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Annual Update 2003/2004 - Treatment of Gastrointestinal Disorders

The goal of this section of *Drugs of the Future* 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. This year's overview attempts to incorporate the information in a unified, user-friendly format and is based on the analysis of a voluminous amount of information from current literature (more than 2,500 journals), congresses (more than 100), company communications (through DailyDrugNews.com), web sites and patents. Subscribers to our Integrity® database (Integrity.prous.com) have the additional opportunity to penetrate further into the different aspects of this class of drugs and therapies, including organic synthesis, experimental pharmacology, pharmacokinetics, metabolism, clinical trials, patents and current literature. All the information available would represent thousands of pages, but has been selected and synthesized for our readers' convenience in this review. Another novelty this year is the inclusion of two different tables: one ordered by indication (condition) and phase of development, and the other by pharmaceutical company (source) and condition. We hope you will enjoy this new format, and gladly accept your comments and suggestions.

J.R. Prous
Editor

Treatment of Gatrointestinal Disorders by Condition

Condition	Phase	Drug	Source
Anal fissures	III	Nitroglycerin[1] (ointment)	Cellegy
	II	SLV-324	Solvay/SLA Pharma
Ascites, cirrhotic	II	SR-121463	Sanofi-Synthélabo
Barrett's esophagus	L-2003	Porfimer sodium[1]	Axcan
Bleeding, gastrointestinal upper	Prereg.	Omeprazole[2,3]	Santarus
Bowel dysfunction, opioid-induced	III	Methylnaltrexone bromide	Progenics
	II	Alvimopan hydrate[3]	Adolor/GlaxoSmithKline
	I/II	Lubiprostone[3]	Sucampo Pharmaceuticals
Cirrhosis	II/III	Interferon beta[1]	Daiichi Pharmaceutical/Toray
	II	Icatibant	Jerini
	II	Interferon alfa-n1[1]	Sumitomo Pharmaceuticals
Constipation	Prereg.	Tegaserod maleate[1,3]	Novartis
	III	Lubiprostone[3]	Sucampo Pharmaceuticals
	II	ABT-224	Abbott
	II	Alvimopan hydrate[3]	Adolor/GlaxoSmithKline
	II	INKP-100[1]	InKine
Crohn's disease	III	Adalimumab[1,3]	Abbott
	III	Alicaforsen sodium[3]	Isis Pharmaceuticals
	III	Certolizumab pegol	Celltech Group
	III	Natalizumab[3]	Biogen Idec/Elan
	II/III	Sargramostim[3]	Schering AG/Berlex
	II/III	Vapreotide acetate[3]	H3 Pharma (Debiopharm)
	II	ABT-874	Abbott
	II	Alequel™	Enzo Biochem
	II	CBP-1011	InKine
	II	Doramapimod	Boehringer Ingelheim
	II	Etiprednol dicloacetate	Ivax
	II	Fontolizumab	Protein Design Labs
	II	MLN-02	Millennium/Genentech
	II	OSI-461	OSI Pharmaceuticals
	II	RDP-58[3]	Genzyme/Procter & Gamble
	II	Rifaximin[1,3]	Salix
	II	Semapimod hydrochloride	Cytokine PharmaSciences
	II	STA-5326	Synta Pharmaceuticals
	II	Teduglutide	NPS Pharmaceuticals
	II	Tocilizumab[3]	Chugai/Roche
	I	Traficet-EN™	ChemoCentryx
	I	Vapaliximab	BioTie Therapies/Seikagaku
Crohn's disease, fistulizing	L-2003	Infliximab[1]	Centocor/Johnson & Johnson/ Schering-Plough
Diarrhea	III	Rotavirus vaccine	Avant Immunotherapeutics/ GlaxoSmithKline
	III	Rotavirus vaccine	Merck & Co.
	II	ETEC vaccine	Iomai
	II	Probactrix™	BioBalance
	II	Ramoplanin[3]	Oscient Pharmaceuticals
	II	Teduglutide	NPS Pharmaceuticals
	II	Tolevamer sodium	Genzyme
	I/II	*Clostridium difficile* toxoid vaccine	Acambis
	I	OPT-80	Optimer Pharmaceuticals
Dyspepsia	II	GW-597599	GlaxoSmithKline
	II	Itopride hydrochloride[1,3]	Axcan
	II	Tegaserod maleate[1,3]	Novartis
	II	Z-338 (YM-443)[3]	Zeria/Yamanouchi
Esophageal variceal bleeding	Prereg.	Vapreotide acetate[3]	H3 Pharma (Debiopharm)
Esophagitis, erosive	Prereg.	Omeprazole[2,3]	Santarus

