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Annual Update 2004/2005 - Treatment of Gastrointestinal Disorders

As in previous issues, the goal of this section is to present a balanced picture of the current status of therapies for gastrointestinal 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 digestive/gastrointestinal cancers is included at the end of this review.

J.R. Prous
Editor

Treatment of Gastrointestinal Disorders by Condition

Condition	Phase	Drug	Source
Cirrhosis	III	Interferon alfa-n1[1]	Sumitomo Pharmaceuticals
Cirrhotic ascites	II	Icatibant	Jerini
	II	SR-121463	Sanofi-Aventis
Constipation	L-2004	Tegaserod maleate[1,2]	Novartis
	Prereg.	Lubiprostone[2]	Sucampo/Takeda
	III	INKP-100[1]	InKine
	III	Methylnaltrexone bromide	Progenics
	II	Alvimopan hydrate[2]	GlaxoSmithKline/Adolor
	II	Naloxone hydrochloride	SLA Pharma
Crohn's disease	III	Adalimumab[1,2]	Abbott
	III	Certolizumab pegol	UCB Pharma/Nektar Therapeutics
	III	Eicosapentaenoic acid/ docosahexaenoic acid	Tillotts
	III	Metronidazole[1], ointment	SLA Pharma
	III	Sargramostim[2]	Schering AG/Berlex
	II	ABT-874	Abbott
	II	Alequel™	Enzo
	II	Etiprednol dicloacetate[2]	Ivax
	II	Fontolizumab	Protein Design Labs
	II	Icosapent	SLA Pharma
	II	IP-1001[2]	Inflabloc
	II	MLN-02	Millennium
	II	OSI-461	OSI Pharmaceuticals
	II	Rifaximin[1,2]	Salix/Altana Pharma
	II	Semapimod hydrochloride	Cytokine PharmaSciences
	II	STA-5326	Synta Pharmaceuticals
	II	Teduglutide	NPS Pharmaceuticals
	II	Tocilizumab[2]	Chugai
	II	Vapreotide acetate[2]	H3 Pharma
	I/II	EGS-21	Enzo
	I	DA-6034	Dong-A
	Discontinued	Alicaforsen sodium[2]	Isis Pharmaceuticals
Delayed gastric emptying (gastroparesis)	Prereg.	INKP-102	InKine
	II	Mitemcinal fumarate[2]	Chugai
	I	ATI-7505	ARYx Therapeutics

Continuation

Treatment of Gastrointestinal Disorders by Condition

Condition	Phase	Drug	Source
Diarrhea	R-2004	Vapreotide acetate[2]	H3 Pharma
	III	Tolevamer sodium	Genzyme
	II	ETEC vaccine	Iomai
	II	OPT-80	Optimer Pharmaceuticals
	II	Ramoplanin[2]	Vicuron/Oscient Pharmaceuticals
	II	Rifalazil	ActivBiotics
	II	Urtoxazumab	Teijin
	I/II	ColoPlus	ColoPlus
	I	*Clostridium difficile* toxoid vaccine	Acambis
	I	ETEC vaccine	Microscience
	I	MDX-066	Medarex
Disorders of absorption	I	ALTU-139	Altus Pharmaceuticals
Dyspepsia	III	Itopride hydrochloride[1,2]	Axcan
	III	Tegaserod maleate[1,2]	Novartis
	II	Acotiamide hydrochloride hydrate[2]	Zeria/Astellas Pharma
	I	Itriglumide	Rottapharm
Esophageal disorders	R-2004	Vapreotide acetate[2]	H3 Pharma
Fecal incontinence	II	SLV-325	Solvay/SLA Pharma
Fissures, anal	II	SLV-324	Solvay/SLA Pharma
Gastritis	III	DA-9601	Dong-A
	II	E-3620	Eisai
	II	Rifalazil	ActivBiotics
Gastroesophageal reflux disease	II	Antigastrin therapeutic vaccine[2]	Aphton
	II	Ilaprazole[2]	Il-Yang
	II	Tegaserod maleate[1,2]	Novartis
	I	ATI-7505	ARYx Therapeutics
	I	AZD-3355	AstraZeneca
	I	AZD-9343	AstraZeneca
	I	Itriglumide[2]	Rottapharm
	I	XP-19986	Xenoport
	Clinical	Tenatoprazole[2]	Negma/Mitsubishi Pharma
Gastrointestinal disorders	R-2004	Vapreotide acetate[2]	H3 Pharma
	II	AZD-7371	AstraZeneca
	II	Human gammaglobulin, oral	PediaMed
	II	Soraprazan	Altana Pharma
Gastrointestinal motility disorders	I	TD-2749	Theravance
Hemorrhagic colitis	II	Urtoxazumab	Teijin
Hemorrhoids	L-2005	OC-108	Mitsubishi Pharma/Lequio Pharma
	II	Nitroglycerin[1], ointment	Cellegy
Hepatitis A+B	L-2005	Hepatitis A/B vaccine	Sinovac
Hepatitis B	L-2005	Entecavir[2]	Bristol-Myers Squibb
	R-2005	Hepatitis B vaccine	GlaxoSmithKline
	Prereg.	Hepatitis B immune globulin	Cangene
	III	Clevudine[2]	Eisai/Bukwang
	III	Telbivudine[2]	Novartis/Idenix
	II/III	Hepatitis B vaccine	Dynavax Technologies
	II	Hepatitis B vaccine	Oxxon Therapeutics
	II	HepeX-B™	XTL Biopharmaceuticals/Cubist Pharmaceuticals
	II	IDN-6556	Pfizer
	II	LB-80380 (ANA-380)[2]	LG Life Sciences/Anadys
	II	Pradefovir mesilate	Valeant/Metabasis Therapeutics
	II	Valtorcitabine dihydrochloride	Novartis/Idenix
	I/II	EHT-899	Enzo
	I/II	Interferon alfa-2b[1]	Flamel Technologies
	I	Hepatitis B vaccine	Innogenetics
	I	Hepatitis B vaccine	Microscience
	I	Hepatitis B vaccine	Roswell Park Cancer Institute

Continuation

Treatment of Gastrointestinal Disorders by Condition

Condition	Phase	Drug	Source
Hepatitis C	III	Interferon beta-1a[1]	Serono
	III	Ursodiol[1]	Mitsubishi Pharma
	III	Viramidine hydrochloride[2]	Valeant
	II/III	Interferon alfa-n3[1]	HemispheRx
	II	Albumin interferon alfa	Human Genome Sciences
	II	Celgosivir	Migenix
	II	Hepatitis C vaccine	Innogenetics
	II	Hepatitis C vaccine	Intercell
	II	IDN-6556	Pfizer
	II	Interferon omega	Intarcia Therapeutics
	II	JTK-003	Japan Tobacco
	II	KPE-02003002	Kemin Pharma
	II	ME-3738	Meiji Seika
	II	Merimepodib[2]	Vertex
	II	UT-231B	United Therapeutics
	II	Valopicitabine	Idenix
	II	Virostat	Bioenvision
	I/II	CpG-10101	Coley Pharmaceutical
	I/II	EGS-21	Enzo
	I/II	EHC-18	Enzo
	I/II	Hepatitis C immune globulin	Nabi Biopharmaceuticals
	I/II	Interferon alfa-2b[1]	Flamel Technologies
	I/II	Isatoribine	Anadys
	I/II	KRN-7000[2]	Kirin Brewery
	I	ANA-971	Anadys
	I	ANA-975	Anadys
	I	HCV-796	ViroPharma/Wyeth
	I	Interferon alfa-2b[1]	OctoPlus/Biolex
	I	Pegylated interferon alfacon-1	InterMune/Nektar Therapeutics
	I	R-1626	Roche
	I	Tarvacin™	Peregrine Pharmaceuticals
	I	VX-950	Vertex
	IND filed	XTL-6865	XTL Biopharmaceuticals
	Discontinued	HCV-086	ViroPharma/Wyeth
	Discontinued	HepeX-C™	XTL Biopharmaceuticals
Hepatitis E	II	Hepatitis E vaccine	GlaxoSmithKline/Genelabs Technologies
Hyperbilirubinemia	III	Stannsoporfin	InfaCare Pharmaceutical
Ileus, postoperative	Prereg.	Alvimopan hydrate[2]	GlaxoSmithKline/Adolor
	II	Lubiprostone[2]	Sucampo/Takeda
	II	Methylnaltrexone bromide	Progenics
Inflammatory bowel disease	II - On hold	683699 (T-0047)	GlaxoSmithKline/Tanabe Seiyaku
	II	270384	GlaxoSmithKline
	II	CCX-282	ChemoCentryx
	II	Delmitide[2]	Procter & Gamble/Genzyme
	II	Dronabinol/Cannabidiol	GW Pharmaceuticals
	II	Rifaximin[1,2]	Salix
	I/II	NAA-004	Nobex
	I	AJM-300	Ajinomoto
	I	Ono-4817	Ono
	I	R-1541	Roche
	I	Z-206	Zeria
Irritable bowel syndrome	Prereg.	Cilansetron[2]	Solvay
	III	Dexloxiglumide[2]	Rottapharm
	III	PTI-901[1,2]	Pain Therapeutics
	III	Ramosetron hydrochloride[1,2]	Astellas Pharma
	II	Asimadoline	Merck KGaA
	II	DDP-225[2]	Dynogen
	II	Dextofisopam	Vela Pharmaceuticals
	II	E-3620	Eisai
	II	Lubiprostone[2]	Sucampo/Takeda
	II	Mitemcinal fumarate	Chugai
	II	Nepadutant	Menarini

Continuation

Treatment of Gastrointestinal Disorders by Condition

Condition	Phase	Drug	Source
Irritable bowel syndrome	II	PD-217014	Pfizer
	II	Renzapride hydrochloride[2]	Alizyme
	II	Rifaximin[1,2]	Salix/Altana Pharma
	II	Talnetant	GlaxoSmithKline
	I	876008	GlaxoSmithKline
	I	Alvimopan hydrate[2]	GlaxoSmithKline/Adolor
	I	MD-1100	Microbia
	I	PGN-1164	Pharmagene
	I	SLV-317	Solvay
Liver diseases	II	IDN-6556	Pfizer
	I/II	Histamine dihydrochloride, oral	Maxim
Nausea/vomiting	Prereg.	Prochlorperazine maleate, transmucosal	BioDelivery Sciences
Nausea/vomiting, chemotherapy-induced	II	APF-530	A.P. Pharma
	II	Granisetron hydrochloride[2], patch	ProStrakan
	II	Vestipitant mesilate	GlaxoSmithKline
	I	679769	GlaxoSmithKline
	I	Granisetron[2] MDTS®	Acrux
	I	Ondansetron hydrochloride[1,2], lingual spray	Hana Biosciences/NovaDel Pharma
Nausea/vomiting, postoperative	II	Palonosetron hydrochloride[1,2]	MGI Pharma/Helsinn
	II	Vestipitant mesilate	GlaxoSmithKline
	I	679769	GlaxoSmithKline
	I	Granisetron[2] MDTS®	Acrux
Nonalcoholic steatohepatitis	II	EGS-21	Enzo
	II	IDN-6556	Pfizer
	II	SPI-8811	Sucampo
Pancreatic disorders	II	Bile salt-stimulated lipase	Arexis
	II	TheraCLEC™	Altus Pharmaceuticals/Dr. Falk
Pancreatitis	II	Semapimod hydrochloride	Cytokine PharmaSciences
Pouchitis	II	Rifaximin[1,2]	Salix/Altana Pharma
	IND filed	Probactrix™	BioBalance
Short bowel syndrome	L-2004	Somatropin (rDNA origin)[1]	Serono
	III	Teduglutide	NPS Pharmaceuticals
Taste disorders	II	Polaprezinc[1,2]	Zeria
Ulcer, NSAID-associated	L-2004	Esomeprazole magnesium[1,2]	AstraZeneca
Ulcer, peptic	III	Revaprazan hydrochloride[2]	Yuhan
	II	AZD-0865	AstraZeneca
	II	Rifalazil	ActivBiotics
	I	Itriglumide[2]	Rottapharm
	I	Z-360	Zeria
Ulcerative colitis	Prereg.	Tacrolimus[1,2]	Astellas Pharma
	III (JP)	Ecabet sodium[1,2]	Tanabe Seiyaku
	III	Infliximab[2]	Schering-Plough/Centocor (Johnson & Johnson)
	III	Nicotine, enema	SLA Pharma
	III	Tetomilast[2]	Otsuka
	II/III	COLAL-PRED™	Alizyme
	II	Alicaforsen sodium[2]	Isis Pharmaceuticals
	II (EU, US)	Ecabet sodium[1,2]	Tanabe Seiyaku
	II	MLN-02	Millennium
	II	Nolpitantium besilate	Sanofi-Aventis
	I/II	Visilizumab[2]	Protein Design Labs
	I	DA-6034	Dong-A
	I	Nicotine, oral	SLA Pharma

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

Treatment of Gastrointestinal Disorders by Source

Source	Condition	Drug	Phase
Abbott	Crohn's disease	ABT-874	II
Acambis	Diarrhea	Clostridium difficile toxoid vaccine	I
Acrux	Nausea/vomiting, chemotherapy-induced	Granisetron[2] MDTS®	I
	Nausea/vomiting, postoperative	Granisetron[2] MDTS®	I
ActivBiotics	Diarrhea	Rifalazil	II
	Gastritis	Rifalazil	II
	Ulcer, peptic	Rifalazil	II
Adolor	Constipation	Alvimopan hydrate[2]	II
	Ileus, postoperative	Alvimopan hydrate[2]	Prereg.
	Irritable bowel syndrome	Alvimopan hydrate[2]	I
Ajinomoto	Inflammatory bowel disease	AJM-300	I
Alizyme	Irritable bowel syndrome	Renzapride hydrochloride[2]	II
Altana Pharma	Crohn's disease	Rifaximin[1,2]	II
	Irritable bowel syndrome	Rifaximin[1,2]	II
	Pouchitis	Rifaximin[1,2]	II
Altus Pharmaceuticals	Disorders of absorption	ALTU-139	I
	Pancreatic disorders	TheraCLEC™	II
Anadys	Hepatitis B	LB-80380 (ANA-380)[2]	II
	Hepatitis C	ANA-971	I
		ANA-975	I
		Isatoribine	I/II
A.P. Pharma	Nausea/vomiting, chemotherapy-induced	APF-530	II
Aphton	Gastroesophageal reflux disease	Antigastrin therapeutic vaccine[2]	II
Arexis	Pancreatic disorders	Bile salt-stimulated lipase	II
ARYx Therapeutics	Delayed gastric emptying (gastroparesis)	ATI-7505	I
	Gastroesophageal reflux disease	ATI-7505	I
Astellas Pharma	Dyspepsia	Acotiamide hydrochloride hydrate[2]	II
	Irritable bowel syndrome	Ramosetron hydrochloride[1,2]	III
	Ulcerative colitis	Tacrolimus[1,2]	Prereg.
AstraZeneca	Gastroesophageal reflux disease	AZD-3355	I
		AZD-9343	I
	Gastrointestinal disorders	AZD-7371	II
	Ulcer, NSAID-associated	Esomeprazole magnesium[1,2]	L-2004
	Ulcer, peptic	AZD-0865	II
Axcan	Dyspepsia	Itopride hydrochloride[1,2]	III
Berlex	Crohn's disease	Sargramostim[2]	III
BioBalance	Pouchitis	Probactrix™	IND filed
BioDelivery Sciences	Nausea/vomiting	Prochlorperazine maleate, transmucosal	Prereg.
Bioenvision	Hepatitis C	Virostat	II
Biolex	Hepatitis C	Interferon alfa-2b[1]	I
Bristol-Myers Squibb	Hepatitis B	Entecavir[2]	L-2005
Bukwang	Hepatitis B	Clevudine[2]	III
Cangene	Hepatitis B	Hepatitis B immune globulin	Prereg.
Cellegy	Hemorrhoids	Nitroglycerin[1], ointment	II
Centocor (Johnson & Johnson)	Ulcerative colitis	Infliximab[2]	III
ChemoCentryx	Inflammatory bowel disease	CCX-282	II
Chugai	Crohn's disease	Tocilizumab[2]	II
	Delayed gastric emptying (gastroparesis)	Mitemcinal fumarate[2]	II
	Irritable bowel syndrome	Mitemcinal fumarate	II
Coley Pharmaceutical	Hepatitis C	CpG-10101	I/II
ColoPlus	Diarrhea	ColoPlus	I/II
Cubist Pharmaceuticals	Hepatitis B	HepeX-B™	II
Cytokine PharmaSciences	Crohn's disease	Semapimod hydrochloride	II
	Pancreatitis	Semapimod hydrochloride	II
Dong-A	Crohn's disease	DA-6034	I
	Gastritis	DA-9601	III
	Ulcerative colitis	DA-6034	I
Dr. Falk	Pancreatic disorders	TheraCLEC™	II
Dynavax Technologies	Hepatitis B	Hepatitis B vaccine	II/III
Dynogen	Irritable bowel syndrome	DDP-225[2]	II
Eisai	Gastritis	E-3620	II
	Hepatitis B	Clevudine[2]	III
	Irritable bowel syndrome	E-3620	II
Enzo	Crohn's disease	Alequel™	II
		EGS-21	I/II
	Hepatitis B	EHT-899	I/II

Continuation

Treatment of Gastrointestinal Disorders by Source

Source	Condition	Drug	Phase
Enzo	Hepatitis C	EGS-21	I/II
		EHC-18	I/II
	Nonalcoholic steatohepatitis	EGS-21	II
Flamel Technologies	Hepatitis B	Interferon alfa-2b[1]	I/II
	Hepatitis C	Interferon alfa-2b[1]	I/II
Genelabs Technologies	Hepatitis E	Hepatitis E vaccine	II
Genzyme	Diarrhea	Tolevamer sodium	III
	Inflammatory bowel disease	Delmitide[2]	II
GlaxoSmithKline	Constipation	Alvimopan hydrate[2]	II
	Hepatitis B	Hepatitis B vaccine	R-2005
	Hepatitis E	Hepatitis E vaccine	II
	Ileus, postoperative	Alvimopan hydrate[2]	Prereg.
	Inflammatory bowel disease	270384	II
		683699 (T-0047)	II - On hold
	Irritable bowel syndrome	876008	I
		Alvimopan hydrate[2]	I
		Talnetant	II
	Nausea/vomiting, chemotherapy-induced	679769	I
		Vestipitant mesilate	II
	Nausea/vomiting, postoperative	679769	I
		Vestipitant mesilate	II
GW Pharmaceuticals	Inflammatory bowel disease	Dronabinol/Cannabidiol	II
H3 Pharma	Crohn's disease	Vapreotide acetate[2]	II
	Diarrhea	Vapreotide acetate[2]	R-2004
	Esophageal disorders	Vapreotide acetate[2]	R-2004
	Gastrointestinal disorders	Vapreotide acetate[2]	R-2004
Hana Biosciences	Nausea/vomiting, chemotherapy-induced	Ondansetron hydrochloride[1,2], lingual spray	I
Helsinn	Nausea/vomiting, postoperative	Palonosetron hydrochloride[1,2]	II
HemispheRx	Hepatitis C	Interferon alfa-n3[1]	II/III
Human Genome Sciences	Hepatitis C	Albumin interferon alfa	II
Idenix	Hepatitis B	Telbivudine[2]	III
		Valtorcitabine dihydrochloride	II
	Hepatitis C	Valopicitabine	II
Il-Yang	Gastroesophageal reflux disease	Ilaprazole[2]	II
InfaCare Pharmaceutical	Hyperbilirubinemia	Stannsoporfin	III
Inflabloc	Crohn's disease	IP-1001[2]	II
InKine	Constipation	INKP-100[1]	III
	Delayed gastric emptying (gastroparesis)	INKP-102	Prereg.
Innogenetics	Hepatitis B	Hepatitis B vaccine	I
	Hepatitis C	Hepatitis C vaccine	II
Intarcia Therapeutics	Hepatitis C	Interferon omega	II
Intercell	Hepatitis C	Hepatitis C vaccine	II
InterMune	Hepatitis C	Pegylated interferon alfacon-1	I
Iomai	Diarrhea	ETEC vaccine	II
Isis Pharmaceuticals	Crohn's disease	Alicaforsen sodium[2]	Discontinued
Ivax	Crohn's disease	Etiprednol dicloacetate[2]	II
Japan Tobacco	Hepatitis C	JTK-003	II
Jerini	Cirrhotic ascites	Icatibant	II
Kemin Pharma	Hepatitis C	KPE-02003002	II
Kirin Brewery	Hepatitis C	KRN-7000[2]	I/II
Lequio Pharma	Hemorrhoids	OC-108	L-2005
LG Life Sciences	Hepatitis B	LB-80380 (ANA-380)[2]	II
Maxim	Liver diseases	Histamine dihydrochloride, oral	I/II
Medarex	Diarrhea	MDX-066	I
Meiji Seika	Hepatitis C	ME-3738	II
Menarini	Irritable bowel syndrome	Nepadutant	II
Merck KGaA	Irritable bowel syndrome	Asimadoline	II
Metabasis Therapeutics	Hepatitis B	Pradefovir mesilate	II
MGI Pharma	Nausea/vomiting, postoperative	Palonosetron hydrochloride[1,2]	II
Microbia	Irritable bowel syndrome	MD-1100	I
Microscience	Diarrhea	ETEC vaccine	I
	Hepatitis B	Hepatitis B vaccine	I
Migenix	Hepatitis C	Celgosivir	II
Millennium	Crohn's disease	MLN-02	II
	Ulcerative colitis	MLN-02	II
Mitsubishi Pharma	Gastroesophageal reflux disease	Tenatoprazole[2]	Clinical

Continuation

Treatment of Gastrointestinal Disorders by Source

Source	Condition	Drug	Phase
Mitsubishi Pharma	Hemorrhoids	OC-108	L-2005
	Hepatitis C	Ursodiol[1]	III
Nabi Biopharmaceuticals	Hepatitis C	Hepatitis C immune globulin	I/II
Negma	Gastroesophageal reflux disease	Tenatoprazole[2]	Clinical
Nektar Therapeutics	Crohn's disease	Certolizumab pegol	III
	Hepatitis C	Pegylated interferon alfacon-1	I
Nobex	Inflammatory bowel disease	NAA-004	I/II
NovaDel Pharma	Nausea/vomiting, chemotherapy-induced	Ondansetron hydrochloride[1,2], lingual spray	I
Novartis	Constipation	Tegaserod maleate[1,2]	L-2004
	Dyspepsia	Tegaserod maleate[1,2]	III
	Gastroesophageal reflux disease	Tegaserod maleate[1,2]	II
	Hepatitis B	Telbivudine[2]	III
		Valtorcitabine dihydrochloride	II
NPS Pharmaceuticals	Crohn's disease	Teduglutide	II
	Short bowel syndrome	Teduglutide	III
OctoPlus	Hepatitis C	Interferon alfa-2b[1]	I
Ono	Inflammatory bowel disease	Ono-4817	I
Optimer Pharmaceuticals	Diarrhea	OPT-80	II
Oscient Pharmaceuticals	Diarrhea	Ramoplanin[2]	II
OSI Pharmaceuticals	Crohn's disease	OSI-461	II
Otsuka	Ulcerative colitis	Tetomilast[2]	III
Oxxon Therapeutics	Hepatitis B	Hepatitis B vaccine	II
Pain Therapeutics	Irritable bowel syndrome	PTI-901[1,2]	III
PediaMed	Gastrointestinal disorders	Human gammaglobulin, oral	II
Peregrine Pharmaceuticals	Hepatitis C	Tarvacin™	I
Pfizer	Hepatitis B	IDN-6556	II
	Hepatitis C	IDN-6556	II
	Irritable bowel syndrome	PD-217014	II
	Liver diseases	IDN-6556	II
	Nonalcoholic steatohepatitis	IDN-6556	II
Pharmagene	Irritable bowel syndrome	PGN-1164	I
Procter & Gamble	Inflammatory bowel disease	Delmitide[2]	II
Progenics	Constipation	Methylnaltrexone bromide	III
	Ileus, postoperative	Methylnaltrexone bromide	II
ProStrakan	Nausea/vomiting, chemotherapy-induced	Granisetron hydrochloride[2], patch	II
Protein Design Labs	Crohn's disease	Fontolizumab	II
	Ulcerative colitis	Visilizumab[2]	I/II
Roche	Hepatitis C	R-1626	I
	Inflammatory bowel disease	R-1541	I
Roswell Park Cancer Institute	Hepatitis B	Hepatitis B vaccine	I
Rottapharm	Dyspepsia	Itriglumide	I
	Gastroesophageal reflux disease	Itriglumide[2]	I
	Irritable bowel syndrome	Dexloxiglumide[2]	III
	Ulcer, peptic	Itriglumide[2]	I
Salix	Crohn's disease	Rifaximin[1,2]	II
	Inflammatory bowel disease	Rifaximin[1,2]	II
	Irritable bowel syndrome	Rifaximin[1,2]	II
	Pouchitis	Rifaximin[1,2]	II
Sanofi-Aventis	Cirrhotic ascites	SR-121463	II
	Ulcerative colitis	Nolpitantium besilate	II
Schering AG	Crohn's disease	Sargramostim[2]	III
Schering-Plough	Ulcerative colitis	Infliximab[2]	III
Serono	Hepatitis C	Interferon beta-1a[1]	III
	Short bowel syndrome	Somatropin (rDNA origin)[1]	L-2004
Sinovac	Hepatitis A+B	Hepatitis A/B vaccine	L-2005
SLA Pharma	Constipation	Naloxone hydrochloride	II
	Crohn's disease	Icosapent	II
		Metronidazole[1], ointment	III
	Fecal incontinence	SLV-325	II
	Fissures, anal	SLV-324	II
	Ulcerative colitis	Nicotine, enema	III
Solvay	Fecal incontinence	SLV-325	II
	Fissures, anal	SLV-324	II
		SLV-317	I
Sucampo	Constipation	Lubiprostone[2]	Prereg.
	Ileus, postoperative	Lubiprostone[2]	II

Continuation

Treatment of Gastrointestinal Disorders by Source

Source	Condition	Drug	Phase
Sucampo	Ileus, postoperative	Lubiprostone[2]	II
	Irritable bowel syndrome	Lubiprostone[2]	II
	Nonalcoholic steatohepatitis	SPI-8811	II
Sumitomo Pharmaceuticals	Cirrhosis	Interferon alfa-n1[1]	III
Synta Pharmaceuticals	Crohn's disease	STA-5326	II
Takeda	Constipation	Lubiprostone[2]	Prereg.
	Ileus, postoperative	Lubiprostone[2]	II
	Irritable bowel syndrome	Lubiprostone[2]	II
Tanabe Seiyaku	Inflammatory bowel disease	683699 (T-0047)	II - On hold
	Ulcerative colitis	Ecabet sodium[1,2]	III (JP)
		Ecabet sodium[1,2]	II (EU, US)
Teijin	Diarrhea	Urtoxazumab	II
	Hemorrhagic colitis	Urtoxazumab	II
Theravance	Gastrointestinal motility disorders	TD-2749	I
Tillotts	Crohn's disease	Eicosapentaenoic acid/docosahexaenoic acid	III
UCB Pharma	Crohn's disease	Certolizumab pegol	III
United Therapeutics	Hepatitis C	UT-231B	II
Valeant	Hepatitis B	Pradefovir mesilate	II
	Hepatitis C	Viramidine hydrochloride[2]	III
Vela Pharmaceuticals	Irritable bowel syndrome	Dextofisopam	II
Vertex	Hepatitis C	Merimepodib[2]	II
Vicuron	Diarrhea	Ramoplanin[2]	II
ViroPharma	Hepatitis C	HCV-086	Discontinued
Wyeth	Hepatitis C	HCV-086	Discontinued
Xenoport	Gastroesophageal reflux disease	XP-19986	I
XTL Biopharmaceuticals	Hepatitis B	HepeX-B™	II
	Hepatitis C	HepeX-C™	Discontinued
		XTL-6865	IND filed
Yuhan	Ulcer, peptic	Revaprazan hydrochloride[2]	III
Zeria	Dyspepsia	Acotiamide hydrochloride hydrate[2]	II
	Inflammatory bowel disease	Z-206	I
	Taste disorders	Polaprezinc[1,2]	II
	Ulcer, peptic	Z-360	I

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

Treatment of Gastrointestinal Disorders

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270384

270384 (GI-270384X) is an ICAM-1 and E-selectin inhibitor in phase II trials at GlaxoSmithKline for the treatment of inflammatory bowel disease. The compound's inhibitory activity involves a late posttranscriptional event in the induction pathway of ICAM-1 and E-selectin expression.

679769

Compound 679769 is a tachykinin NK_1 receptor antagonist in early clinical evaluation at GlaxoSmithKline for the treatment of chemotherapy-induced and postoperative nausea and vomiting, urge incontinence, depression and anxiety.

683699 (T-0047)

The FDA has taken the precautionary measure of placing a clinical hold on investigational new drugs in the α_4 integrin antagonist class being tested in human subjects, including the GlaxoSmithKline/Tanabe Seiyaku compound 683699 (T-0047), which is in phase II development for multiple sclerosis and inflammatory bowel disease. The clinical hold reflects the uncertainty surrounding the cause of two reports of progressive multifocal leukoencephalopathy in patients who had been taking Tysabri (natalizumab), a biological agent marketed by Biogen Idec and Elan for multiple sclerosis, in combination with Avonex (interferon beta-1a) for longer than 2 years. At this point, there is insufficient information to draw conclusions about the link, if any, between α_4 integrin inhibition and the onset of progressive multifocal leukoencephalopathy. While 683699 (T-0047) has the same molecular target as natalizumab, it is not a monoclonal antibody and therefore is chemically unrelated to natalizumab (1-3).

1. *Tanabe Seiyaku reports interim 2003 year-end R&D highlights.* Tanabe Seiyaku Web Site 2004, Feb 2.

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

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

876008

GlaxoSmithKline is conducting phase I trials of 876008, a CRF_1 antagonist, for the treatment of anxiety, depression and irritable bowel syndrome.

ABT-874

ABT-874, a human anti-IL-12 monoclonal antibody isolated and optimized by Cambridge Antibody Technology in collaboration with Abbott, is in phase II clinical trials for the treatment of Crohn's disease and multiple sclerosis (1-3).

The latest results of the multicenter, double-blind, randomized, placebo-controlled IL-12 in Crohn's Disease Study that assessed the efficacy of ABT-874 in active Crohn's disease were presented at a congress last year. Seventy-nine patients with Crohn's Disease Activity Index (CDAI) scores of 220-450 were randomized to receive placebo or ABT-874 (1 or 3 mg/kg) administered s.c. once weekly for 7 weeks. Patients who received 3 mg/kg of ABT-874 with no interruptions between the first and second injections achieved the greatest improvement. Clinical response (reduction of at least 100 points in

Table I: Clinical studies of ABT-874 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Randomized Double-blind Multicenter	ABT-874, 1 mg/kg s.c. 1x/wk x 7 wks ABT-874, 1 mg/kg s.c. on d 1 → [4 wks later] 1x/wk x 6 wks ABT-874, 3 mg/kg s.c. 1x/wk x 7 wks ABT-874, 3 mg/kg s.c. on d 1 → [4 wks later] 1x/wk x 6 wks Placebo	79	A dose of 3 mg/kg of ABT-874 was well tolerated and significantly more effective than placebo in inducing clinical response and clinical remission in patients with moderate to severe Crohn's disease. The greatest therapeutic benefits were associated with weekly s.c. injections of 3 mg/kg given with no interruption	4, 5

baseline CDAI) rates at the end of treatment and after 12 weeks of follow-up for patients receiving 3 mg/kg ABT-874 were significantly greater than in patients on placebo (75% and 69% *vs*. 25% and 13%, respectively). Rates of remission (CDAI < 150) at the end of treatment and after 12 weeks of follow-up were 38% and 50%, respectively, compared to 0% on placebo. ABT-874 was well tolerated and was not associated with an increase in the incidence of antibody-related adverse events compared to placebo. The clinical effects induced by ABT-874 were associated with a lower expression of Th1 cytokines (IL-12, interferon gamma, TNF-α) in mononuclear cells of the lamina propria (4-7) (see Table I).

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

2. *Abbott Laboratories reports Q2 R&D highlights.* Abbott Laboratories Press Release 2004, July 9.

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

4. Mannon, P., Fuss, I., Mayer, L. et al. *Anti-interleukin-12 treats active Crohn's disease.* Gastroenterology 2004, 126(4, Suppl. 2): Abst 162.

5. Fuss, I., Hornung, R., Mannon, P.J. *Anti-interleukin-12 p40 antibody treats active Crohn's disease.* 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst OP-G-225.

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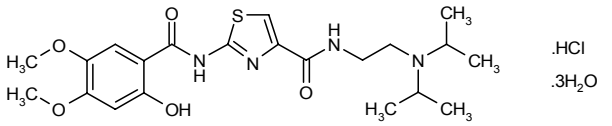
Acotiamide Hydrochloride Hydrate



Zeria expects to launch acotiamide hydrochloride hydrate (Z-338), a gastroprokinetic agent in phase II development in Japan, the E.U. and the U.S., where it is being codeveloped with Astellas Pharma, after 2006 for the treatment of functional dyspepsia. The company plans to outlicense acotiamide in the E.U. prior to beginning phase III studies (1).

Results from a double-blind phase II study in Japanese patients with functional dyspepsia demonstrated the clinical efficacy of acotiamide. After randomization, 127 patients were treated with acotiamide (50, 100 or 300 mg p.o. t.i.d. for 4 weeks) or placebo. With the 100-mg dose, postprandial fullness significantly improved over placebo at weeks 2, 3 and 4, upper abdominal bloating significantly improved at weeks 2 and 3, and early satiety significantly improved at weeks 3 and 4. The 300-mg dose significantly improved postprandial fullness, upper abdominal bloating and early satiety at weeks 1, 2 and 3. Adverse events did not differ among treatment groups and no Q-T prolongation was seen (2) (Table II).

1. *Zeria targets launches after 2006*. DailyDrugNews.com (Daily Essentials) Aug 24, 2004.

2. Matsueda, K., Hongo, M., Sasaki, D., Kusano, M., Harasawa, S., Arakawa, T., Haruma, K., Nakashima, M., Miwa, T., Saitou, Y. *Therapeutic efficacy of novel agent (Z-338) in functional dyspepsia (FD)*. Dig Dis Week (May 14-19, Chicago) 2005, Abst T1148.

Original monograph – Drugs Fut 2003, 28(1): 26.

Table II: Clinical studies of acotiamide hydrochloride hydrate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Dyspepsia	Randomized Double-blind Multicenter	Acotiamide, 50 mg t.i.d. p.o. x 4 wks (n=32) Acotiamide, 100 mg t.i.d. p.o. x 4 wks (n=33) Acotiamide, 300 mg t.i.d. p.o. x 4 wks (n=30) Placebo (n=32)	127	The higher doses of acotiamide significantly improved the symptoms of functional dyspepsia	2

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Adalimumab

Adalimumab (D2E7, Humira®) is a fully human anti-TNF-α monoclonal antibody discovered and developed under a collaboration between Cambridge Antibody Technology and Knoll, which was subsequently acquired by Abbott. In the U.S. and Europe, Abbott currently markets adalimumab for the treatment of rheumatoid arthritis in adults, and it is under regulatory review in the U.S. and the E.U. for early rheumatoid arthritis and psoriatic arthritis. Clinical trials are also under way in juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease (phase III). Abbott has an agreement with Eisai whereby the companies will jointly develop and market adalimumab in Japan for the treatment of rheumatoid arthritis (phase II), Crohn's disease and psoriasis. Abbott retains the sole right to develop the antibody on its own for Crohn's disease and psoriasis indications in the U.S. and Europe (1-6).

A clinical trial evaluated the safety and efficacy of adalimumab in the treatment of Crohn's disease. Sixteen patients with Crohn's disease who had developed intolerance or no longer responded to infliximab were given subcutaneous adalimumab (80 mg at the beginning of the study and 50 mg 2 weeks later). At 4 weeks, 46% of the patients showed clinical response and 8% had achieved complete remission. Four of the 6 patients with perianal and/or rectovaginal fistula at baseline showed improvements, which in 3 patients consisted of complete fistula closure. No evidence of acute or delayed hypersensitivity reactions was found, and only 1 patient experienced injection-site reactions (7) (Table III).

A multicenter, double-blind, randomized clinical trial determined the efficacy of adalimumab in Crohn's disease. A total of 299 patients with moderate to severe active Crohn's disease not previously treated with TNF-α antagonists were randomized to receive placebo or adalimumab (40/20, 80/40 or 160/80 mg) subcutaneously at study weeks 0 and 2. Adalimumab dose-dependently increased the percentage of patients who achieved clinical remission (CDAI < 150) at 4 weeks after the first injection, from 12% on placebo to 24% and 36%, respectively, on 80/40 and 160/80 mg of adalimumab. A greater percentage of patients given adalimumab showed improvements of at least 70 or 100 points in their CDAI scores at the end of the 4-week study period. The baseline levels of C-reactive protein (CRP) of the patients had no effect on their response to adalimumab, and smoking status also had no effect. Most adverse events were mild, and the most common were injection-site reactions (8-10) (Table III).

An open-label clinical trial evaluated the effects and safety profile of adalimumab in 15 patients with moderate to severe active Crohn's disease who discontinued infliximab therapy due to attenuation or loss of response. Each patient was given a subcutaneous injection of 80 mg of adalimumab, followed by a maintenance dose of 40 mg s.c. (increased if response was not maintained) for 6 months. Of 13 evaluable patients, 7 (54%) achieved complete response, 4 (31%) showed partial response and 2 (15%) did not respond to adalimumab. The average time to response was 5.3 weeks. The most common adverse events were injection-site reactions (erythema and discomfort), and no patient experienced immediate- or delayed-type hypersensitivity reactions. Additional studies are needed to determine whether response to adali-

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

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Open	Adalimumab, 80 mg s.c. → [2 wks later] 40 mg s.c. [at week 2]	16	Adalimumab was well tolerated and effective in inducing clinical response (46%) and clinical remission at 4 weeks after receiving the first dose in patients with Crohn's disease	8
Crohn's disease	Randomized Double-blind Multicenter	Adalimumab, 40 mg s.c. on wk 0 → 20 mg s.c. on wk 2 Adalimumab, 80 mg s.c. on wk 0 → 40 mg s.c. on wk 2 Adalimumab, 160 mg s.c. on wk 0 → 80 mg s.c. on wk 2 Placebo	299	Adalimumab was safe and dose-dependently increased the percentage of patients with moderate to severe active Crohn's disease who achieved clinical response and clinical remission at week 4 after the first dose. Clinical remission and response were independent of smoking status	9, 11

mumab may be maintained for long periods of time in these patients (11).

1. *Positive opinion for Humira label extension in E.U*. DailyDrugNews.com (Daily Essentials) May 10, 2004.

2. *FDA approves expanded indication for Humira to improve physical function in RA patients*. DailyDrugNews.com (Daily Essentials) Aug 12, 2004.

3. *Abbott seeks approval of Humira for early RA in U.S. and Europe*. DailyDrugNews.com (Daily Essentials) Dec 27, 2004.

4. *Abbott seeks U.S., European approvals of Humira for psoriatic arthritis*. DailyDrugNews.com (Daily Essentials) Dec 21, 2004.

5. *Canadian approval for Humira*. DailyDrugNews.com (Daily Essentials) Nov 23, 2004.

6. *Eisai and Abbott to develop adalimumab for psoriasis in Japan*. DailyDrugNews.com (Daily Essentials) April 13, 2005.

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AJM-300

AJM-300, a novel orally available integrin inhibitor developed by Ajinomoto, is currently undergoing phase I development for the treatment of inflammatory bowel disease (IBD).

Albumin Interferon Alfa

Albuferon™ (albumin interferon alfa), currently undergoing phase II trials for the treatment of hepatitis C, is a novel, long-acting form of interferon alfa that was modified by Human Genome Sciences using its proprietary albumin fusion technology.

Human Genome Sciences has completed enrollment, randomization and dosing in a phase II trial of Albuferon™ in patients with chronic hepatitis C who are naïve to interferon alfa treatments. The Canadian trial is an open-label, multicenter, randomized, parallel-design, dose-ranging study evaluating the safety, tolerability, pharmacology and optimal dosing of Albuferon™. A total of 56 patients with hepatitis C virus (HCV) genotype 1 were enrolled in the trial and randomized to five dose groups. Patients received two doses of Albuferon™ administered subcutaneously 14 days apart. The pharmacodynamic activity of Albuferon™ is being evaluated based on HCV RNA viral load reductions over a 28-day period of exposure. One of the study objectives is to identify a range of active doses that HGS plans to evaluate in a larger 48-week study of Albuferon™ in combination with ribavirin in patients with HCV genotype 1 who are naïve to interferon treatments. Preliminary data are available from 38 patients who have completed more than 28 days of the ongoing phase II study, including 30 patients enrolled in the 200-, 450- and 670-μg dose cohorts, and 8 patients enrolled in the 900- and 1200-μg dose cohorts. The available data demonstrate that Albuferon™ is well tolerated and has antiviral activity in genotype 1 HCV. A reduction in viral load of 2 log or more at day 28 was observed in 57% (16/28) of the patients who received Albuferon™ at a dose of 450 μg or more. A reduction in viral load of at least 3.0 log at day 28 was observed in a majority (5/8) of the 8 patients in the 900- and 1200-μg dose cohorts. Reductions in viral load of at least 2 log are reported in approximately 42% of genotype 1 HCV patients treated with pegylated interferon alfa products in combination with ribavirin. The pharmacokinetic profile of Albuferon™ supports dosing every 2-4 weeks. The results of the current phase II trial will help identify an optimal range of doses to evaluate in a larger 48-week combination study of Albuferon™ with ribavirin that is planned in treatment-naïve patients. Preliminary 8-week data available from a separate ongoing phase II trial of Albuferon™ in patients with chronic hepatitis C who have failed to respond to previous interferon alfa-based treatment regimens show that Albuferon™ administered at 2- or 4-week intervals in combination with ribavirin is safe, well tolerated and demonstrates antiviral activity in all treatment groups for which data are available. Data from 119 patients in a phase I/II trial of Albuferon™ in interferon alfa-experienced adults with chronic hepatitis C demonstrate that Albuferon™ is well tolerated, has a prolonged half-life, is biologically active and able to reduce viral load with dose-dependent magnitude and durability. On average, patients participating in the trial had been

treated previously for approximately 63 weeks with interferon alfa-containing regimens and 92% of the patients were infected with HCV genotype 1. Patients were treated with one or two doses of Albuferon™ administered subcutaneously 14 days apart. Doses administered ranged from 7 to 900 μg. Preliminary immunogenicity data show that Albuferon™ immunogenicity occurs at rates consistent with those reported for other interferon alfa-based therapies, with no apparent correlation between the emergence of Albuferon™ antibodies and adverse events, antiviral response or pharmacokinetics. The vast majority of Albuferon™ antibody titers were low (< 100 ng/ml). A total of 47% of Albuferon™-treated patients in the combined single- and two-dose cohorts at doses of 120-900 μg experienced an antiviral response, as demonstrated by reductions in viral load of 1.0 log or greater (1-6).

1. *Dosing commences in phase II trial of Albuferon for chronic HCV*. DailyDrugNews.com (Daily Essentials) June 1, 2004.

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

3. *Treatment begins in phase II study of Albuferon plus ribavirin for hepatitis C*. DailyDrugNews.com (Daily Essentials) Dec 2, 2004.

4. *Enrollment completed in phase II HCV study of Albuferon*. DailyDrugNews.com (Daily Essentials) Feb 18, 2005.

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Alequel™

Alequel™ is a complex of autologous colon-derived proteins developed by Enzo Biochem for the management of active Crohn's disease. A double-blind, randomized, placebo-controlled phase II clinical trial evaluated the effects and safety of Alequel™ in 31 patients with moderate to severe Crohn's disease. Comparison of the CDAI scores of the patients at baseline and at the end of the treatment revealed that Alequel™ was associated with a greater rate of clinical response (67% *vs*. 43%) and clinical remission (58% *vs*. 29%) compared to placebo. The quality of life of the patients, evaluated using the Inflammatory Bowel Disease Questionnaire (IBDQ), improved by an average of 43% with Alequel™ and by an average of 12% with placebo. None of the serious adverse events seen with other treatments for Crohn's disease were reported by patients given Alequel™. An ongoing phase II clinical trial will evaluate the efficacy of additional dose levels of Alequel™ in a more diverse population of patients (1, 2).

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Alicaforsen Sodium

Isis has announced results for the first-generation antisense drug alicaforsen sodium (ISIS-2302). Alicaforsen is an inhibitor of ICAM-1, a molecule that plays a key role in a wide range of inflammatory and autoimmune conditions. To evaluate alicaforsen's potential for ulcerative colitis, Isis conducted four phase II trials in more than 300 patients. The trials were designed to characterize the safety profile of an alicaforsen enema, to identify the dose and dose regimen for phase III trials, and to compare the activity of alicaforsen enema to mesalamine enema. Results from the three most recent studies were reported. The data relate to the top-performing alicaforsen enema dose of 240 mg nightly. In a randomized, double-masked, placebo-controlled study in the U.S. and Europe, 112 patients who had ulcerative colitis for a mean of 7.5 years were randomized to receive placebo or one of four alicaforsen enema dose regimens: 240 mg every night, 240 mg every night for 10 days and then every other day, 240 mg every other night or 120 mg every night for 10 days and then every other day. Patients in each dose cohort received their respective enema treatments over a 6-week period. Those who achieved a response were followed for up to 6 months. Once-nightly administration of 240 mg alicaforsen enema for 6 weeks produced greater and more durable responses, as measured by the Disease Activity Index (DAI), than placebo. In addition, alicaforsen-treated patients had improved mucosal healing, decreased rectal bleeding and decreased stool frequency. Based on an intent-to-treat analysis, 59% of patients treated with 240 mg alicaforsen achieved a response as measured by DAI. Six months later at the end of the study, 77% of these patients continued to respond. Patients treated with alicaforsen who achieved a response maintained their response, on average, for over 6 months compared to a duration of response of < 3 months for placebo-treated patients. Alicaforsen-treated patients achieved a mean 51% reduction in DAI at week 18 and 50% at week 30, compared to 18% and 11%, respectively, for patients treated with placebo. Disease improvement observed with alicaforsen was more pronounced in patients with moderate disease than in patients with mild ulcerative colitis. The mean improvement in DAI demonstrated strong trends in favor of the drug or statistical significance compared to placebo. The improvement was confirmed by analyses of

mucosal healing, reduction in rectal bleeding, reduction in stool frequency, and by the Physician Global Assessment. A second phase II study —a mesalamine comparison study— was conducted in 159 patients with mild to moderate left-sided colitis who had ulcerative colitis for a mean of 9.3 years. In the randomized, double-masked, active-controlled U.S. study, patients received 120 mg alicaforsen enema, 240 mg alicaforsen enema or 4.0 g mesalamine enema once nightly for 6 weeks and were allowed to remain on baseline oral medications for their disease. Patients who achieved a response at 6 weeks were followed for up to 1 year. Patients treated with 240 mg alicaforsen nightly for 6 weeks achieved at least equivalent improvements in disease compared to patients treated with mesalamine. Many patients treated with alicaforsen who achieved a response maintained their response for 6 months or longer compared to an average duration of response of < 3 months for mesalamine-treated patients. Across all time points following treatment in the 54-week study, patients treated with alicaforsen demonstrated greater improvement in DAI than patients treated with mesalamine. Improvements in mucosal healing, decreases in rectal bleeding and decreases in stool frequency also demonstrated strong trends in favor of alicaforsen or statistical significance compared to mesalamine. The third reported study, a pharmacokinetic trial, included 12 patients with left-sided colitis who presented with severe mucosal inflammation. In the open-label U.S. trial, patients received 240 mg of alicaforsen enema once nightly for 6 weeks. At the end of the dosing period, patients were evaluated for drug absorption to determine the extent of systemic drug exposure. The patients showed minimal to no systemic absorption of drug (< 1% of dose), demonstrating that it acts locally to treat this local disease. A total of 75% of patients demonstrated improved DAI over the 6-week course of the study and 58% of patients achieved mucosal healing at week 6. Based on the results of these three trials, Isis has selected the best performing dose and dose regimen of 240 mg nightly for phase III trials. However, the company also reported disappointing results from two phase III trials that evaluated alicaforsen in patients with Crohn's disease. These two randomized, double-blind, placebo-controlled studies evaluated alicaforsen in patients with active moderate to severe Crohn's disease. The first trial, which was conducted in North America, enrolled 151 patients and the second trial, which was conducted in Europe and in Israel, enrolled 180 patients. In the studies, patients received either placebo or 300 mg of alicaforsen by intravenous infusion 3 times a week for 4 weeks. Patients were followed for response for 6 months, and alicaforsen-treated patients who achieved clinical remissions were followed for up to 1 year. The primary endpoint for both trials was clinical remission, defined as a CDAI score of 150 or less, by week 12. Alicaforsen did not

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

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Randomized Double-blind	Alicaforsen, 300 mg i.v. 3x/wk x 4 wks Alicaforsen, 200 mg i.v. 3x/wk x 4 wks	331	Alicaforsen was well tolerated but did not demonstrate activity in patients with Crohn's disease	2
Ulcerative colitis	Randomized Open	Alicaforsen, 120 mg [enema] o.d. x 6 wks Alicaforsen, 240 mg [enema] o.d. x 6 wks Mesalamine, 4 mg [enema] o.d. x 6 wks	159	Alicaforsen enema was associated with a higher clinical remission rate and longer lasting responses than mesalamine in patients with acute ulcerative colitis	4
Ulcerative colitis	Open	Alicaforsen, 250 mg [enema] o.d. x 6 wks	15	Alicaforsen improved disease activity and friability in patients with acute ulcerative colitis	5
Ulcerative colitis	Randomized Double-blind	Alicaforsen, 240 mg 1x/d x 10 d → 240 mg 1x/2 d Alicaforsen, 240 mg 1x/d x 6 wks Alicaforsen, 120 mg 1x/d x 10 d → 120 mg 1x/2 d Alicaforsen, 240 mg q x2d x 6 wks Placebo	112	Alicaforsen enema was well tolerated and a dose of 240 mg/day was associated with significant activity in patients with acute ulcerative colitis	6
Ulcerative colitis	Randomized Double-blind Multicenter	Alicaforsen, 0.1 mg/ml i.rect. [enema] o.d. x 28 d (n=8) Alicaforsen, 0.5 mg/ml i.rect. [enema] o.d. x 28 d (n=8) Alicaforsen, 2 mg/ml i.rect. [enema] o.d. x 28 d (n=8) Alicaforsen, 4 mg/ml i.rect. [enema] o.d. x 28 d (n=8) Placebo (n=8)	40	Alicaforsen enema was safe and effective over both the short and long term in patients with distal ulcerative colitis	7

demonstrate statistically significant induction of clinical remissions compared to placebo. In both studies, alicaforsen was well tolerated. As a result of these data, the company has determined it will not invest further in the development of alicaforsen for Crohn's disease (1-6) (Table IV).

