A-4 phosphate	Tubulin	OxiGene
	II	Atrasentan	Endothelin A receptor	Abbott
	II	Cetuximab[1]	EGFR (Erb1)	ImClone/Merck KGaA
	IND (phase II)	Picoplatin	DNA	NeoRx/AnorMED
	II	Indisulam	p21 inducer	Eisai
	II	Aplidine	VEGFR1 (FLT1); VEGF	PharmaMar
	II	BLP-25	MUC-1	Merck KGaA/Biomira
	II	PI-88	VEGF;FGF2; FGF1; heparanase	Progen
	L-2004	Erlotinib hydrochloride	EGFR (Erb1)	OSI Pharmaceuticals/Genentech/ Roche
	II	Ad5CMV-p53		Introgen
	I	Tipifarnib	Farnesyltransferase	National Cancer Institute
	II	Synthadotin	Tubulin	Ilex Oncology
	II	BNP-1350	DNA topoisomerase I	BioNumerik
	II	Bortezomib[1]	Proteasome	Millennium/National Cancer Institute
	III	SRL-172		SR Pharma
	I	IL-4(38-37)-PE38KDEL		Neurocrine Biosciences
	II	Ortataxel	Tubulin	Bayer/National Cancer Institute
	II	11D10	HMFG	National Cancer Institute
	II	Arsenic trioxide[1]		University of Texas System
	II	CpG-7909		Coley Pharmaceutical
	II	Panitumumab	EGFR (Erb1)	Abgenix/Amgen
	II	EGF vaccine	EGF	Center of Molecular Immunology
	III	Paclitaxel poliglumex	Tubulin	Cell Therapeutics
	I	Paclitaxel poliglumex	Tubulin	Chugai
	II	Anhydrovinblastine	Tubulin	Prescient Neuropharma
	I	Lung cancer vaccine	Cancer antigens	Corixa/Zambon
	II	GTI-2040	RRM2	Lorus Therapeutics
	II	CP-547632	VEGFR2 (FLK1/KDR); EGFR (Erb1); PDGFR	Pfizer
	I/II	ABI-007	Tubulin	American BioScience/National Cancer Institute
	II	Ixabepilone	Tubulin	Bristol-Myers Squibb
	II	S-8184	Tubulin	Sonus
	I	TTS-CD3		Active Biotech
	I	Pertuzumab	HER2 (neu/ErbB2)	Chugai
	II	Pertuzumab	HER2 (neu/ErbB2)	Genentech
	I	CTCE-9908	SDF-1	Chemokine Therapeutics
	II	ValboroPro	Dipeptidyl-peptidase IV (CD26)	Point Therapeutics
	II	Vandetanib	VEGFR2 (FLK1/KDR); VEGFR-3 (FLT4); EGFR (Erb1)	AstraZeneca
	I	Matuzumab	EGFR (Erb1)	Merck KGaA
	II	SB-715992	Kinesin-like spindle protein (Eg5)	GlaxoSmithKline
	II	(*R*)-Roscovitine	CDK1,CDK2,CDK7 and CDK9	Cyclacel
	II	TRAIL-R1 MAb	TRAIL-R1	Human Genome Sciences
	II	MVA-Muc1-IL-2	MUC-1	Transgene
	III	IGN-101	EpCAM	Igeneon
	I/II	DN-101		Novacea
	I/II	EP-2101		Epimmune

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Treatment of Respiratory/Thoracic Cancers