Continuation

Treatment of Gatrointestinal Disorders by Condition

Condition	Phase	Drug	Source
Fecal incontinence	II	SLV-325	Solvay/SLA Pharma
Gastritis	Prereg.	Polaprezinc[1,3]	Zeria
	III	DA-9601	Dong-A
	II	E-3620	Eisai
	II	Rifalazil	ActivBiotics
Gastroesophageal reflux disease	Prereg.	Omeprazole[2,3]	Santarus
	II	Antigastrin therapeutic vaccine[3]	Aphton
	II	AZD-0865	AstraZeneca
	II	Ilaprazole[3]	Il-Yang
	II	Tegaserod maleate[1,3]	Novartis
	I	ATI-7505	ARYx Therapeutics
	I	AZD-3355	AstraZeneca
	I	CS-526	Novartis/Ube/Sankyo
	I	Itriglumide[3]	Rotta
	I	Tenatoprazole[3]	Negma/Mitsubishi Pharma
	I	Z-360	Zeria
Gastrointestinal disorders	I	AZD-7371	AstraZeneca
Gastroparesis	II	Mitemcinal fumarate[3]	Chugai
	I	ATI-7505	ARYx Therapeutics
Hemorrhoids	Prereg.	OC-108	Mitsubishi Pharma
	II	Nitroglycerin[1] (ointment)	Cellegy
	II	TJN-219	Tsumura
Hepatitis B	R-2003	Hepatitis B vaccine, prophylactic	Berna Biotech/Corixa
	Prereg.	Hepatitis B immune globulin	Cangene
	Prereg.	Hepatitis B vaccine	GlaxoSmithKline/Corixa
	III	Emtricitabine[1,3]	Gilead
	III	Entecavir[3]	Bristol-Myers Squibb
	III	Peginterferon alfa-2a[1]	Roche
	III	Telbivudine[3]	Idenix/Novartis
	III	Thymalfasin	SciClone
	II/III	Hepatitis B vaccine, prophylactic	Dynavax
	II	EHT-899	Enzo Biochem
	II	Elvucitabine[3]	Achillion
	II	Hepatitis B pharmaccine	Oxxon Pharmaccines
	II	HepeX-B™	XTL Biopharmaceuticals
	II	LB-80380	LG Life Sciences/Anadys
	I/II	Alamifovir	Lilly
	I/II	KRN-7000[3]	Kirin Brewery
	I/II	Remofovir mesilate	Valeant/Metabasis
	I/II	Valtorcitabine dihydrochloride	Idenix/Novartis
	I	Hepatitis B vaccine	Innogenetics/Epimmune
	I	MIV-210 (204937)	Medivir/GlaxoSmithKline
Hepatitis C	III	Interferon beta-1a[1]	Serono
	III	Thymalfasin	SciClone
	III	Ursodiol[1]	Mitsubishi Pharma
	III	Viramidine hydrochloride	Valeant
	II/III	Interferon alfa-n3[1]	HemispheRx/Guangdong Medical Group
	II	Ciluprevir	Boehringer Ingelheim
	II	Hepatitis C vaccine, therapeutic	Innogenetics
	II	Hepatitis C vaccine, therapeutic	Intercell
	II	HepeX-C™	XTL Biopharmaceuticals
	II	Histamine dihydrochloride	Maxim
	II	IDN-6556	Idun
	II	Interferon omega	BioMedicines
	II	ISIS-14803	Isis Pharmaceuticals
	II	JTK-003	Japan Tobacco
	II	KPE-02003002	Kemin Pharma
	II	Merimepodib[3]	Vertex
	II	UT-231B	United Therapeutics
	I/II	Albumin interferon alfa	Human Genome Sciences
	I/II	Celgosivir	Micrologix Biotech