A randomized, double-blind, placebo-controlled trial evaluated the treatment of patients with mild to moderate distal ulcerative colitis with ascending doses of alicaforsen enemas given once daily for 28 days. Disease Activity Index scores were significantly improved by alicaforsen 2 mg/ml (from 5.6 to 1.6) and 4 mg/ml (from 6.3 to 2.5) compared to placebo (from 7.5 to 6.1), and the treatment was well tolerated (7) (Table IV).

1. *Isis reports on alicaforsen trial results*. DailyDrugNews.com (Daily Essentials) Dec 9, 2004.

2. Chey, W.Y., Volfova, M., Konecny, M., Rydzewska, G., Fogel, R., Pare, P., Priebe, W., Marlicz, K., Hajek, J., Karsnodebski, I., Paradowski, L., Yacyshyn, B., Goff, J., Safdi, M., Weiss, M., Sprague, R., Barish, C., Gordon, G., Hardi, R., Miner, P.B., Spainhour, J., De Vos, M., Wedel, M.K., Paul, D.A., Chuang, E., van Deventer, S.J. *Two phase 3 studies of alicaforsen (ISIS-2302), an antisense oligonucleotide to human ICAM-1, in the treatment of moderate to severe Crohn's disease.* Dig Dis Week (May 14-19, Chicago) 2005, Abst 724.

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

4. Miner, P.B., Nichols, T., Schwartz, H., Carlisle, R., Wruble, L., Rider, D., Kaplan, R., Katz, J., Pandek, W., Xia, S., Wedel, M.K., Chuang, E., Chey, W.Y. *A phase 2 trial to assess the safety and efficacy of two dose formulations of alicaforsen enema compared with 4 g mesalamine enema for acute ulcerative colitis*. Dig Dis Week (May 14-19, Chicago) 2005, Abst 491.

5. Miner, P.B., Geary, R.S., Matson, J., Xia, S., Chuang, E., Wedel, M.K. *An open-label study to assess the PK and pharmacologic activity of alicaforsen in patients with active ulcerative colitis.* Dig Dis Week (May 14-19, Chicago) 2005, Abst W1046.

6. van Deventer, S.J., Volfova, M., Flisiak, R., Marlicz, K., Blaszczynska, M., Svoboda, P., Gabalec, L., Paradowski, L., Rydzewska, G., Xia, S., Wedel, M.K., Chuang, E., Miner, P.B. *A phase 2 dose ranging, double-blind, placebo-controlled study of alicaforsen enema in subjects with acute exacerbation of mild to moderate left-sided ulcerative colitis.* Dig Dis Week (May 14-19, Chicago) 2005, Abst 490.

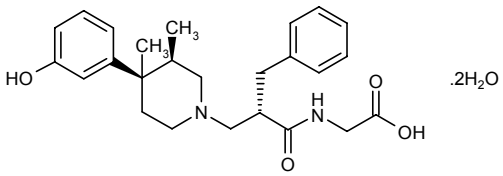
7. van Deventer, S.J.H., Tami, J.A., Wedel, M.K. *A randomised, controlled, double blind, escalating dose study of alicaforsen enema in active ulcerative colitis*. Gut 2004, 53(11): 1646.

Original monograph – Drugs Fut 2002, 27: 439.

ALTU-139

An orally delivered enzyme replacement therapy, ALTU-139 is in phase I trials at Altus Pharmaceuticals for the treatment of fat malabsorption in neonates and low-birth-weight infants.

Alvimopan Hydrate



Alvimopan hydrate (Entereg™) is an investigational peripherally acting mu opioid receptor antagonist (PAMOR) designed to block the negative effects of opioids on the gastrointestinal system without interfering with the analgesic effects on the central nervous system. Adolor and GlaxoSmithKline are collaborating on the worldwide development and commercialization of alvimopan for postoperative ileus, opioid-induced bowel dysfunction associated with extended use of opioids to treat chronic pain (phase IIb), chronic idiopathic constipation not associated with opioid use (phase IIb) and constipation-predominant irritable bowel syndrome (IBS). Adolor completed in June 2004 the submission of an NDA with the FDA, which includes phase III data evaluating more than 2,000 patients in three efficacy studies and one safety study. The FDA granted fast track designation to alvimopan in February 2004 for use in the management of postoperative ileus. The FDA also recently extended the Prescription Drug User Fee Act (PDUFA) target action date from April 25, 2005 to July 25, 2005 for the completion of its review of Adolor's NDA for alvimopan capsules for the management of postoperative ileus. In January 2005, the FDA requested that the company provide information from the GlaxoSmithKline European phase III study (SB-767905/001; see below) of alvimopan. The final component of the requested information, the clinical study report from GSK Study 001, was submitted to the FDA in April. Study 001 was conducted by GlaxoSmithKline in Europe, Australia and New Zealand (1-10).

In a phase I trial, healthy volunteers were treated with morphine 30 mg b.i.d. for 7 or 10 days and were then treated with alvimopan 12 mg or placebo approximately 12 h after the last morphine dose. Among patients given 7 days of morphine, treatment-related adverse events occurred in 0 of 3 patients given alvimopan and in the 1 patient given placebo. In the 10-day morphine group, mostly gastrointestinal adverse events were seen in 5 of 6 and 1 of 3 patients given alvimopan and placebo, respectively (11) (Table V).

A double-blind, placebo-controlled clinical trial determined the pharmacokinetics of alvimopan (6, 12, 18 or 24 mg p.o. on day 1, and then twice daily for nine doses) in 40 healthy volunteers. Alvimopan at doses of 6-18 mg showed a linear pharmacokinetic profile. The values found for peak plasma concentration (5.07-15.88 ng/ml), area under the curve (17.7-54.6 ng.h/ml) and half-life (2.4-5.5 h) were similar at steady state and after single

Table V: Clinical studies of alvimopan hydrate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy Volunteers	Randomized Single-blind	Morphine, 30 mg b.i.d. x 7 d → Alvimopan, 12 mg (n=3) Morphine, 30 mg b.i.d. x 10 d → Alvimopan, 12 mg (n=6) Morphine, 30 mg b.i.d. x 7 d → Placebo (n=1) Morphine, 30 mg b.i.d. x 10 d → Placebo (n=3)	18	Alvimopan was well tolerated in subjects previously exposed to short-term, but not long-term, opioid therapy	11
Constipation	Randomized Double-blind Crossover	Alvimopan, 3 mg b.i.d. x 7 d Placebo	23	Alvimopan increased bowel movement frequency, reduced whole-bowel transit and mean colonic transit times, and improved stool hardness, straining, discomfort and satisfaction in patients with chronic constipation. Alvimopan was associated with a higher incidence of gastrointestinal events compared with placebo, but most of these were mild	16
Surgery, hysterectomy	Randomized Double-blind	Alvimopan, 12 mg p.o. [preoperatively] → p.o. b.i.d. x 7 d Placebo	519	Alvimopan accelerated time to gastrointestinal recovery with a favorable safety profile in patients after total abdominal hysterectomy	19

doses, and were indicative of systemic activity. No evidence of drug accumulation was found (12).

In a double-blind, crossover clinical trial, 23 patients with chronic constipation were given placebo or alvimopan (3 mg b.i.d.) for 7 days. Average values measured at steady state for the area under the curve and the peak plasma concentration were similar to those found in healthy volunteers (13).

Initial topline results from the phase III SB-767905/001 study (Study 001) of alvimopan capsules for the management of postoperative ileus were reported. The multicenter, randomized, double-blind, placebo-controlled parallel-group trial enrolled a total of 911 subjects —741 bowel resection patients and 170 radical hysterectomy patients. The topline results reported are from only the bowel resection subjects who were prespecified as the primary population for the analysis. Under the study protocol, patients were randomized to one of three arms to receive placebo, 6 or 12 mg of alvimopan orally 2 h prior to surgery, and then twice a day beginning on the first postoperative day until hospital discharge or for a maximum of 7 days. The primary endpoint (GI3) of the study was the time to recovery of gastrointestinal function, as defined by the later of the following two events: time from surgery until the patient first tolerates solid foods, and time from surgery until the patient first passes flatus or has a bowel movement. Primary endpoint results did not reach statistical significance. Secondary endpoints included an additional measure of time to recovery of gastrointestinal function (GI2), which measures GI recovery based on tolerating solid food and bowel movement. Results in GI2 were statistically significant for both dose groups compared to the placebo group. Differences in favor of the alvimopan treatment groups as compared to placebo were observed in the secondary endpoint of time to hospital discharge order written, but were not statistically significant. There were a number of findings in Study 001 that highlight differences in perioperative management of bowel resection patients between the U.S. and Europe, and GSK will continue to analyze and evaluate the results of this study (14).

Two ongoing multicenter, double-blind, randomized, placebo-controlled clinical trials are evaluating the effects and safety of alvimopan in the management of bowel dysfunction. Study SB-767905/011, a phase IIb trial conducted in 522 noncancer patients with opioid-induced bowel dysfunction, showed that oral alvimopan (0.5 mg b.i.d., 1 mg once daily or 1 mg b.i.d.) given for 6 weeks was significantly more effective than placebo in increasing weekly frequency of spontaneous bowel movements. Alvimopan was also associated with significant improvements in straining, stool consistency and incomplete evacuation, and was well tolerated. The most common adverse events were abdominal pain, nausea and diarrhea. The second study, SB-767905/007, treated 217 adult patients suffering from chronic idiopathic constipation not caused by opioids with placebo or alvimopan (1, 3 and 8 mg b.i.d.) for 8 weeks. Preliminary data suggest that alvimopan is well tolerated at all doses tested and may induce therapeutic benefits in some patients (15).

Twenty-three adult patients with chronic constipation for at least 6 months were enrolled in a double-blind, crossover clinical trial and randomized to receive alvimopan (3 mg b.i.d.) or placebo for 7 days. Compared to

baseline, alvimopan increased bowel movement frequency and reduced whole-bowel transit and mean colonic transit time by 32% and 19%, respectively. These effects were correlated with improvements in stool hardness, straining, discomfort and patient satisfaction. Alvimopan was well tolerated and although it was associated with a higher incidence of gastrointestinal adverse events compared to placebo, most of these were mild (16) (Table V).

A randomized, placebo-controlled trial evaluated the safety and efficacy of 0.5 or 1 mg alvimopan in 168 patients with opioid-induced bowel dysfunction, with a primary endpoint of more than 1 bowel movement within 8 h of each study dose across the 21-day treatment period. Results showed that, on average, significantly more patients treated with alvimopan reached this endpoint than patients taking placebo. The alvimopan 1 mg group reported improved bowel evacuation and improved satisfaction with the quality of bowel movements compared with placebo. Furthermore, pain intensity scores did not change, suggesting that daily dosing with alvimopan may improve bowel movement frequency and satisfaction without compromising pain relief (17).

Results from a multicenter, randomized, double-blind, placebo-controlled, parallel-group study involving 510 patients (intent-to-treat population = 469) scheduled for bowel resection or radical hysterectomy demonstrated the efficacy of alvimopan (6 or 12 mg p.o. b.i.d. 2 h or more before surgery and until hospital discharge or up to 7 days) in accelerating the recovery of gastrointestinal function. The incidence of adverse events was similar in all groups. Gastrointestinal function recovery time was significantly decreased in patients receiving the two doses of alvimopan (mean difference of 15 and 22 h, respectively, *vs.* placebo). In addition, time to hospital discharge was significantly decreased in the group receiving the higher dose (mean difference of 20 h *vs.* placebo) (18).

The efficacy and safety of alvimopan (12 mg p.o. 2 h before surgery and then b.i.d. for up to 7 days) in accelerating gastrointestinal recovery time were demonstrated in a double-blind, randomized, placebo-controlled phase III trial conducted in 519 women undergoing total abdominal hysterectomy. No significant difference was observed between alvimopan and placebo in the rates of adverse events, of which the most common were nausea, vomiting, constipation and flatulence. Discontinuation rates due to adverse events were similar in both groups. Serious adverse events were observed in 5.6% of the alvimopan-treated patients as compared to 6.6% of placebo-treated patients. Treatment with the agent decreased the time to recovery of both upper and lower gastrointestinal function by 1.9 and 22.2 h, respectively, for the first bowel movement as compared to placebo (19) (Table V).

1. *GlaxoSmithKline reports 2003 year-end R&D highlights*. GlaxoSmithKline Press Release 2004, Feb 12.

2. *First portion of Entereg NDA submitted*. DailyDrugNews.com (Daily Essentials) May 12, 2004.

3. *Second portion of Entereg NDA submitted*. DailyDrugNews.com (Daily Essentials) June 3, 2004.

4. *Complete NDA submitted for Entereg in POI*. DailyDrugNews.com (Daily Essentials) June 30, 2004.

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

6. *Adolor announces FDA update*. Adolor Corp. Press Release 2005, Jan 10.

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

8. *PDUFA action date extended for Entereg NDA*. DailyDrugNews.com (Daily Essentials) April 21, 2005.

9. *Entereg NDA accepted for review*. DailyDrugNews.com (Daily Essentials) Sept 13, 2004.

10. *GlaxoSmithKline reports Q1 R&D highlights*. GlaxoSmithKline Press Release 2004, April 29.

11. Panchal, S. et al. *Safety and tolerability of alvimopan in healthy volunteers following opioid withdrawal*. 24th Annu Sci Meet Am Pain Soc (March 30-April 2, Boston) 2005, Abst 730.

12. Foss, J. et al. *Alvimopan (Entereg(TM)), a novel opioid antagonist, achieves active systemic concentrations*. Clin Pharmacol Ther 2005, 77(2): Abst PII-90.

13. Schmith, V.D. et al. *Alvimopan pharmacokinetics (PK) & pharmacodynamics (PD) in patients with chronic constipation (CC)*. Clin Pharmacol Ther 2005, 77(2): Abst PI-158.

14. *Disappointing topline results from phase III study of alvimopan*. DailyDrugNews.com (Daily Essentials) Dec 28, 2004.

15. *Two phase II clinical trials report benefits with alvimopan in bowel dysfunction*. DailyDrugNews.com (Daily Essentials) March 15, 2005.

16. Garnett, W., Kelleher, D.L., Hickmott, F. et al. *Alvimopan (ALV) shortens whole bowel transit time in adults with chronic constipation (CC)*. Gastroenterology 2004, 126(4, Suppl. 2): Abst W1472.

17. Paulson, D., Kennedy, D., Donovick, R. et al. *Alvimopan, a novel, peripherally-acting, mu-opioid receptor antagonist for the management of opioid-induced bowel dysfunction (OBD): Positive results from a phase III randomized, placebo-controlled, 21-day trial.* 23rd Annu Sci Meet Am Pain Soc (May 6-9, Vancouver) 2004, Abst 796.

18. Wolff, B.G., Michelassi, F., Gerkin, T.M., Techner, L., Gabriel, K., Wallin, B.A. *Alvimopan, a novel, peripherally acting mu opioid antagonist. Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus*. Ann Surg 2004, 240(4): 728.

19. Herzog, T.J., Techner, L.M., Du, W., Wallin, B.A. *A double-blind, randomized, placebo-controlled, phase III clinical trial of the safety of alvimopan (ALV) in patients (pts) undergoing total abdominal hysterectomy (TAH)*. Annu Meet Women's Cancer (March 19-23, Miami Beach) 2005, Abst 233.

Original monograph – Drugs Fut 1994, 19(12): 1078.

ANA-971/ANA-975

ANA-971 is an orally administered prodrug of isatoribine (ANA-245; see below) and a specific toll-like receptor 7 (TLR7) agonist currently in phase I development at Anadys for reducing the risk of hepatitis C virus (HCV) infection relapse.

Anadys has also selected ANA-975, another oral prodrug of isatoribine, as its development candidate for the frontline treatment of chronic HCV infection. Isatoribine represents one of a new class of drugs being developed by Anadys to regulate innate immunity, combat HCV infection and overcome limitations of current anti-HCV therapies. Anadys believes isatoribine interacts as an agonist with TLR7, which is present on certain immune system cells. Interim results of a phase Ib trial show that isatoribine is biologically active in adults with chronic HCV infection and results from dosing a cohort of 6 HCV-infected patients with 800 mg of isatoribine showed a statistically significant reduction in viral load at the end of 1 week, with a median change in viral load from baseline of –0.94 $\log_{10}$ units. Enrollment is under way for an isatoribine phase I/II study. ANA-975 is expected to provide the same combination of antiviral effect and tolerability as isatoribine, but with the benefit of oral administration. The company has initiated an open-label, single-dose phase I trial of ascending doses of ANA-975 in healthy volunteers to evaluate the safety, tolerability and pharmacokinetics following oral administration at doses of 400, 800 and 1200 mg (1, 2).

1. *Anadys selects ANA-975 as development candidate for HCV*. DailyDrugNews.com (Daily Essentials) June 1, 2004.

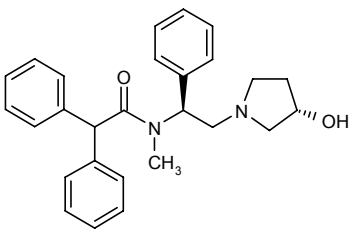
2. *ANA-975 enters phase I study*. DailyDrugNews.com (Daily Essentials) Feb 7, 2005.

Antigastrin Therapeutic Vaccine

The antigastrin therapeutic vaccine Insegia™ is an immunotoxin being developed by Aphton in collaboration with Sanofi Pasteur for the treatment of cancer and by Aphton for gastroesophageal reflux disease (GERD) and gastrointestinal ulcers. It is in phase III trials for the treatment of advanced pancreatic cancer and phase II trials for the treatment of advanced esophageal and stomach cancer, metastatic stomach cancer and GERD. The vaccine contains a portion of the hormone gastrin-17 (G17) and diphtheria toxoid chemically bound together and neutralizes both G17 and the hormone Gly-G17.

Original monograph – Drugs Fut 2001, 26(9): 865.

Asimadoline



Asimadoline is a kappa opioid agonist in phase II trials at Merck KGaA for the treatment of irritable bowel syndrome (IBS). The drug has been shown to reduce the response to heat and gastric and colonic distension.

The effect of asimadoline on pain induced by colonic distension was assessed in a double-blind, randomized, crossover clinical trial in 20 female patients with IBS. On 2 consecutive days, patients underwent left colon distension procedures with a barostat to compare the effects of a single dose of asimadoline (0.5 mg p.o.) and placebo on sensory thresholds. There was no significant difference between treatment groups in pain threshold; however, asimadoline decreased the overall perception of pain, as shown by a significant decrease in the area under the curve of pain intensity at each distension step. Evidence suggested that asimadoline had no significant effects on the perception of nonpainful colonic distension (1).

1. Delvaux, M., Beck, A., Jacob, J., Bouzamondo, H., Weber, F.T., Frexinos, J. *Effect of asimadoline, a kappa opioid agonist, on pain induced by colonic distension in patients with irritable bowel syndrome*. Aliment Pharmacol Ther 2004, 20(2): 237.

ATI-7505

ARYx Therapeutics initiated dosing about a year ago in a phase I trial of ATI-7505, a potent and selective 5-HT_4 receptor agonist and potent prokinetic agent for the treatment of GERD and gastroparesis. The analogue of cisapride was designed to have similar efficacy to cisapride but with improvements and changes to the metabolism and cardiac safety profile of the drug. These changes are expected to overcome the major side effects caused by cisapride. In 2000, safety issues caused by metabolism problems and cardiac safety liabilities led Johnson & Johnson to voluntarily withdraw from the market its own cisapride product, Propulsid®, for GERD patients with severe heartburn (1).

1. *ATI-7505 enters clinic*. DailyDrugNews.com (Daily Essentials) May 3, 2004.

AZD-0865/AZD-3355/AZD-7371/ AZD-9343

AZD-0865 is a potassium-competitive acid blocker in phase II trials at AstraZeneca for the treatment of peptic ulcer.

Twenty-four healthy male volunteers participated in a single-blind clinical trial that evaluated the pharmacokinetics and tolerability of single ascending doses of AZD-0865 (0.08-4.0 mg/kg p.o.). AZD-0865 demonstrated rapid absorption, dose-proportional exposure and a dose-related effect on acid secretion stimulated by pentagastrin. Peak activity was seen within 1 h for doses of 0.5-1.0

mg/kg and inhibition of acid secretion was sustained for up to 14 h at doses of 0.8 and 1.0 mg/kg. AZD-0865 was well tolerated (1).

Several other compounds are also in clinical development at AstraZeneca for gastrointestinal disorders. AZD-7371 is in phase II trials for the treatment of functional gastrointestinal disorders and overactive bladder, and the TLESR (transient lower esophageal spincter relaxations) inhibitors AZD-3355 and AZD-9343 are in early clinical development for the treatment of GERD.

1. Nilsson, C.A., Albrektson, E., Rydholm, H., Röhss, K., Hassan-Alin, M., Hasselgren, G. *Tolerability, pharmacokinetics and effects on gastric acid secretion after single oral doses of the potassium-competitive acid blocker (P-CAB) AZD0865 in healthy male subjects*. Dig Dis Week (May 14-19, Chicago) 2005, Abst T1680.

Bile Salt-Stimulated Lipase

A bile salt-stimulated lipase (BSSL) is in phase II clinical development by Arexis as an enzyme replacement therapy for the treatment of fat malabsorption due to pancreatic insufficiency associated with cystic fibrosis (CF). The patented human recombinant enzyme is the subject of early clinical development to supplement banked breast milk and preterm formula to improve lipolysis in preterm infants. BSSL, a naturally occurring human enzyme which degrades a large spectrum of lipids in food, is present in the mature pancreas and in breast milk. For pharmaceutical use, recombinant human BSSL will be administered orally and manufactured in a cell culture system. In spite of current pancreatic insufficiency therapy, which consists of porcine pancreatic enzyme extracts in combination with nutritional regimens and vitamin supplementation, at least 40-60% of patients are not normalized. Due to new FDA regulations, all pancreatic enzyme products will have to undergo full clinical and manufacturing documentation and receive renewed regulatory approval before mid-2008 in order to stay on the market. Another inconvenience of current pancreatic insufficiency therapy is the large quantity of pancreatic enzyme capsules that are required with each meal, leading to reduced compliance. BSSL received orphan drug status in the E.U. for the CF indication in 2005. Arexis acquired intellectual property and know-how relating to BSSL from originator AstraZeneca in 2004. In September 2004, Arexis presented successful results from its phase II trial of enzyme replacement therapy in CF. The study showed a more rapid and fully restored lipid uptake for CF patients when supplemented with the enzyme BSSL compared to conventional treatments using pancreas extract from pigs. Arexis is planning a dose-finding study and a phase III trial with protocol assistance from regulatory authorities in order to obtain market authorization. The company also recently entered into a collaboration with CMC Biopharmaceuticals for the production of recombinant human BSSL for clinical trials (1, 2).

1. *Arexis receives EU orphan drug status for BSSL for the treatment of cystic fibrosis*. DailyDrugNews.com (Daily Essentials) Feb 10, 2005.

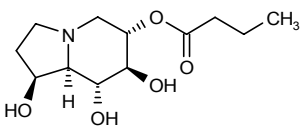
2. *CMC Biopharmaceuticals to produce BSSL for Arexis studies*. DailyDrugNews.com (Daily Essentials) March 11, 2005.

CCX-282

ChemoCentryx is conducting a phase II trial to evaluate the safety and pharmacokinetics of one of its lead products, CCX-282 (Traficet-EN™), in patients with inflammatory bowel disease (IBD). CCX-282 is a novel, orally bioavailable antiinflammatory agent that targets the CCR9 chemokine receptor, found on gut-homing inflammatory cells that are responsible for the persistent inflammation underlying both Crohn's disease and ulcerative colitis, where it controls the migration of these cells into diseased tissue. In preclinical studies, the compound worked both therapeutically and prophylactically. As a small molecule taken orally once a day, CCX-282 is expected to provide advantages in terms of dosing, compliance and cost over existing biological therapeutics. The phase II study has been designed to evaluate the safety and tolerability of CCX-282 in patients, and to monitor certain indicators of clinical activity. The study will enroll 60 patients with moderate to severe Crohn's disease and is being conducted in leading centers located in the U.S., the U.K. and The Netherlands. Patients will receive CCX-282 as a capsule once daily for 28 days. In June 2004, ChemoCentryx completed single- and multiple-dose phase I studies in healthy volunteers. Results from these trials demonstrated that the drug is well tolerated and appropriate for once-daily dosing (1).

1. *Traficet-EN studied in phase II for IBD*. DailyDrugNews.com (Daily Essentials) Jan 13, 2005.

Celgosivir



Migenix (formerly Micrologix Biotech, which acquired MitoKor last year) has initiated enrollment in its Canadian phase II study of celgosivir (MX-3253, formerly MBI-3253; see monograph this issue) in chronic hepatitis C virus (HCV) patients. Approximately 60 treatment-naïve or interferon-intolerant HCV patients (genotype 1), divided into three dosing groups, will be treated for 12 weeks at five sites in Canada. The objective of the study is to eval-

uate HCV viral loads at various time points during the study and at 12 weeks. The study will also assess the safety of celgosivir in HCV patients. Results are expected in the second quarter of calendar 2005. Celgosivir is an oral first-in-class antiviral agent that exerts its effect through the inhibition of the mammalian cell enzyme α-glucosidase I. α-Glucosidase I inhibitors can inhibit the replication of a broad range of enveloped viruses (including HCV) by preventing the correct folding of their envelope glycoproteins. Celgosivir has demonstrated efficacy in a surrogate model of HCV infection and has been well tolerated in over 500 human subjects to date. Celgosivir has been shown to be additive and/or synergistic with the currently approved HCV therapies ribavirin and interferon, and studies are being planned to evaluate celgosivir in combination with these products (1-5).

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

2. *Canadian approval for phase IIa study of MBI-3253*. DailyDrugNews.com (Daily Essentials) Sept 10, 2004.

3. *Enrollment opens in phase II study of MX-3253*. DailyDrugNews.com (Daily Essentials) Oct 18, 2004.

4. *Micrologix Biotech Inc. reports Q4 R&D highlights*. Micrologix Biotech Inc. Press Release 2004, July 12.

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

Certolizumab Pegol

UCB Pharma's certolizumab pegol (CDP-870, Cimzia) is a PEGylated anti-TNF-α antibody fragment developed by Celltech Group, acquired by UCB last year, and currently in late-stage development for Crohn's disease and rheumatoid arthritis. Celltech regained all rights to the antibody from Pfizer in December 2003. Crohn's disease will be the first regulatory submission for certolizumab pegol, planned for this year. Additionally, phase II studies in new indications are planned to begin over the next 12 months. Enrollment was completed ahead of schedule in two pivotal registration studies of certolizumab pegol in Crohn's disease. The response rates in the open phase of one of these studies are in line with those achieved by the only anti-TNF agent available on the market for the treatment of Crohn's disease. The profiling studies (phase IIIb) in rheumatoid arthritis also started late last year following positive results from two phase III clinical trials (1-5). Certolizumab pegol is being developed using Nektar Therapeutics' Advanced PEGylation technology.

Data from a double-blind, randomized, placebo-controlled clinical trial were used to determine the effects of certolizumab pegol on the health-related quality of life of patients with moderate to severe Crohn's disease. A total of 292 adult patients were treated with placebo or certolizumab pegol (100, 200 or 400 mg) given s.c. at weeks 0, 4 and 8. All patients receiving certolizumab pegol showed improvements in their Inflammatory Bowel Disease Questionnaire (IBDQ) scores compared to placebo patients. These improvements increased with dose, and only patients given 400 mg of certolizumab pegol showed significant differences compared to placebo throughout the 12-week follow-up period. The benefits associated with certolizumab pegol were greater in patients with high CRP levels at baseline (6). The results from this and the following study are summarized in Table VI.

A double-blind, placebo-controlled exploratory study assessed the potential advantages of administering certolizumab pegol as a single i.v. dose. Ninety-two patients with active Crohn's disease received a single dose of placebo or 1.25, 5, 10 or 20 mg/kg of certolizumab pegol and were monitored for up to 12 weeks. No significant differences were found in the clinical response rates of patients treated with placebo and those who received certolizumab pegol, although the latter showed a higher remission rate at the 10 mg/kg dose. No additional effect was seen at the highest dose (7).

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

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

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Randomized Double-blind	Certolizumab pegol, 100 mg s.c. 1x/4 wks x 3 (n=73) Certolizumab pegol, 200 mg s.c. 1x/4 wks x 3 (n=72) Certolizumab pegol, 400 mg s.c. 1x/4 wks x 3 (n=72) Placebo (n=73)	292	Certolizumab dose-dependently improved the quality of life in patients with moderate to severe Crohn's disease	6
Crohn's disease	Randomized Double-blind Multicenter	Certolizumab, 1.25 mg/kg i.v. (n=2) Certolizumab, 5 mg/kg i.v. (n=26) Certolizumab, 10 mg/kg i.v. (n=17) Certolizumab, 20 mg/kg i.v. (n=23) Placebo (n=24)	92	Certolizumab pegol was well tolerated and increased the rate of remission in patients with Crohn's disease	7

2. *Celltech and UCB establish development and marketing agreement for CDP-870*. DailyDrugNews.com (Daily Essentials) May 24, 2004.

3. *UCB to acquire Celltech*. DailyDrugNews.com (Daily Essentials) June 1, 2004.

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

5. *Positive preliminary results from second phase III trial of CDP-870 in RA*. DailyDrugNews.com (Daily Essentials) Sept 23, 2004.

6. Rutgeerts, P., Fedorak, R., Schreiber, S., Feagan, B., Innes, A., Jeffery, P., Round, P. *CDP870, a pegylated humanized anti-TNF antibody fragment, improves quality of life in patients with moderate to severe Crohn's disease*. Gastroenterology 2004, 126(4, Suppl. 2): Abst T1306.

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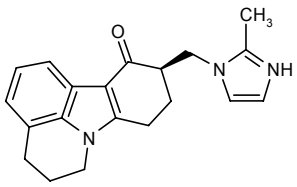
Cilansetron



Cilansetron (Calmactin) is a 5-HT_3 receptor antagonist shown to reduce gastrointestinal motility, secretion and sensation, developed by Solvay for the treatment of irritable bowel syndrome with diarrhea predominance (IBS-D) in both men and women. Solvay recently received a not approvable letter from the FDA regarding the company's NDA for cilansetron requesting additional clinical trials, and the company is examining its options. The NDA submission was based on efficacy and safety studies in over 4,000 patients worldwide (1-5). The company also submitted a registration dossier last year in the U.K.

A randomized, double-blind, placebo-controlled, crossover phase I trial involving 20 healthy women receiving oral contraceptives (daily for the first 21 days of 2 menstrual cycles) examined the effects of cilansetron (2 mg p.o. t.i.d. on days 14-21 of each menstrual cycle) administration on blood levels of ethinylestradiol and norgestimate. Although ethinylestradiol levels were lower during cilansetron treatment, it was concluded that there were no pharmacokinetic or pharmacodynamic interactions between the agent and these oral contraceptives (6).

In a randomized, double-blind trial, 746 patients were treated with cilansetron (2 mg t.i.d.) or placebo for 12 weeks and then re-randomized for another 4 weeks of treatment. At 12 weeks, adequate relief of IBS symptoms was achieved in 55% and 30% of cilansetron- and placebo-treated patients, respectively. More patients treated with cilansetron achieved adequate relief of abdominal pain/discomfort (59% *vs*. 37%) and abnormal bowel habits (54% *vs*. 28%). These response rates significantly declined in patients re-randomized from cilansetron to placebo, while they remained stable in patients continuing cilansetron therapy (7). The results from this and several of the studies described hereunder are depicted in Table VII.

The tolerability of cilansetron was evaluated in 402 patients randomized to cilansetron (2 mg given as needed up to 3 times/day) or placebo for 1 year. Patients in the cilansetron group took fewer tablets and for a longer period of time than patients in the placebo group. Administration of cilansetron was associated with a greater incidence of adverse events (74% *vs.* 55%), although the percentage of patients who discontinued because of these events was similar (10% *vs*. 9%). The most common adverse event was constipation (7% with cilansetron *vs*. 5% with placebo) (8).

Data from two double-blind, randomized, placebo-controlled clinical trials were used to evaluate the efficacy and safety of cilansetron (2 mg t.i.d.) given to 205 and 358 males with IBS-D for 3 and 6 months, respectively. The results from these studies were similar and confirmed that cilansetron was well tolerated and effective in improving the symptoms of IBS-D, abdominal pain/discomfort and abdominal bowel habits. Patients receiving cilansetron showed a greater incidence of constipation compared to placebo patients, and no cases of ischemic colitis were found (9).

A subanalysis of the data from two multicenter, double-blind, randomized phase III clinical trials revealed that cilansetron was effective and well tolerated in women with IBS-D. Cilansetron (2 mg t.i.d.) or placebo was given for 3 months to 487 patients, and for 6 months to another 434 patients. At 3 months, significantly greater improvements were achieved with cilansetron for IBS symptoms, abdominal pain/discomfort and abnormal bowel habits of the patients; these effects were maintained for up to 6 months from the beginning of the study. The incidence of constipation increased with cilansetron (23% after 3 months and 17% after 6 months *vs.* 5% with placebo), but only 1 patient experienced severe constipation. Four patients suffered from suspected ischemic colitis, which was transient and left no sequelae (10).

Two multicenter, double-blind, randomized phase III clinical trials determined the efficacy of cilansetron in providing abdominal pain relief to patients with IBS-D. A similar study design was used in the two trials, and the patients were randomized to receive placebo or cilansetron (2 mg t.i.d.) for 3 (n=692) or 6 months (n=792). The percentage of patients who reported adequate relief of abdominal pain/discomfort in at least 50% of their weekly assessments during the study was significantly greater with cilansetron compared to placebo, both at 3 months (52% *vs.* 37%) and at 6 months (61% *vs*.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Irritable bowel syndrome	Randomized Single-blind	Cilansetron, 2 mg t.i.d. x 16 wks Cilansetron, 2 mg t.i.d. x 12 wks → Placebo x 4 wks Placebo x 12 wks → Cilansetron, 2 mg t.i.d. x 12 wks	746	In patients with diarrhea-predominant irritable bowel syndrome, cilansetron reduced symptoms, which returned upon treatment discontinuation	7
Irritable bowel syndrome	Randomized Double-blind	Cilansetron, 2 mg 3 [max.] x/d x 52 wks (n=308) Placebo (n=94)	402	Long-term administration of cilansetron was safe and well tolerated in patients with diarrhea-predominant irritable bowel syndrome	8
Irritable bowel syndrome	Randomized Double-blind Pooled/meta-analysis	Cilansetron, 2 mg t.i.d. x 3 mo (n=101) Cilansetron, 2 mg t.i.d. x 6 mo (n=186) Placebo (n=276)	563	Cilansetron was well tolerated and effective in reducing symptoms and abdominal pain/discomfort and improving abdominal bowel habits in patients with irritable bowel syndrome with diarrhea predominance	9
Irritable bowel syndrome	Randomized Double-blind Multicenter Pooled/meta-analysis	Cilansetron, 2 mg t.i.d. x 3 mo (n=243) Cilansetron, 2 mg t.i.d. x 6 mo (n=209) Placebo (n=469)	921	Cilansetron given for up to 6 months was significantly more effective than placebo in improving abdominal pain/discomfort and abnormal bowel habits in female patients with diarrhea-predominant irritable bowel syndrome	10
Irritable bowel syndrome	Randomized Double-blind Multicenter	Cilansetron, 2 mg t.i.d. x 6 mo Placebo	792	Cilansetron was well tolerated and more effective than placebo in providing abdominal pain/discomfort relief and improving abdominal habits in patients with irritable bowel syndrome and diarrhea predominance	11,13
Irritable bowel syndrome	Multicenter Pooled/meta-analysis	Cilansetron, 2 mg t.i.d. x 3 mo (n=344) Cilansetron, 2 mg t.i.d. x 6 mo (n=395) Placebo (n=745)	1484	Cilansetron was well tolerated and more effective than placebo in providing sustained relief from symptoms of abdominal pain/discomfort in patients with diarrhea-predominant irritable bowel syndrome	12
Irritable bowel syndrome	Randomized Double-blind Multicenter	Cilansetron, 2 mg t.i.d. x 3 mo (n=344) Placebo (n=348)	692	Cilansetron was significantly more effective than placebo in providing relief from abdominal pain/discomfort and relief from abnormal bowel habits to men and women with diarrhea-predominant irritable bowel syndrome	14

46%). The superiority of cilansetron over placebo was evident after only 1 week of treatment. Cilansetron showed a good safety profile in both studies. Constipation was the adverse event most frequently responsible for patient withdrawal, although no severe complications were reported. The treatment was also associated with improvement in health-related quality of life, with the greatest improvement in subscales (IBS-QOL) evaluating interference with activity, food avoidance and dysphoria (11-16).

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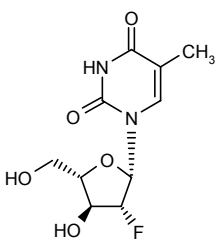
Original monograph – Drugs Fut 1999, 24: 475.

Clevudine



Eisai has inlicensed clevudine (L-FMAU, Levovir), an antihepatitis B pyridine nucleoside analogue, from Bukwang Pharm. Eisai will obtain the exclusive right to develop, manufacture and market clevudine in 10 Asian countries, excluding South Korea. Clevudine acts by inhibiting hepatitis B virus (HBV) DNA polymerase. In South Korea, Bukwang is conducting phase III trials (1).

The tolerability, safety and efficacy of 12-week clevudine therapy (30 and 50 mg/day p.o.) were demonstrated in a 36-week, multicenter, randomized, double-blind, placebo-controlled phase II trial involving 99 HBeAg-positive patients with chronic hepatitis B (HBV DNA > 8 $\log_{10}$ copies/ml). Data were presented for 88 patients who completed the 36-week period, with results showing that at 12 weeks the median change in HBV DNA from baseline for patients receiving clevudine doses of 30 and 50 mg/day was –4.47 and –4.45 $\log_{10}$ copies/ml, respectively, as compared to –0.12 $\log_{10}$ copies/ml for placebo. Antiviral activity was sustained with decreases of 3.32 and 2.99 $\log_{10}$ copies/ml, respectively, seen at week 12 and of 2.28 and 1.40 $\log_{10}$ copies/ml, respectively, at week 24 off therapy. HBV DNA levels were undetectable in 63%, 52% and 0%, respectively, at week 12 and 16%, 9% and 4%, respectively, at week 36 in patients receiving the 30- and 50-mg doses and placebo, and normalization of ALT levels occurred in 53%, 55% and 7% of the patients, respectively, at week 12 and in 71%, 63% and 12%, respectively, at week 36 (2, 3) (Table VIII).

The tolerability and efficacy of clevudine (10, 50, 100 and 200 mg once daily for 28 days) were examined in a multicenter, dose-escalating trial in 32 patients with chronic hepatitis B (median HBV DNA = 7.3-8.8 $\log_{10}$ copies/ml; 27 were HBeAg-positive). Clevudine was well tolerated with no dose-limiting toxicities reported over the dose range examined. Six patients receiving the 100-mg dose had transient elevations in ALT of up to 7.8 times the upper limit of normal, which was associated with improved antiviral activity; no signs of liver failure were detected in these patients. The median changes in HBV DNA from baseline were –2.5, –2.7, –3.0 and –2.6 $\log_{10}$ copies/ml for the four respective dose groups and the median changes at 6 months postdosing were –1.2, –1.4, –2.7 and –1.7 $\log_{10}$ copies/ml, respectively. HBeAg positivity was lost in 6 of the 27 patients who were positive at baseline and 3 of these patients seroconverted to HBe antibody. The pharmacokinetics of clevudine were dose-proportional (4).

Clevudine (30 mg/day p.o.) demonstrated similar activity in patients with hepatitis B infection readministered the drug for 24 weeks to when the patients first received the drug for 12 weeks. Interim data from this multicenter study in South Korea showed similar antiviral activity and rates of ALT normalization in clevudine-naïve patients and those later retreated with the agent (5, 6).

Patients with hepatitis B infection enrolled in an international, randomized, double-blind study (n=31) were treated with clevudine 10, 30 or 50 mg once daily for 12 weeks. The drug was generally well tolerated, with no serious adverse events recorded, and demonstrated

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

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Randomized Double-blind Multicenter	Clevudine, 30 mg/d p.o. x 12 wks (n=32) Clevudine, 50 mg/d p.o. x 12 wks (n=34) Placebo x 12 wks (n=33)	99	Clevudine was well tolerated and exhibited significant antiviral activity with normalization of aminotransferase levels in patients with hepatitis B	2

potent antiviral activity. Doses above 10 mg were the most active (7).

1. *Eisai inlicenses clevudine from Bukwang Pharm*. DailyDrugNews.com (Daily Essentials) Nov 17, 2004.

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3. Lee, H.-S., Chung, Y.-H., Lee, K.S., Byun, K.S., Paik, S.W., Han, J.-Y., Yoo, K., Hwang, S.G., Yoo, B.C., Lee, J.H. *A 12-week clevudine therapy showed durable antiviral activity and normalization of alanine transaminase levels for 6 months after discontinuation of treatment in patients with chronic hepatitis B*. Hepatology 2004, 40(4, Suppl. 1): Abst 1130.

Marcellin, P., Mommeja-Marin, H., Sacks, S.I., Lau, G.K.K., Sereni, D., Bronowicki, J.-P., Conway, B., Trepo, C., Blum, M.R., Yoo, B.C., Mondou, E., Sorbel, J., Snow, A., Rousseau, F., Lee, H.-S. *A phase II dose-escalating trial of clevudine in patients with chronic hepatitis B*. Hepatology 2004, 40(1): 140.

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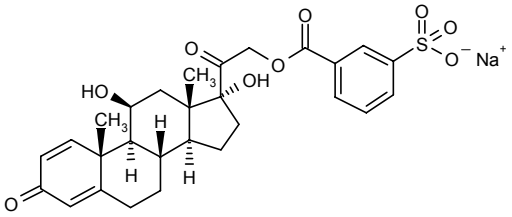
Original monograph – Drugs Fut 1998, 23: 821.

Clostridium difficile Toxoid Vaccine

A *Clostridium difficile* toxoid vaccine, comprised of inactivated *C. difficile* A and B toxins, for the treatment of *C. difficile*-associated diarrhea (CDAD) proved to be immunogenic and well tolerated in phase I clinical trials at Acambis. The company is currently pursuing a modified toxoid vaccine, with additional clinical trials expected this year.

COLAL-PRED®



Alizyme has received approval from the U.K. Medicines and Healthcare products Regulatory Agency (MHRA) for a pivotal phase III trial of COLAL-PRED® for the treatment of patients with acute ulcerative colitis. The randomized, double-blind, controlled, parallel-group study will seek to demonstrate similar efficacy for COLAL-PRED® to conventional oral prednisolone, along with a substantially improved side effect profile. The trial will involve up to 670 patients who have moderate to severe ulcerative colitis. Patients will undergo 8 weeks of treatment and a 4-week follow-up period. In addition to the U.K., the trial is planned to be conducted in a number of other European countries. Pending successful results, Alizyme expects to seek approval for COLAL-PRED® during 2007. COLAL-PRED® comprises a prednisolone derivative (ATL-2502, prednisolone sodium metasulfobenzoate) in Alizyme's proprietary COLAL® drug delivery technology. Data from a phase II trial with COLAL-PRED® indicated that through the local delivery of this drug, the undesirable side effects associated with the use of steroids, such as immunosuppression, are avoided (1).

1. *U.K. clearance for phase III study of COLAL-PRED for acute ulcerative colitis*. DailyDrugNews.com (Daily Essentials) March 29, 2005.

ColoPlus

ColoPlus is a highly nutritional product derived from bovine colostrum that combines immunoglobulins, growth factors and antibacterial peptides and has shown promise in the management of HIV-associated diarrhea. In an open-label, pilot study, 20 patients with this condition entered a 1-week run-in period, were given ColoPlus (35 g p.o. b.i.d.) for 4 weeks and were followed for another 2

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

Indication	Design	Treatments	n	Conclusions	Ref.
Diarrhea, HIV infection	Open	ColoPlus, 35 g p.o. b.i.d. x 4 wks	20	In patients with diarrhea associated with HIV infection, ColoPlus decreased stool frequency by an average of 6.1 evacuations/d and self-reported fatigue by an average of 78%, and induced improvements in body weight, hemoglobin levels, albumin levels and CD4+ cell count	1

weeks. Compared to baseline, ColoPlus decreased stool frequency by an average of 6.1 evacuations/day and self-reported fatigue by an average of 78%. The study treatment also induced average improvements in body weight (by 7.1 kg), hemoglobin levels (by 26.1 g/l), albumin levels (by 11.3 g/l) and $CD4^+$ cell count (by 135%) (1) (Table IX).

1. Chinenye, S., Elfstrand, L., Hagman, C., Ihse, I., Florén, C. *ColoPlus, a new product based on bovine colostrum, alleviates HIV-associated diarrhoea.* 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst MON-G-308.