Condition	Phase	Drug	Target	Source
Non-small cell lung cancer	II	L-Alanosine	Purine nucleotides	Salmedix
	I/II	EMD-273066	EpCAM	Merck KGaA
	II	STA-4783		Synta Pharmaceuticals
	II	GVAX Lung		Cell Genesys
	I/II	GV-1001	Telomerase	GemVax
	IND filed	MTC-MMC	DNA	FeRx
	I	Cancer vaccine	NY-ESO-1	Ludwig Institute for Cancer Research/PowderMed
	III	Neovastat	MMP-2 (gelatinase A); VEGFR2 (FLK1/KDR)	AEterna Zentaris/National Cancer Institute
	II	Sutent	VEGFR1 (FLT1); VEGFR2 (FLK1/KDR); PDGFRβ; Flt3 (FLK2/STK1)	Pfizer
Small cell lung cancer	II	Vandetanib	VEGFR2 (FLK1/KDR); VEGFR-3 (FLT4); EGFR (Erb1)	AstraZeneca
	II	Thalidomide[1]	TNF-α	National Cancer Institute
	R-1998	Lobaplatin	DNA	Hainan Chang An
	II	Lobaplatin		AEterna Zentaris
	II	Satraplatin	DNA	Johnson Matthey
	II	Meclinertant	Neurotensin receptors	Sanofi-Aventis
	II	Lurtotecan	DNA topoisomerase I	OSI Pharmaceuticals
	III	Mitumomab	CD60a (GD3)	ImClone/Merck KGaA
	II	Bevacizumab[1]	VEGF	National Cancer Institute
	I	Imatinib mesilate[1]	Abl kinase, KIT (C-KIT), PDGFRα	National Cancer Institute
	II	Aplidine	VEGFR1 (FLT1); VEGF	PharmaMar
	II	Vincristine sulfate TCS	Tubulin	Inex
	L-2003	Belotecan hydrochloride[1]	DNA topoisomerase I	Chong Kun Dang Pharm.
	II	Rubitecan	DNA topoisomerase I	EORTC
	I/II	huN901-DM[1]	CD56	ImmunoGen/Vernalis
	I	CT-2106	DNA topoisomerase I	Cell Therapeutics
	I/II	INGN-225		Introgen
Lung cancer	II	Antineoplaston A10		Burzynski Research Institute
	II	Diflomotecan	DNA topoisomerase I	Roche/Ipsen
	II	Antineoplaston AS2-1		Burzynski Research Institute
	II	Depsipeptide	HDAC	National Cancer Institute
	II	Sabarubicin hydrochloride	DNA topoisomerase II	Menarini
	R-2003	I-131 ch-TNT-1/B		MediPharm Biotech/Peregrine Pharmaceuticals
	L-2004	Talaporfin sodium		Meiji Seika
	I/II	CHS-828	IKK	Leo
	II	Oncophage	HSPPC-96	Antigenics
	II	Tariquidar	P-glycoprotein (MDR-1)	National Cancer Institute
	I/II	AR20.5	MUC-1	AltaRex
	II	Mage-3		GlaxoSmithKline
	I	Photochlor		National Cancer Institute
	I/II	LE-SN38	DNA topoisomerase I	NeoPharm
	I	rhIGFBP-3		Insmed
	II	Cancer vaccine	TGF-β	NovaRx
	I	SLIT-cisplatin	DNA	Transave
Lung cancer diagnosis	Clinical	LungAlert		IMI International Medical Innovations
	II	Serum-RECAF blood test		BioCurex
Malignant mesothelioma		Decitabine	DNA methyltransferase	National Cancer Institute/ SuperGen
	I			
	III	Mitomycin[1]	DNA	British Thoracic Society
	II	Epirubicin hydrochloride[1]	DNA topoisomerase II	National Cancer Institute
	II	Gemcitabine[1]	Pyrimidine nucleotides	National Cancer Institute/Lilly
	I	Depsipeptide	HDAC	National Cancer Institute
	III	Ranpirnase	Ribosomal RNA	Alfacell
	II	Bevacizumab[1]	VEGF	National Cancer Institute
	II	Vatalanib succinate	VEGFR1 (FLT1); VEGFR2 (FLK1/KDR); VEGFR3 (FLT4)	National Cancer Institute

Continuation

Treatment of Respiratory/Thoracic Cancers

Condition	Phase	Drug	Target	Source
Malignant mesothelioma	I/II	SS(dsFv)-PE38	Mesothelin	National Cancer Institute
	II	L-Alanosine	Purine nucleotides	Salmedix
	L-2004	Pemetrexed disodium[1]	Thymidylate synthase	Lilly
	I	BG-00001		National Cancer Institute
Thymoma and thymic carcinoma	II	Paclitaxel[1]	Tubulin	National Cancer Institute
	II	Carboplatin[1]	DNA	National Cancer Institute

[1]Launched for another indication. CDK: Cyclin-dependent kinase; DHFR: Dihydrofolate reductase; EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor; EpCAM: Epithelial cellular adhesion molecule; FGF: Fibroblast growth factor; GD3: Ganglioside-3; HDAC: Histone deacetylase; HMFG: Human milk fat globule; HSPPC-96: Tumor-derived heat shock protein peptide complex-96; IKK: Inhibitory κB kinase; LTB_4: Leukotriene B_4; MDR-1: Multidrug resistance-1; MMP-2: Matrix metalloproteinase-2; MUC-1: Mucin 1; PDGFR: Platelet-derived growth factor receptor; PKB: Protein kinase B; PKC: Protein kinase C; PPAR: Peroxisome proliferator-activated receptor; RXR: Retinoid X receptor; SDF-1: Stromal cell-derived factor-1; TNF: Tumor necrosis factor; TRAIL:TNF-related apoptosis-inducing ligand; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.