Continuation

Treatment of Gatrointestinal Disorders by Condition

Condition	Phase	Drug	Source
	I/II	EHC-18	Enzo Biochem
	I/II	Hepatitis C immune globulin	Nabi Biopharmaceuticals
	I/II	Isatoribine	Anadys
	I/II	KRN-7000[3]	Kirin Brewery
	I/II	NM-283	Idenix/Novartis
	I	ANA-971	Anadys
	I	CpG-10101	Coley Pharmaceuticals
	I	HCV-086	ViroPharma/Wyeth
	I	Hepatitis C vaccine	Chiron/CSL
	I	PEG-interferon alfacon-1	InterMune/Nektar Therapeutics
	I	R-1479	Roche
	I	R-803	Rigel
	Discontinued	JTK-109	Japan Tobacco
	Discontinued by Roche	Levovirin	Roche/Valeant
Hepatitis E	II	Hepatitis E vaccine	GlaxoSmithKline/Novavax/NIH/ Walter Reed Army Institute
Hyperbilirubinemia	III	Stannsoporfin	WellSpring Pharmaceutical
Inflammatory bowel disease	II	S-3013	Shionogi
	I/II	NAA-004	Nobex
	I	270384	GlaxoSmithKline
	I	683699 (T-0047)	GlaxoSmithKline/Tanabe Seiyaku
	I	AJM-300	Ajinomoto
	I	Budesonide[1] (oral)	West Pharmaceutical Services
	I	Dronabinol/cannabidiol	GW Pharmaceuticals
	I	Ono-4817	Ono Pharmaceutical
Intestinal graft-versus-host disease	III	Beclometasone dipropionate[1] (oral)	DOR BioPharma
Irritable bowel syndrome	III	Cilansetron[3]	Solvay
	III	Dexloxiglumide[3]	Rotta
	III	PTI-901	Pain Therapeutics
	III	Ramosetron hydrochloride[1,3]	Yamanouchi
	II	Asimadoline	Merck KGaA
	II	Dextofisopam	Vela Pharmaceuticals
	II	E-3620	Eisai
	II	Lubiprostone[3]	Sucampo Pharmaceuticals
	II	Nepadutant	Menarini
	II	Probactrix™	BioBalance
	II	Renzapride hydrochloride[3]	Alizyme
	II	Rifaximin[1,3]	Salix
	II	Saredutant[3]	Sanofi-Synthélabo
	II	Talnetant	GlaxoSmithKline
	I	Alvimopan hydrate[3]	Adolor/GlaxoSmithKline
	I	SLV-317	Solvay
	Discontinued (U.S.)	Dexloxiglumide[3]	Forest
Liver diseases	II	ME-3738	Meiji Seika
Nausea/vomiting prophylaxis, chemotherapy-induced	L-2003	Aprepitant[3]	Merck & Co.
	L-2003	Palonosetron hydrochloride[3]	MGI Pharma/Helsinn/Italfarmaco
	R-2004	Indisetron hydrochloride[3]	Kyorin/Nisshin Flour Milling
	II	GW-597599	GlaxoSmithKline
	I	APF-530	A.P. Pharma
Pancreatic disorders	II	Bile salt-stimulated lipase	Arexis
	II	TheraCLEC™	Altus Biologics
Pancreatitis	II/III	Lexipafant	DevCo
	II	Semapimod hydrochloride	Cytokine PharmaSciences
Postgastrectomy syndrome	II	Mosapride citrate [1,3]	Dainippon/Takeda
Postoperative ileus	Prereg.	Alvimopan hydrate[3]	Adolor/GlaxoSmithKline
	II	Lubiprostone[3]	Sucampo Pharmaceuticals
	II	Methylnaltrexone bromide	Progenics