CpG-10101

CpG-10101 (Actilon™) is an oligonucleotide toll-like receptor 9 (TLR9) receptor agonist developed by Coley Pharmaceutical to stimulate the production of antiviral interferons and to induce early and sustained virus-specific memory immune responses in patients infected with HCV. A double-blind phase Ia clinical trial established that administration of two s.c. doses of CpG-10101 (0.25, 1, 4, 10 or 20 mg every 2 weeks) was well tolerated and dose-dependently increased the levels of interferon alfa and other markers of antiviral efficacy in 40 healthy volunteers. An ongoing placebo-controlled phase Ib clinical trial is assessing the effects and safety of CpG-10101 (0.25, 1, 4, 10 or 20 mg s.c. twice weekly) in adult patients with chronic hepatitis C unresponsive or intolerant to previous interferon alfa therapy. Signs of an effective antiviral immune response were seen, and decreases in HCV RNA levels were related to increases in serum interferon gamma-inducible protein-10 (IP-10). Peak plasma levels and maximum change in IP-10 were dose-related. The most common adverse events were mild flu-like symptoms and mild local injection-site reactions (1-4) (Table X).

1. *Update on the safety and antiviral effects of Actilon in hepatitis C.* DailyDrugNews.com (Daily Essentials) Jan 18, 2005.

2. McHutchison, J.G., Bacon, B.R., Gordon, S.C., Afdhal, N.H., Jacobson, I.M., Muir, A., Krieg, A.M., Efler, S., Al-Adhami, M., Davis, H.L., Schmalbach, T.K. *Human pharmacologic activity of a new TLR9 agonist antiviral, CPG 10101 (Actilon(TM)).* Hepatology 2004, 40(4, Suppl. 1): Abst 1224.

3. Bacon, B.R., McHutchison, J.G., Gordon, S.C., Afdhal, N.H., Jacobson, I.M., Shiffman, M., Muir, A., Krieg, A.M., Efler, S., Morris, M., Whisnant, J., Al-Adhami, M., Davis, H., Schmalbach, T. *Safety, pharmacodynamic (PD) and pharmacokinetic (PK) profiles of CPG 10101 (Actilon(TM)), a novel TLR9 agonist: Comparison in normal volunteers and HCV infected individuals*. Dig Dis Week (May 14-19, Chicago) 2005, Abst 525.

4. Schmalbach, T., Efler, S., Morris, M.L., Al-Adhami, M., Laframboise, C., Davis, H., Leese, P. *CPG 10101 (Actilon) oligodeoxynucleotide TLR9 agonist: Pharmacokinetics and pharmacodynamics in normal volunteers*. 44th Intersci Conf Antimicrob Agents Chemother (Oct 30-Nov 2, Washington DC) 2004, Abst V-1151.

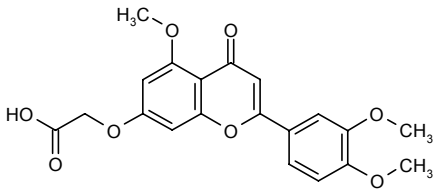
Additional References

Efler, S.M., Ahluwalia, N.K., Zhang, L., Al-Adhami, M., Schmalbach, T.K., Whisnant, J., Krieg, A.M., Davis, H.L. *Different immunostimulatory profiles from two classes of CpG ODN administered subcutaneously in healthy subjects*. Clin Invest Med 2004, 27(4, Suppl.): Abst W23.49.

Table X: Clinical studies of CpG-1010 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis C	Randomized Pooled/meta-analysis	CpG-10101, 0.25 mg s.c. o.d. x 2 on d 1 & 15 CpG-10101, 0.25 mg s.c. o.d. 2x/wk x 4 wks CpG-10101, 1 mg s.c. o.d. x 2 on d 1 & 15 CpG-10101, 1 mg s.c. o.d. 2x/wk x 4 wks CpG-10101, 4 mg s.c. o.d. x 2 on d 1 & 15 CpG-10101, 4 mg s.c. o.d. 2x/wk x 4 wks CpG-10101, 10 mg s.c. o.d. x 2 on d 1 & 15 CpG-10101, 10 mg s.c. o.d. 2x/wk x 4 wks CpG-10101, 20 mg s.c. o.d. x 2 on d 1 & 15 CpG-10101, 20 mg s.c. o.d. 2x/wk x 4 wks Placebo	79	CpG-10101 dose-dependently increased serum levels of IP-10 in healthy volunteers and especially in HCV-infected patients, suggesting that it may induce the expression of interferon and cytokines in both populations. Adverse events were mild and transient	3

DA-6034



Dong-A is evaluating DA-6034, a synthetic flavonoid possessing antiinflammatory activity, in phase I clinical trials as a potential treatment for ulcerative colitis and Crohn's disease.

The safety, tolerability and pharmacokinetics of DA-6034 were investigated in a double-blind, randomized, placebo-controlled phase I study. Healthy volunteers (n=40) were given single or multiple doses of DA-6034 of 10, 20, 50, 100 and 200 mg, and dose-dependent increases in bioavailability were measured, although a low peak plasma concentration (2.518 ± 1.473 ng/ml) was seen with the 200-mg dose. The time to peak plasma concentrations was approximately 98.6 min and the half-life was determined to be 4.1 ± 1.2 h. No significant alterations in vital signs, electrocardiogram or blood biochemistry parameters were observed. DA-6034 was well tolerated, with adverse effects, including transient and mild headache and abdominal pain, occurring in 4 patients (1).

A double-blind, randomized, placebo-controlled phase I clinical trial determined the pharmacokinetic profile of DA-6034 in 67 healthy volunteers. Volunteers were given single (10, 20, 50, 100 and 200 mg) or multiple doses (20, 50 and 100 mg b.i.d. for 7 days) of DA-6034 or placebo. Analysis of serial blood samples showed that DA-6034 is poorly absorbed, and analysis of urine samples revealed that urinary cumulative excretion at 48 h was only 0.3%. These results suggest that most DA-6034 remains located in the gastrointestinal tract, which is its target organ (2).

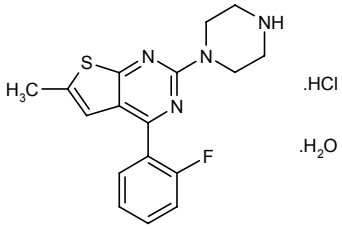
1. Oh, T., Son, M., Chung, J. et al. *Results of the evaluation of safety, tolerability and pharmacokinetic characteristics of DA-6034, a novel treatment for inflammatory bowel disease, in healthy volunteers*. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst TUE-G-387.

2. Lim, K.S. et al. *Evaluation of pharmacokinetic characteristics of a novel anti-IBD drug, DA-6034, in healthy volunteers*. Clin Pharmacol Ther 2005, 77(2): Abst PII-21.

DA-9601

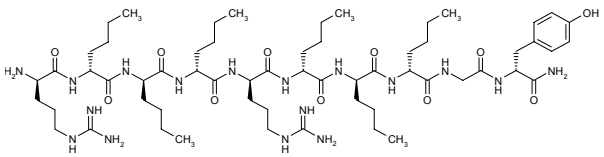
An herbal extract from Dong-A, DA-9601 is currently undergoing phase III clinical trials for the treatment of acute and chronic gastritis and alcoholic gastritis. The extract, *Artemisia asiatica* Nakai, has been used in traditional Asian medicine for the treatment of inflammatory and other disorders, and experimental studies have revealed antioxidant and antiinflammatory effects for DA-9601.

DDP-225



The 5-HT_3 antagonist and dual norepinephrine and 5-HT reuptake inhibitor DDP-225 (MCI-225) is in phase II clinical trials at Dynogen for the treatment of diarrhea-predominant irritable bowel syndrome (IBS). DDP-225 has shown preclinical efficacy in predictive models of IBS, as well as a clean receptor binding profile and no anticholinergic activity, which limits the use of tricyclic antidepressants in treating IBS. DDP-225 is also in preclincial evaluation at Arachnova for the treatment of urinary incontinence (AA-10025), IBS (AA-10026) and pain (AA-10021). Mitsubishi Pharma, originator of the drug, granted Dynogen rights in October 2003, while Arachnova obtained rights from Mitsubishi in 2004. Prior to licensing, Mitsubishi had studied this compound in phase II trials for depression and Alzheimer's disease.

Delmitide

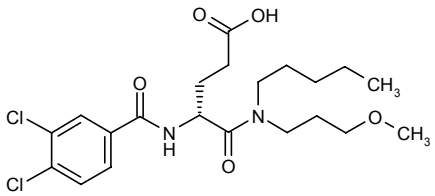


Delmitide (RDP-58) is a triple interferon gamma, TNF-α and IL-12 production inhibitor originally developed by the former SangStat, now Genzyme, for the treatment of gastrointestinal disorders. Genzyme completed phase II trials with delmitide for the oral treatment of inflammatory bowel disease prior to licensing the drug to Procter & Gamble (P&G) in 2004. P&G obtained an exclusive worldwide license to develop, manufacture and commercialize delmitide for the treatment of gastrointestinal and other disorders, including periodontal, topical, ocular and urogenital disorders. Genzyme retains development and commercialization rights to the drug in pulmonary and other disorders,

as well as copromotion rights in oncology-related disorders, such as chemotherapy-induced diarrhea.

Original monograph – Drugs Fut 2004, 29(2): 121.

Dexloxiglumide



Dexloxiglumide (CR-2017) is in phase III clinical development in Europe by Rottapharm for the treatment of constipation-predominant IBS. Forest had been evaluating dexloxiglumide for this indication in the U.S., but discontinued development based on data from two placebo-controlled phase III studies which did not demonstrate statistically significant results. A potent, selective and reversible CCK_1 receptor antagonist, dexloxiglumide increases gastric emptying and intestinal motility, as well as modulating intestinal sensitivity to distension. This mechanism of action differs from that of other compounds indicated for the treatment of IBS that act on 5-HT receptors in the intestine.

A single-blind, placebo-controlled, crossover study conducted in 24 healthy young females showed that multiple-dose dexloxiglumide (200 mg t.i.d. on days 17-20 followed by a single dose on day 21) had no effect on the pharmacokinetics of oral contraceptives (ethinylestradiol + norgestimate). Coadministration was safe and well tolerated and systemic ethinylestradiol and norgestimate exposure was unchanged with dexloxiglumide coadministration (1).

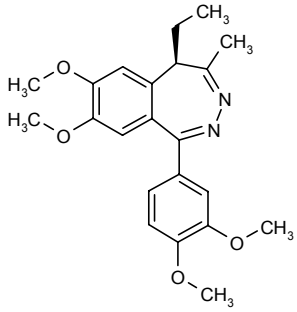
A randomized, placebo-controlled study conducted in 36 female patients with constipation-predominant IBS examined the efficacy of dexloxiglumide (200 mg t.i.d. for 7 days) in accelerating gastrointestinal transit and symptoms. Treatment with the agent significantly accelerated gastric emptying and delayed ascending colon emptying. Overall, the results suggested its potential in functional gut disorders associated with either rapid proximal colonic transit or with delayed gastric emptying (2).

1. Roy, P., Jakate, A.S., Patel, A., Abramowitz, W., Wangsa, J., Persiani, S., Kapil, R. *Effect of multiple-dose dexloxiglumide on the pharmacokinetics of oral contraceptives in healthy women*. J Clin Pharmacol 2005, 45(3): 329.

2. Cremonini, F., McKinzie, S., Burton, D., Thomforde, G., Zinsmeister, A.R., Camilleri, M. *The CCK1 antagonist dexloxiglumide accelerates gastric emptying and delays emptying of the ascending colon in constipation-predominant irritable bowel syndrome (C-IBS) patients.* Am J Gastroenterol 2004, 99(10, Suppl.): Abst 854.

Original monograph – Drugs Fut 1999, 24(7): 725.

Dextofisopam



Phase II trials are in progress at Vela Pharmaceuticals for dextofisopam for the treatment of IBS. The drug acts as an agonist at the $GABA_A$ benzodiazepine receptor site to reduce stress-induced ulcer formation, normalize stretch-induced colonic contractions and reduce visceral hypersensitivity, while having little or no effect on basal colonic motility.

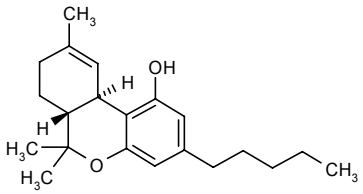
Researchers have recently reported the preclinical and clinical efficacy of dextofisopam, the (*R*)-enantiomer of tofisopam, for treating IBS and IBD. In preclinical animal models of IBS, the agent was shown to attenuate distension-induced contractile activity and decrease abdominal distension in the glass bead expulsion test and the balloon distension test, respectively, without affecting basal upper or lower gastrointestinal tract motility. In the dextran sodium sulfate (DSS)-induced colitis animal model for IBD, administration of dextofisopam (p.o., i.p. or intracolonically) attenuated the signs and symptoms of colitis. The agent had minimal or no effects on basal gastric acid secretion and did not cause gastric irritation. Dextofisopam (single p.o. dose up to 400 mg or up to 600 mg b.i.d. for 7 days) was well tolerated according to results from two phase I trials involving healthy volunteers. No serious adverse events were noted and treatment had little effect on cognitive or motor function. Moreover, preliminary results from an ongoing phase II trial in patients with IBS demonstrated a good safety profile for the agent. Together these results indicate the efficacy of dextofisopam in the treatment of IBS and IBD (1).

A multicenter, double-blind, randomized phase II clinical trial evaluated the potential benefits of dextofisopam in the treatment of IBS. A total of 141 patients with diarrhea-predominant or alternating IBS were given placebo or dextofisopam (200 mg) twice daily for 12 weeks. Patients receiving dextofisopam showed a greater percentage of time with adequate relief of IBS symptoms (57% of study period *vs.* 43% with placebo), together with greater improvements in stool frequency and consistency, compared to placebo-treated patients. Dextofisopam improved bowel function in both forms of IBS, but was especially effective in patients with diarrhea-predominant disease. No significant differences between treatments were found in the incidence of adverse events, and few patients suffered from constipation during the study. Vela has announced that it intends to advance dextofisopam into phase III clinical development (2).

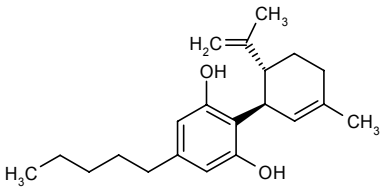
1. Leventer, S.M., Kucharik, R.F., Keogh, J.C., Raudibaugh, K., Galbraith, K., Amchin, J., Keim, K.L. *The potential of dextofisopam for treatment of irritable bowel syndrome and inflammatory bowel syndrome*. Am J Gastroenterol 2004, 99(10, Suppl.): Abst 856.

2. *Dextofisopam reported effective and well tolerated in IBS*. DailyDrugNews.com (Daily Essentials) Jan 14, 2005.

Dronabinol/Cannabidiol



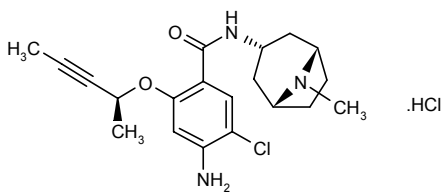
Dronabinol



Cannabidiol

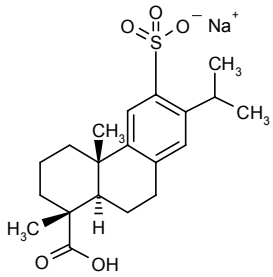
GW Pharmaceuticals is developing its *Cannabis*-based medicinal product extract Sativex® (dronabinol/ cannabidiol) for a number of indications, principally for the treatment of the debilitating symptoms and severe neuropathic pain of multiple sclerosis. It has been submitted for approval for this indication in the U.K., and also in Canada where it will be marketed by licensee Bayer. The oral spray product is a whole-plant extract containing dronabinol (tetrahydrocannabinol, THC, Tetranabinex™) and cannabidiol (CBD, Nabidiolex™). Phase II or III trials are also under way for various types of pain and the product is being tested in phase II studies for its potential in rheumatoid arthritis, inflammatory bowel disease and neurogenic symptoms, as well as phase I studies for psychotic disorders.

E-3620



The 5-HT_3 antagonist/5-HT_4 agonist E-3620 is in phase II trials at Eisai for the treatment of gastrointestinal motility disorders. It is expected to improve the sensation of fullness and anorexia in chronic gastritis and to improve bowel function and abdominal pain in IBS.

Ecabet Sodium



Tanabe Seiyaku's ecabet sodium (TA-2711E, Gastrom®), a gastointestinal mucosal protecting agent currently marketed in Japan for the treatment of peptic ulcers and gastritis, is undergoing phase III clinical trials in Japan and phase II in the U.S. and the E.U. for the treatment of ulcerative colitis. An eye drop formulation is also in phase II development by Senju and licensee ISTA in Japan and the U.S., respectively, for the treatment of dry eye syndrome, or keratoconjunctivitis sicca (1-3).

1. *Tanabe Seiyaku reports interim 2003 year-end R&D highlights*. Tanabe Seiyaku Web Site 2004, Feb 2.

2. *ISTA licenses U.S. rights for ecabet sodium for dry eye*. DailyDrugNews.com (Daily Essentials) Nov 22, 2004.

3. *ISTA submits IND for phase IIb study of ecabet sodium for dry eye syndrome*. DailyDrugNews.com (Daily Essentials) March 23, 2005.

Original monograph – Drugs Fut 1988, 13: 966.

EGS-21

Enzo Biochem's subsidiary Enzo Therapeutics initiated a phase II trial of EGS-21, a β-D-glucosylceramide immunomodulating compound, for the treatment of non-alcoholic steatohepatitis (NASH, or fatty liver) earlier this year, which will be funded in part with a USD 1 million grant from the Israel-U.S. Binational Industrial Research and Development Foundation (BIRD). The trial is being conducted at Hadassah-Hebrew University Hospital in Jerusalem, Israel. The grant was awarded following the successful completion of numerous preclinical animal model studies and a recently completed phase I safety study of EGS-21 in human subjects. EGS-21 was shown to alleviate the symptoms of the disease and its associated metabolic syndrome in animal model systems. Administration of the compound led to significant reductions in the hepatic fat content (as assessed by MRI and

liver biopsies), body weight and serum liver enzyme levels, as well as marked improvement in glucose tolerance tests and the lipid profile. Results demonstrated that EGS-21 acts on the immunoregulatory natural killer (NK) T-cells and could therefore impact the immune response in the body by modulating its function and adjusting it to a normal state. EGS-21 is being studied as a treatment for a broad range of immune-mediated diseases, including HBV- and HCV-associated liver disease, various cancers, Crohn's disease and other forms of inflammatory bowel disease, HIV, diabetes and graft-versus-host disease. A phase II trial is expected to begin soon comparing EGS-21 and the company's Alequel™ for the treatment of Crohn's disease, and another phase II trial to evaluate the effect of EGS-21 in the treatment of chronic active hepatitis C has been approved (1-3).

1. *Enzo Biochem to begin phase I trial of EGS-21*. DailyDrugNews.com (Daily Essentials) May 25, 2004.

2. *Enzo Biochem receives grant to conduct study of EGS-21 for fatty liver disease*. DailyDrugNews.com (Daily Essentials) Jan 20, 2005.

3. *Enzo Biochem reports first half and fiscal second quarter operating results*. Enzo Biochem 2005, March 14.

EHC-18

Enzo's EHC-18 is an immunomodulator in phase I/II trials at Hadassah University Medical Center in Jerusalem, Israel, for the treatment of hepatitis C.

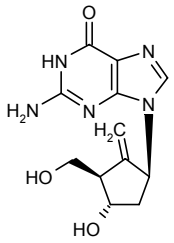
EHT-899

EHT-899 is an immunoregulating product from Enzo in phase I/II clinical trials for the oral treatment of hepatitis B. EHT-899 is a proprietary formulation of an HBV viral protein designed to eliminate the undesirable immune response provoked by HBV infection. The product also apparently enhances a secondary immune response to clear the viral infection, resulting in a reduction in liver damage and a decrease in viral load.

Eicosapentaenoic Acid/ Docosahexaenoic Acid

Epanova™ is a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two natural anti-inflammatory agents produced by plankton from the southern Pacific, which is currently undergoing phase III clinical trials (EPIC, for Epanova™ in Crohn's Disease) at Tillotts for the maintenance of remission in Crohn's disease. After collection, EPA and DHA are concentrated, highly purified and converted to a free fatty acid form, before soft gelatin capsules are filled. A special coating is then applied to delay the release of the active agents after ingestion, with the aim of improving tolerability. A previous hard gel capsule formulation (Purepa®) was shown to prolong remission in a phase II trial in Crohn's disease patients, in the absence of serious side effects. Tillotts is seeking licensees to market the product worldwide.

Entecavir



Subsequent to approval by the FDA in March, Bristol-Myers Squibb launched entecavir (Baraclude™) for the treatment of chronic hepatitis B infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. Entecavir, a guanosine nucleoside analogue, is an oral antiviral therapy specifically designed to selectively block the replication of hepatitis B virus (HBV) in the body by interfering with the virus's ability to infect cells via inhibition of HBV polymerase. The clinical trial program was the largest ever (over 2,300 patients) conducted in chronic hepatitis B and the first to compare two antivirals, entecavir *versus* lamivudine. In these studies after 48 weeks, entecavir demonstrated statistically significant improvements compared to lamivudine in liver histology, HBV viral load reductions to undetectable levels (< 300 copies/ml) and normalization of alanine aminotransferase (ALT) levels (1 times the upper limit of normal or less). Entecavir demonstrated comparable safety to lamivudine with a favorable resistance profile. An MAA is also under review in Europe (1-5).

In an open phase I study, the pharmacokinetics and tolerability of entecavir were evaluated in 16 healthy controls and in 16 subjects with moderate to severe hepatic impairment. A single oral dose of 1.0 mg was well tolerated in all study subjects and drug exposure was not altered in those with hepatic impairment (6).

Three open phase I studies assessed the pharmacokinetics of entecavir, lamivudine, adefovir and tenofovir alone and in combination in healthy subjects. In these studies, entecavir did not alter the pharmacokinetics of lamivudine, adefovir or tenofovir, and these agents did not alter entecavir pharmacokinetics (7).

A study used 711 plasma samples from 354 subjects with mild to severe renal impairment to construct a pharmacokinetic model with single-dose data to determine the

effect of creatinine clearance (CL_{CR}) on the pharmacokinetics of entecavir (1 mg) and to support dose selection for this patient population. Entecavir clearance increased linearly with increasing CL_{CR}. According to the model, dose adjustments of 50%, 30% and 20%, respectively, of the starting dose were recommended in patients with CL_{CR} values of 30-50 ml/min or less, < 30 ml/min and in patients with end-stage renal disease on dialysis; dose adjustments were not needed in patients with CL_{CR} of > 80 ml/min or 50-80 ml/min or less (8).

The ETV-026 study was a multicenter, double-blind phase III clinical trial that randomized 286 chronic hepatitis B patients unresponsive to lamivudine to either continue receiving lamivudine (100 mg once daily) or switch to entecavir (1.0 mg once daily) for 48 weeks. At the end of the study, patients treated with entecavir showed greater improvements in liver histology, virological response and normalization of ALT levels than patients still on lamivudine. No significant differences were found between the safety profiles of the two study groups (9). Data from this and three other phase II/III clinical trials (ETV-014, ETV-022 and ETV-027) were used to compare the safety profiles of entecavir (0.5 or 1.0 mg once daily) and lamivudine (100 mg once daily) in patients with chronic hepatitis B. No significant differences between treatments were found in the incidence of adverse events except for ALT flares, which were more common among lamivudine-treated patients. Most adverse events were mild or moderate, and the most common were headache, upper respiratory tract infection, cough, nasopharyngitis, fatigue and upper abdominal pain. The number of patients who developed malignant melanoma or died was low during the treatment period and the 24-week follow-up period (10-12). The results from these and several of the following studies are shown in Table XI.

The ETV-022 study was a phase III clinical trial in which entecavir (0.5 mg once daily) or lamivudine (100 mg once daily) was administered to 709 HBeAg-positive, nucleoside-naïve patients with chronic hepatitis B for 48 weeks. More patients given entecavir achieved serum HBV DNA levels below 0.7 MEq/ml (91% *vs*. 65%), serum HBV DNA levels below 400 copies/ml (69% *vs*. 38%) and serum ALT levels below 1.25 x ULN (78% *vs.* 70%) at the end of the treatment period. Sustained virological response, which was defined as serum HBV DNA levels below 0.7 MEq/ml and loss of HBeAg expression, was maintained by 82% of entecavir-treated patients and 73% of lamivudine-treated patients at 24 weeks after the end of treatment. After 24 weeks off treatment, more than 70% of entecavir-treated patients sustained their responses, a figure superior to that seen with lamivudine (13-16).

In a multicenter, randomized, double-blind phase III trial (ETV-027), 648 nucleoside-naïve, $HBeAg^-$ patients with chronic hepatitis B were treated with entecavir 0.5 mg/day or lamivudine 100 mg/day for up to 96 weeks. At 48 weeks, entecavir was superior to lamivudine in terms of histological improvement, HBV DNA change, and a composite endpoint of HBV DNA and ALT normalization (17).

Analysis of data from the phase III ETV-022 and ETV-027 trials established that neither HBV DNA nor ALT levels at baseline had any significant effect on the virological response of hepatitis B patients to entecavir therapy (18).

The therapeutic benefits of entecavir in the management of recurrent HBV viremia in HIV/HBV coinfection were evaluated in a double-blind phase II clinical trial. Sixty-eight patients with HIV/HBV coinfection who experienced HBV viremia while receiving lamivudine were randomized to supplement their baseline therapy with placebo or entecavir (1.0 mg) once daily for 24 weeks, followed by open-label entecavir for another 24 weeks. The reduction in HBV viral load at the end of the first 24-week treatment period was significantly greater with entecavir compared to placebo. Entecavir was also associated with a greater percentage of patients achieving normalized ALT levels (49% *vs*. 17% with placebo). No significant differences between study treatments were found after an average follow-up of more than 40 weeks. No patients showed significant changes in HIV viral load or $CD4^+$ T-cell count during the study (19).

The double-blind, placebo-controlled ETV-056 clinical trial assessed the effects of entecavir (1.0 mg once daily) given for up to 36 weeks to 145 Chinese patients with hepatitis B unresponsive to lamivudine. Entecavir was significantly more effective than placebo in reducing plasma HBV levels and normalizing plasma ALT levels. The incidence of adverse events was similar (33% with entecavir *vs*. 28% with placebo), although entecavir-treated patients experienced less ALT flares (2% *vs.* 10%) (20).

An analysis of data from 28 reported trials indicated that entecavir, lamivudine and adefovir were more effective than placebo in patients with $HBeAg^+$ and $HBeAg^–$ chronic hepatitis B infection. In addition, entecavir was superior to adefovir for all efficacy measures in $HBeAg^+$ patients and for virological endpoints in $HBeAg^–$ patients; entecavir was superior to lamivudine for all efficacy measures except ranked assessment of necrosis/inflammation and fibrosis in $HBeAg^{+/–}$ patients and $HBeAg^+$ seroconversion (21).

Analysis of phase III trial data showed that the efficacy of entecavir in nucleoside-naïve patients with chronic hepatitis B was similar in $HBeAg^+$ and $HBeAg^–$ patients and in patients with varying baseline ALT levels (22).

Entecavir was at least as effective as lamivudine in terms of histological improvement and viral load reduction in chronic hepatitis B patients, regardless of previous interferon treatment, geographic region, gender or Asian race (23).

Entecavir resistance was not identified in samples from 659 nucleoside-naïve patients with chronic hepatitis B infection treated with a dose of 0.5 mg for at least 1 year. Resistance-related virological rebounds were noted in 1% of lamivudine-refractory subjects (24).

Genotypic analysis of 604 serum samples from patients with chronic hepatitis B treated for 1 year with entecavir showed that entecavir genotypic resistance emerged only in patients refractory to lamivudine, with an incidence of 5.8% (25).

1. *Entecavir submitted for U.S., European marketing approval for hepatitis B*. DailyDrugNews.com (Daily Essentials) Oct 6, 2004.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Randomized Double-blind Multicenter	Entecavir, 10 mg o.d. x 48 wks Lamivudine, 100 mg o.d. x 48 wks	286	In patients with chronic hepatitis B unresponsive to lamivudine therapy, switching to entecavir further improved both liver histology and virological response, and promoted normalization of alanine aminotransferase levels	9
Hepatitis B	Randomized Double-blind Multicenter Pooled/meta-analysis	Entecavir, 0.5 mg o.d. x 62 [median] wks (n=354) Entecavir, 1.0 mg o.d. x 63 [median] wks (n=141) Lamivudine, 100 mg o.d. x 52-57 [median] wks (n=500)	995	Both entecavir regimens were as well tolerated as lamivudine in patients with chronic hepatitis B	10
Hepatitis B	Pooled/meta-analysis	Entecavir, 0.5-1.0 mg o.d. (n=862) Lamivudine (n=858)	1720	Entecavir and lamivudine showed similar safety profiles in HBV-infected patients not previously treated with nucleosides or who had not responded to lamivudine	11
Hepatitis B	Open	Entecavir, 0.5 mg o.d. x 48 wks Lamivudine, 100 mg o.d. x 48 wks	709	The percentage of patients with chronic hepatitis B who achieved a complete response after 48 weeks of administration was significantly greater with entecavir compared to lamivudine. More than 80% of entecavir-treated patients maintained their antiviral response throughout a follow-up period of 24 weeks	13
HIV infection, Hepatitis B	Randomized Double-blind	Entecavir, 1.0 mg o.d. + Lamivudine x 24 wks (n=51) Placebo + Lamivudine x 24 wks (n=17)	68	Entecavir was safe and significantly more effective than placebo in reducing hepatitis B viral load and normalizing alanine aminotransferase levels in patients with HIV/hepatitis B coinfection and recurrent hepatitis B viremia	19
Hepatitis B	Randomized Double-blind Multicenter	Entecavir, 1.0 mg o.d. x 12 wks (n=116) Placebo (n=29)	145	Entecavir was significantly more effective than placebo in reducing plasma viral DNA levels and improving alanine transaminase levels in Chinese patients with chronic hepatitis B	20

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

3. *Baraclude receives FDA approval*. DailyDrugNews.com (Daily Essentials) March 31, 2005.

4. *Baraclude available in U.S*. DailyDrugNews.com (Daily Essentials) April 26, 2005.

5. *FDA Advisory Committee recommends approval of Baraclude for hepatitis B*. DailyDrugNews.com (Daily Essentials) March 15, 2005.

6. Bifano, M., Yan, J.-H., Xie, J., Zhang, D., Freund, J., Hanna, G., Lacreta, F., Grasela, D. *Hepatic impairment does not alter single-dose pharmacokinetics and safety of entecavir*. Hepatology 2004, 40(4, Suppl. 1): Abst 1149.

7. Bifano, M. et al. *Lack of pharmacokinetic interaction when entecavir is administered with lamivudine, adefovir, or tenofovir*. 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 473.

8. LaCreta, F., Mould, D., Bifano, M., Grasela, D.M., Pfister, M. *Simulation-based support of dose recommendations of entecavir for renally impaired subjects*. Clin Pharmacol Ther 2005, 77(2): Abst PI-45.

9. Sherman, M., Yurdaydin, C., Sollano, J. et al. *Entecavir is superior to continued lamivudine for the treatment of lamivudine-refractory, HBeAg(+) chronic hepatitis B: Results of phase III study ETV-026*. Hepatology 2004, 40(4, Suppl. 1): Abst 1152.

10. Sollano, J., Schiff, E., Carrilho, F. et al. *Entecavir is well-tolerated for treatment of chronic hepatitis B: Phase III safety analysis in nucleoside-naïve and lamivudine-refractory patients*. Hepatology 2004, 40(4, Suppl. 1): Abst 1153.

11. Gish, R.G., Sherman, M., Lok, A.S., Pockros, P.J., Raptopoulou-Gigi, M., Sollano, J.D., Chang, T.-T., Cooney, E., Hindes, R.G., Yang, J.Y., Cross, A.P., Wilber, R.B. *Entecavir is well tolerated for the treatment of nucleoside-naïve and lamivudine-refractory chronic hepatitis B: Phase 2/3 safety results*. Dig Dis Week (May 14-19, Chicago) 2005, Abst 323.

12. Manns, M.P., Raptopoulou-Gigi, M., Sollano, J., Gish, R.G., Chang, T.T., Sherman, M., Yurdaydin, C., Shouval, D., Lok, A.S., Cooney, E., Hindes, R., Yang, J., Cross, A., Wilber, R. *Entecavir is well tolerated for the treatment of nucleoside-naive and lamivudine-refractory chronic hepatitis B: Phase II/III safety results*. 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 511.

13. Gish, R.G., Martin, P., Schiff, E.R., De Man, R.A., Pederson, C., Chang, T.-T., Apelian, D., Zhu, J., Cross, A.P., Wilber, R.B. *Entecavir leads to sustained response off-treatment in nucleoside-naïve, HBeAg(+) patients who met on-treatment response endpoints at 48 weeks of therapy in phase 3 study ETV-022.* Dig Dis Week (May 14-19, Chicago) 2005, Abst 321.

14. Chang, T.T., Gish, R., De Man, R., Gadano, A., Sollano, J., Han, K.H., Goodman, Z., Zhu, J., Cross, A., Dehertogh, D., Apelian, D. *Entecavir is superior to lamivudine for the treatment of HBeAg(+) chronic hepatitis B: Results of phase III study ETV-022 in nucleoside-naive patients*. Hepatology 2004, 40(4, Suppl. 1): Abst 70.

15. Gish, R.G., De Man, R.A., Pedersen, C., Bialkowska, J., Chang, T.T., Apelian, D., Zhu, J., Cross, A., Wilber, R. *Sustained response off-treatment to entecavir and lamivudine after 48 weeks of treatment in nucleoside-naive, HBeAg(+) patients: 24-week follow-up results of phase 3 study ETV-022*. 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 490.

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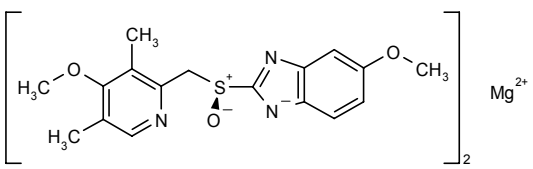
Esomeprazole Magnesium



The European mutual recognition procedure was successfully completed last year for new indications of

AstraZeneca's esomeprazole magnesium (Nexium®). The new indications are for the healing of gastric ulcers and for the prevention of gastric and duodenal ulcers associated with nonsteroidal antiinflammatory drug (NSAID) therapy in patients at risk. The U.S. FDA also approved the compound in late 2004 for reducing the risk of gastric ulcers associated with NSAID therapy and issued an approvable letter for its use in healing gastric ulcers associated with NSAID therapy. Regulatory applications for the use of esomeprazole for the healing of NSAID-associated gastric ulcers and the prevention of NSAID-associated gastric and duodenal ulcers in patients at risk were also submitted in other global markets in 2004. Further approvals are anticipated in the coming months. Esomeprazole has proven to be fast and effective in healing and preventing ulcers in patients taking NSAIDs, including cyclooxygenase type 2 (COX-2)-selective NSAIDs. It is also in phase II clinical testing for the treatment of extraesophageal reflux disease. Esomeprazole, an established treatment for gastroesophageal reflux disease (GERD), is a proton pump inhibitor (PPI) that has been shown to provide more effective control of gastric acid secretion than all other PPIs. It works by deactivating the proton pumps that produce stomach acid, thereby reducing the amount of acid that is in the stomach, helping to treat heartburn and other symptoms of GERD (1-3).

A randomized clinical trial evaluated the rate of recurrent ulcer bleeding in 320 patients who developed upper gastrointestinal bleeding while receiving continuous low-dose aspirin that healed with PPIs and were negative for *Helicobacter pylori* infection. Each patient was given clopidogrel (75 mg p.o. once daily) or a combination of aspirin (80 mg p.o. once daily) plus esomeprazole (20 mg p.o. b.i.d.) for 12 months. The cumulative incidence of recurrent ulcer bleeding during the study period was significantly higher with clopidogrel (8.6%) compared to the aspirin/esomeprazole regimen (0.7%). The mechanism underlying the appearance of recurrent ulcer bleeding with clopidogrel has not yet been elucidated, although evidence suggests that it may be associated with previous damage in the gastric mucosal barrier or the coexistence of major conditions that predispose the patients to the development of ulcers (4). The results from this and several of the following studies are described in Table XII.

Two multicenter, randomized, double-blind, placebo-controlled, parallel-group studies involving a total of 1,429 patients (*H. pylori*-negative) on continuous nonselective or COX-2-selective NSAID therapy for a chronic condition (osteoarthritis, rheumatoid arthritis) examined the efficacy of esomeprazole (20 or 40 mg p.o. once daily for 6 months) in preventing gastric and duodenal ulcers. Treatment was well tolerated and resulted in a significant reduction in ulcer incidence compared to placebo (ulcer-free rate = 94.8% and 95.4%, respectively, for doses of 20 and 40 mg *vs*. 83% on placebo). The absolute risk reduction in gastric and duodenal ulcers by month 6 was 11.8% and 12.4% for the respective dose groups. Esomeprazole was also more effective than placebo in maintaining improvements in health-related quality of life, improving symptom severity and preventing upper gastrointestinal symptom relapse. Compared to placebo, significantly more patients treated with esomeprazole (20 and 40 mg) had no heartburn (75.5% and 81.3%, respectively, *vs.* 62.4%) or acid regurgitation (78.1% and 86.5%, respectively, *vs.* 67.3%). Results were comparable in patients taking nonselective and COX-selective NSAIDs. Adverse event frequency was similar for both treatment groups and placebo (5-9).

Two other multicenter, randomized, double-blind, parallel-group studies in a total of 809 patients (*H. pylori*-negative) on continuous nonselective or COX-2-selective NSAID therapy for a chronic condition compared the efficacy of esomeprazole (20 or 40 mg once daily p.o. for 8

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

Indication	Design	Treatments	n	Conclusions	Ref.
Bleeding, gastrointestinal	Randomized Double-blind	Aspirin, 80 mg p.o. o.d. + Esomeprazole, 20 mg p.o. b.i.d. x 12 mo (n=159) Clopidogrel, 75 mg p.o. o.d. x 12 mo (n=161)	320	Aspirin combined with esomeprazole was more effective than clopidogrel in preventing recurrence of ulcer bleeding in patients who developed gastrointestinal bleeding while receiving low-dose aspirin	4
Ulcer, duodenal, Ulcer, gastric	Randomized Multicenter	Esomeprazole, 20 mg p.o. o.d. [before breakfast] x 6 mo Esomeprazole, 40 mg p.o. o.d. [before breakfast] x 6 mo Placebo	1429	Esomeprazole significantly reduced the incidence of gastric and duodenal ulcer and was well tolerated in patients at risk of developing ulcer on long-term NSAID therapy	7, 9
Ulcer, gastric, Ulcer, peptic	Randomized Double-blind Multicenter Pooled/ meta-analysis	Esomeprazole, 40 mg o.d. (n=262) Esomeprazole, 20 mg o.d. (n=276) Ranitidine, 150 mg b.i.d. (n=271)	809	Esomeprazole was superior to ranitidine, although both drugs were well tolerated in patients with gastric ulcer receiving either COX-2-selective or nonselective NSAIDs	10, 11

weeks) with ranitidine (150 mg b.i.d.) in healing gastric ulcers. Both agents were well tolerated. Patients receiving esomeprazole 20 and 40 mg had significantly higher gastric ulcer healing rates compared to ranitidine-treated patients (86.6% and 88.6%, respectively, *vs*. 75.3%). Of those patients receiving nonselective NSAIDs (n=686), healing rates were significantly higher in the esomeprazole-treated groups compared to the ranitidine-treated group (86% and 87.6%, respectively, *vs*. 74.4%). Healing rates for patients receiving COX-2-selective NSAIDs (n=121) were 91.2% and 94.6%, respectively, compared to 80% for ranitidine (10-12).

1. *Nexium completes European mutual recognition procedure for new indications*. DailyDrugNews.com (Daily Essentials) Sept 20, 2004.

2. *FDA approves new indication for Nexium*. DailyDrugNews.com (Daily Essentials) Nov 30, 2004.

3. *New intravenous formulation of Nexium receives FDA approval*. DailyDrugNews.com (Daily Essentials) April 5, 2005.

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Original monograph – Drugs Fut 1999, 24(11): 1178.

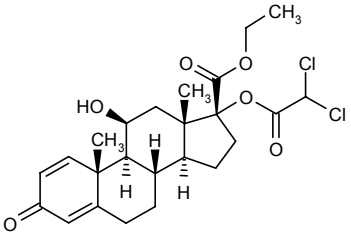
ETEC Vaccines

A clinical trial conducted by Microscience at St. George's Vaccine Institute, St. George's Hospital Medical School in London, demonstrated the safety and immunogenicity of the company's new oral vaccine intended to protect against infectious enterotoxigenic *Escherichia coli* (ETEC) disease, the most common cause of travelers' diarrhea. The dose-escalating, open-label study involved 36 volunteers and was designed to assess safety and determine the serum antibody and mucosal responses raised by the novel vaccine. The results showed that the vaccine had an excellent safety profile and was highly immunogenic. After a single dose, 50% of the volunteers mounted high levels of immune responses against a known protective antigen of ETEC. After two doses, the response rate rose to 70%. Microscience is now moving into a phase II program, which will include trials to demonstrate protection against the disease and to develop an optimal dosing regimen that will be administered over a few days to provide rapid immunity. The spi-VEC™ vaccine consists of harmless *Salmonella* bacteria that have been modified to carry an ETEC antigen. The *Salmonella* bacteria then act as a vehicle to deliver the antigen directly to cells of the immune system, resulting in efficient antigen presentation and strong immune responses (1).

Iomai is also developing an ETEC vaccine based on its noninvasive (patch) vaccine delivery technology. Iomai's transcutaneous immunization (TCI) technology combines the use of powerful adjuvants with the targeting of Langerhans cells in the skin. The ETEC vaccine is currently in phase II evaluation for traveler's diarrhea.

1. *Latest trial results move British company ahead in the race to develop new oral vaccine to protect against travellers' diarrhoea*. Microscience Press Release 2004, March 8.

Etiprednol Dicloacetate



Etiprednol dicloacetate (BNP-166, Cronaze) 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 is in phase II development at Ivax for the treatment of asthma and Crohn's disease.

Fontolizumab

Fontolizumab (HuZAF™) is a humanized monoclonal antibody in phase II trials at Protein Design Labs for the treatment of Crohn's disease. Fontolizumab binds to and potently neutralizes human interferon gamma, thereby inhibiting the development of Th1 cells, preventing the activation of macrophages, monocytes and natural killer (NK) cells, and preventing the induction or increase in MHC molecule expression.

In March 2004, Protein Design Labs reported results of two double-blind, randomized, placebo-controlled trials of fontolizumab in Crohn's disease. The primary endpoint for both trials was the response to the initial intravenous dose. PDL reported that fontolizumab did not meet the primary endpoint at study day 28 in either trial following administration of a single i.v. dose. Fontolizumab did, however, demonstrate statistically significantly greater activity compared to placebo at several subsequent time points following administration of a second i.v. dose in the HARMONY II clinical trial (1).

A double-blind, randomized, placebo-controlled study evaluated the potential of fontolizumab in the treatment of Crohn's disease. Each of the 45 patients enrolled was first treated with a single dose of placebo or fontolizumab (0.1, 1.0 and 4.0 mg/kg i.v.), and those who responded were re-randomized to receive placebo or fontolizumab (50% of initial dose) once every 3 months. The analysis of serum samples collected at different times after administration suggested that fontolizumab had a 2-compartment pharmacokinetic profile, with peak plasma concentrations of 1.0-73.3 μg/ml and an average elimination half-life of 9-23 days. Fontolizumab was minimally immunogenic, dose-dependently improved the CDAI scores and reduced the serum levels of IP-10 of the patients (2) (Table XIII).

Fontolizumab was associated with a response rate of 89% and a remission rate of 11% in a recently reported open study in 11 patients with moderate to severe Crohn's disease. The patients received fontolizumab 10 mg/kg at weeks 0, 2, 6 and 10. At week 12, the mean decrease in disease activity scores was 174 points. No serious treatment-related adverse events were seen and no discontinuations due to such events occurred. One grade 2 infusion reaction occurred but did not prevent the patient from completing treatment. An amended protocol has added 23 patients to the study, who will receive fontolizumab at weeks 0, 2, 6, 10, 14, 18, 22, 26 and 30 (3) (Table XIII).

Patients administered fontolizumab i.v. have increased serum levels of interferon gamma. In an *in vitro* study, U937 cells were incubated with serum samples from patients administered fontolizumab. Although the samples contained 130-1056 pg/ml interferon gamma, none contained active interferon gamma. Thus, serum interferon gamma levels may be increased following i.v. fontolizumab, but interferon gamma activity is not (4).

The tolerability, safety and efficacy of fontolizumab (4 or 10 mg/kg as 1 infusion or 2 infusions on days 0 and 28) were examined in a randomized, double-blind, placebo-controlled trial in 133 patients with moderate to severe Crohn's disease (CDAI = 228-457). The C_{max} values obtained for the two dose groups were 93 ± 17 and 211 ± 43 μg/ml, respectively. There was a tendency for a response on day 28, such that 37.8% and 44.2% of subjects in the respective fontolizumab dose groups responded (*i.e.*, a decrease in CDAI of 100 points or more) as compared to 32.6% in the placebo group; the differences, however, were not significant. On the other hand, on days 28, 42, 56 and 84, significant improvements in CDAI were observed in patients who received 2 infusions compared to placebo. Mean serum CRP levels were significantly decreased on day 42 for the low-dose group and on days 28, 42 and 56 for the high-dose group (5).

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

2. Ding, H., Maia, M., Keller, S. et al. *Fontolizumab (HuZAF(TM)) pharmacokinetics (PK), pharmacodynamics (PD), immunogenic-*

Table XIII: Clinical studies of fontolizumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Randomized Double-blind	Fontolizumab, 0.1 mg/kg i.v. (n=6) Fontolizumab, 1.0 mg/kg i.v. (n=14) Fontolizumab, 4.0 mg/kg i.v. (n=15) Placebo (n=10)	45	Fontolizumab was minimally immunogenic and improved the Crohn's Disease Activity Index scores in patients with moderate to severe Crohn's disease	2
Crohn's disease	Open	Fontolizumab, 10 mg/kg x wks 0, 2, 6, 10 (n=11) Fontolizumab, 10 mg/kg x wks 0, 2, 6, 10, 14, 18, 22, 26, 30 (n=20)	31	Fontolizumab was active in patients with moderate to severe Crohn's disease	3

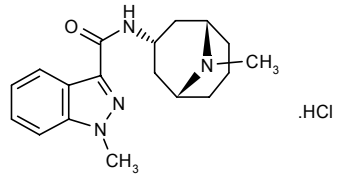
ity and exposure/response relationship in patients (pts) with moderate and severe Crohn's disease (CD). Gastroenterology 2004, 126(4, Suppl. 2): Abst T1302.

3. de Villiers, W.J., Katz, S., Salzberg, B.A., Kostova, N., Kotsev, I., Pearce, T. *Chronic dosing of fontolizumab (HuZAF(TM)), a humanized anti-IFN-gamma antibody, in patients with moderate to severe Crohn's disease (CD).* Dig Dis Week (May 14-19, Chicago) 2005, Abst 720.

4. Fang, Y., Keller, S., Fanget, M., Maia, M., Caras, I. *Circulating immune complexes of HuZAF and IFN-gamma have no detectable IFN-gamma activity*. Clin Invest Med 2004, 27(4, Suppl.): Abst T12.37.

5. Van Assche, G., Pearce, T. *Fontolizumab (HuZAF(TM)), a humanized anti-IFN-gamma antibody, has clinical activity and excellent tolerability in moderate to severe Crohn's disease (CD)*. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst OP-G-226.

Granisetron Hydrochloride, New Formulations



Granisetron hydrochloride (Kytril) is a 5-HT_3 antagonist that was launched over 10 years ago by Roche for the treatment of nausea and vomiting associated with chemotherapy and radiation therapy. The compound was originally developed at GlaxoSmithKline, but global rights were divested to Roche in September 2000. A number of companies are testing novel formulations of granisetron.

Acrux is conducting phase I clinical trials with a transdermal formulation of granisetron hydrochloride, intended for the treatment of chemotherapy-related emesis and postoperative nausea and vomiting. Granisetron MDTS® employs the company's Patchless Patch™ delivery method using a liquid spray or aerosol formulation to form a nonocclusive reservoir of drug and ACROSS™ penetration enhancer within the skin. The phase I proof-of-concept trial in 6 healthy volunteers will compare the absorption of granisetron administered via the company's transdermal spray with the absorption of the drug from the approved oral tablet formulation (1, 2).

A.P. Pharma has initiated a phase II program in cancer patients with its lead product candidate APF-530 for the prevention of both acute and delayed chemotherapy-induced nausea and vomiting (CINV). Combining the company's proprietary Biochronomer™ bioerodible drug delivery system with granisetron, APF-530 is designed to provide therapeutic levels of the drug in order to give 4-5 days of continuous relief from CINV following a single s.c. injection. Granisetron, one of a class of 5-HT_3 antagonists, is currently administered by i.v. injection and is approved for the acute phase only. In the new open-label, multicenter, active-control, dose-ascending phase II trial, patients undergoing moderately emetogenic chemotherapy will receive APF-530 containing one of three doses of granisetron. The primary endpoints are pharmacokinetics, safety and tolerability. The trial will be conducted at various U.S. and international clinical sites and will include at least 30 patients. The first seven U.S. sites selected are in various stages of initiation. In phase I studies evaluating four dose formulations of APF-530 in healthy human subjects, pharmacokinetic results indicated a dose-proportional increase in plasma levels of granisetron, and measurable plasma levels were observed over a 5-day period (3, 4).

ProStrakan has an antiemetic patch containing granisetron hydrochloride in phase II evaluation for acute and delayed chemotherapy-induced emesis. A patent has been granted to the company covering the manufacture and use of acrylic adhesive patches comprising nonacidic hydroxyl moieties for facilitating the transdermal administration of granisetron hydrochloride to cancer patients. The claim embodies a method for ensuring a reduction in the adverse events commonly associated with this type of therapy, as well as side effects associated with other therapeutic options, such as emesis resulting from fractionated chemotherapy and postoperative nausea and vomiting (5).

1. *Phase I study of Acrux transdermal spray to prevent nausea in cancer patients*. DailyDrugNews.com (Daily Essentials) March 18, 2005.

2. *Quarterly shareholder update, December 2004-February 2005.* Acrux Press Release 2005, March 1.

3. *A.P. Pharma reports initial data for APF-112 and APF-530*. DailyDrugNews.com (Daily Essentials) Aug 17, 2004.

4. *APF-530 enters phase II for CINV in cancer patients*. DailyDrugNews.com (Daily Essentials) May 2, 2005.

5. Altenschöpfer, P. and Watkinson, A.C. (ProStrakan Group Ltd.) *Transdermal granisetron*. WO 0469141.

Original monograph – Drugs Fut 1989, 14: 875.

HCV-086

ViroPharma announced results from the phase Ib proof-of-concept study with HCV-086, an orally dosed HCV inhibitor being codeveloped with Wyeth, earlier this year. This randomized, double-blind, placebo-controlled, sequential-group study of ascending multiple doses was designed to assess the safety, tolerability and antiviral effect of HCV-086 in subjects with chronic HCV infection. In each of five different dose groups, subjects with a variety of HCV genotypes were assigned to receive HCV-086 or placebo for 14 days. The results of the study indicated that after 14 days of treatment, the greatest mean change in plasma HCV RNA concentrations (–0.32 $\log_{10}$ IU/ml)

occurred in the highest dose group. The joint steering committee of the ViroPharma-Wyeth collaboration decided that overall the antiviral activity of HCV-086 does not support further development of the compound. HCV-086 demonstrated favorable pharmacokinetics and was generally safe and well tolerated, although in the highest dose group gastrointestinal adverse events occurred in several subjects and caused discontinuation of treatment in two subjects (1, 2).

1. *Proof-of-concept study begins for HCV-086*. DailyDrugNews.com (Daily Essentials) June 11, 2004.

2. *ViroPharma and Wyeth discontinue development of HCV-086*. DailyDrugNews.com (Daily Essentials) March 17, 2005.

HCV-796

ViroPharma has begun dosing in a phase I trial for HCV-796, a novel RNA polymerase (NS5B) inhibitor being developed as a potential new product to treat HCV infection. ViroPharma is conducting the trial with Wyeth, its partner for antiviral compounds for HCV. The phase Ia study is a placebo-controlled trial designed to assess the safety and tolerability of single ascending doses of HCV-796 in healthy adult volunteers, as well as to gather pharmacokinetic data. The study is being conducted at a U.S. clinical research facility. Phase Ib proof-of-concept studies of HCV-796 in HCV-positive adults are expected to begin during the second quarter of 2005. Data will be available from that trial in the fourth quarter of 2005. Preclinical studies have shown that HCV-796 may be more potent than other anti-HCV compounds developed to date by the two companies (1, 2).

1. *IND submission for HCV-796*. DailyDrugNews.com (Daily Essentials) Jan 12, 2005.

2. *Phase I program begins for HCV-796*. DailyDrugNews.com (Daily Essentials) Feb 17, 2005.

Hepatitis A/B Vaccine

Sinovac Biotech has commenced market launch of Bilive™, its combined hepatitis A and B vaccine, in China. Bilive™ is recommended to protect people against both hepatitis A and hepatitis B virus infections. It will be sold in two forms based on the age of vaccinees. Bilive™ junior is for use in nonimmune children and adolescents from ages 1 to 15 years, and Bilive™ adult is for use in nonimmune adults and adolescents 16 years of age and older. Bilive™ is a combined vaccine formulation comprising purified inactivated hepatitis A virus antigen and recombinant hepatitis B surface (HBsAg), absorbed onto aluminum hydroxide. The vaccine induces the body's immune system to generate antibodies as a reaction against hepatitis A and hepatitis B viruses (1, 2).

1. *Sinovac Biotech Ltd. issues corporate update on approval of its hepatitis A & B vaccine-Bilive 'TM' and its application to the American Stock Exchange*. Sinovac Biotech Press Release 2004, Oct 13.

2. *Chinese launch of Bilive vaccine*. DailyDrugNews.com (Daily Essentials) April 5, 2005.

Hepatitis B Immune Globulin

Cangene's hepatitis B immune globulin, also known as hepatitis B hyperimmune, is a highly purified and specialized antibody that has been filed for regulatory approval in the U.S. and Canada for the postexposure prevention of hepatitis B infection.

Hepatitis B Vaccines

Oxxon Therapeutics (the former Oxxon Pharmaccines) is developing a PrimeBoost immunotherapeutic encoding the HBV surface antigen and designed to induce the immune system to mount a targeted and potent immune response against HBV. The product is in phase II trials in patients with chronic HBV, with different arms testing the immunotherapeutic alone and in combination with standard antiviral therapy.

Dynavax Technologies has completed enrollment and administered the first round of immunizations in a phase II/III trial of HBV-ISS, its prophylactic HBV vaccine candidate containing the HBV surface antigen (HBsAg) and the company's immunostimulatory sequence (ISS) that stimulates a Th1 immune response and suppresses Th2 immune responses. The study, being conducted at the National University Hospital and Singapore General Hospital, both in Singapore, began enrollment in June 2004. The double-blind study compares Dynavax's HBV vaccine candidate with GlaxoSmithKline's marketed HBV vaccine Engerix-B® in 94 subjects, aged 40-70 years, who had not previously been immunized against HBV. The full immunization schedule will consist of 3 injections over 6 months, with antibody levels measured 1 month after each injection. The primary endpoint will be comparative protective antibody levels measured after the third injection. Comparative protective antibody levels measured after the first injection are a secondary endpoint. Pending successful results, phase III studies will begin in the first half of 2005 to confirm efficacy on a larger scale. In parallel, the vaccine will be tested more broadly in young adults and adolescents. Data from Dynavax's phase II prophylactic HBV vaccine trial in young adults showed superior efficacy after both one and two immunizations

as compared to Engerix-B®. Protective hepatitis B antibody responses were produced more quickly and with fewer injections with Dynavax's HBV vaccine (see below) (1, 2). Dynavax has an agreement with Berna Biotech under which the latter supplies Dynavax with its proprietary HBsAg for the HBV vaccine in exchange for an option to commercialize the vaccine.

The efficacy of HBV-ISS in the induction of a protective antibody response against HBV infection was evaluated in a placebo-controlled phase II clinical trial in 99 healthy seronegative adult subjects who were randomized to receive either HBV-ISS (at weeks 0 and 8) followed by placebo at week 24, or a licensed hepatitis B vaccine (at weeks 0, 8 and 24). The percentage of patients who achieved a protective antibody response was greater with HBV-ISS at 4 weeks after the first dose (79% *vs.* 12%), at 1 week after the second dose (98% *vs.* 18%) and at 4 weeks after the second dose (100% *vs.* 64%). At 1 year, all patients treated with HBV-ISS and 89% of those given the licensed HBV vaccine still had protective antibody levels. The incidence of adverse events was similar in both study groups, although mild tenderness at the injection site was more common in the HBV-ISS patients. The most common adverse events were headache and fatigue (3).

Innogenetics took over sponsorship of a phase I safety and tolerability study for a hepatitis B therapeutic vaccine candidate (INNO-102), acquired from Genencor and based on Epimmune's polyepitope technology, last year. Final results of the study demonstrated that doses of 0.4 or 4 mg i.m. of the DNA vaccine administered every 4 weeks for a total of 4 doses were safe and well tolerated in healthy volunteers. The next step in the clinical development program will be to deliver the hepatitis B polyepitope using a DNA vaccine and a viral vector in order to maximize the immune response (4).

GlaxoSmithKline (GSK) has received European approval for its hepatitis B vaccine Fendrix® (hepatitis B [rDNA] vaccine [adjuvanted, adsorbed]). Fendrix® prevents hepatitis B in patients with renal insufficiency, including specific high-risk groups such as prehemodialysis and hemodialysis patients, from 15 years of age upwards. Fendrix® contains the GSK Bio hepatitis B antigen (HBsAg) and a novel proprietary GSK Bio adjuvant system (AS04), which includes the lipid A derivative MPL® from Corixa (5, 6).

An oral vaccine administered in genetically engineered potatoes has shown promise against HBV, according to researchers at Roswell Park Cancer Institute (RPCI) and their colleagues at Arizona State University. The vaccine, which consists of only one protein from the virus, may be safer than other oral vaccines that use weakened living viruses. In a placebo-controlled, double-blind phase I study, 42 adult healthcare workers who previously responded to a licensed injectable vaccine received an oral booster dose delivered in transgenic potatoes that expressed the HBsAg. Blood serum antibodies increased in 10 of 16 volunteers (62.5%) who ate 3 doses of potatoes and in 9 of 17 volunteers (52.9%) who ate 2 doses of transgenic potatoes. It did not increase in volunteers who consumed the nonengineered potatoes (7, 8).

Microscience's phase I study of its spi-VEC™ oral hepatitis B vaccine designed for the treatment of subjects chronically infected with HBV has met its primary objectives and successfully demonstrated safety and immunogenicity. The open-label, dose-escalating study was conducted in 30 healthy adult volunteers to evaluate the safety and immunogenicity of a candidate oral immunotherapy given on 2 occasions, 56 days apart. The primary aim was to assess safety and to determine the cellular immune responses against hepatitis B core antigen (HBcAg) raised by 2 dose levels of this novel vaccine. The immunological data demonstrated that all subjects mounted a T-cell proliferative response to both the HBcAg and to groups of peptides representing the whole sequence of HBcAg, indicating that the antigen had been successfully delivered to the immune system in all subjects. In addition, 95% of responders in the high-dose group elicited a Th1-biased response characterized by the secretion of interferon gamma and the absence of IL-5 secretion by stimulated T-cells. The data support the further development of the immunotherapeutic vaccine and Microscience is now planning a phase II program in subjects chronically infected with the virus. The spi-VEC™ vaccine consists of a harmless *Salmonella* bacterium that has been modified to carry the hepatitis B core antigen. The *Salmonella* bacterium acts as a vehicle to deliver the antigen directly to cells of the immune system, resulting in effective antigen presentation with resultant strong immune responses. The immunogenicity of HBcAg is well reported in the literature from various animal models and is expected to translate to an advantage over surface antigen preparations in terms of the magnitude of the immune response elicited in chronic carriers. The spi-VEC™ platform technology is also being harnessed to develop oral vaccines to protect against typhoid, traveler's diarrhea (see above) and anthrax (9, 10).

1. *Singapore study for Dynavax HBV prophylactic vaccine*. DailyDrugNews.com (Daily Essentials) June 29, 2004.

2. *Enrollment completed in phase II/III trial of Dynavax HBV vaccine*. DailyDrugNews.com (Daily Essentials) Sept 6, 2004.

3. Halperin, S.A., Dobson, S., McNeil, S., Langley, J.M., Smith, B., McCall-Sani, R., Levitt, D. *Hepatitis B virus surface antigen (HBV) co-administered with an immunostimulatory phosphorothioate oligonucleotide (HBV-ISS) achieves protective antibody levels more quickly and with fewer doses than a licensed hepatitis B vaccine*. 44th Intersci Conf Antimicrob Agents Chemother (Oct 30-Nov 2, Washington DC) 2004, Abst G-557a.

4. *Innogenetics completes first US clinical trial on time: Excellent safety and tolerability results of hepatitis B therapeutic vaccine phase I study*. Innogenetics Press Release 2005, March 31.

5. *Positive opinion for Fendrix in Europe*. DailyDrugNews.com (Daily Essentials) Oct 26, 2004.

6. *Fendrix hepatitis B vaccine approved in Europe*. DailyDrugNews.com (Daily Essentials) Feb 9, 2005.

7. *Roswell Park study evaluates oral hepatitis B vaccine*. Roswell Park Cancer Institute Press Release 2005, Feb 14.

8. Thanavala, Y., Mahoney, M., Pal, S., Scott, A., Richter, L., Natarajan, N., Goodwin, P., Arntzen, C.J., Mason, H.S. *Immunogenicity in humans of an edible vaccine for hepatitis B*. Proc Natl Acad Sci USA 2005, 102(9): 3378.

9. *Phase I results of spi-VEC vaccine for hepatitis B*. DailyDrugNews.com (Daily Essentials) July 30, 2004.

10. *spi-VEC oral hepatitis B vaccine shows promise in phase I study*. DailyDrugNews.com (Daily Essentials) Nov 8, 2004.

Hepatitis C Immune Globulin

Preliminary results from a phase I/II clinical trial of Nabi Biopharmaceuticals' hepatitis C immune globulin (human) (Civacir®), a polyclonal antibody-based therapy being developed to prevent HCV disease in HCV-positive liver transplant patients, demonstrated that the product was well tolerated in both high- and low-dose treatment arms. In addition, a trend towards a reduction in HCV levels was observed at the higher dose (1, 2). Civacir® is also being developed for the treatment of chronic hepatitis C. It holds orphan drug status in both the U.S. and the E.U.

1. *Nabi Biopharmaceuticals reports 2003 year-end R&D highlights*. Nabi Biopharmaceuticals Press Release 2004, Feb 18.

2. *Nabi Biopharmaceuticals reports Q1 R&D highlights*. Nabi Biopharmaceuticals Press Release 2004, April 21.

Hepatitis C Vaccines

A therapeutic hepatitis C vaccine (INNO-101) based on the purified viral envelope E1 protein subtype 1b is currently in phase IIb development at Innogenetics.

Intercell's novel therapeutic hepatitis C vaccine Transvax™ has met the primary endpoints in an international, multicenter phase II study in nearly 200 healthy and chronically infected interferon/ribavirin nonresponders. Results showed helper and cytotoxic T-cell response in the most difficult and to date untreatable group of chronic patients. The vaccine had an excellent safety profile with no significant side effects. The results pave the way for an additional phase II trial in hepatitis C patients with less compromised immune systems, for example individuals recently diagnosed with hepatitis C and awaiting interferon/ribavirin treatment. In this new patient group, the primary endpoint of the study will be the reduction of the viral load and a further confirmation of efficacy. The vaccine is based on proprietary developed virus-derived T-cell-specific peptides and formulated with the company's first-generation adjuvant polyarginine. Using a method called "transloading", the antigens are efficiently transferred into cells, where they are recognized by the human immune system, which then mounts an immune response (1).

1. *Intercell's phase II study of hepatitis C vaccine meets endpoints*. DailyDrugNews.com (Daily Essentials) July 28, 2004.

Hepatitis E Vaccine

Genelabs Technologies has received a USD 750,000 payment from GlaxoSmithKline Biologicals (GSK Bio) based on a milestone relating to clinical trial results for GSK's investigational prophylactic hepatitis E vaccine, currently in phase II. Genelabs previously granted GSK an exclusive worldwide license to develop and commercialize hepatitis E virus (HEV) vaccines. Genelabs scientists were the first to clone and characterize HEV, and the company owns a portfolio of patents covering HEV genomes and encoded peptides (1).

1. *Genelabs receives milestone from GSK for hepatitis E vaccine*. DailyDrugNews.com (Daily Essentials) Nov 16, 2004.

HepeX-B™

HepeX-B™ (XTL-001) is an injectable combination of libivirumab (Ab17) and exbivirumab (Ab19), two fully human monoclonal antibodies that target the hepatitis B virus (HBV) surface antigens, selected using XTL's preclinical Trimera™ model. The antibody product is currently in phase IIb clinical development at XTL Biopharmaceuticals for the prevention of hepatitis B reinfection in liver transplant patients. Worldwide development and commercialization rights for the product were licensed to Cubist Pharmaceuticals in 2004. HepeX-B™ has been granted orphan drug designation in both the U.S. and Europe.

Cubist and XTL reported that the first scheduled review has been conducted by an independent data and safety monitoring board (DSMB) of the first group of 15 patients enrolled in the ongoing open-label phase II trial examining the safety and efficacy of HepeX-B™ for the prevention of HBV reinfection in patients who have received liver transplantation for end-stage HBV infection, and who have been maintained on hepatitis B immune globulin (HBIg). Based upon a review of the data provided by XTL, the DSMB, convened by Duke Clinical Research Institute at Duke University, has recommended continuation of the trial. Patients are being enrolled in the trial in the U.S. and in Israel. Centers in several Western European countries will be opened shortly. The trial is the second of two planned phase II trials. In clinical studies, HepeX-B™ maintained serum levels similar to or higher than the current first-line treatment, HBIg, using 1,000 times less drug (1).

The antiviral effects of the antibody combination were evaluated in a clinical trial in which once-weekly doses of 10-80 mg were administered for 4 weeks to patients with chronic HBV infection. Reductions in the plasma levels of HBV DNA and HBsAg antigen induced by HepeX-B™ were correlated with the plasma levels of anti-HBs antibodies. Effective neutralization of plasma HBsAg antigen was achieved with the antibody combination at doses above 10-20 mg in patients with baseline HBsAg levels of < 4 μg/ml, whereas patients with greater viral loads seemed to need higher doses (2, 3).

1. *First safety review completed for phase II study of HepeX-B*. DailyDrugNews.com (Daily Essentials) Nov 26, 2004.

2. Andrews, J. *Correlates of response in patients with chronic HBV infection receiving libivirumab and exbivirumab (HepeX-B(TM))*. 42nd Annu Meet Infect Dis Soc Am (Sept 30-Oct 3, Boston) 2004, Abst 956.

3. Andrews, J. *Correlates of response in patients with chronic HBV infection receiving libivirumab and exbivirumab (HepeX-B(TM))*. Hepatology 2004, 40(4, Suppl. 1): Abst 1128.

HepeX-C™/XTL-6865

In April, XTL Biopharmaceuticals submitted an IND with the FDA to commence a phase Ia/Ib trial of XTL-6865, the company's dual-MAb product for preventing HCV reinfection in liver transplant patients and for the treatment of chronic HCV. XTL-6865 contains Ab68 and Ab65, antibodies targeting different epitopes on the HCV E2 envelope protein. The company is seeking to conduct a dose-escalating trial of XTL-6865 in patients with chronic HCV to evaluate safety and biological activity of the product, followed by a study in liver transplant patients. A single-antibody version (Ab68) of the product, referred to as HepeX-C™ (also known as XTL-002), was tested in phase I (see below) and II clinical trials. In a phase IIa trial (Study 2002-09) for the prevention of HCV reinfection in liver transplant patients, HepeX-C™ proved to be safe and well tolerated at doses up to 240 mg for 12 weeks. Higher doses were not tested due to a clinical hold as a result of an intraoperative death of the first patient tested at the dose of 480 mg, which was later determined by the medical examiner to be related to pulmonary emboli. Although the FDA later cleared the clinical hold, XTL decided to discontinue the study and focus further development efforts on the dual-antibody product. No other serious drug-related adverse events were reported during this study. The 120- and 240-mg dose groups experienced a significantly greater reduction in viral load than the placebo group during the first week when dosed daily, although this effect was less evident when the antibody was dosed less frequently. In preclinical studies evaluating Ab68 and Ab65 for the prevention of HCV reinfection, both antibodies induced immunoprecipitation of HCV particles in sera from infected patients with diverse genotypes via the formation of immune complexes and endocytosis, without activating complement-dependent cytotoxicity. The antibodies prevented HCV reinfection *in vitro* in human hepatoma cell lines and *in vivo* in the HCV Trimera™ model in mice. This study demonstrates the viral neutralizing properties of Ab68 and Ab65, indicating that they may be promising immunotherapies to prevent HCV reinfection in liver transplant patients (1-8).

Study 2002-07 was a dose-finding clinical trial that determined the effects of HepeX-C™ in patients with chronic HCV infection. Each patient was given intravenous HepeX-C™ at doses ranging from 10 to 120 mg. HepeX-C™ dose-dependently increased the levels of anti-E2 antibodies and decreased HCV RNA concentration in plasma, with the greatest effects being detected at a dose of 120 mg. The authors suggested that doses of 120 mg or more may provide effective viral suppression in liver transplant recipients (9).

The tolerability, safety and efficacy of single-dose (0.25, 1, 2.5, 10 and 40 mg) and subsequent multiple-dose (10, 20, 40, 80 and 120 mg) HepeX-C™ were examined in two phase Ia and phase Ib studies, respectively, in a total of 40 patients with chronic HCV infection (HCV RNA = 2.6×10^3-1×10^6 IU/ml; anti-E2 antibodies = 5-550 μg/ml). Treatment was well tolerated, with no serious adverse events observed. Viral load reductions were found to be infusion-related. In the phase Ia study, 8 of 15 patients had transient reductions in HCV RNA of 2-100-fold. In the phase Ib, reductions in HCV RNA of at least 1 and 0.75 log were observed in 8 and 18 of the 25 patients, respectively (10) (Table XIV).

1. *Partial clinical hold in phase IIa trial of HepeX-C*. DailyDrugNews.com (Daily Essentials) May 14, 2004.

2. *XTL Biopharmaceuticals to enroll new patients in HepeX-C study.* DailyDrugNews.com (Daily Essentials) Aug 30, 2004.

3. *HepeX-C development progresses.* DailyDrugNews.com (Daily Essentials) Nov 22, 2004.

Table XIV: Clinical studies of HepeX-C™ (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis C	Randomized Open Pooled/ meta-analysis	HepeX-C™, 10 mg i.v. 1x/3 wks → 3x/wk x 1 wk HepeX-C™, 20 mg i.v. 1x/3 wks → 3x/wk x 1 wk HepeX-C™, 40 mg i.v. 1x/3 wks → 3x/wk x 1 wk HepeX-C™, 80 mg i.v. 1x/3 wks → 3x/wk x 1 wk HepeX-C™, 120 mg i.v. 1x/3 wks → 3x/wk x 1 wk	40	HepeX-C™ administered as multiple doses was well tolerated and effective in reducing serum HCV RNA levels in patients with chronic HCV infection	10

4. Eren, R. et al. *Preclinical evaluation of two neutralizing human monoclonal antibodies against HCV: A potential treatment to prevent HCV re-infection in liver transplant patients.* 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 560.

5. *XTL Biopharmaceuticals Ltd. provides update on clinical programs and planned operations.* XTL Biopharmaceuticals Press Release 2005, March 31.

6. *XTL Biopharmaceuticals Ltd. reports progress in HepeX-C program.* XTL Biopharmaceuticals Press Release 2004, Nov 18.

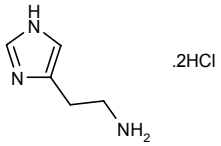
7. *XTL Biopharmaceuticals Ltd. presents new HepeX-C data at AASLD*. XTL Biopharmaceuticals Press Release 2004, Nov 3.

8. XTL Biopharmaceuticals Web Site.

9. Andrews, J. *Changes in HCV RNA with monoclonal Ab HCV-AB(XTL)-68 in patients with HCV infection*. 42nd Annu Meet Infect Dis Soc Am (Sept 30-Oct 3, Boston) 2004, Abst 968.

10. Ilan, E., Zauberman, A., Graham, N., Nussbaum, O., Terkieltaub, D., Galun, E., Terrault, N., Eren, R., Dagan, S. *Clinical evaluation of a human monoclonal antibody against the envelope protein (E2) of HCV for prevention of HCV infection*. Antivir Res 2004, 62(2): Abst 65.

Histamine Dihydrochloride, Oral Formulation

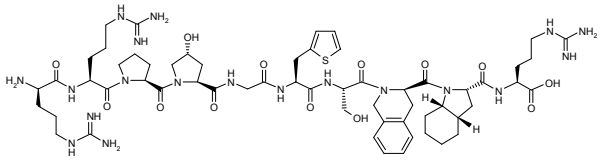


Maxim is developing an oral formulation of histamine dihydrochloride (HD-O) for the treatment of chronic liver diseases, including alcoholic liver disease and nonalcoholic steatohepatitis. Phase Ia and Ib clinical trials in healthy volunteers have been completed. Histamine binds to the H_2 receptor on phagocytes, temporarily helping to prevent the production and release of oxygen free radicals, thereby reducing oxidative stress and potentially preventing disease progression and helping to reverse liver damage. Maxim's histamine dihydrochloride for s.c. injection (Ceplene™) is in phase III trials for the treatment of acute myeloid leukemia.

Human Gammaglobulin, Oral

Oral human gammaglobulin is in phase II trials at PediaMed for the treatment of gastrointestinal dysfunction in autistic children. The drug is a sterilized immune globulin product prepared from pooled human donor plasma that consists primarily of IgG. Through its acquisition of Protein Therapeutics last year, the company holds exclusive worldwide rights to patents and applications for the use of oral immunoglobulin for the treatment of a wide variety of autoimmune diseases from Research Corporation Technologies.

Icatibant



Icatibant is a potent and specific bradykinin B_2 receptor antagonist in phase III trials at Jerini for the oral treatment of hereditary angioedema. The company has also evaluated icatibant in phase II trials for the treatment of patients with refractory ascites in liver cirrhosis (RAIL) and in phase I for the treatment of edema in patients with severe burn injuries. Jerini acquired an exclusive worldwide license to develop icatibant from the former Aventis Pharma (Sanofi-Aventis) in 2001 (1-4),

The efficacy of icatibant (0.15 mg/kg/day by continuous 3-day infusion) in increasing the natriuretic response after a sodium load (on day 2) was demonstrated in a randomized, crossover, placebo-controlled, proof-of-concept trial in 8 patients with liver cirrhosis (Child Pugh score = 5-8) and 8 healthy subjects. Treatment with the agent was well tolerated and significantly increased sodium excretion (6.9 mmol/h), urine osmolarity (18-54 mmol/h) and urine flow (41.4 ml/h) in patients with cirrhosis at 6-12 h postsodium load as compared to placebo; potassium excretion was also increased but values were not significantly different from placebo. The body weight of icatibant-treated patients was also significantly reduced (0.53 kg) at 48 h after sodium load compared to placebo. Treatment responses to sodium load in healthy volunteers were prompt and similar in subjects treated with both icatibant and placebo. Renal function was not altered during treatment and the agent did not cause orthostatic hypotension, reflex tachycardia or Q-T_c prolongation (5). A more recent phase II efficacy study in 35 patients with severe RAIL, however, did not demonstrate significant beneficial effects on sodium excretion and body weight. Based on these results, the company believes that further clinical trials will be necessary and is considering partnering the program (see Jerini Web Site).

1. *Icatibant awarded orphan drug status for edema in severe burn patients*. DailyDrugNews.com (Daily Essentials) July 9, 2004.

2. *Fast track status for subcutaneous icatibant in HAE*. DailyDrugNews.com (Daily Essentials) July 27, 2004.

3. *Phase II proof-of-concept study successfully completed for icatibant in HAE*. DailyDrugNews.com (Daily Essentials) Aug 31, 2004.

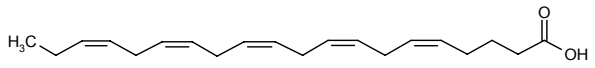
4. *U.S./Canadian pivotal study commences for icatibant in hereditary angioedema*. DailyDrugNews.com (Daily Essentials) Sept 10, 2004.

5. Russmann, S., Buclin, T., Decosterd, L., Baumann, S., Brunner-Ferber, F., Naga, B., Rosenkranz, B., Knolle, J., Biollaz, J., Reichen, J. *Icatibant, a potent bradykinin B2 receptor antagonist, improves natriuresis and diuresis after sodium challenge in patients with liver cirrhosis*. Hepatology 2004, 40(4, Suppl. 1): Abst 1092.

Table XV: Clinical studies of IDN-6556 (from Prous Science Integrity®).

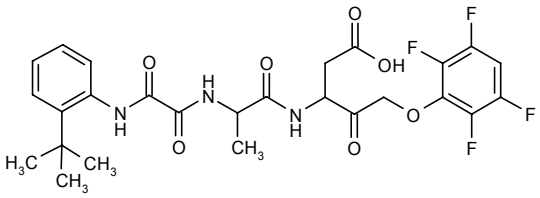
Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis C, Steatohepatitis, nonalcoholic	Randomized Double-blind Multicenter	IDN-6556, 25 mg o.d. x 14 d IDN-6556, 100 mg o.d. x 14 d IDN-6556, 200 mg o.d. x 14 d IDN-6556, 5 mg b.i.d. x 14 d IDN-6556, 50 mg b.i.d. x 14 d IDN-6556, 100 mg b.i.d. x 14 d Placebo	49	IDN-6556 reduced serum levels of alanine aminotransferase and aspartate aminotransferase in patients with hepatitis C and nonalcoholic steatohepatitis. IDN-6556 was also well tolerated and mostly associated with mild and transient adverse events	1

Icosapent



SLA Pharma is evaluating icosapent (EPA, eicosapentaenoic acid) in phase II clinical trials for use in Crohn's disease.

IDN-6556



IDN-6556 is a first-in-class, small-molecule pan-caspase inhibitor developed by Idun Pharmaceuticals, recently acquired by Pfizer, and currently undergoing phase II trials in liver transplantation and in patients infected with HCV. In a recent phase IIa study, oral IDN-6556 was well tolerated and significantly improved markers of liver damage in HCV patients who had previously failed to respond to existing drugs for HCV. IDN-6556 may represent a new class of drugs that protect the liver from inflammation and cellular damage induced by viral infections and other causes. In preclinical models of liver disease, it has demonstrated both antiinflammatory and antifibrotic activity (1-3).

A total of 49 patients with hepatic diseases (48 with chronic hepatitis C and 1 with NASH) were enrolled in an ongoing multicenter, double-blind, randomized clinical trial assessing the benefits of using IDN-6556 to inhibit apoptosis in these conditions. Each patient received placebo or IDN-6556 (25, 100 and 200 mg/day, 5, 50 and 100 mg b.i.d.) for 14 days. At the end of the study, all doses of IDN-6556 were more effective than placebo in reducing serum levels of ALT and aspartate aminotransferase (AST). The greatest efficacy was found with 100 mg of IDN-6556 given twice daily. IDN-6556 was safe and mostly associated with mild and transient adverse events (4) (Table XV).

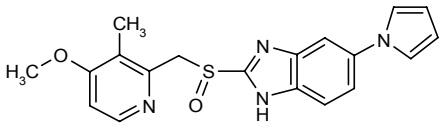
1. *Phase II study evaluates IDN-6556 in HCV patients*. DailyDrugNews.com (Daily Essentials) Aug 3, 2004.

2. *Pfizer to acquire Idun Pharmaceuticals*. DailyDrugNews.com (Daily Essentials) Feb 28, 2005.

3. *Pfizer Inc. first-quarter 2005 performance report*. Pfizer Press Release 2005, April 19.

3. Schiff, E.R., Pockros, P., Shiffman, M.L. et al. *Oral IDN-6556, an anti-apoptotic caspase inhibitor, lowers aminotransferases in HCV patients*. Gastroenterology 2004, 126(4, Suppl. 2): Abst 126.

Ilaprazole



Ilaprazole (IY-81149, Aldenon®) is a substituted benzimidazole proton pump inhibitor from Il-Yang currently undergoing multinational phase IIb trials for the treatment of GERD and ulcers. The drug has been shown to significantly inhibit acute gastric erosions and accelerate ulcer healing through H^+/K^+-ATPase inhibition. Axcan acquired an option to license worldwide rights except for Korea and China as a result of an agreement between the companies in January 2000.

Original monograph – Drugs Fut 1999, 24: 618.

Infliximab

Infliximab (Remicade®), a chimeric monoclonal antibody that binds to TNF-α, was initially launched in 1998 for the treatment of Crohn's disease. Subsequently, it was introduced in the E.U., the U.S. and Japan for rheumatoid arthritis, and in the U.S. and the E.U. for ankylosing spondylitis and psoriatic arthritis. The antibody was discovered by Centocor (Johnson & Johnson), which markets the product in the U.S.; licensee Schering-Plough markets it outside the U.S., Japan and certain other Asian countries, where Tanabe Seiyaku holds commercial rights.At present, infliximab is awaiting registration in Japan for the treatment of Behçet's disease. Phase III tri-

als are under way for the use of infliximab in the treatment of psoriasis, juvenile idiopathic arthritis, pediatric Crohn's disease and ulcerative colitis. Infliximab has received fast track designation from the FDA for the treatment of active ulcerative colitis and two multicenter, randomized, double-blind, placebo-controlled, parallel-treatment phase III trials are evaluating its safety and efficacy in such patients. Centocor is planning simultaneous submissions for the treatment of active ulcerative colitis in the U.S. and Europe (1).

A randomized, open-label, methylprednisolone-controlled trial examined the efficacy of infliximab in inducing and maintaining remission in 20 patients with moderate to severe glucocorticoid-dependent ulcerative colitis. Patients received 3 infliximab infusions (5 mg/kg/infusion) at 0, 2 and 6 weeks, followed by infliximab infusions every 8 weeks (group A) or methylprednisolone (0.7-1 mg/kg/day) for 1 week followed by tapering to a minimal dose to achieve a symptom-free condition (group B). No significant adverse events were observed with infusions. Remission after the first infusion was observed in all patients in group A, with a significant decrease in disease activity index (DAI) scores (1.6 ± 0.7 from 8.9 ± 1.4) and progressive discontinuation of glucocorticoids. Clinical remission was maintained in 9 of 10 patients at 1 year; 1 patient relapsed at 3 months and required shorter intervals between infusions to achieve remission. In group B, all patients had clinical remission at 1 week, with significant reductions in DAI (1.9 ± 0.3 from 8.7 ± 1.4); 8 of 10 patients continued on minimal steroid doses with no relapses seen after 1 year. Two patients from this group who relapsed at 6 and 8 months achieved clinical remission after subsequent treatment with infliximab. Health-related quality of life according to the IBDQ increased in both groups, although the improvement was significantly greater in group A (2, 3) (Table XVI).

A randomized pilot study examined the efficacy of infliximab for acute, non-steroid-refractory ulcerative colitis. The 13 patients involved had acute moderate or severe ulcerative colitis (median baseline activity score = 13.5) and were randomized to receive either 3 infliximab infusions (5 mg/kg at 0, 2 and 6 weeks) or high-dose prednisolone (1.5 mg/kg daily for 2 weeks followed by 1 mg/kg for 1 week and a subsequent tapering regimen with a weekly reduction of 5 mg). Of the patients receiving infliximab and prednisolone, respectively, 5 of 6 and 6 of 7 were treated successfully after 3 and 13 weeks (4) (Table XVI).

The safety and efficacy of infliximab (5 or 10 mg/kg at weeks 0, 2 and 6, and then every 8 weeks through week 46) were examined in a multicenter, randomized trial (ACT 1) conducted in a total of 364 patients with active moderate or severe ulcerative colitis who were also treated with corticosteroids and/or 6-mercaptopurine/azathioprine. Treatment was generally well tolerated and the safety profile was similar to that previously reported. Clinical response rates in groups receiving either dose of the agent were significantly higher than on placebo at week 8 (69.4% and 61.5%, respectively, *vs*. 37.02%) and at week 30 (52.1% and 50.8%, respectively, *vs*. 29.8%). Clinical remission rates were also significantly greater than on placebo (38.8% and 32%, respectively, *vs*. 14.9% at week 8; 33.9% and 36.9%, respectively, *vs*. 15.7% at week 30). In addition, significantly more patients had mucosal healing as compared to placebo (62% and 59%, respectively, *vs*. 33.9% at week 8; 50.4% and 49.2%, respectively, *vs.* 24.8% at week 30). Treatment with infliximab also facilitated corticosteroid withdrawal while sustaining remission (5).

The safety and efficacy of infliximab (5 or 10 mg/kg at weeks 0, 2 and 6, 14 and 22) were examined in a multicenter, randomized trial (ACT 2) conducted in 364 patients with active ulcerative colitis refractory to at least 1 standard therapy including 5-ASA, corticosteroids or immunosuppressants. Treatment was generally well tolerated and the safety profile was similar to that previously reported. Clinical response rates in groups receiving either dose of the agent were significantly higher than on placebo at week 8 (64.5% and 69.2%, respectively, *vs.* 29.3%) and at week 30 (47.1% and 60%, respectively, *vs*. 26%). Clinical remission rates were also significantly greater than on placebo (33.9% and 27.5%, respectively, *vs.* 5.7% at week 8; 25.6% and 35.8%, respectively, vs. 10.6% at week 30). In addition, significantly more patients

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

Indication	Design	Treatments	n	Conclusions	Ref.
Ulcerative colitis	Randomized	Infliximab, 5 mg/kg i.v. infusion on wk 0, 2 & 6 → 1x/8 wks (n=10) Methylprednisolone, 0.7-1 mg/kg o.d. x 1 wk → tapered to minimum effective dose (n=10)	20	Infliximab had similar efficacy to methylprednisolone and displayed possible efficacy in the short-term maintenance of remission and steroid withdrawal in patients with moderate to severe steroid-dependent ulcerative colitis	3
Ulcerative colitis	Randomized	Infliximab, 5 mg/kg i.v. infusion on wk 0, 2 & 6 (n=6) Prednisolone, 1.5 mg/kg p.o. o.d. x 2 wks → 1 mg/kg x 1 wk → tapering 5 mg/wk (n=7)	13	Infliximab demonstrated efficacy in the acute treatment of moderate to severe ulcerative colitis	4

had mucosal healing as compared to placebo (60.3% and 61.7%, respectively, *vs*. 30.9% at week 8; 46.3% and 56.7%, respectively, *vs*. 30.1% at week 30). Treatment with infliximab also facilitated corticosteroid withdrawal while sustaining remission (6).

The short- and long-term efficacy of infliximab (5 mg/kg for a median of 6 infusions preceded by oral acetaminophen and diphenhydramine) was demonstrated in a retrospective study in 12 pediatric patients with acute moderate to severe ulcerative colitis (including 3, 3, 5 and 1 cases of fulminant colitis, acute exacerbation of colitis, steroid-dependent colitis and steroid-refractory colitis, respectively). Complete and partial short-term (2 weeks after the first infusion) responses were obtained in 9 and 3 patients, respectively. A significant reduction in the mean per-patient dose of corticosteroid from 45 mg/day at the first infusion to 22.2 and 7.8 mg/day at 4 and 8 weeks, respectively, was also observed with treatment. There were 8 long-term responders at a median follow-up time of 10.4 months. Infliximab was more effective in those patients who were also receiving 6-mercaptopurine (7).

Infliximab 5 mg/kg was evaluated as rescue therapy in patients with moderately severe ulcerative colitis (n=45) included in a placebo-controlled study. More placebo-treated patients underwent colectomy within 90 days (66.7% *versus* 29.2%), and no deaths or severe complications were seen in the infliximab group (8).

The efficacy and safety of infliximab (5 mg/kg by infusion) were shown in 6 patients with chronic active ulcerative colitis and 1 patient with acute steroid-refractory ulcerative colitis. The agent was well tolerated and no adverse events were reported. Clinical/biochemical inflammatory activity was significantly decreased by 85.7% in 6 of the 7 patients. In addition, 5 of 6 patients with corticosteroid-dependent disease were weaned off steroids (9).

1. *Fast track designation for Remicade for ulcerative colitis*. DailyDrugNews.com (Daily Essentials) Dec 21, 2004.

2. Armuzzi, A., Lupascu, A., Fedeli, P., De Pascalis, B., Gasbarrini, G., Gasbarrini, A. *Infliximab in moderate to severe glucocorticoid dependent ulcerative colitis: A randomised methylprednisolone controlled trial*. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst TUE-G-366.

3. Armuzzi, A., Lupascu, A., Fedeli, P., De Pascalis, B., Gasbarrini, G., Gasbarrini, A. *Infliximab in the treatment of moderate to severe glucocorticoid dependent ulcerative colitis: A randomized methylprednisolone controlled trial.* Gastroenterology 2004, 126(4, Suppl. 2): Abst T1297.

4. Ochsenkühn, T., Sackmann, M., Göke, B. *Infliximab for acute, not steroid-refractory ulcerative colitis: A randomized pilot study.* Eur J Gastroenterol Hepatol 2004, 16(11): 1167.

5. Rutgeerts, P., Feagan, B.G., Olson, A., Johanns, J., Travers, S., Present, D., Sands, B.E., Sandborn, W., Olson, A.*A randomized placebo-controlled trial of infliximab therapy for active ulcerative colitis: ACT 1 trial*. Dig Dis Week (May 14-19, Chicago) 2005, Abst 689.

6. Sandborn, W.J., Rachmilewitz, D., Hanauer, S.B., Lichtenstein, G.R., de Villiers, W.J., Olson, A., Johanns, J., Travers, S., Colombel, J. *Infliximab induction and maintenance therapy for ulcerative colitis: The ACT 2 trial*. Dig Dis Week (May 14-19, Chicago) 2005, Abst 688.

7. Eidelwein, A.P., Cuffari, C., Abadom, V., Oliva-Hemker, M. *Infliximab efficacy in pediatric ulcerative colitis*. Inflamm Bowel Dis 2005, 11(3): 213.

8. Jaernerot, G., Hertervig, E., Friis-Liby, I., Blomquist, L., Karlen, P., Graennoe, C., Stroem, M., Danielsson, A., Vilien, M., Verbaan, H., Hellstroem, P., Curman, B. *Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: A randomised placebo controlled study*. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst TUE-G-356.

9. Bermejo, F., López-Sanromán, A., Hinojosa, J., Castro, L., Jurado, C., Gómez-Belda, A.B. *Infliximab induces clinical, endoscopic and histological responses in refractory ulcerative colitis*. Rev Esp Enferm Dig 2004, 96(2): 94.

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Jaernerot, G., Hertervig, E., Friis-Liby, I.-L., Blomquist, L., Karlen, P., Graennoe, C., Stroem, M., Danielsson, A., Vilien, M., Verban, H., Hellstroem, P., Curman, B. *Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: A randomised placebo controlled study*. Falk Symp. Inflamm Bowel Dis: Transl Basic Res Clin Pract (May 7-8, Dubrovnik) 2004, Abst 122.

Maté Jiménez, J. *Infliximab in the treatment of severe ulcerative colitis*. Rev Esp Enferm Dig 2004, 96(2): 89.

Shen, E.H., Das, K.M. *Current therapeutic recommendations: Infliximab for ulcerative colitis*. J Clin Gastroenterol 2004, 38(9): 741.

INKP-100

INKP-100 (Visicol®), a sodium phosphate product, was initially launched in 2001 by InKine in the U.S. as tablets for bowel cleansing in preparation for colonoscopy. Currently, low-dose INKP-100 is undergoing phase III studies as a laxative in patients with constipation. INKP-100 is licensed to Zeria (Z-205) for development and marketing in Japan, where it is awaiting approval for bowel cleansing, and to Paladin in Canada, where it is known as Diacol® and is in late-stage development for the primary indication.

An open-label, randomized, dose-ranging study examined the safety and efficacy of sodium phosphate tablets (starting dose of 4 and 8 1.5-g tablets for groups A and B, respectively, each morning for 28 days and subsequent titration by 2 tablets) in 40 adults with chronic functional constipation or constipation-predominant IBS. Treatment was generally well tolerated. The constipation response rate in groups A and B was 100% and 96%,

respectively. The median time to first bowel movement was 21 and 4 h in groups A and B, respectively, although there was no significant difference in this parameter between groups by the end of day 2 (81% and 82%, respectively). Significant and sustained improvements in stool consistency, straining, cramping and bloating/distension were observed in both groups. Net downward titration occurred in 2 of 16 and 14 of 24 patients in groups A and B, respectively; net upward titration occurred in 6 and 3 patients, respectively. Group B had a significant change in potassium levels from baseline (–0.14 ± 0.46 mEq/l). Four patients withdrew from group B due to adverse events, none of which was serious. It was concluded that 2-4 tablets/day is a feasible starting dose (1, 2).

1. Rose, M., Katz, S., Malik, P., Pambianco, D., Medoff, J., Pruitt, R., Poulos, J., Rank, J. *Study of sodium phosphate (NaP, Visicol) tablets for constipation.* Am J Gastroenterol 2004, 99(10, Suppl.): Abst 331.

2. Medoff, J., Katz, S., Malik, P., Pambianco, D., Pruitt, R., Poulos, J., Rank, J., Rose, M. *Open-label, dose-ranging pilot study of 4 weeks of low-dose therapy with sodium phosphate tablets in chronically constipated adults*. Clin Ther 2004, 26(9): 1479.

INKP-102

INKP-102, a next-generation purgative sodium phosphate tablet developed at InKine, is currently awaiting registration in the U.S. for colon cleansing prior to colonoscopy. INKP-102 tablets are smaller in size and easier to swallow than the company's currently marketed sodium phosphate tablet product Visicol® (see above). The NDA was based on data from two multicenter, randomized, investigator-blind trials comparing INKP-102 to 40 Visicol® tablets, including a phase II dose-ranging trial and a phase III pivotal trial. Based on the results of these trials, the dose of INKP-102 proposed for marketing is 32 tablets (48 g), compared to the approved dose of 40 tablets (60 g) for Visicol®. The clinical trials indicated that the 32-tablet INKP-102 dose was comparable or significantly superior to 40 Visicol® tablets in all tested efficacy parameters, and met the primary efficacy endpoint of noninferiority for the overall colon-cleansing response rate in the phase III trial. In the combined safety database, the 32-tablet INKP-102 dose was significantly superior to Visicol® tablets in several key safety parameters. In the phase III trial, patient acceptance was significantly greater with INKP-102 compared to patients who took Visicol® tablets. Significantly more patients who took 32 INKP-102 tablets indicated that they would be willing to take the same preparation again for a future colonoscopy compared to those who took Visicol® tablets. Results from the phase II trial were supportive (1-6).