Continuation

Treatment of Gatrointestinal Disorders by Condition

Condition	Phase	Drug	Source
Short bowel syndrome	L-2004	Somatropin[1]	Serono
	III	Teduglutide	NPS Pharmaceuticals
Steatohepatitis, nonalcoholic	II	IDN-6556	Idun
	I/II	SPI-8811	Sucampo Pharmaceuticals
Ulcer	R-2003	Esomeprazole magnesium[1,3]	AstraZeneca
	R-2003	Helizide™	Axcan
	Prereg.	Omeprazole[2,3]	Santarus
	III	Revaprazan hydrochloride[3]	Yuhan
	II	Rifalazil	ActivBiotics
	II	Soraprazan	Altana Pharma
	I	CS-526	Novartis/Ube/Sankyo
	I	E-3309	Eisai
	I	*H. pylori* vaccine	Iomai
	I	Itriglumide[3]	Rotta
	I	Tenatoprazole[3]	Negma/Mitsubishi Pharma
	I	Z-360	Zeria
Ulcerative colitis	Prereg.	Beclometasone dipropionate[1] (oral + enema)	Chiesi
	Prereg.	Tacrolimus[1,3]	Fujisawa
	III	COLAL-PRED™	Alizyme
	III	Infliximab[1]	Centocor/Johnson & Johnson/ Schering-Plough
	III	OPC-6535	Otsuka
	III	SPD-476	Shire
	II/III	Ecabet sodium[1,3]	Tanabe Seiyaku/Tanabe AAI
	II	Alicaforsen sodium[3]	Isis Pharmaceuticals
	II	BXT-51072	Oxis (Axonyx)
	II	CBP-1011	InKine
	II	Etiprednol dicloacetate[3]	Ivax
	II	Kappaproct®	InDex Pharmaceuticals/Serono
	II	MLN-02	Millennium/Genentech
	II	Nolpitantium besilate	Sanofi-Synthélabo
	II	PLD-116	Pliva
	II	RDP-58[3]	Genzyme/Procter & Gamble
	II	SPD-480	Shire
	II	TC-2403	Targacept/Dr. Falk
	I/II	Visilizumab[3]	Protein Design Labs
	I	Traficet-EN™	ChemoCentryx
	I	Vapaliximab	BioTie Therapies/Seikagaku
	Discontinued	Daclizumab[1]	Protein Design Labs

[1]Launched for another indication. [2]New formulation. [3]Monograph previously published in Drugs of the Future.