1. *InKine completes enrollment in phase II study of INKP-102*. DailyDrugNews.com (Daily Essentials) May 17, 2004.

2. *Phase II results for INKP-102*. DailyDrugNews.com (Daily Essentials) July 21, 2004.

3. *Phase III study of INKP-102 commences enrollment*. DailyDrugNews.com (Daily Essentials) Sept 13, 2004.

4. *Enrollment completed in phase III colonoscopy study of INKP-102*. DailyDrugNews.com (Daily Essentials) Dec 14, 2004.

5. *Promising results reported for the purgative INKP-102 in colonoscopy patients*. DailyDrugNews.com (Daily Essentials) Feb 28, 2005.

6. *InKine submits NDA for next generation purgative product*. DailyDrugNews.com (Daily Essentials) May 5, 2005.

Interferon Alfa-2b, New Formulations

Several companies are developing novel, longer acting formulations of interferon alfa-2b.

OctoPlus and Biolex have entered a collaboration for the codevelopment of a controlled-release formulation of a recombinant human alfa interferon. The product, named Locteron™, combines OctoPlus's proprietary biodegradable PolyActive™ drug delivery technology with Biolex's BLX-883 (interferon alfa-2b), a recombinant interferon alfa produced in its proprietary LEX System™. Locteron™ is designed to be more convenient for patients than the current pegylated interferon alfa products on the market, as it is expected to be administered every 2 weeks rather than every week as for available products. Initial focus will be on the treatment of hepatitis C. Locteron™ is expected to enter clinical trials in mid-2005. In preclinical studies, OctoPlus has demonstrated that BLX-883 formulated with PolyActive™ is comparable to commercially available interferon alfa, can be produced cost-effectively and is gradually released after injection, avoiding both high peak and low trough plasma levels. Dosing in a clinical study evaluating the safety, pharmacokinetics and pharmacodynamics of an immediate-release formulation commenced in February 2005 (1, 2).

Flamel Technologies' long-acting interferon alfa-2b XL, based on the company's Medusa® platform, is in phase I/II clinical evaluation for hepatitis B and C. Results from animal studies indicated that it appears to maintain the activity of native interferon, unlike pegylated interferon alfa-2b. The product is available for licensing.

1. *Biolex seeks approvals for phase I trials of BLX-883*. DailyDrugNews.com (Daily Essentials) Jan 13, 2005.

2. *OctoPlus and Biolex to jointly develop controlled-release alfa interferon*. DailyDrugNews.com (Daily Essentials) Feb 18, 2005.

Interferon Alfa-n1

Sumitomo Pharmaceuticals is assessing the potential of interferon alfa-n1 (Sumiferon®; licensed from GlaxoSmithKline) in combination with ribavirin for several

new indications. Phase III trials are under way in liver cirrhosis and for preventing the recurrence of hepatocellular carcinoma. The natural interferon alfa has been on the market in Japan for several years mainly for use in several cancers and leukemias and chronic hepatitis B and C.

Interferon Alfa-n3

HemispheRx's injectable formulation of human leukocyte-derived interferon alfa-n3 (Alferon N Injection®) is the only natural-source multispecies interferon product currently sold in the U.S., and also approved in several other countries, for the intralesional treatment of condylomata acuminata. Phase III trials are in preparation in patients with hepatitis C and West Nile virus infections. The hepatitis C trials are expected to begin soon in China in collaboration with Guangdong Medical Group.

Interferon Beta-1a

Serono's recombinant interferon beta-1a, widely introduced as Rebif® for the treatment of multiple sclerosis, is being tested in a phase III trial in Asian patients with chronic hepatitis C.

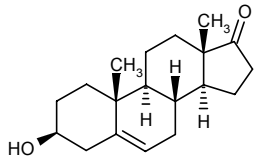
A multicenter, randomized, parallel-group, dose-finding study with a 24-week follow-up period examined the efficacy of interferon beta-1a (44 or 88 μg s.c. 3 times weekly for 48 weeks) in 267 patients with chronic hepatitis C who were unresponsive to prior interferon alfa therapy. The majority of adverse events reported were mild to moderate. Thirty-six patients withdrew due to adverse events. Trends for a dose-response relationship were observed for loss of detectable serum HCV RNA (virological response) and normalization of serum alanine aminotransferase (biochemical response). After 48 weeks of treatment, 8.3% of the patients had a virological response, of which 3.4% were sustained virological responses. Of the 23 Chinese patients involved in the study, 5 (21.7%) had sustained virological responses. Race was found to be the only variable related to sustained virological response. Complete viral clearance also occurred significantly earlier in Chinese as compared to non-Chinese patients (1).

1. Cheng, P.N., Marcellin, P., Bacon, B., Farrell, G., Parsons, I., Wee, T., Chang, T.-T. *Racial differences in responses to interferon-beta-1a in chronic hepatitis C unresponsive to interferon-alpha: A better response in Chinese patients*. J Viral Hepat 2004, 11(5): 418.

Interferon Omega

Interferon omega, a naturally occurring human type 1 interferon manufactured using a novel genetic engineering process licensed from Boehringer Ingelheim, is in phase II trials at Intarcia Therapeutics (the former BioMedicines) for the treatment of hepatitis C. Intarcia is also developing a long-acting formulation using Alza's DUROS® delivery system which allows the continuous delivery of interferon omega for 3 or more months via a subcutaneous implant.

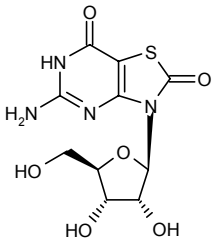
IP-1001



Pharmadigm, now named Inflabloc Pharmaceuticals, has successfully completed a USD 3 million Series B venture financing, the proceeds from which will be used to initiate phase II studies of its lead product targeting Crohn's disease, as well as to continue development in other inflammatory therapeutic areas. The company's lead product, IP-1001, is a proprietary oral prasterone (dehydroepiandrosterone, DHEA) combination product for the treatment of chronic and subchronic inflammatory diseases (1).

1. *Pharmadigm completes financing, changes corporate name to Inflabloc*. DailyDrugNews.com (Daily Essentials) Aug 31, 2004.

Isatoribine

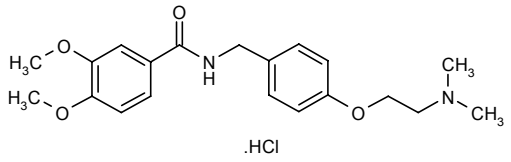


Isatoribine is a TLR7 receptor agonist which has completed phase I clinical development at Anadys as an intravenous therapy for the treatment of chronic hepatitis C.

The effects of isatoribine were evaluated in an open-label, dose-escalating clinical trial involving the i.v. administration of doses of 200-800 mg once daily to 32 patients with chronic HCV infection. Isatoribine dose-dependently decreased HCV viral load and increased plasma levels of 2'5'-oligoadenylate synthetase (a biomarker for interferon alfa activity), although both parameters returned to baseline values within 7 days after the end of treatment. All adverse events were mild or moderate, and the most common were insomnia, joint pain and asthenia (1).

1. Horsmans, Y., Berg, T., Desager, J.-P. et al. *Isatoribine, a toll-like receptor 7 agonist, significantly reduced plasma viral load in a clinical proof-of-concept study in patients with chronic hepatitis C virus infection*. Hepatology 2004, 40(4, Suppl. 1): Abst 270.

Itopride Hydrochloride



Axcan Pharma has enrolled over 1,000 patients in its phase III clinical trials in Canada and the U.S. to demonstrate the safety and efficacy of itopride hydrochloride (Itax™) in the treatment of functional dyspepsia. Itopride is a dopamine D2 antagonist with gastroprokinetic and antiemetic properties for the treatment of gastrointestinal symptoms caused by reduced gastrointestinal motility. Each study will assess the efficacy of 100-mg tablets of itopride in the treatment of functional dyspepsia. The primary efficacy endpoint will be the assessment of abdominal symptom relief. The secondary endpoint will assess changes in the quality of life of patients undergoing itopride or placebo therapy. Axcan will monitor adverse drug reactions and conduct standard laboratory measurements in order to determine the safety of itopride. In addition, the company plans to include repeated 12-lead electrocardiograms as part of its phase III protocols in order to confirm the absence of cardiac adverse events, as already observed in the phase I and II studies. Pending positive outcomes from the studies, Axcan expects to file for regulatory approval in the U.S. for the treatment of functional dyspepsia in the first half of 2006, with regulatory filings in Canada and selected Western European countries following later in the year. The company also plans to study its use in diabetic gastroparesis. Axcan licensed itopride from Abbott in September 2003 for North America, the E.U. (excluding the U.K., France, Germany, Italy and Spain) and Latin America. The product has been marketed in Japan by the Abbott-owned Hokuriku and Astellas (formerly Fujisawa) since 1995 as Ganaton® for the treatment of gastroparesis (1-3).

Cardiac safety results of Axcan's supratherapeutic study for itopride showed the agent to have no clinically relevant effects on heart rate, cardiac conduction and cardiac repolarization. The electrocardiogram (ECG) trial was intended to determine the cardiotoxic potential of itopride. The randomized, placebo- and positive-controlled, parallel-design, multiple-dose trial involved 162 healthy male and female volunteers aged 18-45 years. Itopride at a dose of 100 mg 3 times daily and at a supratherapeutic dose of 400 mg 3 times daily was compared to placebo and moxifloxacin, an antibiotic that produces a 5-10-ms effect on cardiac repolarization, as defined by changes in the individually corrected Q-T interval ($Q\text{-}T_{cI}$). An expert centralized ECG laboratory analyzed more than 13,000 digital ECGs using a high-resolution manual on-screen caliper method with annotations. All subjects received placebo on day 1 in a single-blind fashion. ECGs were recorded using a digital continuous 12-lead (H-12) system over 24 h at baseline and steady state. The study confirmed an expected 8-ms placebo-corrected $Q\text{-}T_c$ prolongation in the moxifloxacin group. However, itopride at clinical and supratherapeutic doses showed a 1- and 2-ms placebo-corrected change and 2- and 3-ms change using the maximum $Q\text{-}T_{cI}$ duration derived by taking the longest interval at any time point in each subject. Therefore, the variation in $Q\text{-}T_c$ for the itopride groups was well within the 5-ms safety margin considered by experts as having no impact on cardiac safety (4).

A randomized, double-blind, placebo-controlled phase II study examined the safety and efficacy of itopride (50, 100 or 200 mg t.i.d. for 4 and 8 weeks) in 554 patients with dyspepsia. Treatment was well tolerated; 523 patients completed the trial and data were available from 424. In terms of change in overall severity of patients' functional dyspepsia as measured by the Leeds Dyspepsia Questionnaire (LDQ), all itopride groups showed statistically significant improvement after 8 weeks of treatment. Of patients treated with placebo, 46.6% were symptom-free or markedly improved compared to 60.8%, 63.2% and 71.4% of patients, respectively, treated with itopride at doses of 50, 100 and 200. Response in terms of pain and fullness was significantly better in the itopride groups (77.3% for 50 mg, 78.9% for 100 mg and 76.2% for 200 mg) in comparison to the placebo group (63.6%). After 8 weeks of treatment, itopride was significantly better in controlling symptoms than placebo. No cardiac adverse events or $Q\text{-}T_c$ prolongation were observed with treatment (5).

The efficacy of itopride (50 mg/day p.o.) in accelerating postoperative ileus restoration was demonstrated in a randomized, double-blind trial conducted in 50 patients scheduled for laparoscopic cholecystectomy. A significantly higher incidence of nausea was observed in the placebo group on the day of surgery and on postoperative days 1 and 2 as compared to the group receiving itopride; the incidence of vomiting was similar between groups. Normalization of the EEG curve (performed 6, 24 and 48 h postsurgery) as an indicator of gastric motility was accelerated in itopride-treated patients as compared to placebo (6).

The effect of itopride (150 mg/day p.o. for 2 weeks) on gastric emptying was examined in a study in 12 patients with type 2 diabetes diagnosed with gastroparesis and who exhibited reduced vibration sensation in the lower leg and low nerve impulse transmission velocity. Following treatment with the agent, the pre- and postprandial electrical gastrography dominant frequencies measured significantly increased from 58.1% and 41.7%, respectively, at baseline to 72.9% and 71.4%, respectively. In addition, gastric emptying of radiopaque markers

after 2 h of ingestion was significantly increased with treatment from 5% at baseline to 24%. A significant increase in blood acetaminophen concentrations at 1 h after a meal (from 9.7 μg/ml to 14 μg/ml) was also observed after treatment (7).

1. *Axcan to begin phase III clinical trials with Itax*. DailyDrugNews.com (Daily Essentials) May 17, 2004.

2. *Axcan Pharma reports Q2 R&D highlights*. Axcan Pharma Press Release 2004, May 6.

3. *More than 1000 patients enrolled in Axcan's ITAX phase III dyspepsia studies*. Axcan Pharma Press Release 2005, June 9.

4. *Axcan's high dose safety study on ITAX in healthy subjects shows no cardiac adverse drug reaction - Results of a large, high dose, electrocardiogram trial completed in 162 healthy subjects.* Axcan Pharma Press Release 2004, Dec 15.

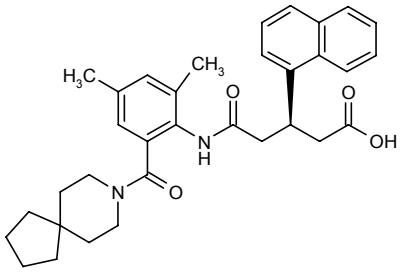
5. Holtmann, G, Schnittker, J., Boos, G., Matiba, B., Talley, N.J. *A randomized, double-blind, placebo-controlled dose finding study of itopride for the treatment of patients with functional dyspepsia*. Gastroenterology 2004, 126(4, Suppl. 2): Abst 748.

6. Frasko, R., Gurlich, R., Maruna, P. *Randomized clinical trial of itopride for the treatment of postoperative ileus after laparoscopic cholecystectomy.* 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst OP-G-43.

7. Basque, J.-R. et al. *Efficacy of itopride hydrochloride on gastric emptying in patients with diabetic gastroparesis*. Dig Dis Week (May 14-19, Chicago) 2005, Abst S969.

Original monograph – Drugs Fut 1995, 20(12): 1220.

Itriglumide



Rottapharm's itriglumide (CR-2945) is a potent and selective cholecystokinin CCK_2 receptor antagonist shown in phase I trials to be safe and well tolerated following single oral doses to healthy volunteers and to dose-dependently inhibit gastrin-induced gastric acid secretion. The compound has potential for the treatment of peptic ulcers, dyspepsia and GERD, as well as panic disorders and anxiety.

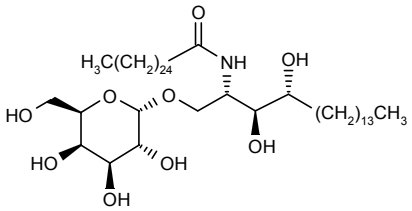
JTK-003

JTK-003 is an RNA-directed RNA polymerase (NS5B) inhibitor in phase II trials at Japan Tobacco for the oral treatment of hepatitis C.

KPE-02003002

KPE-02003002, a synthetic derivative of a phytochemical with several chiral centers, is undergoing phase II clinical trials for the treatment of HCV infection. The compound was discovered through a collaboration between Kemin Pharma, the National Institutes of Health (NIH) and the Rega Institute for Medical Research.

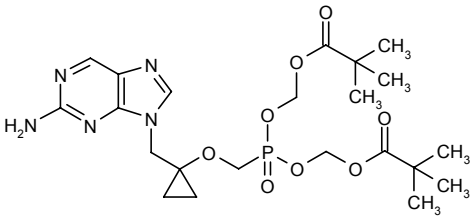
KRN-7000



KRN-7000 (AGL-582), or α-galactosylceramide, is an immunostimulant developed by Kirin Brewery and currently in phase I/II trials for the treatment of hepatitis C, as well as phase I trials for the treatment of cancer.

Original monograph – Drugs Fut 1996, 21: 152.

LB-80380 (ANA-380)



LB-80380 (ANA-380) is in phase II trials at Anadys and LG Life Sciences for the treatment of hepatitis B. The drug is a nucleotide analogue and an orally active double prodrug of LB-80317. The prodrug was developed to correct the low cell permeability and poor oral bioavailability of the parent drug LB-80317, and produces LB-80317 intracellularly as a result of a series of metabolic events. In April 2004, Anadys acquired an exclusive license from LG Life Sciences for the commercialization of LB-80380 worldwide excluding China, Korea, India and Southeast Asia. A double-blind, randomized, placebo-controlled, dose-escalating phase I/IIa trial demonstrated that oral administration of LB-80380 (30, 60, 120 or 240 mg p.o. once daily) over 4 weeks was well tolerated and reduced HBV viral load by 99.9% in the chronic HBV-infected patients treated in the study, although values returned to baseline after a follow-up period of 12 weeks. In a multicenter, dose-finding phase II clinical trial, LB-80380 (30, 60 or 90 mg p.o.) was administered once daily for 12

Table XVII: Clinical studies of LB-80380 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Randomized Double-blind	LB-80380, 30 mg p.o. o.d. x 28 d (n=6) LB-80380, 60 mg p.o. o.d. x 28 d (n=6) LB-80380, 120 mg p.o. o.d. x 28 d (n=6) LB-80380, 240 mg p.o. o.d. x 28 d (n=6) Placebo (n=4)	28	LB-80380 was well tolerated and decreased serum viral DNA levels in patients with chronic hepatitis B	2
Hepatitis B	Open Multicenter	LB-80380, 30 mg o.d. + Lamivudine, 100 mg x 4 wks → LB-80380, 30 mg o.d. x 8 wks (n=13) LB-80380, 60 mg o.d. + Lamivudine, 100 mg x 4 wks → LB-80380, 60 mg o.d. x 8 wks (n=13) LB-80380, 90 mg o.d. + Lamivudine, 100 mg x 4 wks → LB-80380, 90 mg o.d. x 12 wks (n=14)	40	LB-80380 given for 12 weeks was safe and effective in reducing plasma viral DNA levels in patients infected with lamivudine-resistant hepatitis B virus	3

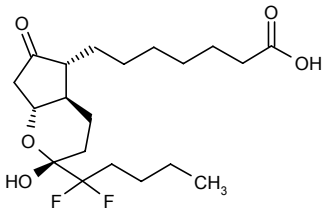
weeks to 40 HBeAg-positive patients infected with lamivudine-resistant HBV; each patient also received concomitant lamivudine (100 mg) during the first 4 study weeks. An interim analysis revealed that plasma HBV DNA levels decreased dose-dependently with a lamivudine/LB-80380 combination, and continued to do so after discontinuation of lamivudine. At the end of the study, baseline plasma HBV DNA levels of patients treated with 30 and 60 mg/day of LB-80380 decreased by about 2.8 and 3.2 $\log_{10}$ units, respectively. All doses were well tolerated and no serious adverse events were reported (1-3) (see Table XVII).

1. *First two cohorts enrolled in phase II study of ANA-380 for HBV*. DailyDrugNews.com (Daily Essentials) Sept 17, 2004.

2. Yuen, M.F., Kim, J., Averett, D. et al. *Phase I/II double-blind, randomized, placebo-controlled study of the novel anti-HBV agent LB80380/ANA380 in patients with chronic HBV infection*. Hepatology 2004, 40(4, Suppl. 1): Abst 23.

3. Lai, C.L. et al. *Interim report for a phase II, multi-centre, dose-escalating study of LB80380/ANA380 in hepatitis B patients with lamivudine-resistant YMDD mutant HBV*. 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 72.

Lubiprostone



Sucampo has submitted an NDA to the FDA seeking approval to market lubiprostone (SPI-0211, RU-0211), a novel prostaglandin compound with a unique mechanism of action, for the treatment of chronic idiopathic constipation and associated symptoms in adults. Lubiprostone, administered orally, has been shown to work locally in the gastrointestinal tract by activating specific chloride channels on cells lining the small intestine and increasing intestinal fluid secretion. The NDA included results from two phase III pivotal efficacy studies, results of a randomized withdrawal study and three long-term safety studies, including two 12-month safety studies. The pivotal studies demonstrated that lubiprostone produced rapid and sustained effects in treating the symptoms of constipation, performing significantly better than placebo in men and women over age 18 for all constipation variables tested. Results from the randomized withdrawal study indicated no rebound effect after treatment discontinuation. Based on an agreement reached in October 2004, Takeda will market lubiprostone, once approved, in the U.S. and Canada. Takeda also has the option for marketing rights in other territories, including Japan and Europe. Lubiprostone has also completed a phase II trial in constipation-predominant irritable bowel syndrome (IBS-C), and phase III trials are expected to begin shortly. Furthermore, lubiprostone is being evaluated for other bowel dysfunctions and gastrointestinal disturbances, *i.e.*, IBS, postoperative bowel dysfunction and opioid-induced bowel dyfsunction (1-3).

In the above-mentioned randomized withdrawal trial, lubiprostone (24 μg b.i.d.) was administered to 128 patients with constipation for 4 weeks, followed by randomization to continue receiving lubiprostone or switch to placebo for 3 weeks. Compared to baseline, lubiprostone increased weekly spontaneous bowel movement frequency from 1.36 to 6.20 at 4 weeks and significantly improved other parameters (*e.g.,* bowel movement consistency and straining, abdominal bloating and discomfort, and constipation severity). Switching to placebo was associated with a reduction in spontaneous bowel movement frequency and a higher relapse rate (44.4% *vs.* 18.2%) compared to lubiprostone therapy, but no evidence of a rebound effect was found. No patients showed drug-related serious adverse events (4) (Table XVIII).

Table XVIII: Clinical studies of lubiprostone (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Constipation	Randomized Double-blind	Lubiprostone, 24 µg b.i.d. x 7 wks Lubiprostone, 24 µg b.i.d. x 4 wks → Placebo	128	Lubiprostone significantly increased the frequency of small bowel movements and was well tolerated in patients with constipation. Switching to placebo was associated with a decrease in the frequency of small bowel movements, but no evidence of a rebound effect was found	4

1. *Positive results from RW study of SPI-0211 for constipation*. DailyDrugNews.com (Daily Essentials) May 13, 2004.

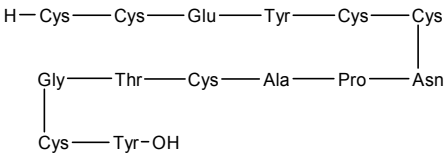
2. *Sucampo and Takeda enter collaboration and license agreement for lubiprostone*. DailyDrugNews.com (Daily Essentials) Nov 4, 2004.

3. *Sucampo submits lubiprostone NDA*. DailyDrugNews.com (Daily Essentials) April 5, 2005.

4. Johanson, J.F., Gargano, M.A., Holland, P.C., Patchen, M.L., Ueno, R. *Phase III, randomized withdrawal study of RU-0211, a novel chloride channel activator for the treatment of constipation*. Gastroenterology 2004, 126(4, Suppl. 2): Abst 749.

Original monograph – Drugs Fut 2004, 29(4): 336.

MD-1100



Microbia has initiated a phase I trial of MD-1100, an orally administered compound with a novel mechanism of action under investigation for the treatment of constipation-predominant IBS. The phase I studies will evaluate the safety, pharmacokinetic and pharmacodynamic properties of MD-1100 in healthy volunteers. MD-1100 is a potent superagonist of guanylate cyclase C, a receptor found on the surface of intestinal cells. Preclinical studies show that MD-1100 acts on the key defining attributes of IBS, increasing gastrointestinal transit and secretion while decreasing gastrointestinal pain. Microbia designed MD-1100 to specifically target the intestine without more general systemic exposure (1). Additional target indications for MD-1100 include GERD, chronic constipation and dyspepsia.

1. *MD-1100 enters phase I study for IBS*. DailyDrugNews.com (Daily Essentials) Nov 4, 2004.

MDX-066

In the fall of 2004, the FDA allowed an IND for The Massachusetts Biologic Laboratories (MBL) of the University of Massachusetts Medical School (UMMS) and Medarex to initiate a phase I trial of MDX-066 (CDA-1), a novel, fully human monoclonal antibody designed to treat *C. difficile*-associated diarrhea (CDAD). The dose-escalation trial of MDX-066 will enroll up to 30 healthy volunteers. The participants will be monitored for any adverse side effects and their blood will be tested to measure the concentration of the antibody in their systems. MDX-066 is believed to target and neutralize the effects of toxin A, a toxin produced by *C. difficile*. By binding to toxin A, MDX-066 used in conjunction with antibiotic treatment would potentially forestall the disease state that arises from the toxin's effect on the intestinal tract. Published epidemiological studies of hospitalized patients at risk for CDAD have shown a positive correlation between detectable levels of antibody in the blood to toxin A and protection from disease or relapse (1).

1. *Phase I cleared to begin for CDA-1 for C. difficile associated diarrhea*. DailyDrugNews.com (Daily Essentials) Oct 1, 2004.

Additional References

Mandell, R.B., Babcock, G.J., Hill, A.C., Coccia, J.A., Zhang, H., Lowy, I., Graziano, R.F., Ambrosino, D.M., Thomas, W.D. *Neutralizing human monoclonal antibodies against Clostridium difficile toxin A*. 44th Intersci Conf Antimicrob Agents Chemother (Oct 30-Nov 2, Washington DC) 2004, Abst B-1697.

MDX-1100

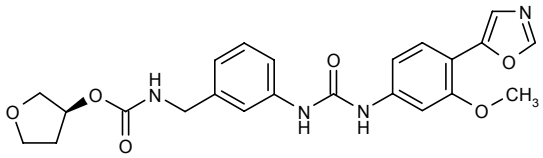
MDX-1100 is a fully human antibody designed to target IP-10 (also known as CXCL10), a chemokine involved in the migration of activated T-cells and monocytes to sites of inflammation. Medarex acquired full rights to the antibody as part of its acquisition of Ability Biomedical in August 2004. The company just recently announced FDA allowance of its IND to begin phase I clinical trials of MDX-1100 as a treatment for ulcerative colitis. The multicenter trial is expected to enroll up to 32 patients with ulcerative colitis and will examine the safety and preliminary efficacy of single escalating doses of the antibody (1).

1. Medarex announces phase I clinical trial of MDX-1100, a fully human anti-IP10 antibody, for the treatment of ulcerative colitis. Medarex Press Release 2005, May 11.

ME-3738

ME-3738 is an IL-6 agonist in phase II clinical development by Meiji Seika for the oral treatment of chronic hepatitis C.

Merimepodib



Vertex has commenced enrollment in a phase IIb study of merimepodib (VX-497), an orally active inhibitor of IMP dehydrogenase (IMPDH), for the treatment of HCV infection in patients who are nonresponders to prior treatment with pegylated interferon and ribavirin. The U.S.-based trial will enroll approximately 315 patients who will receive merimepodib or placebo in combination with Pegasys® (peginterferon alfa-2a) and Copegus® (ribavirin), both provided by Roche. As part of the supply agreement with Roche, Vertex will share data and data analysis with Roche during the course of the study. The double-blind, placebo-controlled, randomized METRO (MErimepodib TRiple cOmbination) study will evaluate the antiviral activity of two doses of merimepodib in combination with Pegasys® and Copegus®. Patients will receive 50 or 100 mg of merimepodib or placebo twice daily in combination with standard doses of Pegasys® and Copegus® for an initial period of 24 weeks. At the end of 24 weeks, patients with undetectable HCV RNA will receive combination therapy with Pegasys® and Copegus® only for an additional 24 weeks. Patients completing the 48-week treatment period will be followed for an additional 24-week treatment-free period. More than 40 sites will take part in the trial. The study aims to evaluate the safety, pharmacokinetics and efficacy of merimepodib in combination with pegylated interferon. The primary endpoint is to evaluate the antiviral activity of merimepodib and perform an assessment of the proportion of merimepodib-treated patients who achieve a sustained virological response compared to placebo at week 72. Secondary endpoints include evaluation of the antiviral activity in merimepodib-treated patients at 12, 24, and 48 weeks. IMPDH inhibitors such as merimepodib may enhance the antiviral activity of ribavirin by depleting guanosine triphosphate (GTP) and increasing the rate of incorporation of ribavirin into viral RNA, rendering the virus nonfunctional. Six-month results from a phase II study demonstrated that relative to placebo treatment, merimepodib treatment produced a statistically significant, dose-dependent increase in the percentage of treatment-refractory patients with HCV genotype 1 who achieved undetectable levels of HCV RNA at 6 months. In combination with the standard of care, merimepodib may help to increase the sustained viral response rate in HCV patients (1, 2).

A phase II clinical trial in 31 HCV-infected patients nonresponsive to previous standard therapy with interferon alfa plus ribavirin evaluated the potential benefits of merimepodib in this indication. Each patient was randomized to receive placebo or merimepodib (25 or 50 mg b.i.d.) plus pegylated interferon alfa and ribavirin. A logistic regression analysis on pharmacokinetic data from 28 patients who completed 12 weeks of treatment suggested that higher levels of exposure to merimepodib were associated with greater reductions in HCV viral load but did not increase the risk of anemia associated with ribavirin (3) (Table XIX).

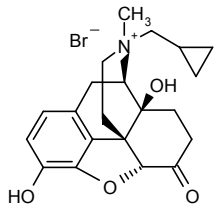
1. *Vertex plans METRO study for merimepodib*. DailyDrugNews.com (Daily Essentials) May 27, 2004.

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

3. Zha, J., Garg, V., McNair, L., Marcellin, P., Alam, J., Purdy, S., Ette, E. *Pharmacokinetic-pharmacodynamic relationships of merimepodib and ribavirin in pegylated interferon-alfa/ribavirin/merimepodib treated genotype-1 HCV patients non-responsive to previous therapy with interferon-alfa/ribavirin*. Hepatology 2004, 40(4, Suppl. 1): Abst 193.

Original monograph – Drugs Fut 2000, 25: 809.

Methylnaltrexone Bromide



Progenics has completed phase I trials of two different oral formulations of its investigational drug methylnaltrex-

Table XIX: Clinical studies of merimepodib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis C	Randomized Double-blind Crossover	Merimepodib, 25 mg b.i.d. + Peginterferon alfa + Ribavirin x 12 wks Merimepodib, 50 mg b.i.d. + Peginterferon alfa + Ribavirin x 12 wks Placebo + Peginterferon alfa + Ribavirin x 12 wks	31	Compared with placebo, merimepodib decreased the viral load in patients with chronic hepatitis C without increasing the risk for anemia associated with ribavirin therapy	3

one bromide (MNTX), a peripheral opioid receptor antagonist. Preliminary analysis of data from 61 healthy volunteers who received study medication at 3 dose levels indicated that the drug was well tolerated and exhibited predictable pharmacokinetics. An oral formulation and dose levels have been selected that will be studied in phase II trials in chronic pain patients with opioid-induced constipation. Progenics is evaluating three dosage forms of MNTX in clinical trials: subcutaneous MNTX for opioid-induced constipation in patients with advanced medical illness (phase III; see below), intravenous MNTX for the treatment of postoperative ileus (phase II; see below) and oral MNTX for the relief of opioid-induced constipation in patients with chronic pain (phase I/II) (1-3).

A multicenter, double-blind, randomized, placebo-controlled phase II clinical trial established that MNTX improved the management of bowel dysfunction following major abdominal surgery. A total of 65 patients who underwent segmental colectomies mainly due to cancer or diverticular disease were given placebo or MNTX (0.3 mg/kg i.v.) every 6 h for up to 7 days after surgery. MNTX significantly accelerated gastrointestinal recovery and allowed a faster discharge of the patients from the hospital. MNTX was also well tolerated and no serious drug-related adverse events were found (4).

A double-blind, randomized, placebo-controlled phase III clinical trial assessed the effects of MNTX in the treatment of opioid-induced constipation. A total of 154 hospice patients with advanced medical illness and opioid-induced constipation unresponsive to laxatives or stool softeners were given a single dose of placebo or MNTX (0.15 or 0.30 mg/kg s.c.). The percentage of patients who experienced laxation within 4 h after treatment was significantly lower with placebo (13%) compared to MNTX (62% and 50% with 0.15 and 0.30 mg/kg, respectively). The percentage of patients with laxation within 24 h was, respectively, 33%, 68% and 64%. The median time to laxation decreased dose-dependently with MNTX (70 and 45 min, respectively, with 0.15 and 0.30 mg/kg) compared to placebo (< 24 h). The most common adverse events were transient abdominal cramping and flatulence (5).

The results of a randomized, double-blind study in healthy male or postmenopausal female volunteers (n=54) suggested that peripheral opiate agonists may relieve the constipating effects of codeine. After a 7-day evaluation of colonic transit time (CTT) and bowel habits, study subjects received codeine (60 mg/day) for 7 days and underwent CTT measurement. After drug washout, subjects were given codeine (60 mg/kg) plus methylnaltrexone and again underwent CTT measurement. It was found that codeine often prolonged CTT but also promoted colonic transit in some individuals. Methylnaltrexone dose-dependently reversed the effects of codeine and was well tolerated. Pharmacokinetic analyses of the effects of methylnaltrexone are ongoing (6).

1. *Oral MNTX formulations complete phase I trials*. DailyDrugNews.com (Daily Essentials) May 27, 2004.

2. *Target enrollment reached in phase II study of methylnaltrexone for POI*. DailyDrugNews.com (Daily Essentials) Oct 11, 2004.

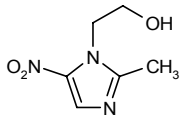
3. *Target enrollment reached in phase III study of methylnaltrexone*. DailyDrugNews.com (Daily Essentials) Dec 9, 2004.

4. *Improved gastrointestinal recovery found with MNTX after abdominal surgery*. DailyDrugNews.com (Daily Essentials) Jan 24, 2005.

5. *MNTX shows efficacy in the treatment of opioid-induced constipation*. DailyDrugNews.com (Daily Essentials) March 17, 2005.

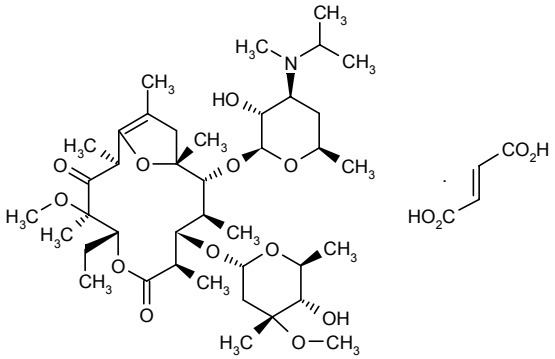
6. Gruss, H.-J., Sutton, A., Horton, P., Clauss, R., Barras, N. *Codeine-induced slow transit in healthy volunteers and its alteration by peripheral opiate agonists.* Dig Dis Week/106th Annu Meet Am Gastroenterol Assoc (May 14-19, Chicago) 2005, Abst T1142.

Metronidazole, Ointment



SLA Pharma is conducting phase III clinical trials with metronidazole ointment for the treatment of perianal Crohn's disease.

Mitemcinal Fumarate



Mitemcinal fumarate (GM-611) is a motilin receptor agonist in phase II trials at Chugai for the treatment of delayed gastric emptying (gastroparesis) in diabetes and IBS.

The GM-611-03 study was a multicenter, double-blind phase IIa clinical trial that randomized 106 patients with symptomatic diabetic (n=60) or idiopathic gastroparesis (n=46) to receive placebo or mitemcinal fumarate at doses of 10, 20 or 30 mg b.i.d. or 20 mg t.i.d. orally for 28

days. At the end of the treatment period, mitemcinal improved gastric emptying in both types of patients, but statistical significance was only reached in patients with diabetic gastroparesis. The most common adverse events included hypoglycemia, diarrhea, sinusitis, headache, dyspepsia, flu-like illness and constipation, but only 2 patients reported serious adverse events (viral syndrome and diabetic ketoacidosis) during the study. All patients treated with mitemcinal showed a slight increase in the levels of hepatic enzymes (1, 2) (Table XX).

The GM-611-05 study was a randomized, double-blind, placebo-controlled phase IIb clinical trial that evaluated the effects of mitemcinal in patients with idiopathic and diabetic gastroparesis. The patients were treated with mitemcinal (5 or 10 mg b.i.d.) or placebo for 90 days and recorded symptoms in a daily diary with global symptom assessment each week. A complete response (a monthly response for all 3 study months) was seen in 22.9%, 24.4% and 26.9% of patients in the placebo, 5 and 10 mg mitemcinal groups, respectively. This effect was stronger in patients with type 1 diabetes, who achieved complete response rates of 17.1%, 21.7% and 29.3%, respectively. More severe baseline symptoms were also associated with a greater treatment effect. Safety profiles did not differ significantly between mitemcinal and placebo (3) (Table XX).

A pharmaceutical formulation suitable for repeated use comprising the motilin receptor agonist mitemcinal fumarate, or a pharmaceutically acceptable salt thereof, has been claimed for the prevention and/or treatment of dyschezia (4).

1. Kipnes, M., Schmitt, C., Dibaise, J., Fang, J., Sarosiek, I. *Safety of mitemcinal fumarate (GM-611) in patients with symptomatic gastroparesis*. 64th Annu Meet Sci Sess Am Diabetes Assoc (June 4-8, Orlando) 2004, Abst 558-P.

2. Kipnes, M.S., Schmitt, C.M., DiBaise, J.K., Fang, J.C., Sarosiek, I. *Effect of mitemcinal fumarate (GM-611) on gastric emptying, safety and tolerability in patients with diabetic or idiopathic gastroparesis*. 86th Annu Meet Endocr Soc (June 16-19, New Orleans) 2004, Abst P3-577.

3. McCallum, R.W., Fogel, R., Fang, J.C., Altman, R.S., Faichney, J., Goldstein, B.J. *Mitemcinal fumarate (GM-611) provided symptomatic relief of diabetic gastroparesis, especially in type 1 diabetes: Results of a 12-week, multi-center, double-blind, placebo-controlled, randomized phase 2b study (GM-611-05).* Dig Dis Week (May 14-19, Chicago) 2005, Abst T1149.

4. Kamei, K. et al. (Chugai Pharmaceutical Co. Ltd.) *Therapeutic and/or preventive agent for dyschezia*. WO 0437273.

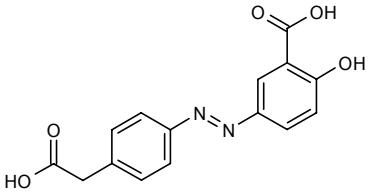
Original monograph – Drugs Fut 1994, 19(10): 910.

MLN-02

Millennium has gained back the rights for MLN-02, an investigational humanized monoclonal antibody that binds to the T-cell integrin $\alpha_4\beta_7$ and prevents the migration of T-cells to the gut, from Genentech. In phase II trials, MLN-02 met its primary efficacy endpoint in patients with ulcerative colitis and its secondary endpoint in patients with Crohn's disease. Millennium is now proceeding with the development of the molecule, including optimizing a commercial manufacturing process (1).

1. *Millennium Pharmaceuticals reports Q2 R&D highlights*. Millennium Pharmaceuticals Press Release 2004, July 22.

NAA-004

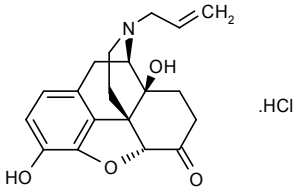


NAA-004 (Apaza™) is a dual antiinflammatory and immunomodulating therapy in phase I/II trials at Nobex for the treatment of inflammatory bowel disease. The drug couples the antiinflammatory action of 5-aminosalicylic acid (5-ASA) and the immunomodulating effects of 4-aminophenylacetic acid (4-APAA). Upon reaching the colon, bacteria cleave the azo bond joining the two substances, thereby releasing the active compounds locally.

Table XX: Clinical studies of mitemcinal fumarate (from Prous Science Integrity®).

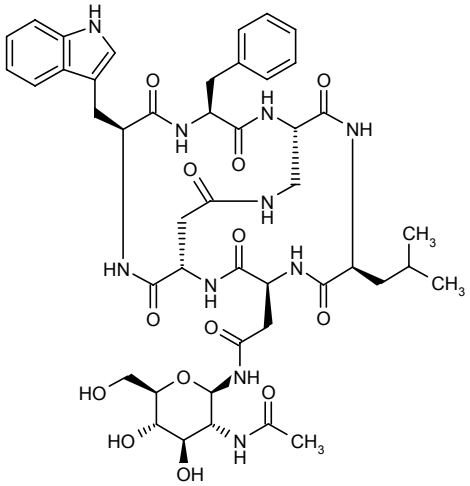
Indication	Design	Treatments	n	Conclusions	Ref.
Gastroparesis, diabetic	Randomized Double-blind Multicenter	Mitemcinal, 10 mg p.o. b.i.d. x 28 d (n=21) Mitemcinal, 20 mg p.o. b.i.d. x 28 d (n=21) Mitemcinal, 20 mg p.o. t.i.d. x 28 d (n=21) Mitemcinal, 30 mg p.o. b.i.d. x 28 d (n=21) Placebo (n=22)	106	Mitemcinal was well tolerated and significantly improved gastric emptying in patients with diabetic gastroparesis, but had no significant effects in patients with idiopathic gastroparesis	2
Gastroparesis	Randomized Double-blind	Mitemcinal, 5 mg p.o. b.i.d. x 90 d Mitemcinal, 10 mg p.o. b.i.d. x 90 d Placebo	392	A nonsignificant dose-response effect on gastroparesis symptoms was seen with mitemcinal treatment which was stronger in patients with type 1 diabetes	3

Naloxone Hydrochloride



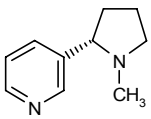
Naloxone hydrochloride is an opioid receptor antagonist presently being evaluated in phase II trials at SLA Pharma for the oral treatment of opioid-induced constipation.

Nepadutant



Nepadutant is a glycosylated bicyclic peptide discovered by Menarini that acts as a potent, selective and competitive tachykinin NK_2 receptor antagonist. The company is currently conducting phase IIa clinical studies for the treatment of IBS. In animal models of IBS, nepadutant corrected colon visceral hyperalgesia, recognized as the main pathophysiological event underlying IBS symptoms.

Nicotine, Enema/Oral Formulations

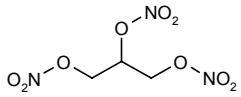


SLA Pharma is developing nicotine products for the treatment of ulcerative colitis. An enema formulation is currently in phase III trials and an oral capsule formulation is undergoing phase I clinical testing.

Additional References

Ingram, J.R. et al. *Nicotine enemas for treatment of ulcerative colitis: A study of the pharmacokinetics and adverse events associated with three doses of nicotine*. Aliment Pharmacol Ther 2004, 20(8): 859.

Nitroglycerin, Ointment



Cellegy's nitroglycerin ointment (Rectogesic® outside the U.S., Cellegesic®) is currently available in Australia, New Zealand, the U.K. and South Korea for the treatment of pain associated with chronic anal fissures. In December 2004, the company received a not approvable letter from the FDA and regulatory approval in Canada is pending; Cellegy recently submitted a response to the FDA letter containing new analyses of data from its phase III trials. In terms of clinical development, Cellegy is also developing nitroglycerin ointment in phase II trials for the treatment of various complications of hemorrhoids, and a phase I/II trial is under way to evaluate its potential for the treatment of dyspareunia. ProStrakan is the company's European marketing partner (1-7).

1. *Cellegy submits NDA for Cellegesic to treat chronic anal fissure pain*. Cellegy Pharmaceuticals, Inc. Press Release 2004, June 30.

2. *Cellegy announces Cellegesic(TM) approvable in the U.K. for treating chronic anal fissure pain*. Cellegy Pharmaceuticals, Inc. Press Release 2004, July 7.

3. *Cellegesic NDA accepted for review*. DailyDrugNews.com (Daily Essentials) Sept 10, 2004.

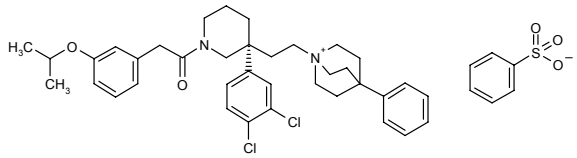
4. *Rectogesic approved in U.K.* DailyDrugNews.com (Daily Essentials) Sept 17, 2004.

5. *Not approvable letter for Cellegesic*. DailyDrugNews.com (Daily Essentials) Dec 29, 2004.

6. *Cellegy Pharmaceuticals' Cellegesic(TM) granted "Priority Review" by U.S. Food and Drug Administration*. Cellegy Pharmaceuticals, Inc. Press Release 2004, Oct 14.

7. *Cellegy submits Cellegesic written response*. DailyDrugNews.com (Daily Essentials) April 20, 2005.

Nolpitantium Besilate



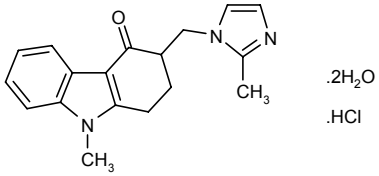
Nolpitantium besilate (SR-140033) is a tachykinin NK_1 antagonist in phase IIb clinical development by Sanofi-Aventis for the treatment of ulcerative colitis.

OC-108

Mitsubishi Pharma has introduced the internal hemorrhoid sclerotherapy agent OC-108 (Zione Injection) in Japan following its approval in July last year. OC-108 is a compounding agent for local injection with active ingredients of aluminum potassium sulfate and tannic acid. It is a preparation based on Xiaozhiling, an internal hemorrhoid sclerotherapy agent approved in China, but modified with certain additives. It was jointly developed in Japan by the venture business Lequio Pharma and Mitsubishi Pharma. Aluminum potassium sulfate produces acute inflammation when injected into the hemorrhoid; the formation of granulation tissue, which is the repair reaction to this, is followed by fibrosis, which causes the prolapsed hemorrhoid to sclerose and retract. Within a short time after administration, the vascular permeability-enhancing action of aluminum potassium sulfate produces local thickening of the blood, reducing the volume of blood flow and resulting in a rapid improvement in hemorrhagic symptoms. Tannic acid suppresses the excessive acute inflammation produced by aluminum potassium sulfate and mitigates secondary tissue damage. OC-108 appears to be effective against prolapsed internal hemorrhoids and also offers a new option to patients in whom surgery is indicated (1).

1. *Japanese sales release of Zione Injection products*. DailyDrugNews.com (Daily Essentials) April 7, 2005.

Ondansetron Hydrochloride, Lingual Spray



Hana Biosciences has reported positive results from a pilot pharmacokinetic clinical trial that was conducted using its lingual spray version of ondansetron hydrochloride, a 5-HT_3 antagonist, for the treatment of chemotherapy-induced nausea and vomiting. The study was designed to compare the pharmacokinetic profile of 8 mg of ondansetron lingual spray to an 8-mg oral tablet of GlaxoSmithKline's Zofran® in 9 healthy male volunteers. Each volunteer was given a Zofran® tablet and the same dose of the lingual spray version at weekly intervals. Plasma ondansetron levels were measured and analyzed for standard pharmacokinetic parameters. Hana's ondansetron lingual spray demonstrated faster drug delivery than the tablet. Time to achievement of measurable drug concentrations was approximately 20 min shorter for the spray when compared to the oral tablet. During the first 20 min postdose, the lingual spray formulation achieved statistically significant increases in the total amount of drug delivered and in the mean ondansetron concentration. The mean maximum plasma concentration (C_{max}) and bioavailability, as measured by area under the curve (AUC), achieved during the entire 12-h observation period for the lingual spray did not exceed those of the oral tablet. There was no evidence of safety or tolerability issues. Hana intends to file an IND to commence an abbreviated clinical development program designed to support a 505(b)(2) submission. Pivotal trials are expected to begin in 2005 and the company expects the ondansetron lingual spray to be available in 2007. The company also plans to study ondansetron lingual spray in the breast cancer setting, as well as in pediatrics and radiation therapy. Hana acquired the rights to market the novel lingual spray formulation in the U.S. and Canada from NovaDel Pharma in 2004. The new formulation, expected to offer greater convenience to patients, utilizes NovaDel's patented lingual spray drug delivery technology (1-3).

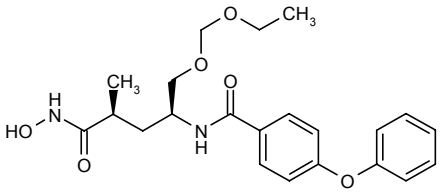
1. *NovaDel Pharma licenses lingual ondansetron spray to Hana Biosciences*. DailyDrugNews.com (Daily Essentials) Nov 3, 2004.

2. *NovaDel initiates pilot study of lingual spray formulation of ondansetron*. DailyDrugNews.com (Daily Essentials) Feb 11, 2005.

3. *Positive results from pilot PK study of ondansetron lingual spray*. DailyDrugNews.com (Daily Essentials) March 22, 2005.

Original monograph – Drugs Fut 1990, 15(1): 37.

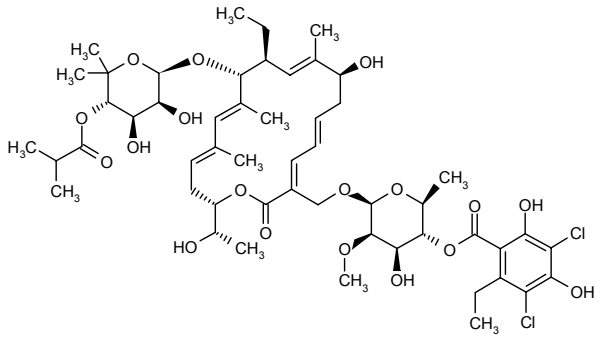
Ono-4817



Phase I trials are ongoing with Ono-4817 (Ono Pharmaceutical), a matrix metalloproteinase (MMP) inhibitor in development for the treatment of inflammatory bowel disease and osteoarthritis (1).

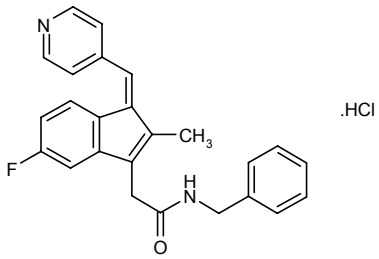
1. *Ono Pharmaceuticals reports Q4 R&D highlights*. Ono Pharmaceuticals Web Site 2004, May 18.

OPT-80



OPT-80 (tiacumicin B) is a narrow-spectrum antibiotic in phase II clinical development at Optimer Pharmaceuticals for the treatment of *C. difficile*-associated diarrhea (CDAD), for which it holds fast track status from the FDA.

OSI-461



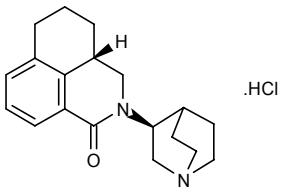
OSI Pharmaceuticals' SAAND (selective apoptotic antineoplastic drug) OSI-461, a second-generation follow-on candidate to Aptosyn® (exisulind), is currently being evaluated in a series of preliminary phase II studies in chronic lymphocytic leukemia, renal cell carcinoma and prostate cancer. In addition, data from a phase II study of OSI-461 in patients with moderate to severe Crohn's disease have been reported. OSI-461 was tested at 200 mg b.i.d. for up to 8 weeks in patients with moderately to severely active Crohn's disease. Clinical response rate was the primary endpoint, and clinical remission rate was among the secondary endpoints. OSI is currently conducting a phase I study in cancer patients to explore whether increases in systemic exposure of OSI-461 can be achieved by administering the drug with food and will consider the most appropriate next steps for the entire OSI-461 program based upon the results of this study (1-3).

1. *OSI Pharmaceuticals reports Q1 R&D highlights*. OSI Pharmaceuticals Press Release 2004, Jan 28.

2. *OSI Pharmaceuticals reports Q2 R&D highlights*. OSI Pharmaceuticals Press Release 2004, May 11.

3. *OSI Pharmaceuticals reports Q3 R&D highlights*. OSI Pharmaceuticals Press Release 2004, Aug 10.

Palonosetron Hydrochloride



The FDA approved the selective second-generation 5-HT_3 receptor antagonist palonosetron hydrochloride (Aloxi™) injection in 2003 for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and for the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. MGI Pharma, which obtained an exclusive U.S. and Canadian license to the product from Helsinn in 2001, began launch in the U.S. in September 2003. The companies are also collaborating on the development of palonosetron for the postoperative nausea and vomiting indication, currently in phase II, and an oral formulation. E.U. marketing approval for the prevention of acute nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy was just recently obtained. Helsinn has signed a number of licensing and distribution agreements in most European countries: with Cambridge Laboratories for the U.K.; Ribosepharm for Germany; Italfarmaco for Italy and Spain; Galenica for Greece; CSC for Austria and several central and Eastern European countries; and PharmaSwiss for Slovenia, the Baltic States and several other Eastern countries; it is also licensed to Taiho for Japan. Palonosetron has up to 30 times higher receptor binding affinity than currently available compounds and an extended 40-h plasma half-life (1-5).

Pharmaceutical formulations comprising 5-HT_3 receptor antagonists such as palonosetron, or a pharmaceutically acceptable salt thereof, have been claimed for the suppression of postoperative nausea and vomiting, as well as general emesis. The claim embodies the application of minimal doses of the active drug (*e.g.*, 0.025-0.075 mg) in order to offset the potential onset of deleterious side effects (6).

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

2. *MGI Pharma reports Q2 R&D highlights*. MGI Pharma Press Release 2004, July 14.

3. *Cambridge Laboratories acquires U.K. rights to palonosetron*. DailyDrugNews.com (Daily Essentials) Sept 9, 2004.

4. *Aloxi receives European approval*. DailyDrugNews.com (Daily Essentials) April 29, 2005.

5. *European CHMP recommends approval of Aloxi*. DailyDrugNews.com (Daily Essentials) Dec 23, 2004.

6. Baroni, L. et al. (Helsinn Healthcare SA) *Use of palonosetron treating post-operative nausea and vomiting*. WO 0473714.

Original monograph – Drugs Fut 1996, 21(9): 906.

PD-217014

The calcium channel modulator PD-217014 is in phase II trials at Pfizer for the treatment of irritable bowel syndrome and overactive bladder.

Pegylated Interferon Alfacon-1

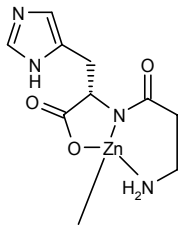
Pegylated interferon alfacon-1 is a bioengineered interferon in phase I trials at InterMune and Nektar Therapeutics for the treatment of hepatitis C. The drug utilizes Nektar's PEGylation technology, a process whereby a long, rapid-moving PEG polymer chain is attached to the drug to protect the molecule from immune response and other clearance mechanisms, thereby sustaining drug bioavailability.

PGN-1164

Pharmagene has initiated clinical evaluation of the lead compound PGN-1164 from its R1 program. The compound is a 5-HT_{2B} receptor antagonist and is in development as an oral product for the treatment of IBS. The first phase I study, which is being conducted by a U.K. contract research organization, is a combined single- and multiple-dose safety/tolerance and pharmacokinetic trial evaluating ascending doses. A total of 36 healthy volunteers will participate in the study, the results of which will be available late in 2005. Pharmagene has shown for the first time that the excitatory effects of 5-HT in human colon are mediated by 5-HT_{2B} receptors. Pharmagene believes that the increase of 5-HT levels in IBS patients leads to increased sensitivity of smooth muscle, inappropriate contractility and cramping, particularly by activation of the 5-HT_{2B} receptor. The use of a drug to block the 5-HT_{2B} receptor is therefore expected to allow normal activity to be restored (1).

1. *R1 program commences clinical trials*. Pharmagene Press Release 2005, Jan 24.

Polaprezinc

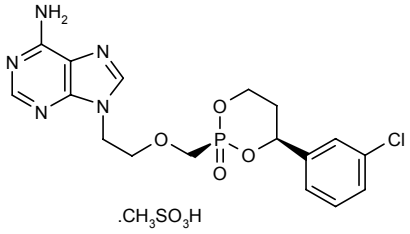


Zeria plans to seek an additional indication for the gastroprokinetic agent polaprezinc (Z-103, Promac®), introduced over 10 years ago for the treatment of peptic ulcer and currently in phase II for dysgeusia (1).

1. *Zeria targets launches after 2006*. DailyDrugNews.com (Daily Essentials) Aug 24, 2004.

Original monograph – Drugs Fut 1989, 14(12): 1176.

Pradefovir Mesilate



Pradefovir mesilate (remofovir mesilate, ICN-2001-3, MB-6866, Hepavir B) is in phase II trials at Valeant, under license from Metabasis Therapeutics, for the treatment of hepatitis B. It is a prodrug of PMEA (adefovir) that was developed using Metabasis Therapeutics' proprietary liver-targeting prodrug technology HepDirect™ (1).

Forty-five adult Asian patients with compensated HBV infection participated in a randomized, placebo-controlled phase I clinical trial that determined the safety, efficacy and pharmacokinetics of pradefovir (5, 10, 20 or 30 mg/day p.o.). Compared with placebo, pradefovir at doses of 10 mg/day and higher significantly reduced serum HBV DNA levels after 28 days of treatment. Both the peak plasma concentration and the level of drug exposure of pradefovir and adefovir increased with dose. The time to peak plasma concentration of both compounds was 1 h or less at all dose levels, suggesting that pradefovir is quickly absorbed and transformed to adefovir. All study treatments were well tolerated and mostly associated with mild adverse events, the most common of which was upper respiratory tract infections. No patients withdrew from the study due to adverse events

Table XXI: Clinical studies of pradefovir mesilate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Randomized Double-blind	Pradefovir, 5 mg/d p.o. x 28 d Pradefovir, 10 mg/d p.o. x 28 d Pradefovir, 20 mg/d p.o. x 28 d Pradefovir 30 mg/d p.o. x 28 d Placebo	45	Pradefovir was well tolerated and more effective than placebo in reducing serum virus levels in patients with hepatitis B	2
Hepatitis B	Randomized	Pradefovir, 5 mg p.o. o.d. x 28 d (n=8) Pradefovir, 10 mg p.o. o.d. x 28 d (n=8) Pradefovir, 30 mg p.o. o.d. x 28 d (n=8) Pradefovir, 60 mg p.o. o.d. x 28 d (n=8) Placebo (n=8)	40	Once-daily pradefovir significantly decreased serum HBV DNA levels in patients with chronic hepatitis B, and was mostly associated with mild adverse events	3

(2). The results from this and the following study are shown in Table XXI.

A multicenter, randomized, placebo-controlled clinical trial evaluated the safety and pharmacokinetics of pradefovir (5, 10, 30 and 60 mg p.o. once daily) in 40 adult patients with chronic HBV. After 28 days of treatment, all pradefovir doses significantly decreased the patients' baseline serum HBV DNA levels. Pradefovir was quickly absorbed and converted to adefovir, and both peak plasma concentration and AUC for the two compounds increased with dose. Most adverse events were mild, and the most common was headache (3).

1. *Remofovir mesylate enters phase II*. DailyDrugNews.com (Daily Essentials) Aug 5, 2004.

2. Lin, C.-C., Chao, Y.-C., Lai, M.-Y. et al. *Safety, tolerance, pharmacokinetics and pharmacodynamics of remofovir, a liver-targeting prodrug of PMEA in HBV patients following daily dosing for 28 days*. Hepatology 2004, 40(4, Suppl. 1): Abst 1141.

3. Lau, D. et al. *Safety, tolerablity, pharmacokinetics and pharmacodynamics of remofovir in chronic HBV patients in US and Canada following daily dosing for 28 days*. 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 74.

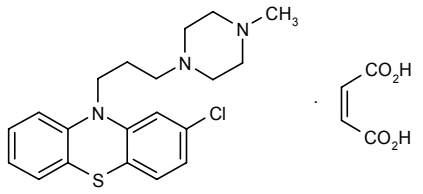
Probactrix™

Earlier in the year, the FDA informed BioBalance, a wholly owned subsidiary of New York Health Care, that it has comments related to BioBalance's IND for Probactrix™ that require additional information and has placed the proposed trials on clinical hold. This first IND was seeking approval to conduct clinical trials of the proprietary biotherapeutic agent Probactrix™ in patients suffering from pouchitis, an inflammation of an internal pouch created in patients who have part of their colon removed to treat ulcerative colitis or familial adenomatous polyposis (FAP). The FDA is expected to formally communicate the precise nature of these issues in writing to BioBalance. Probactrix™ is a patented, single strain of nonpathogenic *E. coli* in a proprietary formulation that enhances the administration of the probiotic. The mechanism of action is believed to involve inhibition of the growth of pathogenic bacteria in the digestive tract and preventing their recolonization. The active ingredient in Probactrix™ has a long history of use for a variety of gastrointestinal conditions, which has been well documented in published foreign studies (1, 2).

1. *IND filing for clinical testing of Probactrix for pouchitis*. DailyDrugNews.com (Daily Essentials) Jan 10, 2005.

2. *FDA raises questions over Probactrix IND*. DailyDrugNews.com (Daily Essentials) Feb 10, 2005.

Prochlorperazine Maleate, Transmucosal

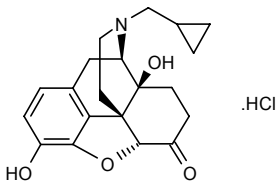


BioDelivery Sciences International (BDSI) has submitted an NDA for a novel transmucosal formulation of prochlorperazine maleate (Emezine®), a currently approved dopamine D2 antagonist for the treatment of nausea and vomiting. This formulation is conveniently administered by placing the dissolving tablet between the upper lip and gum, thereby delivering the drug across the membrane of the mouth. BDSI believes that Emezine® will offer a patient-friendly alternative to injections or suppositories for the treatment of nausea and vomiting associated with a wide range of conditions such as surgery,

chemotherapy and migraine attacks. BDSI licensed Emezine® from Reckitt Benckiser (1).

1. *NDA submission for Emezine*. DailyDrugNews.com (Daily Essentials) May 4, 2005.

PTI-901



Phase III trials are currently ongoing at Pain Therapeutics for PTI-901, a low-dose oral formulation of the potent opioid receptor antagonist naltrexone hydrochloride, used for the treatment of opioid dependency and alcoholism, for the treatment of IBS. PTI-901 is the first in a new class of drugs designed to restore the balance of opioids in the gut. An imbalance of opioid activity in the gut is believed to contribute to the symptoms of IBS. Two phase III trials were initiated in late 2003, one in women and the other in men. The trial in women recently completed patient enrollment (1-4).

1. *Pain Therapeutics reports 2003 year-end R&D highlights*. Pain Therapeutics Press Release 2004, Jan 27.

2. *Pain Therapeutics reports Q2 R&D highlights*. Pain Therapeutics Press Release 2004, July 20.

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

4. *Pain Therapeutics completes patient enrollment of women's study in irritable bowel syndrome*. Pain Therapeutics Press Release 2005, June 21.

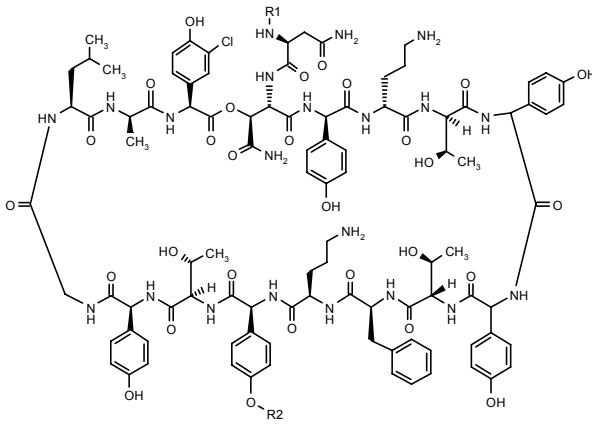
R-1541

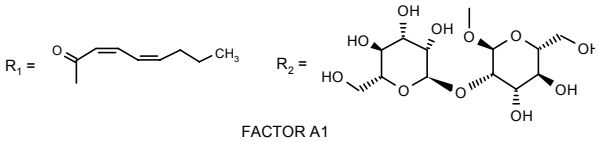
R-1541, an integrin receptor antagonist, is currently in phase I development at Roche for the treatment of IBD.

R-1626

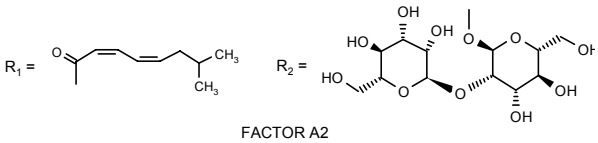
The polymerase inhibitor R-1626 is in phase I trials at Roche for the treatment of hepatitis C.

Ramoplanin

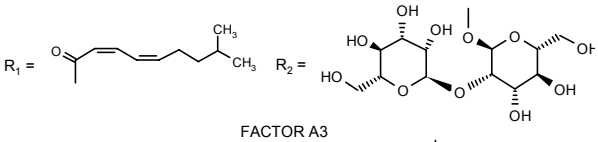




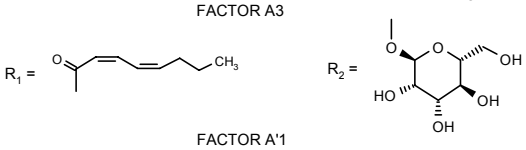
FACTOR A1



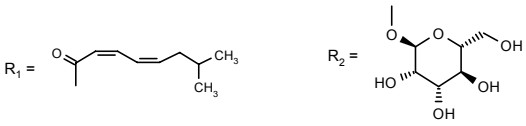
FACTOR A2



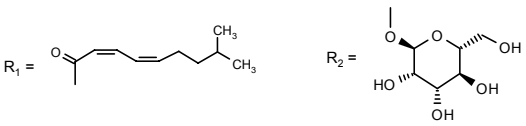
FACTOR A3



FACTOR A'1



FACTOR A'2



FACTOR A'3

Ramoplanin is an oral glycolipodepsipeptide antibiotic in phase II trials at Oscient Pharmaceuticals and Vicuron for the treatment of *C. difficile*-associated diarrhea (CDAD). The antibiotic is not absorbed systemically from the gastrointestinal tract following oral dosing and exerts its bactericidal activity in the gastrointestinal tract. Ramoplanin was originally developed by Vicuron, which later entered a collaboration with the former

Genome Therapeutics, now Oscient Pharmaceuticals. In February 2004, the drug was granted fast track status for the treatment of CDAD.

Oscient reported encouraging preliminary results from the recently completed phase II trial of ramoplanin for the treatment of CDAD. The 3-arm, open-label, non-inferiority study compared ramoplanin 200 mg twice daily, ramoplanin 400 mg twice daily and vancomycin 125 mg 4 times daily. Patients were enrolled regardless of the severity of their CDAD disease at 24 U.S. sites and were dosed for 10 days. The response rates at the test-of-cure visit (7-14 days post-therapy), the primary endpoint of the trial, were 71% in the ramoplanin 400 mg arm and 78% in the vancomycin arm. Although response rates for these two arms were comparable, noninferiority was not statistically demonstrated because the observed response rates of all arms, including the vancomycin arm, were lower than the previously published vancomycin response rates. The trial was designed and powered based on published data in the scientific literature that suggested the vancomycin response rate would be approximately 95%. There was a dose-response relationship in the ramoplanin arms with a higher response rate seen with the 400-mg dose of ramoplanin. Ramoplanin 400 mg and vancomycin had response rates at the end of therapy (a secondary endpoint) of 85.2% and 85.7%, respectively. The data will be used to select a dose of ramoplanin for the phase III program. Preclinical data suggest that ramoplanin may have potential in controlling several antibiotic-resistant Gram-positive bacteria such as vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *S. aureus*. However, the company reassessed priorities for the clinical development of ramoplanin last year. Enrollment had been slow in a phase III study for the prevention of VRE bloodstream infections; the RAVE (Ramoplanin Against VRE) trial in up to 950 neutropenic cancer patients at risk for bloodstream infections caused by VRE was only two-thirds complete 4 years after initiation and the company decided to close enrollment in this study and focus resources on the CDAD indication. Oscient will decide at a later date how to pursue a label claim for VRE (1-4).

1. *Phase II ramoplanin trial in C. difficile-associated diarrhea completes enrollment*. DailyDrugNews.com (Daily Essentials) June 28, 2004.

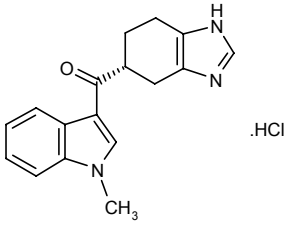
2. *Oscient updates status of leading programs*. DailyDrugNews.com (Daily Essentials) July 22, 2004.

3. *Encouraging topline data from phase II ramoplanin study*. DailyDrugNews.com (Daily Essentials) Aug 16, 2004.

4. Leach, T., Pullman, J., Prieto, J. *Ramoplanin versus vancomycin in the treatment of Clostridium difficile diarrhea: A phase 2 study.* 44th Intersci Conf Antimicrob Agents Chemother (Oct 30-Nov 2, Washington DC) 2004, Abst K-985a.

Original monograph – Drugs Fut 1990, 15(7): 689.

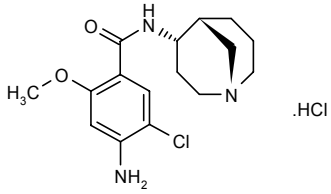
Ramosetron Hydrochloride



Ramosetron hydrochloride (YM-060) is a 5-HT_3 antagonist originally launched in Japan in 1996 for the prophylaxis of chemotherapy-induced nausea/vomiting by the former Yamanouchi (now Astellas Pharma). At present, phase III trials are under way in Japan and phase II trials in Europe for the oral treatment of irritable bowel syndrome (IBS).

Original monograph – Drugs Fut 1992, 17(1): 28.

Renzapride Hydrochloride



Alizyme has successfully completed its thorough cardiovascular safety trial of renzapride, conducted under an open IND in the U.S. The trial was a positive- and placebo-controlled, crossover study in 44 male and female healthy volunteers. It was single-blind with respect to renzapride and placebo and open-label with respect to the positive control. The study evaluated the effects of single oral therapeutic (4 mg) and supratherapeutic (20 mg) doses of renzapride and moxifloxacin at a dose (400 mg) known to affect heart rhythm by prolonging the Q-T_c interval by a small amount. Cardiac rhythm parameters were continuously monitored by ECG. Neither dose of renzapride affected the heart rhythm using a number of approved data analysis methods. Moxifloxacin demonstrated a clear effect on heart rhythm, consistent with reported findings from other studies. Alizyme is currently investigating renzapride in phase II trials for the treatment of IBS. Renzapride is a potent, full 5-HT_4 receptor agonist and 5-HT_3 receptor antagonist. The unique dual pharmacological profile of renzapride differentiates it from other drugs currently in development for the treatment of IBS. Renzapride was discovered by Beecham Research Laboratories, where it was investigated initially as a gastrointestinal prokinetic agent for the treatment of GERD. Following a collaborative agreement, Alizyme obtained full ownership of patents relating to renzapride from SmithKline Beecham prior to its merger with GlaxoWellcome (1).

Table XXII: Clinical studies of renzapride hydrochloride (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Irritable bowel syndrome	Randomized Double-blind Multicenter	Renzapride, 1 mg o.d. x 2 wks Renzapride, 2 mg o.d. x 2 wks Renzapride, 4 mg o.d. x 2 wks Placebo	510	Renzapride was well tolerated and more effective than placebo in improving abdominal pain/discomfort, stool consistency and the frequency of bowel movements in patients with constipation-predominant irritable bowel syndrome	2
Irritable bowel syndrome	Randomized Double-blind	Renzapride, 1 mg x 2 wks (n=12) Renzapride, 2 mg x 2 wks (n=12) Renzapride, 4 mg x 2 wks (n=12) Placebo (n=12)	48	Renzapride was safe and dose-dependently improved bowel function scores and accelerated colonic transit in patients with constipation-predominant irritable bowel syndrome	3
Irritable bowel syndrome	Randomized Double-blind Multicenter	Renzapride, 1 mg o.d. x 56 d Renzapride, 2 mg o.d. x 56 d Renzapride, 4 mg o.d. x 56 d Placebo	168	Renzapride was generally well tolerated and was more effective than placebo in inducing relief of overall symptoms and bowel dysfunction associated with mixed-symptom irritable bowel syndrome	4

The effects of renzapride on the symptoms of abdominal pain/discomfort and bowel dysfunction associated with constipation-predominant IBS were determined in a double-blind, randomized, placebo-controlled phase IIb clinical trial conducted at 80 primary healthcare centers in the U.K. A total of 510 patients were given renzapride (1, 2 and 4 mg) or placebo once daily for 12 weeks. Only patients receiving 4 mg/day of renzapride showed greater relief of abdominal pain/discomfort symptoms compared to placebo. The dose levels of 2 and 4 mg/day significantly increased the frequency of bowel movements and improved stool consistency. No clinically relevant adverse events were found in the electrocardiograms of renzapride-treated patients (2). The results from this and the following studies are summarized in Table XXII.

A total of 48 patients with constipation-predominant IBS and no evacuation disorder were included in a double-blind clinical trial and randomized to receive placebo or renzapride (1, 2 and 4 mg) for 2 weeks. Renzapride dose-dependently improved bowel function scores and accelerated colonic transit; these effects were considered to be clinically relevant with the 4-mg dose compared to placebo. No significant adverse effects were found in the study groups (3).

A multicenter, double-blind, randomized, placebo-controlled, phase IIb clinical trial assessed the efficacy and safety of renzapride (1, 2 and 4 mg once daily) in 168 patients with mixed-symptom (alternating) IBS. The average numbers of days with relief of overall IBS symptoms measured after 56 days of treatment were 18.6 days for 1 mg/day, 21.5 days for 2 mg/day, 19.0 days for 4 mg/day and 22.4 days for placebo. The 2 mg/day dose was associated with a greater average daily responder rate for relief of overall symptoms and relief of bowel dysfunction compared to placebo, but the differences were not significant. Greater effects were found for renzapride in female patients and during the second half of the study (days 29-58) (4).

1. *Alizyme completes thorough cardiovascular safety trial of renzapride*. DailyDrugNews.com (Daily Essentials) April 27, 2005.

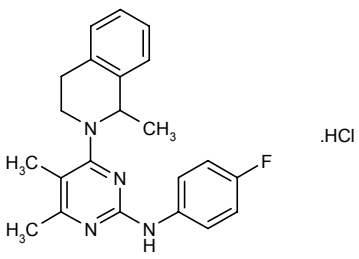
2. Meyers, N.L., Palmer, R.J., George, A. *Efficacy and safety of renzapride in patients with constipation-predominant IBS: A phase IIB study in the UK primary healthcare setting*. Gastroenterology 2004, 126(4, Suppl. 2): Abst W1457.

3. Camilleri, M., McKinzie, S., Fox, J. et al. *Renzapride accelerates colonic transit and improves bowel function in constipation-predominant irritable bowel syndrome (C-IBS)*. Gastroenterology 2004, 126(4, Suppl. 2): Abst W1466.

4. Henderson, J.C., Palmer, R.M.J., Meyers, N.L., Spiller, R.C. *A phase IIb clinical study of renzapride in mixed-symptom (alternating) irritable bowel syndrome*. Gastroenterology 2004, 126(4, Suppl. 2): Abst W1476.

Original monograph – Drugs Fut 1987, 12(11): 1009.

Revaprazan Hydrochloride

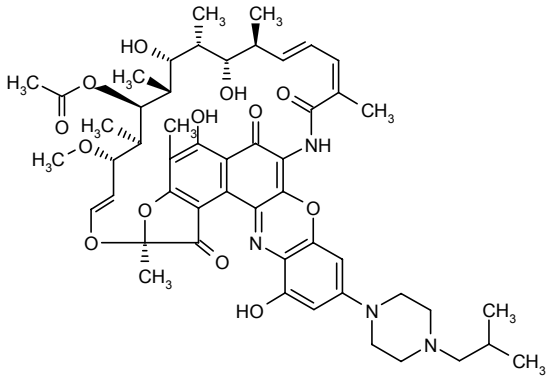


Revaprazan hydrochloride (YH-1885), an H^+/K^+-ATPase inhibitor discovered at Yuhan, is currently

undergoing phase III clinical trials for the treatment of peptic ulcer

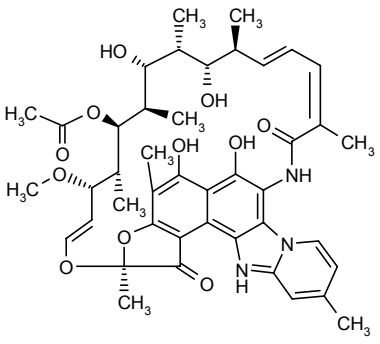
Original monograph – Drugs Fut 2004, 29(5): 455.

Rifalazil



Rifalazil is a novel second-generation rifamycin antibiotic in phase II clinical trials at ActivBiotics for the treatment of gastritis and peptic ulcer caused by *H. pylori*, as well as for the treatment of *C. difficile*-associated diarrhea (CDAD); it has also been tested in phase II trials for the treatment of *Chlamydia trachomatis* infections in men with nongonococcal urethritis. ActivBiotics acquired exclusive worldwide rights to develop and market rifalazil from Kaneka in January 2001. In 2002, ActivBiotics and DepoMed signed a memorandum of understanding pursuant to which DepoMed is developing rifalazil as a controlled-release oral tablet. Rifalazil has shown potent and highly active bactericidal activity against several key pathogenic bacteria. As the drug does not induce or inhibit the P-450 enzymatic pathway, the risk of unwanted drug interactions and liver toxicity is significantly reduced. In addition, rifalazil is metabolically stable and is broadly distributed throughout the body. Due to the drug's long half-life, therapeutic levels for the effective treatment of bacterial infections can be maintained for up to 2 weeks after a single dose.

Rifaximin



The FDA approved Salix's rifaximin (Xifaxan™) in mid-2004 for the treatment of travelers' diarrhea caused by noninvasive strains of *E. coli* in patients 12 years of age and older. A nonsystemic, gastrointestinal-selective, oral antibiotic, rifaximin was subsequently launched in the U.S. in August. In clinical trials, rifaximin was shown to be effective in shortening the duration of diarrhea caused by noninvasive strains of *E. coli*. This effect was achieved with minimal systemic absorption, thus reducing the potential for development of antimicrobial resistance and other systemic concerns such as drug-drug interactions. Salix, which licensed rifaximin from Alfa Wassermann, is also evaluating rifaximin for the treatment of other gastrointestinal-related diseases, including hepatic encephalopathy, Crohn's disease, pouchitis and small bowel overgrowth in irritable bowel syndrome (IBS) patients. The company has also taken preliminary steps to formulate a more potent and effective formulation of rifaximin. The drug was first approved in Italy in 1987. Salix has a copromotion agreement with Altana Pharma (1-6).

A prospective, multicenter, randomized study conducted in 36 Greek patients examined the efficacy of rifaximin (400 mg b.i.d. for the first 7 days of every month) in preventing relapses of diverticulitis. Patients received either rifaximin plus a high-fiber diet or a high-fiber diet alone (control) for 6 months. Adverse events and compliance were similar in both groups. According to per-protocol analysis, rifaximin-treated patients had significantly fewer relapses of diverticulitis as compared to the control group (5.6% *vs.* 33.3%); this difference was not significant on an intent-to-treat analysis. The mean CRP levels were significantly lower in rifaximin-treated patients (7).

Rifaximin (400 mg b.i.d.) was administered to 8 patients with moderate to severe refractory Crohn's disease in an open-label study. In these patients, the Harvey Bradshaw index of disease activity decreased significantly with treatment (by a mean of 7.1). The median time to response was 8.9 days and rifaximin was well tolerated (8). The results of this and the studies that follow are summarized in Table XXIII.

Rifaximin at doses of 200 mg t.i.d. or 400 mg b.i.d. was well tolerated and effective in 30 patients with refractory mild to moderate Crohn's disease. Review of patient medical records showed that improvement was achieved in 7 of 16 patients with ileitis, 4 of 6 patients with ileocolitis and 5 of 8 patients with colitis. Only 1 adverse event was reported (9).

An open-label study was conducted to assess the treatment of pouchitis with rifaximin (400 mg b.i.d.) given for 14 days. Of the 10 patients enrolled in the study, 9 responded to treatment and complete responses were seen after a mean of 7 days. Complete remission was obtained in 8 of the 9 patients who responded. Rifaximin reduced mean bowel frequency, fecal urgency and abdominal pain. No adverse events were seen (10).

Rifaximin was effective in treating small bowel bacterial overgrowth in an open-label study. Of the 14 patients treated with rifaximin (400 mg b.i.d.) for 2 weeks, 13

Table XXIII: Clinical studies of rifaximin (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Open	Rifaximin, 400 mg b.i.d.	8	Rifaximin was well tolerated and significantly reduced Crohn's disease activity	8
Crohn's disease	Retrospective	Rifaximin, 200 mg t.i.d. (n=10) Rifaximin, 400 mg b.i.d. (n=20)	30	Rifaximin was effective and well tolerated in patients with refractory Crohn's disease	9
Pouchitis	Open	Rifaximin, 400 mg b.i.d. x 14 d	10	Rifaximin reduced symptoms and induced remission in most study patients with pouchitis	10
Infection, gastrointestinal	Open	Rifaximin, 400 mg b.i.d. p.o. x 14 d	14	Rifaximin was safe and effective in inducing remission in patients with small bowel bacterial overgrowth	11
Infection, gastrointestinal, Irritable bowel syndrome	Randomized Open	Rifaximin, 600 mg/d x 7 d Rifaximin, 800 mg/d x 7 d Rifaximin, 1200 mg/d x 7 d	90	Rifaximin demonstrated dose-related efficacy in eradicating small intestinal bacterial overgrowth in patients with irritable bowel syndrome	12

responded, with complete responses seen after a mean 10 days. All of the responders except 1 achieved complete remission. Bowel frequency, fecal urgency and abdominal pain were all reduced, and no adverse events were seen (11).

In a large open-label study, rifaximin demonstrated dose-related efficacy in reducing small intestinal bacterial overgrowth in patients with IBS. Ninety such patients were randomized to 7 days of treatment with rifaximin (600, 800 or 1200 mg/day). One month after the end of treatment, the eradication rates in these dose groups were 16.6%, 26.6% and 60%, respectively. The incidence of side effects did not increase with increasing doses (12).

1. *Salix Pharmaceuticals reports 2003 year-end R&D highlights*. Salix Pharmaceuticals Press Release 2004, Feb 3.

2. *Salix Pharmaceuticals reports Q1 R&D highlights*. Salix Pharmaceuticals Press Release 2004, April 26.

3. *Xifaxan approved for travelers' diarrhea caused by noninvasive E. coli*. DailyDrugNews.com (Daily Essentials) May 28, 2004.

4. *Shipment of Xifaxan underway*. DailyDrugNews.com (Daily Essentials) July 15, 2004.

5. *Salix Pharmaceuticals reports Q2 R&D highlights*. Salix Pharmaceuticals Press Release 2004, Aug 9.

6. *Salix and Altana sign Xifaxan copromotion agreement*. DailyDrugNews.com (Daily Essentials) March 9, 2005.

7. Antonakopoulos, N., Kyrlagkitsis, I., Karagiannis, J.A., Triantafillidis, J.K., Karamanolis, D.G. *Cyclic chemoprevention with rifaximin prevents from relapses of diverticulitis: A multicenter randomised study in Greek population*. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst MON-G-319.

8. Bosworth, B.P., Scherl, E.J. *A novel nonabsorbable antibiotic (rifaximin) in the treatment of moderate to severe Crohn's disease*. Dig Dis Week (May 14-19, Chicago) 2005, Abst W1013.

9. Kornbluth, A., Hunt, M., George, J., Latzman, G., Rochester, J., Fried-Boxt, E., Legnani, P. *Efficacy and safety of rifaximin in the treatment of mild-moderate Crohn's disease: Results of an open-label pilot study.* Dig Dis Week (May 14-19, Chicago) 2005, Abst W1029.

10. Baidoo, L., Kundu, R., Su, C., Lewis, J.D., Stein, R., Bronski, W., Lichtenstein, G.R. *Rifaximin is an effective antibiotic for the treatment of pouchitis*. Dig Dis Week (May 14-19, Chicago) 2005, Abst M1975.

11. Baidoo, L., Kundu, R., Berenbaum, P.L., Stein, R., Wolf, D., Su, C., Lewis, J.D., Lichtenstein, G.R. *Rifaximin is effective therapy for small bowel bacterial overgrowth*. Dig Dis Week (May 14-19, Chicago) 2005, Abst W1732.

12. Lauritano, C., Gabrielli, M., Lupascu, A., Nucera, G., Santoliquido, A., Flore, R., La Mura, R., Scarpellini, E., Tondi, P., Cammarota, G., Gasbarrini, G., Gasbarrini, A. *A dose-finding study of rifaximin for the treatment of small intestinal bacterial overgrowth in patients with irritable bowel syndrome*. Dig Dis Week (May 14-19, Chicago) 2005, Abst T1145.

Original monograph – Drugs Fut 1982, 7(4): 260.

Additional References

Abdelrazeq, A.S., Lund, J.N., Kelly, S.M., Leveson, S.H. *Rifaximin-ciprofloxacin combination therapy is effective in patients with chronic, active, refractory pouchitis*. Gastroenterology 2004, 126(4, Suppl. 2): Abst W1397.

Sharara, A.I., Aoun, E., Mounzer, R., Sidani, S., El Hajj, I. *Rifaximin in abdominal bloating and flatulence trial (RAFT): A randomized double-blinded placebo-controlled trial*. Am J Gastroenterol 2004, 99(10, Suppl.): Abst 862.

Sargramostim

Schering AG's U.S. affiliate Berlex has initiated enrollment for two phase III trials of sargramostim (Leukine®,

rhuGM-CSF), a potential new treatment for Crohn's disease. The trials are part of N.O.V.E.L.™ (New Opportunities to Verify Evolving Logic in Crohn's disease), a worldwide clinical trials program for sargramostim in Crohn's disease. N.O.V.E.L. 3, a multicenter, randomized, double-blind, placebo-controlled phase III study, is enrolling patients in the U.S. and will evaluate disease response and remission following retreatment with sargramostim in patients who have demonstrated response to an initial cycle of treatment. N.O.V.E.L. 4, another multicenter, randomized, double-blind, placebo-controlled phase III study, is scheduled to begin recruiting in approximately 10 countries outside the U.S. It will evaluate induction of disease response and remission in patients treated with sargramostim. More than 1,000 patients will be involved in the overall global N.O.V.E.L. program, which also includes N.O.V.E.L. 1, a recently completed multicenter, randomized, double-blind, placebo-controlled phase II trial, N.O.V.E.L. 2, a phase II trial in steroid-dependent patients in the U.S. and Canada which has completed enrollment, and N.O.V.E.L. 5, an open-label extension trial for all patients who have previously participated in a N.O.V.E.L. trial. Pediatric trials are also under development. In N.O.V.E.L. 1, patients receiving sargramostim experienced significantly greater clinical response and remission rates than those receiving placebo. Follow-up to N.O.V.E.L. 1 showed that patients treated with sargramostim maintained improvements in disease severity and quality of life even after therapy was completed. Sargramostim, a growth factor that helps fight infection and disease in appropriate patients by enhancing cells of the immune system, is believed to address the primary defect of Crohn's disease by improving cell function within the mucosal barrier that protects the gastrointestinal tract. Approved in the U.S. in 1991, sargramostim is indicated for use following induction chemotherapy in older adults with acute myelogenous leukemia (AML) to shorten the time to neutrophil recovery and reduce the incidence of severe and life-threatening infections. It is also approved for use in myeloid reconstitution following allogeneic and autologous bone marrow transplantation, peripheral blood stem cell (PBSC) mobilization and subsequent myeloid reconstitution in patients undergoing PBSC transplantation, and bone marrow transplantation failure or engraftment delay (1, 2).

A double-blind clinical trial randomized 124 patients with moderate to severe active Crohn's disease (defined as CDAI scores of 220-475) to receive sargramostim (6 μg/kg) or placebo once daily for 8 weeks. Patients treated with sargramostim showed higher rates of clinical response and remission both at the end of the treatment period (48% and 40%, respectively, *vs.* 26% and 19%, respectively, with placebo) and after follow-up for 30 days (42% and 33%, respectively, *vs.* 21% and 14%, respectively, with placebo). The quality-of-life scores of the patients also improved significantly more with sargramostim compared to placebo. It was found that response and remission rates in sargramostim-treated patients were not affected by baseline CRP levels. Sargramostim was generally well tolerated, although it was associated with higher incidences of bone pain and mild to moderate injection-site reactions (3-5) (see Table XXIV).

The efficacy and safety profile of sargramostim in moderate to severe Crohn's disease were evaluated in an ongoing open-label clinical trial. Sixty patients with a median baseline CDAI score of 306 initiated treatment consisting of repeated 8-week cycles of sargramostim (6 μg/kg/day s.c.) for up to 1 year. An interim analysis conducted on 42 patients who completed at least 1 cycle of sargramostim showed that 53% achieved a clinical response of at least 100 points and 40% achieved clinical remission (CDAI = 150 or less). The most common adverse events were mild to moderate injection-site reactions, bone pain, headache, fatigue and nausea and vom-

Table XXIV: Clinical studies of sargramostim (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Randomized Double-blind	Sargramostim, 6 μg/kg s.c. o.d. x 8 wks (n=81) Placebo (n=43)	124	The rates of clinical response and remission in patients with moderate to severe active Crohn's disease were significantly higher with sargramostim compared to placebo both at 8 weeks of treatment and after follow-up for 30 days. Sargramostim was generally well tolerated, although it was associated with higher incidences of bone pain and mild to moderate injection-site reactions. Sargramostim induced response and remission independent of CRP levels	3, 5
Crohn's disease	Open	Sargramostim, 6 μg/kg/d x 1 y		Once-daily sargramostim was well tolerated and showed efficacy in the management of patients with active Crohn's disease. The incidence of injection-site reactions and bone pain decreased with exposure to sargramostim	6

iting. The incidence of bone pain and injection-site reactions decreased with continuous exposure to sargramostim (6-8) (see Table XXIV).

1. *Enrollment underway in two phase III Leukine studies for Crohn's disease*. DailyDrugNews.com (Daily Essentials) July 6, 2004.

2. *Enrollment completed in phase II study of Leukine for Crohn's disease*. DailyDrugNews.com (Daily Essentials) May 10, 2005.

3. Korzenik, J., Dieckgraefe, B., Valentine, J.F. *Duration of sargramostim effects in patients with moderately-to-severely active Crohn's disease (CD): Follow-up results from a randomized, double-blind, placebo-controlled trial.* Gastroenterology 2004, 126(4, Suppl. 2): Abst 582.

4. Korzenik, J., Dieckgraefe, B., Valentine, J., Hausman, D., Gibert, M. *Sargramostim induces response and remission in patients with moderately-to-severely active Crohn's disease (CD): Results from a randomized, double-blind, placebo-controlled trial.* 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst OP-G-229.

5. Korzenik, J., Dieckgraefe, B., Valentine, J.F. *Sargramostim therapy induces response independent of C-reactive protein levels in patients with moderately-to-severely active Crohn's disease (CD).* Gastroenterology 2004, 126(4, Suppl. 2): Abst T1291.

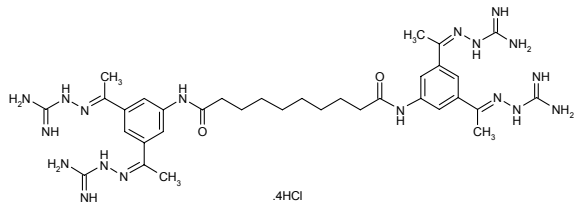
6. Stone, C., Korzenik, J., Hausman, D., Gilbert, M., Valentine, J. *Safety of repeated cycles of sargramostim in patients with active Crohn's disease (CD): Experience from an open label extension trial*. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst OP-G-230.

7. Korzenik, J., Stone, C., Valentine, J., Hausman, D. *Safety of repeated cycles of sargramostim in patients with moderately-to-severely active Crohn's disease (CD): Experience from an open label extension trial.* Gastroenterology 2004, 126(4, Suppl. 2): Abst W1390.

8. Valentine, J. et al. *Repeated cycles of sargramostim for active Crohn's disease (CD): Update from an open label trial (N.O.V.E.L. 5)*. Dig Dis Week (May 14-19, Chicago) 2005, Abst 721.

Original monograph – Drugs Fut 1989, 14(3): 243.

Semapimod Hydrochloride



.4HCl

Semapimod hydrochloride (CNI-1493) is a synthetic guanylhydrazone which is in phase II trials at Cytokine PharmaSciences for the treatment of Crohn's disease and pancreatitis. The compound inhibits signal transduction pathways by preventing the phosphorylation of p38 MAP kinase and JNK, and it also inhibits the production of proinflammatory cytokines and nitric oxide. Semapimod has successfully completed proof-of-principle studies in psoriasis and it demonstrated good safety and biological activity in a phase I study in cancer patients. The compound was originally developed at the Picower Institute for Medical Research.

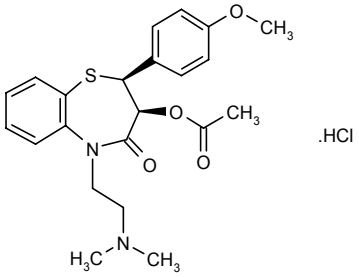
A double-blind clinical trial randomized 33 Crohn's disease patients with CDAI scores of 250-400 at baseline to receive placebo or semapimod hydrochloride 30 or 60 mg i.v. once daily for 5 days. Both the CDAI and the IBDQ cores of the patients tended to improve with semapimod, but the clinical trial was discontinued prematurely due to poor accrual, multiple infusions and discomfort associated with infusion-site reactions (irritation and/or phlebitis). Additional studies are being conducted to determine the feasibility of using shorter treatment schedules and other formulations in order to increase the acceptability of semapimod (1) (Table XXV).

1. Buchman, A.L., Katz, S., Barish, C., Elkin, R., Korzenik, J., Plase, T. *Semapimod treatment of Crohn's disease*. Gastroenterology 2004, 126(4, Suppl. 2): Abst T1299.

SLV-317

Solvay is conducting phase I clinical trials with the NK_1 receptor antagonist SLV-317 for the treatment of IBS.

SLV-324



.HCl

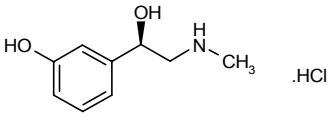
SLV-324 (formerly referred to as Anoheal®) is a 2% cream formulation of diltiazem hydrochloride which is

Table XXV: Clinical studies of semapimod hydrochloride (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Randomized Double-blind	Semapimod, 30 mg i.v. o.d. x 5 d (n=13) Semapimod, 60 mg i.v. o.d. x 5 d (n=10 Placebo (n=10)	33	Semapimod induced clinical responses and improved the quality of life in patients with Crohn's disease, but was associated with a higher incidence of infusion-site reactions and/or phlebitis	1

being assessed in phase II clinical trials at SLA Pharma and Solvay for the treatment of anal fissures. Solvay obtained North American marketing rights to the product in 2002.

SLV-325



SLV-325 (formerly referred to as Incostop®) is a topical gel formulation of phenylephrine hydrochloride in phase II clinical development at SLA Pharma and Solvay for the treatment of fecal incontinence. In 2002, Solvay acquired North American marketing rights to the product from SLA Pharma.

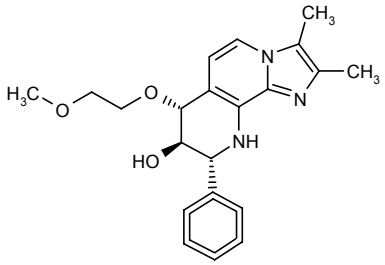
Somatropin (rDNA origin)

Somatropin (rDNA origin) is a recombinant human growth hormone developed by Serono and available for a number of years for the treatment of a variety of growth deficit indications, as well as cachexia. The company launched the product last year in the U.S. under the trade name Zorbtive™ for use in the treatment of patients with short bowel syndrome (SBS). Phase III trials are also under way for the treatment and maintenance therapy of HIV-associated lipodystrophy or HIV-associated adipose redistribution syndrome (HARS). In a pivotal clinical trial, a 4-week regimen of somatropin in conjunction with specialized nutritional support could significantly reduce the dependence of SBS patients on intravenous feeding, as measured by total volume, total calories and frequency of infusion. Patients taking somatropin and a supplemented specialized diet reduced the average number of days they had to use intravenous nutrition by 4.2 days per week compared to baseline, which was a significant reduction compared to the average reduction seen in the control group. The proportion of patients who were able to completely discontinue intravenous feeding was greater among those who received somatropin. Results persisted at the 12-week post-treatment follow-up assessment (1, 2).

1. *Zorbtive launched for short bowel syndrome*. DailyDrugNews.com (Daily Essentials) May 6, 2004.

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

Soraprazan

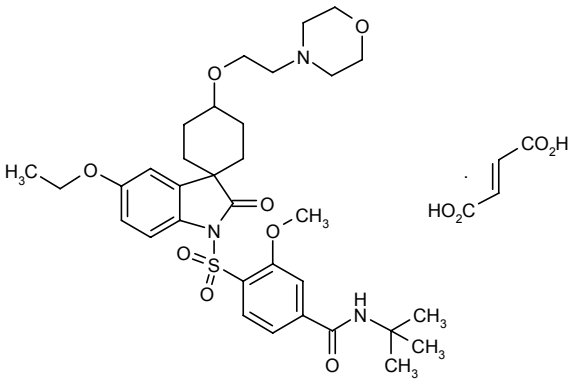


Soraprazan is an acid pump antagonist (APA) with a rapid onset of action undergoing phase II clinical trials at Altana Pharma for the treatment of acid-induced gastrointestinal diseases.

SPI-8811

Sucampo's SPI-8811 (RU-8811) is a novel prostaglandin metabolite currently in phase II development for the treatment of cystic fibrosis and various types of liver disease, including nonalcoholic steatohepatitis. SPI-8811, a potent and specific CIC-2 Cl^- channel activator, acts as an ion transport modulator that facilitates the transport of chloride ions across cell membranes and increases bile fluid secretion and bile fluid Cl^- concentration, without affecting Na^+ or K^+ concentrations.

SR-121463



SR-121463, a vasopressin (AVP) V_2 antagonist and pure aquaretic compound in development at Sanofi-Aventis, is currently undergoing phase III clinical trials for the treatment of hyponatremia due to the syndrome of inappropriate antidiuretic hormone secrection (SIADH) and phase IIb trials for cirrhotic ascites.

Table XXVI: Clinical studies of STA-5326 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Open	STA-5326, 14 mg b.i.d. x 4 wks (n=12) STA-5326, 35 mg/d x 4 wks (n=12)	24	STA-5326 demonstrated activity and acceptable safety in patients with Crohn's disease	2

STA-5326

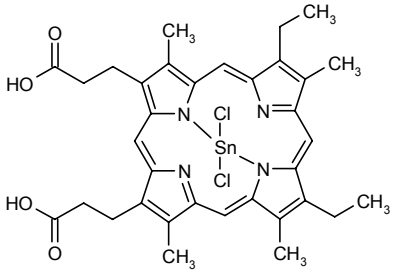
Synta's STA-5326 is a first-in-class, orally active small molecule that selectively inhibits IL-12. STA-5326 has successfully completed two phase I studies in healthy volunteers and is undergoing multiple phase II studies for patients with Crohn's disease and psoriasis (1). It is also being considered for the treatment of rheumatoid arthritis and multiple sclerosis.

An open-label, dose-ranging study examined the safety and efficacy of escalating doses of STA-5326 for 4 weeks in patients with moderate to severe Crohn's disease. Efficacy and safety results were presented for 22 and 18 patients, respectively. Only 1 serious adverse event was reported but was not related to treatment. The agent had an acceptable safety profile, the most common adverse events related to treatment being dizziness, fatigue and positive ANA (antinuclear antibody test); the incidence was similar in both dose groups. One patient discontinued at 14 mg b.i.d. for treatment-related adverse events. Clinical response rates at weeks 2 and 4 were 18% and 9%, respectively, at the 14 mg b.i.d. dose and 45% and 64%, respectively, at the 35 mg/day dose; the remission rates were 9% and 36% for respective doses at both time points (2) (Table XXVI).

1. *Synta closes financing round*. DailyDrugNews.com (Daily Essentials) Nov 24, 2004.

2. Burakoff, R., Barish, C., Farraye, F.A., Pruitt, R., Shafran, I., Dahl, T.A., Hsia, A.Y., Sherman, M.L., Bleday, R. *An open-label, dose-ranging study of STA-5326, an oral interleukin-12 (IL-12) inhibitor, for the treatment of patients with moderate-to-severe Crohn's disease (CD)*. Dig Dis Week (May 14-19, Chicago) 2005, Abst W1014.

Stannsoporfin



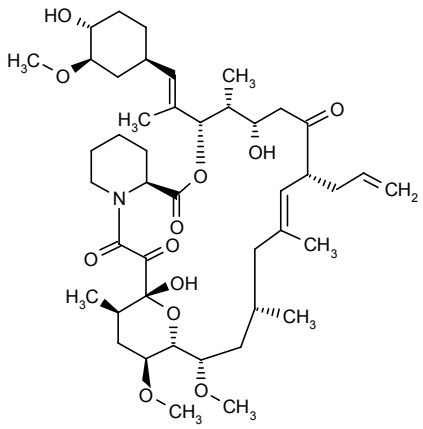
InfaCare Pharmaceutical's stannsoporfin (Stanate®), its first-in-class heme oxygenase inhibitor for the treatment of hyperbilirubinemia in infants, has been released from clinical hold allowing phase III clinical trials to continue. Following a series of collaborative meetings with the FDA, agreement was reached over the developmental path towards NDA filing. Stannsoporfin is being developed as a new therapeutic tool to rapidly treat high levels of bilirubin in jaundiced infants. Administered by a single intramuscular injection, stannsoporfin effectively turns off the body's production of bilirubin and allows the baby's normal mechanisms to eliminate the bilirubin from the bloodstream. New guidelines recently issued by the American Academy of Pediatrics regarding diagnostic and therapeutic steps to reduce the incidence of hyperbilirubinemia suggest that, once approved, stannsoporfin should be considered as an alternative to exchange transfusion in severely jaundiced newborns. InfaCare just recently entered into a licensing agreement with Recordati for the rights to develop and market stannsoporfin in Europe and certain territories of North Africa and the Middle East. InfaCare licensed rights to stannsoporfin from WellSpring Pharmaceutical, which originally acquired worldwide rights from Rockefeller University (1-3).

1. *Partial clinical hold lifted from Stanate*. DailyDrugNews.com (Daily Essentials) Nov 3, 2004.

2. *InfaCare and Recordati complete international licensing agreement for Stanate®, a new drug candidate to treat jaundice in newborns*. InfaCare Pharmaceutical Press Release 2005, June 13.

3. *New Stanate® synthesis patent issued by US patent office*; *new drug in late stage development for jaundice in babies.* InfaCare Pharmaceutical Press Release 2004, Dec 8.

Tacrolimus



The immunosuppressant tacrolimus (FK-506) continues to undergo active clinical development worldwide for

Table XXVII: Clinical studies of tacrolimus (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Ulcerative colitis	Randomized Double-blind	Tacrolimus, 0.025 mg/kg [adjusted to C_{min} 5-10 ng/ml] p.o. b.i.d. x 2 wks Tacrolimus, 0.025 mg/kg [adjusted to C_{min} 10-15 ng/ml] p.o. b.i.d. x 2 wks Placebo	60	Oral tacrolimus was well tolerated and improved stool frequency and rectal bleeding in patients with moderate to severe refractory ulcerative colitis	1, 2
Crohn's disease	Open	Tacrolimus, 0.05 mg/kg p.o. b.i.d.	10	Tacrolimus was safe and active in the treatment of fistulizing Crohn's disease refractory to infliximab	3, 4

a variety of conditions in different formulations, including rheumatoid arthritis (oral), lupus nephritis (oral), psoriasis (gel/cream) and asthma (inhalation). In 2004, the former Fujisawa (now Astellas Pharma) submitted a supplemental NDA in Japan for the use of oral tacrolimus in the treatment of ulcerative colitis.

A double-blind, randomized, placebo-controlled clinical trial assessed the safety and efficacy of tacrolimus in the treatment of moderate to severe active ulcerative colitis unresponsive to steroid therapy. Sixty patients were treated orally with placebo, low-dose tacrolimus (adjusted to trough levels of 5-10 ng/ml) or high-dose tacrolimus (adjusted to trough levels of 10-15 ng/ml) for 2 weeks. None of the patients included in the study achieved complete response, although partial remission of symptoms was seen in 38.1% of patients with low-dose tacrolimus, 68.4% with high-dose tacrolimus and 10.0% with placebo. Both tacrolimus regimens significantly improved stool frequency and rectal bleeding, and were well tolerated (1, 2). The results from this and the following study are summarized in Table XXVII.

The long-term efficacy and safety of tacrolimus in fistulizing Crohn's disease refractory to infliximab were determined in an open-label clinical trial. Ten patients with enterocutaneous or perianal fistulas refractory to conventional therapy were treated with tacrolimus (0.05 mg/kg p.o.) twice daily. The analysis of the Perianal Crohn's Disease Activity Index (PCDAI) and the Magnetic Resonance-based Score (MRS) after 4-8 months of treatment showed complete response and partial response for 4 and 5 patients, respectively. Tacrolimus suppressed the need for concomitant steroids or immunosuppressive therapy, and response was maintained throughout a follow-up period of 6-24 months. Most adverse events were mild, although 1 patient withdrew from the study due to headache (3, 4).

1. Ogata, H., Matsui, T., Nakamura, M., Iida, M., Takazoe, M., Suzuki, Y., Hibi, T. *The effectiveness of oral tacrolimus therapy against refractory ulcerative colitis: A placebo-controlled, double-blind, randomized study*. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst OP-G-325.

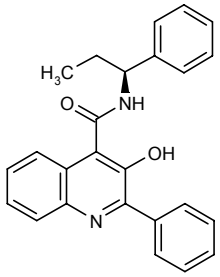
2. Ogata, H., Matsui, T., Nakamura, M., Iida, M., Takazoe, M., Suzuki, Y., Hibi, T. *The effectiveness of oral tacrolimus therapy against refractory ulcerative colitis: A placebo-controlled, double-blind, randomized study*. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst OP-G-260.

3. Gonzalez Lama, Y., Abreu, L., Vera, M.I. et al. *Long term oral tacrolimus is safe and effective in refractory to infliximab fistulizing Crohn's disease*. Gastroenterology 2004, 126(4, Suppl. 2): Abst 436.

4. Gonzalez-Lama, Y., Abreu, L., Vera, M.I., Pastrana, M., Tabernero, S., Revilla, J., Durán, J.G., Escartin, P. *Long-term oral tacrolimus therapy in refractory to infliximab fistulizing Crohn's disease: A pilot study*. Inflamm Bowel Dis 2005, 11(1): 8.

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

Talnetant



The NK_3 antagonist talnetant is in phase II development at GlaxoSmithKline for the treatment of irritable bowel syndrome (IBS) and schizophrenia (1).

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

Tarvacin™

Peregrine Pharmaceuticals recently received FDA clearance of its IND to initiate a phase I trial using Tarvacin™ to treat patients with chronic hepatitis C virus (HCV) infection. The objectives of the phase I protocol are to evaluate safety, pharmacokinetics and viral load in patients chronically infected with HCV who have failed standard treatment. An IND filing for Tarvacin™ was previously cleared for patients with solid tumors and a phase

I trial is under way. Preclinical studies using Tarvacin™ for the treatment of viral diseases have yielded promising results in Lassa fever, influenza and cytomegalovirus. Based on its antiviral mechanism, the drug has potential for the treatment of enveloped viruses, including hepatitis B and C, HIV, herpes, influenza, including severe acute respiratory syndrome (SARS) and avian flu, and potential bioterrorism threats such as Marburg virus and Lassa fever. Tarvacin™ is a chimeric monoclonal antibody that binds to the phospholipid phosphatidylserine. It was initially discovered by researchers at UT Southwestern, who have worked closely with Peregrine to explore Tarvacin™ for cancer. Peregrine has a sponsored research agreement with researchers at UT Southwestern to study the use of Tarvacin™ and its parent antibody 3G4 for the treatment of cancer and viral diseases. In addition, the researchers at UT Southwestern have also received grants to study the use of antiphospholipid therapy (APT) agents for the treatment of viral infections and diseases. The company recently entered a collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) to screen Tarvacin™ and other APT agents for activity agaisnt a broad spectrum of enveloped viral pathogens of health and bioterrorism concern. Tarvacin™ is Peregrine's first product under its APT technology platform. It is based on the finding that aminophospholipids, basic components of the inner surface of the cellular membrane, become exposed on the outside of the cellular membrane in response to certain disease states, making them a potential therapeutic target (1-6).

1. *IND submission to begin clinical testing of Tarvacin*. DailyDrugNews.com (Daily Essentials) Sept 28, 2004.

2. *Peregrine discusses Tarvacin IND with FDA*. DailyDrugNews.com (Daily Essentials) Oct 28, 2004.

3. *Tarvacin cleared to enter new phase I study*. DailyDrugNews.com (Daily Essentials) Feb 1, 2005.

4. *NIAID to test Tarvacin for antiviral potential*. DailyDrugNews.com (Daily Essentials) April 8, 2005.

5. *Peregrine submits Tarceva IND for HCV*. DailyDrugNews.com (Daily Essentials) May 6, 2005.

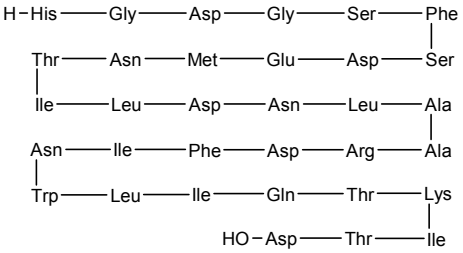
6. *Tarvacin cleared to enter phase I study for HCV.* DailyDrugNews.com (Daily Essentials) June 2, 2005.

TD-2749

Theravance has enrolled the first subjects in a phase I study designed to assess the safety, tolerability and pharmacokinetics of its investigational gastrointestinal prokinetic agent TD-2749. TD-2749 is a selective 5-HT_4 receptor agonist discovered by Theravance through the application of multivalent drug design in a drug discovery program dedicated to finding new medicines for gastrointestinal motility disorders such as chronic constipation, constipation-predominant irritable bowel syndrome (C-IBS), opioid-induced constipation, functional dyspepsia and diabetic gastroparesis. The program aims to develop a once-a-day oral medicine that is more effective than the market-leading medicines (1).

1. *Enrollment under way in phase I study of TD-2749 for GI motility dysfunction*. DailyDrugNews.com (Daily Essentials) Jan 5, 2005.

Teduglutide

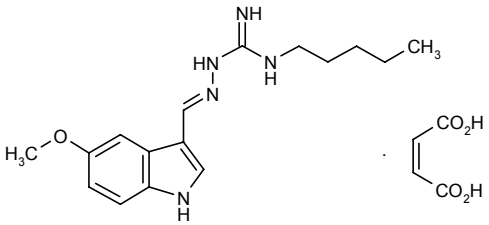


NPS Pharmaceuticals is conducting a phase II study with teduglutide, a glucagon-like peptide-2 (GLP-2) receptor agonist, in patients with Crohn's disease and a pivotal phase III trial in patients with short bowel syndrome. The company signed a mutual termination agreement with Technology Partnership Canada (TPC) last year, which relieves NPS of any potential obligations related to the development or commercialization of teduglutide (1, 2). Orphan drug status has been granted in the U.S. and Europe for the treatment of short bowel syndrome.

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

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

Tegaserod Maleate



Last year, the FDA approved a supplemental indication for Novartis's promotility agent tegaserod maleate (Zelnorm®) for the treatment of chronic idiopathic constipation in male and female patients under the age of 65 years. The new indication is supported by safety and efficacy data from the two largest and longest multinational, randomized, double-blind, placebo-controlled phase III trials conducted in chronic constipation. The two 3-month

trials included more than 2,600 male and female patients (see below). One of the studies also included a 13-month extension safety study of 840 patients. Tegaserod was found to significantly increase the frequency of complete spontaneous bowel movements, as well as to provide relief of the multiple symptoms of chronic constipation that patients complain about most, including straining, hard stools, incomplete evacuation, infrequent defecation, bloating and abdominal discomfort. In April, a precaution statement was added to U.S. labeling regarding postmarketing cases of ischemic colitis and severe diarrhea. Tegaserod acts as a partial agonist at 5-HT_4 receptors in the gastrointestinal tract and mimics the natural effects of 5-HT by activating these receptors, which normalizes impaired motility in the gastrointestinal tract, inhibits visceral sensitivity and stimulates intestinal secretion. Tegaserod treats dysmotility symptoms caused by chronic constipation and IBS with constipation. First approved in the U.S. in July 2002 for the short-term treatment of women with IBS whose primary bowel symptom is constipation, tegaserod, also known in some countries as Zelmac®, is now approved in more than 55 countries for this indication. It is under regulatory review in the E.U. for IBS, with a decision expected this year. It is also approved for use in chronic constipation in 10 countries, including Mexico and Latin America. The drug continues to be studied for gastroesophageal reflux disease (GERD; phase II) and dyspepsia (phase III) (1-5).

The efficacy of tegaserod (6 mg b.i.d. for 4 weeks) in treating constipation in 15 parkinsonian patients was examined in a 6-week, randomized, double-blind, placebo-controlled study. Treatment was well tolerated, with no adverse events reported in the group receiving tegaserod. After 4 weeks of treatment, although constipation decreased an average of 0.3 points in the treatment group as compared to an increase of 0.8 points on placebo, the difference was not significant. Similarly, abdominal discomfort decreased by 0.3 points in the tegaserod group as compared to an increase of 1 point on placebo, but this difference was again not significant. The agent had no effect on parkinsonian symptoms according to changes in the UPDRS. It was concluded that tegaserod does not possess anticonstipation effects in this patient population (6) (Table XXVIII).

Two double-blind, randomized, placebo-controlled trials assessed the efficacy of tegaserod (2 or 6 mg b.i.d. for 12 weeks) in improving bowel frequency and other constipation symptoms in patients with chronic constipation. A total of 2,612 patients were included. Treatment was well tolerated, with no consistent differences in the frequency of adverse events observed between groups. Responder rates obtained during weeks 1-4 in both studies were significantly greater in the tegaserod groups compared to placebo. In addition, significant improvements in the majority of secondary efficacy variables were observed in the tegaserod groups compared to placebo (7, 8).

Patients with chronic constipation completing a 14-week study were eligible for inclusion in a 13-month evaluation of the safety and tolerability of tegaserod. The extension study was completed by 451 patients who continued their previous tegaserod dose or were switched from placebo to tegaserod 6 mg b.i.d. In this study, safety and tolerability did not deteriorate with long-term drug administration (9).

In a crossover study, 42 patients with functional heartburn were randomized to tegaserod 6 mg b.i.d. or placebo, each given for 14 days. Data culled from a multisymptom questionnaire showed that tegaserod improved several gastrointestinal symptoms related to upper dysmotility, while placebo did not affect the same symptoms (10).

Patients with functional dyspepsia (n=16) and healthy volunteers (n=12) were included in a randomized, double-blind, placebo-controlled, crossover evaluation of tegaserod 6 mg b.i.d. for 7 days. Postprandial gastric compliance was increased in patients with functional dyspepsia and gastric accommodation was increased in healthy volunteers treated with tegaserod (11) (Table XXVIII).

Gastric myoelectrical activity was measured in 8 patients with functional dyspepsia and delayed gastric emptying treated with tegaserod 6 mg b.i.d. for 4 weeks. Tegaserod significantly lowered total symptom scores, significantly accelerated gastric emptying and improved alterations in gastric myoelectrical activity (12).

Salivary protective components were evaluated in 38 patients with GERD after 7 days of treatment with

Table XXVIII: Clinical studies of tegaserod maleate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Constipation, Parkinson's disease	Randomized Double-blind	Tegaserod, 6 mg b.i.d. x 4 wks + Stool bulking agents (n=8) Placebo + Stool bulking agents (n=7)	15	Tegaserod was well tolerated but ineffective in the treatment of patients with constipation associated with Parkinson's disease	6
Dyspepsia, Healthy volunteers	Randomized Double-blind Crossover	Tegaserod, 6 mg b.i.d. x 7 d Placebo	28	Tegaserod was associated with improvement in postprandial gastric compliance in patients with functional dyspepsia and in gastric accommodation in healthy volunteers	11

tegaserod 6 mg b.i.d. or placebo in a randomized, double-blind, crossover study. Tegaserod treatment significantly increased salivary flow rates and secretion of salivary bicarbonate and nonbicarbonate buffers under basal conditions and during mastication. The agent also increased salivary epidermal growth factor (EGF) under basal conditions and significantly increased salivary EGF during mastication (13).

An oral suspension of the 5-HT_4 receptor partial agonist tegaserod has been claimed. The claim pertains in particular to a powdered (crushed tablet) formulation suspended in a taste-masking beverage and is expected to be of therapeutic value in the prevention and/or treatment of IBS, GERD, functional dyspepsia, postoperative ileus and chronic constipation (14).

1. *Zelnorm labeling updated with new risk information*. DailyDrugNews.com (Daily Essentials) May 5, 2004.

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

3. *Zelnorm recommended for approval for chronic constipation with restrictions*. DailyDrugNews.com (Daily Essentials) July 19, 2004.

4. *FDA approves Zelnorm for chronic constipation*. DailyDrugNews.com (Daily Essentials) Aug 25, 2004.

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

6. Sullivan, K.L., Staffetti, J.F., Hauser, R.A., Maldonado, J.L., Dunne, P.B., Zesiewicz, T.A. *A double-blind, randomized trial of tegaserod (Zelnorm) for the treatment of constipation in Parkinson's disease*. Mov Disord 2004, 19(Suppl. 9): Abst P805.

7. Johanson, J.F. *Tegaserod for chronic constipation*. Aliment Pharmacol Ther 2004, 20(Suppl. 7): 20.

8. Bardhan, K., Schwarz, R., Kanty-Okulewicz, M., Jones, J., Hugot, S., Nault, B. *Tegaserod is effective in relieving the multiple symptoms of chronic constipation (CC): Pooled data from two phase III studies*. Gastroenterology 2004, 126(4, Suppl. 2): Abst W1469.

9. Mueller-Lissner, S., Kamm, M., Haeck, P., Musoglu, A., Huorka, M., Guillot, J., Jones, J., Nault, B. *Long-term safety and tolerability of tegaserod in chronic constipation (CC)*. Gastroenterology 2004, 126(4, Suppl. 2): Abst W1468.

10. Rodriguez-Stanley, S., Zubaidi, S., Proskin, H.M., Kralstein, J.R., Miner, P.B. *Tegaserod significantly improves several upper gastrointestinal dysmotility symptoms in patients with functional heartburn*. Dig Dis Week (May 14-19, Chicago) 2005, Abst T1690.

11.Thumshirn, M., Fruehauf, H., Stutz, B., Tougas, G., Salter, J., Fried, M. *Effects of tegaserod on gastric motor and sensory function in patients with functional dyspepsia and healthy controls.* Dig Dis Week (May 14-19, Chicago) 2005, Abst T1158.

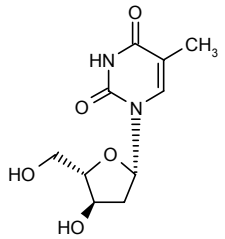
12. van der Voort, I.R., Schmidtmann, M., Fach, K., Werner, C., Andresen, V., Wiedenmann, B., Klapp, B.F., Moennikes, H. *Tegaserod improves gastric emptying and alters myoelectrical activity in dyspeptic patients*. Gastroenterology 2004, 126(4, Suppl. 2): Abst W1473.

13. Jaworski, T., Majewski, M., Sarosiek, J., Sarosiek, I., Gupta, V., Sostarich, S., Roeser, K., Edlavitch, S., McCallum, R.W., Wallner, G., Kralstein, J. *Enhancement of salivary buffering capacity and epidermal growth factor in patients with gastroesophageal reflux disease during tegaserod administration*. Dig Dis Week (May 14-19, Chicago) 2005, Abst T1691.

14. Bizot, M.-N. et al. (Novartis AG) *Oral suspension of tegaserod*. WO 0487135.

Original monograph – Drugs Fut 1999, 24(1): 38.

Telbivudine



Telbivudine (LTD-600) is a once-daily oral treatment for chronic HBV infection presently in phase III clinical evaluation by Idenix and partner Novartis. Phase II data have shown efficacy exceeding lamivudine. The ongoing international phase III GLOBE trial, which includes China, is designed to evaluate telbivudine head to head against lamivudine. Enrollment was completed ahead of schedule in April 2004. Both companies plan to submit U.S., E.U. and international marketing applications for telbivudine beginning in the fourth quarter of 2005 and extending into 2006 (1, 2).

Two clinical trials that compared the pharmacokinetics of telbivudine (200 or 600 mg/day) alone or combined with lamivudine (100 mg/day) or adefovir (10 mg/day) found no significant interactions between these drugs in 32 healthy volunteers (3).

A single dose of telbivudine 600 mg was administered to 24 patients with normal or impaired hepatic function and to 36 subjects with normal or impaired renal function in a pharmacokinetic study. While dose adjustments did not appear to be necessary in individuals with hepatic impairment, drug clearance was reduced in subjects with impaired renal function to a degree suggesting a need for dose adjustment (4).

In the first clinical study of telbivudine, 43 patients with HBeAg-positive chronic hepatitis B received doses of 25, 50, 100, 200, 400 and 800 mg/day for 4 weeks. All doses were well tolerated and plasma pharmacokinetics were dose-proportional. Dose-related antiviral activity was also observed, with over 99% reduction in serum viral load seen with the 800 mg/day dose (5).

A viral dynamic study determined the antiviral effects of telbivudine monotherapy (400 or 600 mg/day), lamivudine monotherapy (100 mg/day) or a combination of both regimens in 104 adult patients with HBeAg-positive chronic hepatitis B. Hepatitis B viral load showed a biphasic evolution with all study regimens over 1 year of treatment. Telbivudine-containing regimens were associated

Table XXIX: Clinical studies of telbivudine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Randomized Double-blind	Telbivudine, 400-600 mg/d x 1 y → 600 mg/d x 1 y Telbivudine, 400-600 mg/d x 1 y → 600 mg/d x 1 y + Lamivudine, 100 mg/d x 2 y Lamivudine, 100 mg/d x 2 y	90	Telbivudine alone or combined with lamivudine was significantly more effective than lamivudine alone in inducing hepatitis B virus DNA suppression and normalizing serum alanine aminotransferase levels in patients with chronic hepatitis B. No significant differences were found between the effects of telbivudine monotherapy and the combination regimen	9

with greater viral load reductions during the first 2 study weeks and a faster second-phase viral clearance for the rest of the treatment period (6-8). Patients completing this phase IIb trial were allowed to continue treatment with lamivudine (100 mg/day), telbivudine (600 mg/day, previously 400 or 600 mg/day) or combination of lamivudine (100 mg/day) and telbivudine (600 mg/day, previously 400 or 600 mg/day). At 2 years of treatment, telbivudine remained superior to lamivudine in terms of the HBV clearance rate and the ALT normalization rate (9) (see Table XXIX).

Viremia was analyzed in 36 $HBeAg^+$, treatment-naïve patients with chronic hepatitis B treated with telbivudine 25, 50, 100, 200, 400 or 800 mg/day for 4 weeks in a phase I/II study. The treatment was associated with a biphasic decline in HBV viremia, with first-phase effectiveness estimated at approximately 99% with doses of 25-200 mg. Second-phase clearance and post-treatment relapse were dose-dependent (10).

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

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

3. Zhou, X.J. et al. *Absence of pharmacokinetic drug-drug interaction between telbivudine and lamivudine or adefovir in healthy subjects*. 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 544.

4. Zhou, X.J., Myers, M., Chao, G., Dubuc, G., Brown, N.A. *Clinical pharmacokinetics of telbivudine, a potent antiviral for hepatitis B, in subjects with impaired hepatic or renal function*. Hepatology 2004, 40(4, Suppl. 1): Abst 1166.

5. Brown, N.A., Lai, C.-L., Lim, S.G. *A dose-finding study of once-daily oral telbivudine in HBeAg-positive patients with chronic hepatitis B virus infection*. Hepatology 2004, 40(3): 719.

6. Zhou, X.J. et al. *HBV viral dynamics of telbivudine vs. lamivudine and the combination: Relevance of early viral suppression to better long-term clinical response*. 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 543.

7. Zhou, X.J., Boehme, R.E., Brown, N.A., Lai, C.L. *HBV viral dynamics in a comparative clinical trial of telbivudine (LdT), lamivudine, and the combination in patients with chronic hepatitis B*. 44th Intersci Conf Antimicrob Agents Chemother (Oct 30-Nov 2, Washington DC) 2004, Abst V-1155.

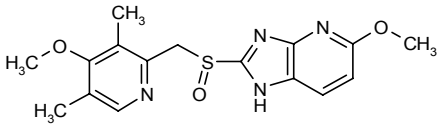
8. Zhou, X.-J., Boehme, R., Chao, G., Brown, N.A., Lai, C. *HBV viral dynamics of telbivudine vs. lamivudine and the combination: Relevance of early viral suppression to better long-term clinical response*. Dig Dis Week (May 14-19, Chicago) 2005, Abst M948.

9. Lai, C.-L., Leung, N.W., Teo, E., Tong, M., Wong, F., Hann, H.Y., Han, S.H., Poynard, T., Qiao, X., Pietropaolo, K., Lloyd, D., Brown, N.A. *Phase IIb extended-treatment trial of telbivudine (LdT) vs lamivudine vs combination treatment in hepatitis B patients: Two-year results*. Dig Dis Week (May 14-19, Chicago) 2005, Abst 320.

10. Neumann, A.U., Zhou, X.J., Boehme, R.E., Chao, G., Fang, C., Brown, N.A., Lai, C.L. *Viral dynamics for LdT (telbivudine)-treated hepatitis B patients: High degree of initial inhibition with dose-dependent second-phase HBV clearance suggests a new model for HBV dynamics*. Hepatology 2004, 40(4, Suppl. 1): Abst 186.

Original monograph – Drugs Fut 2003, 28(9): 870.

Tenatoprazole



Tenatoprazole is an H^+/K^+-ATPase inhibitor developed by Mitsubishi Pharma and licensed to Negma, where clinical trials are apparently under way for the treatment of GERD.

The maintenance of the effects induced by tenatoprazole and esomeprazole on gastric acid output were assessed in a single-blind, randomized, crossover clinical trial that enrolled 30 healthy volunteers. Each patient received tenatoprazole (40 mg/day p.o.) or esomeprazole (40 mg/day p.o.) for 7 days, and gastric pH was measured at baseline, at the end of the treatment period, and 3 and 5 days after administration of the last dose. Compared with esomeprazole, tenatoprazole was more effective in increasing gastric pH and its effects were maintained for a longer period of time, although no significant differences between treatments were found at 5 days after the last dose. Both drugs were well tolerated

Table XXX: Clinical studies of tenatoprazole (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Single-blind Crossover	Tenatoprazole, 40 mg p.o. o.d. x 7 d Esomeprazole, 40 mg p.o. o.d. x 7 d	30	Tenatoprazole was more effective than esomeprazole in reducing nighttime gastric acid output in healthy male volunteers	1
Healthy volunteers	Randomized Open Crossover	Tenatoprazole, 40 mg p.o. o.d. x 2 d Esomeprazole, 40 mg p.o. o.d. x 2 d	24	Tenatoprazole achieved a better control of gastric acid output in heathy volunteers compared to esomeprazole during the first 48 h of therapy	2
Healthy volunteers	Randomized Crossover	Tenatoprazole, 40 mg o.d. x 2 d Esomeprazole, 40 mg o.d. x 2 d	25	Tenatoprazole was significantly more effective in achieving better overall and nocturnal gastric pH control compared to esomeprazole, despite a comparable effect on diurnal gastric pH in healthy male volunteers	3
Healthy volunteers	Randomized Open Crossover	Tenatoprazole, 20 mg p.o. o.d. x 7 d Tenatoprazole, 40 mg p.o. o.d. x 7 d Esomeprazole, 40 mg p.o. o.d. x 7 d	18	Tenatoprazole at a daily dose of 40 mg was significantly more effective than esomeprazole in reducing gastric acid output and the incidence of nocturnal acid breakthroughs in healthy volunteers	4

(1). The results from this and the following studies are summarized in Table XXX.

The early effects of tenatoprazole were evaluated in an open-label, crossover clinical trial that randomized 24 healthy volunteers to receive tenatoprazole (40 mg/day p.o.) or esomeprazole (40 mg/day p.o.) for 2 days. The median gastric pH value achieved with tenatoprazole was higher compared to esomeprazole (3.88 *vs*. 3.45) during the first 24-h period, but these differences disappeared during the second 24-h period. At nighttime, tenatoprazole was associated with significantly higher median gastric pH values both during the first night (4.24 *vs*. 2.92) and the second night (4.53 *vs.* 3.24) (2, 3).

Tenatoprazole 20 and 40 mg was compared with esomeprazole 40 mg in a randomized, open, crossover study in 18 healthy volunteers. Treatments were given once daily for 7 days. Intragastric acid inhibition was greater with tenatoprazole 40 mg compared to tenatoprazole 20 mg, and tenatoprazole 40 mg was superior to esomeprazole 40 mg during a 24-h period and during the night (4).

1. Chowdhury, S.K., James, C., Fiorentini, P., Taccoen, A., Cohen, P., Armstrong, D., Hunt, R.H. *Tenatoprazole (T) and esomeprazole (E): The effect of a prolonged plasma half-life on gastric pH in healthy males*. Gastroenterology 2004, 126(4, Suppl. 2): Abst 449.

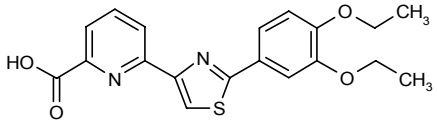
2. Galmiche, J.-P., Bruley des Varannes, S., Sacher-Huvelin, S. et al. *Early effects of tenatoprazole 40 mg and esomeprazole 40 mg on intragastric pH in Caucasian healthy volunteers*. Gastroenterology 2004, 126(4, Suppl. 2): Abst M1442.

3. Galmiche, J.P., Sacher-Huvelin, S., Bruley des Varannes, S., Vavasseur, F., Taccoen, A., Fiorentini, P., Homerin, M. *A comparative study of the early effects of tenatoprazole 40 mg and esomeprazole 40 mg on intragastric pH in healthy volunteers*. Aliment Pharmacol Ther 2005, 21(5): 575.

4. Galmiche, J.-P., Ducrotte, P., Bruley des Varannes, B., Sacher-Huvelin, S., Vavasseur, F., Taccoen, A., Fiorentini, P., Homerin, M.*Tenatoprazole, a novel proton pump inhibitor with a prolonged half-life. Effects of a 7-day dosing on diurnal and nocturnal intragastric pH, and comparison with esomeprazole in Caucasian healthy volunteers*. Gastroenterology 2004, 126(4, Suppl. 2): Abst M1449.

Original monograph – Drugs Fut 1994, 19(11): 1018.

Tetomilast



Tetomilast (OPC-6535) is a phosphodiesterase type 4 (PDE4) and superoxide production inhibitor under development by Otsuka and currently undergoing phase III trials as a once-daily oral treatment for ulcerative colitis and phase II clinical trials for the treatment of chronic obstructive pulmonary disease (COPD).

A double-blind, randomized, placebo-controlled clinical trial determined the efficacy and safety of tetomilast (25 and 50 mg p.o.) given once daily for 8 weeks to 186 patients with active ulcerative colitis with or without 5-ASA. Clinical improvement, which was defined as a

Table XXXI: Clinical studies of tetomilast (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Ulcerative colitis	Randomized Double-blind	Tetomilast, 25 mg p.o. o.d. x 8 wks (n=62) Tetomilast, 50 mg p.o. o.d. x 8 wks (n=62) Placebo (n=62)	186	Once-daily tetomilast was more effective than placebo in improving the DAI scores and reducing rectal bleeding in patients with ulcerative colitis. Response to treatment was greater among patients with more severe disease	1, 3

3-point reduction in the DAI score, was achieved by 55% and 48% of patients, respectively, receiving 25 and 50 mg of tetomilast and 40% of placebo-treated patients, and improvement was observed independent of 5-ASA treatment. Tetomilast improved both rectal bleeding and physician global assessment, and the percentage of patients who achieved clinical remission was significantly higher in the 50-mg group than in any other study group. The efficacy of tetomilast was greater among patients with more severe disease scores at baseline (1-3) (Table XXXI).

1. Hanauer, S.B., Miner, P.B., Keshavarzian, A., Isaacs, K.L., Goff, J.S., Harris, M.S. *Randomized, double-blind, placebo-controlled, parallel arm, safety and efficacy trial of once-daily, oral OPC-6535 in the treatment of active ulcerative colitis (UC)*. Gastroenterology 2004, 126(4, Suppl. 2): Abst 814.

2. Hanauer, S.B., Keshavarzian, A., Schollenberger, J., Harris, M.S. *Once-daily, oral OPC-6535 in the treatment of active ulcerative colitis: Effect of concomitant 5-ASA use*. Am J Gastroenterol 2004, 99(10, Suppl.): Abst 823.

3. Schreiber, S.W., Forbes, A., Feagan, B.G., Ali, M., Harris, M.S. *Randomized, multi-center, double-blind, placebo-controlled trial of once-daily, oral OPC-6535 in the treatment of active ulcerative colitis: Use of the disease activity index (DAI) to define study population and treatment response*. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst TUE-G-367.

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

TheraCLEC™

The Center for Drug Evaluation and Research (CDER)'s Division of Gastrointestinal and Coagulation Drug Products has selected Altus's TheraCLEC™ for participation in the Continuous Marketing Application (CMA) Pilot 2 program. TheraCLEC™ is the first in a new class of oral enzyme replacement therapies from Altus and is being developed for the treatment of malabsorption as a result of pancreatic insufficiency. It is being evaluated in a large multicenter phase II trial. TheraCLEC™ received U.S. orphan drug designation in January 2002 and fast track designation in December 2003. The European Medicines Evaluation Agency (EMEA) also granted orphan drug designation last year. The compound is intended to replace digestive enzymes to promote and maintain proper digestion, nutrition and growth in affected patients. Altus's European marketing partner for the compound is Dr. Falk Pharma (1, 2).

1. *TheraCLEC selected for CMA Pilot 2 program*. DailyDrugNews.com (Daily Essentials) Sept 15, 2004.

2. *European orphan drug designation for TheraCLEC*. DailyDrugNews.com (Daily Essentials) Oct 15, 2004.

Tocilizumab

Tocilizumab (atlizumab, R-1569, MRA, Actemra®) is a humanized anti-IL-6 receptor antibody originally developed by Chugai and Osaka University and approved recently in Japan for the treatment of Castleman's disease. Chugai and Roche are evaluating the product in phase III trials for the treatment of systemic-onset juvenile idiopathic arthritis and adult rheumatoid arthritis. Phase II trials with tocilizumab are also reportedly under way for the treatment of multiple myeloma and Crohn's disease, as are phase I trials in systemic lupus erythematosus. Under a 2003 licensing agreement, Roche is responsible for promoting tocilizumab worldwide with the exception of Japan, South Korea and Taiwan, while both companies copromote the product in the U.K., France and Germany and Chugai reserves an option for copromotion in the U.S., Italy and Spain (1-3).

The anti-IL-6 antibody was investigated in 36 patients with active Crohn's disease in a randomized, placebo-controlled study. Patients received tocilizumab 8 mg/kg by i.v. infusion biweekly, placebo biweekly, or alternating MRA and placebo for 12 weeks. Significantly more patients given biweekly tocilizumab responded compared to placebo (80% *vs*. 31%); the regimen also suppressed acute-phase responses and was well tolerated. Remission was achieved in 20% of tocilizumab-treated patients compared to none of those on placebo (4, 5) (Table XXXII).

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

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

3. *Japanese manufacturing approval for tocilizumab for Castleman's disease*. DailyDrugNews.com (Daily Essentials) April 13, 2005.

Table XXXII: Clinical studies of tocilizumab (from Prous Science Integrity®).

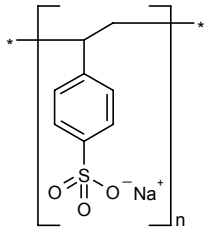
Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Randomized Double-blind	Tocilizumab, 8 mg/kg i.v. 2x/wk 1x/2 wks x 12 wks (n=10) Tocilizumab, 8 mg/kg i.v. 2x/wk 1x/4 wks [alternating with Placebo 1x/2 wks] x 12 wks (n=13) Placebo (n=13)	36	Biweekly infusion of tocilizumab was safe, well tolerated and produced significant improvement in acute-phase responses in patients with active Crohn's disease	5

4. Ito, H. *Treatment of Crohn's disease with anti-IL-6 receptor antibody*. J Gastroenterol 2005, 40(Suppl. 16): 32.

5. Ito, H., Takazoe, M., Fukuda, Y., Hibi, T., Kusugami, K., Andoh, A., Matsumoto, T., Yamamura, T., Azuma, J., Nishimoto, N., Yoshizaki, K., Shimoyama, T., Kishimoto, T. *A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease*. Gastroenterology 2004, 126(4): 989.

Original monograph – Drugs Fut 2003, 28(4): 315.

Tolevamer Sodium



The first patients have been treated in Genzyme's phase III study to test the safety and efficacy of tolevamer sodium, an investigational polymer therapy for patients with *C. difficile*-associated diarrhea (CDAD). The randomized, double-blind phase III study will be conducted at more than 250 clinical sites in North America, Europe and Australia in over 1,000 patients. Enrollment is expected to take approximately 18 months to complete. The study will include three arms and have a primary endpoint of noninferiority to the standard prescribed oral dose of vancomycin, measured by the percent of patients with resolution of CDAD. Half of the patients enrolled in the study will receive tolevamer in a new liquid formulation designed for ease of use. The study will also evaluate tolevamer against metronidazole, the most commonly prescribed antibiotic treatment for CDAD. Because tolevamer is a nonantibiotic and will not harm the normal protective intestinal bacteria that prevent *C. difficile* proliferation, it is expected to reduce the rate of recurrent CDAD. The study is also designed to measure the superiority of tolevamer based on the number of CDAD recurrences against both vancomycin and metronidazole. Tolevamer is being developed as a new, nonabsorbed therapy that could be the first nonantibiotic treatment approved for CDAD. Tolevamer is designed to bind and remove from the body toxins released by *C. difficile* that damage the intestine. To date, tolevamer has been evaluated in a large phase II efficacy study, two open-label clinical trials in CDAD patients, a phase I trial in healthy volunteers and an additional phase I tolerability study evaluating the new liquid formulation. Data from this last study show the new liquid formulation of tolevamer to be well tolerated at all dose levels tested up to a maximum of 15 g. The daily dose of tolevamer in the phase III study is 9 g (1, 2).

A multicenter, double-blind, randomized phase II clinical trial compared the efficacy and safety of the antibiotic vancomycin and the toxin-binding polymer tolevamer sodium in the treatment of CDAD. A total of 289 patients with first-episode or recurrent mild to moderate CDAD were treated with vancomycin (125 mg p.o. once daily) or tolevamer (1 or 2 g t.i.d.) until resolution. No significant differences were found between the median times to resolution of diarrhea (TTROD) for vancomycin and the 6 mg/day tolevamer dose, whereas the median TTROD was longer with the 3 mg/day tolevamer dose (4.0 days *vs*. 2.0 days with vancomycin). The 6 mg/day tolevamer dose was associated with a lower rate of recurrence compared to vancomycin (10% *vs.* 19%), but the differences were not statistically significant. The incidence of adverse events was similar in all study groups (3, 4) (Table XXXIII).

In a substudy of a multinational, randomized, double-blind phase II trial, fecal samples were collected from 30 participants at the study sites. In normal intestinal microflora controls, an average of 4 species of anaerobic *Bacteroides* were detected in counts of $10^{10\text{-}12}$/g feces wet weight. *Bacteroides* counts were lower in most of the patients with CDAD, including half of the patients in whom the counts were below the limit of detection. While vancomycin treatment eliminated vegetative *C. difficile*, the *Bacteroides* genera did not return to normal during or after treatment. An increase in anaerobic organisms was seen in patients responding to tolevamer, however, although recovery of anaerobic microflora was not complete at 14 days (5) (Table XXXIII).

1. *Genzyme Corp. reports Q1 R&D highlights*. Genzyme Corp. Press Release 2004, April 15.

2. *Treatment begins in phase III study of tolevamer in CDAD*. DailyDrugNews.com (Daily Essentials) April 7, 2005.

3. Louie, T., Peppe, J., Watt, C.K. et al. *A phase 2 study of the toxin binding polymer tolevamer in patients with C. difficile-associated diarrhea*. Gastroenterology 2004, 126(4, Suppl. 2): Abst T1785.

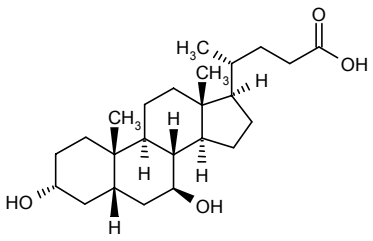
Table XXXIII: Clinical studies of tolevamer sodium (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Diarrhea	Randomized Double-blind Multicenter	Tolevamer, 1 g t.i.d. [until resolution] Tolevamer, 2 g t.i.d. [until resolution] Vancomycin, 125 mg p.o. o.d. [until resolution]	289	Tolevamer (2 g t.i.d.) was well tolerated and as effective as vancomycin in the treatment of *C. difficile*-associated diarrhea. This tolevamer dose was associated with a lower incidence of recurrence compared to vancomycin, but the differences between study groups were not statistically significant	3, 4
Diarrhea	Randomized Multicenter	Tolevamer, 2 g t.i.d. x 14 d Tolevamer, 1 g t.i.d. x 14 d Vancomycin, 125 mg q.i.d. x 10 d	30	Tolevamer was associated with restoration of components of the anerobic intestinal microflora. Patients who responded to toxin-binding therapy exhibited nonemergence of toxins with an increase in the numbers of anerobic organisms during treatment of *C. difficile*-associated diarrhea. Vancomycin eliminated vegetative *C. difficile* with variable spore persistence, and *Bacteroides* remained suppressed in the majority of patients	5

4. Davidson, D., Peppe, J., Louie, T. *A phase 2 study of the toxin binding polymer tolevamer in patients with C. difficile associated diarrhoea*. Clin Microbiol Infect 2004, 10(Suppl. 3): Abst P548.

5. Louie, T., Byrne, B., Emery, J. et al. *Tolevamer (GT160-246) binds Clostridium cytotoxins A/B and is associated with restoration of components of the anaerobic intestinal microflora during treatment of C. difficile-associated diarrhoea*. Clin Microbiol Infect 2004, 10(Suppl. 3): Abst P855.

Ursodiol



A naturally occurring bile acid, ursodiol has been available for a number of years from Axcan for the treatment of primary biliary cirrhosis and cholestatic liver diseases. It is presently the subject of a phase III clinical development program at Mitsubishi Pharma for the treatment of hepatitis C.

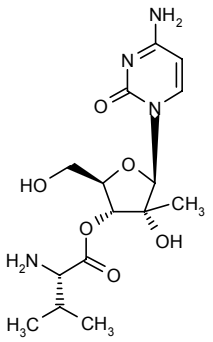
Urtoxazumab

Urtoxazumab (TMA-15), a humanized monoclonal antibody in development at Teijin, is being tested in phase II clinical trials for the treatment of bloody diarrhea and hemorrhagic colitis caused by *E. coli* O157:H7 infection.

UT-231B

UT-231B is currently undergoing phase II clinical trials at United Therapeutics as a treatment for hepatitis C. Research suggests that UT-231B, a therapeutic iminosugar, alters the assembly of the viruses, thereby preventing them from being able to continue infecting and replicating in other cells.

Valopicitabine



The nucleoside RNA polymerase inhibitor valopicitabine (NM-283) is in phase IIa clinical trials at Idenix for the oral, once-daily treatment of HCV in combination with

pegylated interferon in treatment-naïve patients. In addition, Idenix is conducting a phase IIb clinical trial comparing valopicitabine as monotherapy to valopicitabine combined with pegylated interferon or pegylated interferon combined with ribavirin for the treatment of HCV-infected patients unresponsive to treatment with standard therapy. Valopicitabine was codiscovered by Idenix and the University of Cagliari. Novartis has an an option to license and jointly develop valopicitabine for the treatment of chronic hepatitis C.

Idenix has announced the results of the first human clinical trial of valopicitabine. In the double-blind, randomized, dose-escalating phase I/II trial, valopicitabine demonstrated consistent, dose-related antiviral effects in adult patients with chronic hepatitis C. The trial was designed to evaluate the safety, pharmacokinetics and antiviral activity of valopicitabine during 15 days of treatment, with a 2-week follow-up period. The design of the phase I/II clinical trial included five once-daily dosing cohorts: 50, 100, 200, 400 and 800 mg, and one twice-daily dosing cohort of 200 mg. Two further cohorts explored methods for optimizing tolerance of higher daily doses. The patient cohort that received the highest overall dose exposure of valopicitabine achieved a mean viral load reduction of 92% within 15 days of treatment. The once-daily 800 mg cohort is currently ongoing. To date, a total of 82 patients comprising seven dose groups have completed treatment, including 68 patients receiving assigned doses of valopicitabine and 14 receiving placebo. For the three highest dose groups in the clinical trial, antiviral responses over the 15-day treatment period exceeded the average serum viral level reduction observed in hepatitis C patients who respond to treatment with the current standard of therapy (ribavirin in combination with pegylated interferon). The overall safety profile for valopicitabine was satisfactory, with no dose-limiting toxicities. All 82 compliant patients completed treatment and follow-up; 1 patient was discontinued from the study for noncompliance. At the higher doses, some patients had mild to moderate gastrointestinal side effects that most often appeared in the first 2 days of treatment and typically resolved quickly. No patients changed or discontinued treatment due to side effects. Pharmacokinetic data revealed that valopicitabine was well absorbed and there was no significant drug accumulation, as day 15 drug levels were comparable to day 1 levels. Furthermore, drug levels were proportional to the dose (1, 2).

Sixty adult HCV-infected patients with compensated noncirrhotic liver disease participated in a placebo-controlled phase I/II clinical trial that determined the pharmacokinetics of valopicitabine (50, 100, 200, 400 or 800 mg p.o.) given once daily for 15 days. Valopicitabine was quickly absorbed and converted to its active metabolite NM-107 and the minor metabolite NM-106. Both the level of exposure and the peak plasma concentration of valopicitabine, NM-107 and NM-106 increased with dose and were correlated with greater reductions in serum HCV viral load (3).

In a phase I/II study, patients with HCV genotype 1 infection were treated with valopicitabine 50-800 mg/day or placebo for 15 days. The drug demonstrated rapid absorption, extensive conversion to the target moiety, dose-proportional plasma exposure and anti-HCV activity appeared to be dose-related. No serious adverse events or dose-limiting toxicity were observed (4, 5).

A placebo-controlled phase I/II clinical trial assessed the antiviral efficacy, safety and pharmacokinetics of valopicitabine (50-800 mg/day for 15 days) in 95 HCV-infected adults with compensated noncirrhotic chronic liver disease and serum HCV RNA levels greater than 5 $\log_{10}$ copies/ml. Most (87%) patients had not responded to previous interferon therapy and the others were treatment-naïve. The serum HCV RNA levels of the patients decreased dose-dependently with valopicitabine (61-99%) but increased by an average of 7% with placebo. All valopicitabine regimens were well tolerated; gastrointestinal side effects were mostly mild and self-limiting, and were more common at doses of 400 mg/day and above (6) (Table XXXIV).

An ongoing multicenter, randomized phase IIa clinical trial is evaluating the antiviral efficacy of valopicitabine plus peginterferon alfa in 28 treatment-naïve patients with chronic hepatitis C genotype 1 infection. Each patient was given valopicitabine (800 mg p.o. once daily) alone or combined with once-weekly peginterferon alfa-2b (1.0

Table XXXIV: Clinical studies of valopicitabine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis C	Randomized Double-blind Multicenter	Valopicitabine, 50-800 mg/d x 15 d Placebo	95	Valopicitabine was well tolerated and effectively reduced serum viral RNA levels in patients with hepatitis C	6
Hepatitis C	Open Multicenter	Valopicitabine, 800 [max.] mg p.o. o.d. x 24 wks Valopicitabine, 800 [max.] mg p.o. o.d. x 1 wk → Id. + Peginterferon alfa-2b, 1.0 µg/kg 1x/wk x 24 wks	28	After 10-12 weeks of treatment, a combination of valopicitabine plus peginterferon alfa-2b was well tolerated and more effective than valopicitabine alone in reducing viral load in patients infected with hepatitis C virus genotype 1	8, 9

μg/kg, starting on day 8) for 24 weeks. An interim analysis conducted after 19 patients had received treatment for 10-12 weeks revealed average HCV viral load reductions of 1.0 log_{10} IU/ml with valopicitabine alone and 3.2 log_{10} IU/ml with valopicitabine plus peginterferon alfa-2b. Of the 12 patients treated for at least 10 weeks, 11 had substantial decreases in HCV RNA (1.7-6.2 log_{10} IU/ml) and 9 had a > 2 log_{10} IU/ml decrease, associated with a sustained response to current standard therapy; 4 patients were PCR-negative (HCV RNA < 10 IU/ml). After 12 weeks of treatment, the average reductions in baseline serum HCV RNA levels with combination therapy and valopicitabine alone were 99.94% and 87.4%, respectively. Both study treatments were well tolerated. Idenix has begun a phase IIb clinical trial to determine the efficacy of valopicitabine plus pegylated interferon in HCV-infected patients unresponsive to at least 3 months of treatment with standard therapy (7-9) (Table XXXIV).

1. *Idenix reports phase I/II clinical trial data for NM-283 as treatment of hepatitis C*. DailyDrugNews.com (Daily Essentials) May 20, 2004.

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

3. Zhou, X.J. et al. *Pharmacokinetics and pharmacodynamics of valopicitabine (NM283), a new nucleoside HCV polymerase inhibitor: Results from a phase I/II dose-escalation trial in patients with HCV-1 infection*. 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 626.

4. Godofsky, E., Afdhal, N., Rustgi, V., Shick, L., Duncan, L., Zhou, X.-J., Chao, G., Fang, C., Fielman, B., Myers, M., Brown, N. *A phase I/II dose escalation trial assessing tolerance, pharmacokinetics, and antiviral activity of NM283, a novel antiviral treatment for hepatitis C*. Gastroenterology 2004, 126(4, Suppl. 2): Abst 407.

5. Zhou, X.-J., Afdhal, N., Godofsky, E., Dienstag, J., Rustgi, V., Schick, L., Duncan, L., Fielman, B., Chao, G., Brown, N.A. *Pharmacokinetics and pharmacodynamics of valopicitabine (NM283), a new nucleoside HCV polymerase inhibitor: Results from a phase I/II dose-escalation trial in patients with HCV-1 infection*. Dig Dis Week (May 14-19, Chicago) 2005, Abst S926.

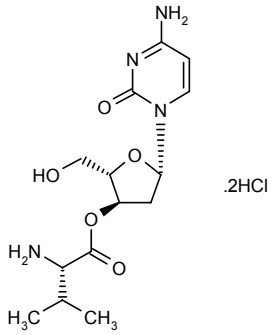
6. Afdhal, N., Godofsky, E., Dienstag, J. et al. *Final phase I/II trial results for NM283, a new polymerase inhibitor for hepatitis C: Antiviral efficacy and tolerance in patients with HCV-1 infection, including previous interferon failures*. Hepatology 2004, 40(4, Suppl. 1): Abst LB 03.

7. *A valopicitabine plus pegylated interferon regimen shows promise in hepatitis C*. DailyDrugNews.com (Daily Essentials) Jan 13, 2005.

8. Afdhal, N. et al. *Enhanced antiviral efficacy of valopicitabine (NM283) plus PEG-interferon in hepatitis C patients with HCV genotype-1 infection: Results of a phase IIA multicenter trial.* 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 93.

9. Rodriguez-Torres, M., Lawitz, E., Godofsky, E., Afdhal, N., Chao, G., Constance, B.F., Knox, S., Brown, N.A. *Valopicitabine (NM283) alone and in combination with PEG-interferon in patients with genotype 1 chronic hepatitis C: Preliminary results from an ongoing phase II, multicenter study*. Dig Dis Week (May 14-19, Chicago) 2005, Abst 522.

Valtorcitabine Dihydrochloride



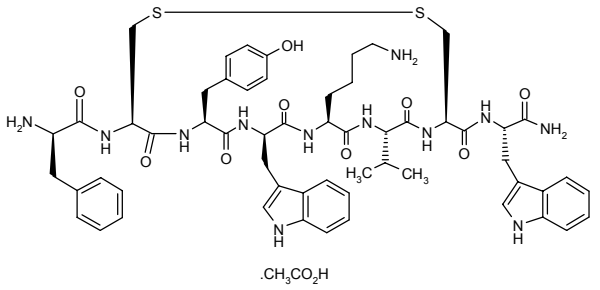
Valtorcitabine dihydrochloride is a DNA polymerase inhibitor in phase II trials at Idenix and Novartis for the treatment of hepatitis B. The drug is an orally bioavailable prodrug of NM-107, a nucleoside analogue that directly inhibits HCV RNA polymerase. Valtorcitabine has been shown to dose-dependently decrease plasma HBV DNA levels. It is being developed as a fixed-dose combination with telbivudine (see above).

The efficacy, safety and pharmacokinetics of two different forms of valtorcitabine were assessed in a phase I/II clinical trial. Cohorts of patients with chronic hepatitis B and positive for HBeAg were randomized to receive placebo, a 3',5'-divalyl prodrug form of valtorcitabine (50, 100, 200 or 400 mg/day) or a more stable 3'-monovalyl form (300, 600, 900 or 1200 mg/day) for 28 days. An interim analysis revealed that valtorcitabine dose-dependently decreased plasma HBV DNA levels, with maximal antiviral effects achieved at doses of 900 mg/day or more. All study treatments were well tolerated (1, 2).

1. Lai, C.L., Brown, N.A., Yuen, M.F. et al. *Valtorcitabine provides potent suppression of hepatitis B virus in patients with chronic hepatitis B: Results of a phase I/II clinical trial*. Hepatology 2004, 40(4, Suppl. 1): Abst 24.

2. Lim, S.G. et al. *Final results of a phase I/II dose escalation trial of valtorcitabine in patients with chronic hepatitis B*. 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 34.

Vapreotide Acetate



The Mexican Health Authority has granted the first approval for H3 Pharma's immediate-release vapreotide

acetate (Docrised®) for the treatment of esophageal variceal bleeding (EVB) and four other indications (acromegaly, gastrointestinal fistulas, AIDS-related diarrhea and neuroendocrine tumors). H3 Pharma plans to sign a commercialization agreement with a partner to make the product available in Mexico as soon as possible. The company also recently received an approvable letter from the FDA (Sanvar® IR in the U.S.) for the acute treatment of acute EVB secondary to portal hypertension, requesting additional supportive efficacy data and additional information related to manufacturing aspects. Immediate-release vapreotide is the only somatostatin analogue to demonstrate benefits in the treatment of EVB in association with endoscopic therapy in a reliable clinical study. In a phase III study in 227 patients at 22 centers, it was shown to significantly reduce active bleeding. Survival with hemostasis at 5 days was achieved significantly more often with vapreotide than with placebo. In patients with control of bleeding at day 5, vapreotide significantly increased hemostasis and survival through day 42. Vapreotide will be used in association with endoscopic treatment to improve hemostasis in emergency in cirrhotic patients presenting variceal bleeding. It is also the only somatostatin analogue that is stable at room temperature for extended periods of time. The product has orphan drug status in the U.S. (1-3). A sustained-release formulation is also in phase II development for Crohn's disease.

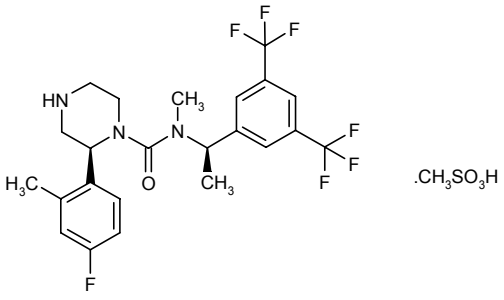
1. *Mexican approval for Sanvar IR*. DailyDrugNews.com (Daily Essentials) Aug 31, 2004.

2. *Approvable letter for Sanvar IR for esophageal variceal bleeding*. DailyDrugNews.com (Daily Essentials) Jan 10, 2005.

3. *Debiopharm purchases outstanding shares of H3 Pharma*. DailyDrugNews.com (Daily Essentials) March 4, 2005.

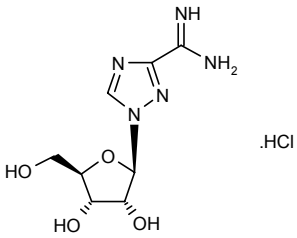
Original monograph – Drugs Fut 1989, 14(11): 1052.

Vestipitant Mesilate



Vestipitant mesilate (597599, GW-597599) is a tachykinin NK_1 receptor antagonist in development at GlaxoSmithKline for several different disorders. Phase II trials are in progress for depression and anxiety in combination with paroxetine, and vestipitant alone is being evaluated in phase II for postoperative and chemotherapy-induced nausea and vomiting.

Viramidine Hydrochloride



Viramidine hydrochloride, a nucleoside (guanosine) analogue, is being developed in oral form by Valeant for the treatment of chronic hepatitis C in conjunction with pegylated interferon. Viramidine is a liver-targeted oral prodrug of ribavirin that is rapidly absorbed and extensively taken up by the liver, where it is converted to the active metabolite. Valeant announced the final results of its proof-of-concept phase II clinical trial comparing the efficacy of ribavirin and viramidine in chronic hepatitis C. A total of 180 treatment-naïve patients were randomized to receive pegylated interferon alfa-2a (180 μg s.c. once weekly) combined with either ribavirin (1000/1200 mg daily) or viramidine (400, 600 or 800 mg b.i.d.) for 24 weeks (if infected with HCV genotypes 2 or 3) or 48 weeks (if infected with HCV genotype 1). Sustained virological response, which was evaluated at 24 weeks after the end of treatment, was obtained in 44% of ribavirin-treated patients and in 23%, 37% and 29% of patients treated with 400, 600 and 800 mg of viramidine, respectively. The analysis of blood samples showed that the average level of ribavirin in red blood cells was significantly lower with viramidine 600 mg b.i.d. than with ribavirin 1200 mg/day after 4 and 12 weeks of treatment. Anemia was more common with ribavirin (27%) compared to viramidine (0%, 2% and 11%, respectively, with 400, 600 and 800 mg), but other adverse events such as fatigue, headache, insomnia, depression and myalgia showed a similar incidence in all study groups. These results are in accordance with the liver-targeting, red blood cell-sparing mechanism of action of viramidine and confirmed that 600 mg b.i.d. was the best dose for phase III studies with viramidine. The company also announced that it has finished enrolling patients in the pivotal VISER2 (Viramidine's Safety and Efficacy vs. Ribavirin) phase III clinical trial, the second of two global phase III trials after VISER1, commenced in late 2003. Each trial includes approximately 1,000 patients at 100 sites and compares viramidine and ribavirin in conjunction with pegylated interferon (1-7) (see Table XXXV).

Six healthy adult male subjects aged 50 years or more participated in a study that evaluated the absorption, metabolism and excretion of viramidine hydrochloride. Each subject was given a single oral dose of 600 mg of [^{14}C]-labeled viramidine (total radioactivity of 52.2 microcuries). Analysis of samples of plasma, red blood cells, urine and feces obtained at different times after dosing revealed that viramidine was quickly absorbed

Table XXXV: Clinical studies of viramidine hydrochloride (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis C	Randomized	Viramidine, 400 mg p.o. b.i.d. + Pegylated interferon alfa, 180 µg/wk s.c. (n=47) Viramidine, 600 mg p.o. b.i.d. + Pegylated interferon alfa, 180 µg/wk s.c. (n=43) Viramidine, 800 mg p.o. b.i.d. + Pegylated interferon alfa, 180 µg/wk s.c. (n=45) Ribavirin, 1000/1200 mg/d (n=45)	180	Viramidine and pegylated interferon alfa in combination showed comparable efficacy to ribavirin, but was better tolerated, with a lower incidence of anemia, in patients with chronic hepatitis C. The 600 mg dose of viramidine was the best dose	3, 4, 6, 7

and converted to ribavirin. Time to peak plasma concentrations was 1.5 h for viramidine, 2 h for ribavirin and 3.5 h for total radioactivity. Most plasma radioactivity was in the form of ribavirin (59% *vs*. 5.5% as viramidine), and most ribavirin was trapped inside red blood cells. Overall, 50.9% and 26.1% of total radioactivity was excreted in urine and feces, respectively, and only a small percentage (3.2%) of viramidine was excreted unchanged (8).

The pharmacokinetics of ascending multiple doses of viramidine (400, 600 or 800 mg b.i.d. for 4 weeks) were determined in 24 adults with compensated hepatitis C infection. The agent was rapidly absorbed and converted to ribavirin. Steady state was achieved by day 22. Exposure of plasma and red blood cells to viramidine and ribavrin increased with the 400- and 600-mg doses, but no further increases were seen with 800 mg. The half-lives for viramidine and ribavirin were long in both plasma (66-76 and 340-410 h, respectively) and red blood cells (200-240 and 360-430 h, respectively). Only negligible amounts of the compounds were excreted in urine. Low renal clearance was observed for both viramidine and ribavirin (5-8 and 4-7 l/h, respectively). There was significant accumulation of viramidine in red blood cells, but not in plasma; ribavirin accumulated in both plasma and red blood cells (9).

1. *Second of two phase III trials for Viramidine underway*. DailyDrugNews.com (Daily Essentials) June 16, 2004.

2. *Update on the efficacy and safety of viramidine in chronic hepatitis C*. DailyDrugNews.com (Daily Essentials) Jan 24, 2005.

3. Arora, S., Gish, R., Nelson, D., Hong, Z., Lin, C.-C. *Clinical study of viramidine in treatment of hepatitis C supports RBC-sparing mechanism of action*. Gastroenterology 2004, 126(4, Suppl. 2): Abst 84.

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5. Gish, R.G., Nelson, D., Arora, S., Fried, M.W., Reddy, K.R., Xu, Y., Murphy, B. *Virologic response and safety outcomes in therapy-naive patients treated for chronic hepatitis C with viramidine in combination with pegylated interferon alfa-2a.* 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 91.

6. Gish, R.G., Arora, S., Nelson, D., Fried, M.W., Reddy, K.R., Xu, Y., Murphy, B. *End-of-treatment (EOT) response in therapy-naïve patients treated for chronic hepatitis C with viramidine in combination with pegylated interferon alfa-2a*. Hepatology 2004, 40(4, Suppl. 1): Abst 519.

7. Gish, R.G., Nelson, D., Arora, S., Fried, M.W., Reddy, K.R., Xu, Y., Kim, M.C., Murphy, B.S. *Virologic response and safety outcomes in therapy-naive patients treated for chronic hepatitis C with viramidine in combination with pegylated interferon alfa-2a*. Dig Dis Week (May 14-19, Chicago) 2005, Abst 2.

8. Lin, C.-C. et al. *Absorption, metabolism and excretion of [14C]viramidine in human.* 40th Annu Meet Eur Assoc Study Liver (April 13-17, Paris) 2005, Abst 580.

9. Arora, S., Xu, C., Teng, A., Peterson, J., Yeh, L.-T., Gish, R., Lau, D., Rossi, S., Lin, C.-C. *Ascending multiple-dose pharmacokinetics of viramidine, a prodrug of ribavirin, in adult subjects with compensated hepatitis C infection*. J Clin Pharmacol 2005, 45(3): 275.

Original monograph – Drugs Fut 2004, 29(7): 687.

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Lin, C.-C. et al. *Dosing with viramidine in HCV patients resulted in lower plasma and RBC ribavirin levels and exhibited smaller decreases in hemoglobin compared to ribavirin dosing*. Hepatology 2004, 40(4, Suppl. 1): Abst 515.

Virostat

The first patients have been enrolled in an international phase II investigator-sponsored trial to evaluate the clinical efficacy of Virostat (methylene blue) for the treatment of chronic hepatitis C. The trial is being conducted at specialist centers in Europe and Egypt and will assess the ability of Virostat to reduce viral load and improve quality of life in patients with chronic hepatitis C. Virostat has shown potent virucidal activity *in vitro* and is effective against viruses such as HIV and West Nile virus in laboratory tests. Bioenvision obtained global development and marketing rights from the Oklahoma Medical Research Foundation (OMRF) for Virostat for antiviral indications (1).

1. *Enrollment open in phase II study of Virostat for hepatitis C* . DailyDrugNews.com (Daily Essentials) Feb 21, 2005.

Visilizumab

Protein Design is focusing on the development of novel therapies for inflammatory bowel disease with the ongoing development of visilizumab (Nuvion®), a human-

ized anti-CD3 antibody product for the potential treatment of patients with severe ulcerative colitis who fail to respond to treatment with intravenous steroids, for which it holds fast track designation. A phase I/II trial in patients with severe ulcerative colitis who had not responded to intravenous steroids was commenced in the fourth quarter of 2003 and was designed to explore four dose levels (5, 7.5, 10 and 12.5 μg/kg by i.v. bolus on days 1 and 2). In the 32-patient phase I portion, a strong signal of activity was observed in the first dose cohort given 7.5 μg/kg on days 1 and 2, in which all 8 patients achieved remission. A continued strong signal of activity was subsequently observed in the second dose cohort of 5 μg/kg administered on days 1 and 2, in which 19 of 24 patients responded to treatment and 13 achieved remission. PDL is now enrolling visilizumab-naïve patients into the phase II portion of the study at the 5 μg/kg dose level. This study also incorporates an optional retreatment phase. To date, 4 patients have received a second course of visilizumab in the optional retreatment phase, all of whom had taken part in the completed phase I trial, achieved a response and later relapsed within 1 year. Two met the protocol-defined criteria for dose-limiting toxicity (DLT): 1 had slow recovery of the $CD3^+/CD4^+$ T-cell count at day 60 and the other had an asymptomatic elevation of Epstein-Barr virus (EBV) levels. Despite these DLTs, an independent data safety monitoring board concluded that this phase could continue. PDL has discussed with the FDA in an end-of-phase I meeting the future development pathway for visilizumab for the treatment of intravenous steroid-refractory ulcerative colitis. As a result of discussions, PDL is now considering a plan to conduct two pivotal clinical trials and a retreatment study of visilizumab in the setting of intravenous steroid-refractory ulcerative colitis. The first pivotal study will be a phase II/III trial, instead of a phase III trial, and is expected to begin in 2005. If certain criteria are met at an interim analysis, the second pivotal trial would then be initiated. The retreatment study would begin at the time of the phase II/III study. While the mechanism of action of visilizumab in ulcerative colitis is still being characterized, early research has demonstrated that it induces selective apoptosis of activated, but not resting human T-cells in *in vitro* cell biology experiments. Research studies continue on visilizumab's effects on the resting T-cell populations that appear not susceptible to *in vitro* apoptosis (1-8).

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

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

3. *Protein Design Labs plots Nuvion development pathway*. DailyDrugNews.com (Daily Essentials) March 30, 2005.

4. *Enrollment to resume in optional retreatment arm of phase I/II Nuvion study*. DailyDrugNews.com (Daily Essentials) Aug 12, 2004.

5. Plevy, S., Salzberg, B., van Assche, G. et al. *A humanized anti-CD3 monoclonal antibody, visilizumab, for treatment of severe steroid-refractory ulcerative colitis: Results of a phase I study*. Gastroenterology 2004, 126(4, Suppl. 2): Abst 579.

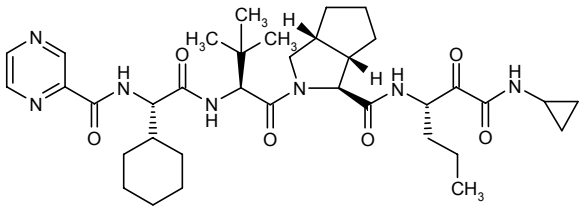
6. Targan, S., Salzberg, B., Dignass, A.U. *Visilizumab, a humanized anti-CD3 monoclonal antibody is active in the treatment of severe steroid-refractory ulcerative colitis (UC): Preliminary results of a phase III study*. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst OP-G-258.

7. Keller, S., Delanoy, M., Zhao, V., Albano, A., Fang, Y., Tang, K., Chang, Y., Singer, R., Lowder, J., Vexler, V., Caras, I. *Treatment with visilizumab causes a rapid and reversible increase in circulating levels of selected cytokines, chemokines and growth factors in patients with intravenous steroid-refractory ulcerative colitis*. Dig Dis Week (May 14-19, Chicago) 2005, Abst W1028.

8. Targan, S.R., Salzberg, B.A., Mayer, L., Hommes, D., Hanauer, S., Mahadevan, U., Reinisch, W., Plevy, S.E., Dignass, A.U., Van Assche, G., Buchman, A., Mechkov, G., Krastev, Z., Lowder, J.N. *A phase I-II study: Multiple dose levels of visilizumab are well tolerated and produce rapid and sustained improvement in ulcerative colitis patients refractory to treatment with IV steroids (IVSR-UC)*. Dig Dis Week (May 14-19, Chicago) 2005, Abst 493.

Original monograph – Drugs Fut 2002, 27(5): 469.

VX-950



Phase I testing is under way at Vertex for VX-950, an investigational oral HCV NS3-4A protease inhibitor for the treatment of HCV infection. Following successful completion of the first phase Ia trial assessing safety, tolerability and pharmacokinetics of escalating single doses in healthy volunteers, a phase Ib study in HCV-infected patients has commenced. The double-blind, placebo-controlled study will evaluate the tolerability, pharmacokinetics and viral kinetics of multiple ascending doses of VX-950 over a period of up to 14 days. Approximately 60 subjects, both healthy volunteers and patients with chronic HCV infection, will be enrolled at two centers. The study may include patients with HCV who are either treatment-naïve or -experienced. The study will first assess healthy volunteers receiving multiple doses of VX-950 for a 5-day period. Subsequently, three different doses of VX-950 will be evaluated in HCV patients over 14 days of treatment in serially configured dose groups. The study is said to be the first to involve 14 days of administration of an HCV protease inhibitor in patients with chronic HCV infection. Data from the three dose groups will be studied

when the third dose is complete. The study is expected to be completed in the first half of 2005. In the phase Ia study, VX-950 (25-1250 mg) was well tolerated and demonstrated oral bioavailability. Combined clinical and preclinical pharmacokinetic results indicate that VX-950 can be administered in a dose regimen that may achieve liver concentrations substantially greater than target concentrations (IC_{50} and IC_{90} in preclinical studies). VX-950 is Vertex's lead oral HCV protease inhibitor and one of a new class of direct antivirals in development for the treatment of HCV. Preclinical studies have shown that VX-950 significantly reduces levels of HCV RNA in both an *in vitro* replicon system and infectious virus assays. VX-950 reduced HCV RNA 10,000-fold (4 $\log_{10}$) in 9 days in an *in vitro* replicon assay. Preclinical pharmacokinetic studies have indicated that VX-950 is orally bioavailable and achieves excellent exposure in the liver. Vertex and Mitsubishi Pharma have signed an agreement to develop and commercialize VX-950 in Japan and certain Far East countries. Mitsubishi will have exclusive rights to develop and commercialize VX-950 in Japan and certain Far East countries, while Vertex will retain exclusive development and marketing rights to VX-950 in the rest of the world, including North America and Europe (1-5).

Twenty-five healthy male volunteers were included in a phase I clinical trial that assessed the safety and pharmacokinetics of VX-950 (single doses of 25-1000 mg p.o.). The median apparent elimination half-life of VX-950 was 4 h at doses of 450 mg or more, and 2 h at doses of 25-300 mg. Analysis of plasma drug exposure levels suggested that these VX-950 doses provided liver exposure levels above the IC_{90} for 12 h after administration. Most adverse events (*e.g.,* fatigue, headache and nausea) were mild and nonspecific (6) (Table XXXVI).

The effects and safety of multiple doses of VX-950 are being evaluated in the VX04-950-101 study, an ongoing phase Ib clinical trial in which placebo or VX-950 (450, 750 or 1250 mg p.o.) is administered for 5 days to 24 healthy volunteers and for 14 days to 36 patients with chronic hepatitis C. Preliminary data from the healthy volunteers included in the study have shown that VX-950 is well tolerated and is mostly associated with mild adverse events. No serious adverse events have been observed, and no subjects have discontinued the study due to safety issues. VX-950 has also shown good bioavailability, and steady state was reached within 24-48 h after the first dose. From the results obtained and from preclinical data on plasma-to-liver drug concentration ratios, it was predicted that the doses would result in liver exposure exceeding the IC_{90} (7) (Table XXXVI).

1. *VX-950 enters phase I for HCV*. DailyDrugNews.com (Daily Essentials) June 14, 2004.

2. *Vertex and Mitsubishi sign agreement for VX-950 in Japan and Far East*. DailyDrugNews.com (Daily Essentials) June 16, 2004.

3. *Vertex initiates phase Ib study for VX-950*. DailyDrugNews.com (Daily Essentials) Nov 11, 2004.

4. *Vertex completes dosing in phase Ia study of VX-950 for HCV*. DailyDrugNews.com (Daily Essentials) Sept 9, 2004.

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

6. Chu, H.-M., McNair, L., Purdy, S. *Results of a phase I single-dose escalation study of the hepatitis C protease inhibitor VX-950 in healthy volunteers*. Hepatology 2004, 40(4, Suppl. 1): Abst LB 20.

7. Reesink, H.W. , Zeuzem, S., van Vliet, A., McNair, L., Purdy, S., Chu, H., Jansen, P.L. *Initial results of a phase 1B, multiple-dose study of VX-950, a hepatitis C virus protease inhibitor*. Dig Dis Week (May 14-19, Chicago) 2005, Abst 527.

XP-19986

XenoPort has initiated phase I trials of XP-19986, a drug designed to overcome the deficiencies of baclofen. The initial phase I trial aims to demonstrate the safety and pharmacokinetic properties of different formulations of XP-19986. A single dose of different strengths of each formulation of XP-19986 will be administered to healthy adults and the extent of the oral absorption and metabolism of XP-19986 will be measured. In future clinical trials, XenoPort plans to explore the therapeutic utility of XP-19986 in the treatment of spasticity and gastroesophageal reflux disease. XP-19986 is designed to overcome the deficiencies (short duration in blood after oral dosing and limited absorption in the colon) of baclofen, a marketed drug that is a 50:50 mixture of (*R*)- and (*S*)-isomers. Studies have shown that the beneficial therapeutic properties of baclofen are attributable to the (*R*)-isomer. XP-19986 is a new chemical entity that is a transported prodrug of (*R*)-baclofen and is designed to engage natural transport mechanisms found on intestinal

Table XXXVI: Clinical studies of VX-950 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers		VX-950, 25-1000 mg p.o. Placebo	25	Single oral doses of VX-950 were well tolerated and mostly associated with mild adverse events	6
Healthy volunteers	Open	VX-950, 450 mg p.o. o.d. x 5 d VX-950, 750 mg p.o. o.d. x 5 d VX-950, 1250 mg p.o. o.d. x 5 d Placebo	24	Once-daily VX-950 was well tolerated and mostly resulted in mild adverse events in healthy volunteers	7

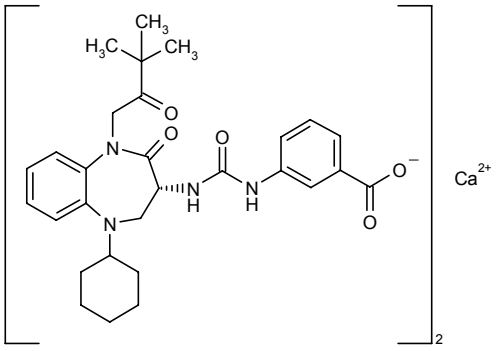
cell membranes, thereby gaining efficient entry into the bloodstream. XP-19986 is then rapidly converted to (*R*)-baclofen by high-capacity enzymes. The other metabolic breakdown products of XP-19986 are natural substances with favorable safety characteristics. XP-19986 is expected to be formulated in a sustained-release pill to provide improved therapy. Baclofen is regularly prescribed for multiple sclerosis, spinal disease/injury, pain conditions and spastic conditions. Recent clinical trials also suggest its utility for treating GERD. Unlike acid-suppressing agents, baclofen exerts its effects on the function of the lower esophageal sphincter that controls the passage of material between the esophagus and the stomach. Baclofen reduces the frequency of TLESRs, and therefore the passage of gastric contents into the esophagus, and may potentially be effective alone or in combination with acid suppressants (1).

1. *XenoPort advances XP-19986 into phase I trials*. DailyDrugNews.com (Daily Essentials) March 31, 2005.

Z-206

Z-206 is in phase I trials at Zeria for the treatment of IBD.

Z-360



Z-360 is a CCK_2 (CCK_B/gastrin) antagonist and gastrointestinal motility-activating agent in early clinical development at Zeria for the treatment of peptic ulcers.

Annual Update 2004/2005 - Treatment of Digestive/Gastrointestinal Cancers

The group of digestive/gastrointestinal cancers includes esophageal, gastrointestinal (stomach and small intestine), colorectal, anal, hepatobiliary (liver and bile duct) and gallbladder cancers (1). Pancreatic cancer, which affects the pancreas, a hormone-producing gland, was covered in a previous table (2).

Approximately 250,000 new cases of digestive/gastrointestinal cancer are expected in the U.S. in 2005, with 140,000 cases of colorectal cancer and almost 20,000 cases of hepatobiliary cancer. Colorectal cancer is the third most common cancer both in men and in women, with an estimated 56,000 deaths from colorectal cancer expected to occur in 2005 (3).

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

References

1. NCI website (www.cancer.gov)

2. Cancer Statistics 2005 (American Cancer Society, Inc., www.cancer.org)

Itziar Escudero

Treatment of Digestive/Gastrointestinal Cancers

Condition	Phase	Drug	Target	Source
Esophageal cancer	I	MS-275	HDAC	National Cancer Institute
	III	Leucovorin/UFT[1]	Pyrimidine nucleotides	Bristol-Myers Squibb
	II	Anti-Gastrin 17	Gastrin 17	Aphton
	II	Antineoplaston AS2-1		Burzynski Research Institute
	II	Celecoxib[1]	COX-2	Cornell Univresity
	II	Ad5CMV-p53		Introgen
	II	OncoGel	Tubulin	MacroMed
	II	Bortezomib[1]	Proteasome	National Cancer Institute
	II	Arsenic trioxide		National Cancer Institute
	II	Paclitaxel[1]	Tubulin	National Cancer Institute
	II	Oxaliplatin[1]	DNA	National Cancer Institute
	II	3-AP	Ribonucleoside-diphosphate reductase	National Cancer Institute
	II	Erlotinib hydrochloride[1]	EGFR	National Cancer Institute
	II	GS-7904L	Thymidylate synthase	OSI Pharmaceuticals
	II	SP-1049C	DNA topoisomerase II	Supratek
	I/II	Photochlor		National Cancer Institute
	I	Benzyl aminolevulinate		PhotoCure
	I	Banoxantrone	DNA topoisomerase II	Kudos Pharmaceuticals/Novacea
Gastrointestinal cancer	II	Matuzumab	EGFR	EMD Pharmaceuticals
	II	Bevacizumab[1]	VEGF	National Cancer Institute
	II	Gefitinib[1]	EGFR	National Cancer Institute
	I/II	OncoVEX(GM-CSF)		BioVex
Stomach cancer	I/II	Indisulam	CDK2	Eisai
	III	Sunitinib malate	VEGFR-1 and -2, PDGFRβ, Flt3	Pfizer
	II/III	PN-401		Wellstat Therapeutics

Continuation

Treatment of Digestive/Gastrointestinal Cancers

Condition	Phase	Drug	Target	Source
Stomach cancer	II/III	PN-401		Wellstat Therapeutics
	II	AMG-706	VEGFR-1, -2 and -3, PDGFR	Amgen
	II	HSPPC-96	HSP	Antigenics
	II	Anti-Gastrin 17	Gastrin 17	Aphton
	II	Capecitabine[1]	Pyrimidine nucleotides	Chugai
	II	SC-1	CD55	H3 Pharma
	II	LMB-9	CD174 (Lewis y)	Ivax
	II	Irinotecan hydrochloride[1]	DNA topoisomerase I	National Cancer Institute
	II	Oxaliplatin[1]	DNA	National Cancer Institute
	II	FR-901228	HDAC	National Cancer Institute
	II	Bryostatin[1]	PKC	National Cancer Institute
	II	Irofulven	Caspase 8 and 9	National Cancer Institute
	II	Erlotinib hydrochloride[1]	EGFR	National Cancer Institute
	II	Bortezomib[1]	Proteasome	National Cancer Institute
	II	Arsenic trioxide		National Cancer Institute
	II	Lapatinib	EGFR, HER2	National Cancer Institute
	II	GS-7904L	Thymidylate synthase	OSI Pharmaceuticals
	I/II	SC-1	CD55	H3 Pharma/OncoMab
	I/II	RAV-12	RAAG-12	Raven
Small intestine cancer	I	Spisulosine		PharmaMar
	I	Ixabepilone	Tubulin	National Cancer Institute
	I	XK-469	DNA topoisomerase II	National Cancer Institute
	I	Azacitidine[1]	DNA methyltransferase	National Cancer Institute
	I	Decitabine	DNA methyltransferase	National Cancer Institute
	I	Lenalidomide	TNF-α	National Cancer Institute
Colorectal cancer	Reg.	ColorectAlert		IMI International Medical Innovations/Procyon
	III	Cetuximab[1]	EGFR	ImClone
	II/III	CTP-37	hCG	AVI BioPharma
	II/III	Celecoxib[1]	COX-2	EORTC/National Cancer Institute
	II/III	105AD7	CD55	University of Nottingham
	II	E-7010	Tubulin	Abbott
	II	Liposomal NDDP	DNA	Antigenics
	II	HSPPC-96	HSP	Antigenics
	II	Gefitinib[1]	EGFR	AstraZeneca/National Cancer Institute
	II	Serum-RECAF blood test		BioCurex
	II	Antineoplaston A10		Burzynski Research Institute
	II	Antineoplaston AS2-1		Burzynski Research Institute
	II	DJ-927	Tubulin	Daiichi Pharmaceutical
	II	Indisulam	CDK2	Eisa
	II	GS-7904L	Thymidylate synthase	EORTC
	II	GBC-590	Galectin 3	GlycoGenesys
	II	Mapatumumab	TRAIL-R1	Human Genome Sciences
	II	IMMU-111	CD66e (CEA)	Immunomedics
	II	Pemetrexed disodium[1]	Thymidylate synthase	Lilly
	II	GTI-2040	RRM2	Lorus Therapeutics/National Cancer Institute
	II	HyCAMP	DNA topoisomerase I	Meditech Research Limited/Novozymes
	II	Thalidomide[1]	TNF-α	National Cancer Institute
	II	FR-901228	HDAC	National Cancer Institute
	II	Imatinib mesilate[1]	Abl, c-Kit, PDGFRα, PDGFRβ, Bcr-Abl	National Cancer Institute
	II	RAS peptides vaccine	Ras	National Cancer Institute
	II	SB-715992	KNSL1 (Eg5)	National Cancer Institute
	I/II	Amonafide	DNA topoisomerase II	ChemGenex Pharmaceuticals
	I/II	EP-2101		Epimmune
	I/II	GV-1002	Telomerase and p21 Ras	GemVax
	I/II	GV-1003		GemVax
	I/II	IDD-5		IDM
	I/II	IMMU-100	CD66e (CEA)	Immunomedics
	I/II	IMMU-101	CD66e (CEA)	Immunomedics
	I/II	INGN-241		Introgen
	I/II	EMD-273066	EpCAM	Merck KGaA
	I/II	ZYC-300	CYP1B1	MGI Pharma

Continuation

Treatment of Digestive/Gastrointestinal Cancers

Condition	Phase	Drug	Target	Source
Colorectal cancer	I/II	LE-SN38	DNA topoisomerase I	NeoPharm
	I/II	Combretastatin A-4 phosphate	Tubulin	OxiGene
	I/II	RAV-12	RAAG-12	Raven
	I	CPX-1		Abiogen
	I	AMG-706	VEGFR-1, -2 and -3, PDGFR	Amgen
	I	APC-8024	HER2	Dendreon
	I	Bortezomib[1]	Proteasome	EORTC
	I	rhIGFBP-3	IGF-1	Insmed
	I	LMB-9	CD174 (Lewis y)	Ivax/National Cancer Institute
	I	Erlotinib hydrochloride[1]	EGFR	National Cancer Institute
	I	AZD-2171	VEGFR-1, -2 and -3	National Cancer Institute
	I	Cotara		Peregrine Pharmaceuticals
	I	TAS-102	Thymidine phosphorylase	Taiho
	IND filed	AP-5346	DNA	Access Pharmaceuticals
	IND filed	CX-3543	DNA	Cylene Pharmaceuticals
	IND filed	huC242-DM4	CanAg	ImmunoGen
Metastatic colorectal cancer	L-2004	Bevacizumab	VEGF	Genentech
	III	Panitumumab	EGFR	Abgenix/Amgen
	III	Leucovorin/UFT[1]	Pyrimidine nucleotides	National Cancer Institute
	III	Vatalanib succinate	VEGFR-1, -2 and -3	Novartis/Schering AG
	II	CoFactor		Adventrx Pharmaceuticals
	II	Theratope	Sialyl Tn	Biomira
	II	RPR-113090	Adenosine A_3 receptor	Can-Fite Biopharma
	II	IGN-101	EpCAM	Igeneon
	II	Diflomotecan	DNA topoisomerase I	Ipsen/Roche
	II	Patrin-2	O^6-Alkylguanine-DNA alkyltransferase	Kudos Pharmaceuticals
	II	CEA-TRICOM	CEA	National Cancer Institute
	II	11D10	HMFG	National Cancer Institute
	II	ALVAC-CEA-B7.1	CEA	Sanofi Pasteur/National Cancer Institute
	II	ALVAC-CEA	CEA	Sanofi Pasteur
	II	MVA-5T4	5T4	Oxford BioMedica
	II	Davanat/5-FU	Pyrimidine nucleotides	Pro-Pharmaceuticals
	I/II	NV-1020		MediGene
	I/II	PG-CPT	DNA topoisomerase I	Cell Therapeutics
	I/II	Thymectacin	Thymidylate synthase	Celmed BioSciences
	I/II	Rexin-G		Epeius Biotechnologies
	I	Flt3ligand	Flt3	National Cancer Institute
	I	125I-HuCC49-DeltaCH2		National Cancer Institute
Anal cancer	I	AEE-788	VEGFR-2, EGFR, HER2	Novartis
	III	Octreotide acetate[1]		National Cancer Institute
	III	Mitomycin[1]	DNA	National Cancer Institute/EORTC
	III	Fluorouracil[1]	Pyrimidine nucleotides	National Cancer Research Institute
	II/III	Cisplatin[1]	DNA	EORTC/National Cancer Institute
	II	Oxaliplatin[1]	DNA	M.D. Anderson Cancer Center
Hepatobiliary cancer	I	LMB-9	CD174 (Lewis y)	National Cancer Institute
	II	Porfimer sodium[1]		Axcan
Liver cancer	II	Lapatinib	EGFR, HER2	National Cancer Institute
	Prereg.	Cisplatin[1]	DNA	Nippon Kayaku
	III	Sorafenib	Raf kinase, VEGFR, PDGFR	Bayer/Onyx
	III	Nolatrexed dihydrochloride	Thymidylate synthase	Eximias Pharmaceutical
	III	Seocalcitol		Leo
	III	Cisplatin[1]	DNA	National Cancer Institute
	III	ADI-PEG 20	Arginine	Phoenix Pharmacologics
	III	Interferon alfa-n1[1]		Sumitomo Pharmaceuticals
	II/III	Polyprenoic acid	RAR, RXR	Nikken Chemicals
	II	Menatetrenone[1]		Eisai
	II	Sho-saiko-to		Memorial Sloan-Kettering Cancer Center
	II	Irofulven		MGI Pharma
	II	Mitomycin[1]	DNA	National Cancer Institute
	II	SB-715992	KSLP1(Eg5)	National Cancer Institute
	II	Flavopiridol	CDK2	National Cancer Institute
	II	Bevacizumab	VEGF	National Cancer Institute

Continuation

Treatment of Digestive/Gastrointestinal Cancers

Condition	Phase	Drug	Target	Source
Liver cancer	II	Gefitinib[1]	EGFR	National Cancer Institute
	II	Erlotinib hydrochloride[1]	EGFR	National Cancer Institute
	II	Bortezomib[1]	Proteasome	National Cancer Institute
	II	Ixabepilone	Tubulin	National Cancer Institute
	II	Oxaliplatin[1]	DNA	National Cancer Institute
	II	Kahalalide F		PharmaMar
	II	PI-88	VEGF, FGF-1 and -2, heparanase	Progen
	II	BrachySil		pSivida
	II	Thymalfasin[1]		SciClone
	II	[188Re]-HDD-lipiodol		Seoul National University
	II	Miriplatin	DNA	Sumitomo Pharmaceuticals
	I/II	Doxorubicin Transdrug	DNA topoisomerase II	BioAlliance Pharma
	I/II	MTC-DOX	DNA topoisomerase II	FeRx
	I/II	DENSPM	Ornithine decarboxylase	Genzyme
	I/II	IMMU-105	AFP	Immunomedics
	I/II	PHY-906		PhytoCeutica
	I	Heat-activated doxorubicin liposomes	DNA topoisomerase II	Celsion
	I	MB-7133		Metabasis
	I	CEA-TRICOM	CEA	National Cancer Institute
	I	NS-9		Nippon Shinyaku
	I	Spisulosine		PharmaMar
	I	PI-166		Progen
	I	Occlusin		Virexx
Metastatic cancer (to liver)	IND filed	PH-10		Provectus
	III	Becatecarin	DNA topoisomerase II	Exelixis
Bile duct tumor	I	Interleukin-12		National Cancer Institute
	II	3-AP	Ribonucleoside-diphosphate reductase	National Cancer Institute
Gallbladder cancer	II	TS-11	Pyrimidine nucleotides	Taiho
	II	Bortezomib[1]	Proteasome	National Cancer Institute
	II	Ixabepilone	Tubulin	National Cancer Institute
	II	Lapatinib	EGFR, HER2	National Cancer Institute

[1]Launched for another indication. EGFR: Epidermal growth factor receptor; hCG: Human chorionic gonadotropin; COX-2: Cyclooxygenase type 2; HSP: Heat shock protein; CDK: Cyclin-dependent kinase; TRAIL-R1: Tumor necrosis factor-related apoptosis-inducing ligand death receptor 1; CEA: Carcinoembryonic antigen; RRM2: Ribonucleotide reductase M2; TNF: Tumor necrosis factor; HDAC: Histone deacetylase; PDGFR: Platelet-derived growth factor receptor; KNSL1: Kinesin-like spindle protein 1; VEGFR: Vascular endothelial growth factor receptor; EpCAM: epithelial cell adhesion molecule; HMFG: Human milk fat globule; RAR: Retinoic acid receptor; RXR: Retinoid X receptor; FGF: Fibroblast growth factor; AFP: α-fetoprotein; PKC: Protein kinase C.