Treatment of Gastrointestinal Disorders by Source

Source	Condition	Drug	Phase
A.P. Pharma	Nausea/vomiting prophylaxis, chemotherapy-induced	APF-530	I
Abbott	Constipation	ABT-224	II
	Crohn's disease	ABT-874	II
		Adalimumab[1,3]	III
Acambis	Diarrhea	*Clostridium difficile* toxoid vaccine	I/II
Achillion	Hepatitis B	Elvucitabine[3]	II
ActivBiotics	Gastritis	Rifalazil	II
	Ulcer	Rifalazil	II
Adolor	Bowel dysfunction, opioid-induced	Alvimopan hydrate[3]	II
	Constipation	Alvimopan hydrate[3]	II
	Irritable bowel syndrome	Alvimopan hydrate[3]	I
	Postoperative ileus	Alvimopan hydrate[3]	Prereg.
Ajinomoto	Inflammatory bowel disease	AJM-300	I
Alizyme	Irritable bowel syndrome	Renzapride hydrochloride[3]	II
	Ulcerative colitis	COLAL-PRED™	III
Altana Pharma	Ulcer	Soraprazan	II
Altus Biologics	Pancreatic disorders	TheraCLEC™	II
Anadys	Hepatitis B	LB-80380[3]	II
	Hepatitis C	ANA-971	I
		Isatoribine	I/II
Aphton	Gastroesophageal reflux disease	Antigastrin therapeutic vaccine[3]	II
Arexis	Pancreatic disorders	Bile salt-stimulated lipase	II
ARYx Therapeutics	Gastroesophageal reflux disease	ATI-7505	I
	Gastroparesis, diabetic	ATI-7505	I
AstraZeneca	Gastroesophageal reflux disease	AZD-0865	II
		AZD-3355	I
	Gastrointestinal disorders	AZD-7371	I
	Ulcer	Esomeprazole magnesium[1,3]	R-2003
Avant Immunotherapeutics	Diarrhea	Rotavirus vaccine	III
Axcan	Barrett's esophagus	Porfimer sodium[1]	L-2003
	Dyspepsia	Itopride hydrochloride[1,3]	II
	Ulcer	Helizide™	R-2003
Berlex	Crohn's disease	Sargramostim [1,3]	II/III
Berna Biotech	Hepatitis B	Hepatitis B vaccine, prophylactic	R-2003
BioBalance	Diarrhea	Probactrix™	II
	Irritable bowel syndrome	Probactrix™	II
Biogen Idec	Crohn's disease	Natalizumab	III
BioMedicines	Hepatitis C	Interferon omega	II
BioTie Therapies	Crohn's disease	Vapaliximab	I
	Ulcerative colitis	Vapaliximab	I
Boehringer Ingelheim	Crohn's disease	Doramapimod	II
	Hepatitis C	Ciluprevir	II
Bristol-Myers Squibb	Hepatitis B	Entecavir[3]	III
Cangene	Hepatitis B	Hepatitis B immune globulin	Prereg.
Cellegy	Anal fissures	Nitroglycerin[1] (ointment)	III
	Hemorrhoids	Nitroglycerin[1] (ointment)	II
Celltech Group	Crohn's disease	Certolizumab pegol	III
Centocor	Crohn's disease, fistulizing	Infliximab[1]	L-2003
	Ulcerative colitis	Infliximab[1]	III
ChemoCentryx	Crohn's disease	Traficet-EN™	I
	Ulcerative colitis	Traficet-EN™	I
Chiesi	Ulcerative colitis	Beclometasone dipropionate[1] (oral + enema)	Prereg.
Chiron	Hepatitis C	Hepatitis C vaccine	I
Chugai	Crohn's disease	Tocilizumab[3]	II
	Gastroparesis, diabetic/idiopathic	Mitemcinal fumarate[3]	II
Coley Pharmaceuticals	Hepatitis C	CpG-10101	I
Corixa	Hepatitis B	Hepatitis B vaccine, prophylactic	R-2003
		Hepatitis B vaccine	Prereg.
CSL	Hepatitis C	Hepatitis C vaccine	I
Cytokine PharmaSciences	Crohn's disease	Semapimod hydrochloride	II
	Pancreatitis	Semapimod hydrochloride	II
Daiichi Pharmaceuticals	Cirrhosis	Interferon beta[1]	II/III

Continuation

Treatment of Gastrointestinal Disorders by Source

Source	Condition	Drug	Phase
Dainippon	Postgastrectomy syndrome	Mosapride citrate [1,3]	II
DevCo	Pancreatitis, acute	Lexipafant	II/III
Dong-A	Gastritis	DA-9601	III
DOR BioPharma	Intestinal graft-versus-host disease	Beclometasone dipropionate[1] (oral)	III
Dr. Falk	Ulcerative colitis	TC-2403	II
Dynavax	Hepatitis B	Hepatitis B vaccine, prophylactic	II/III
Eisai	Gastritis	E-3620	II
	Irritable bowel syndrome	E-3620	II
	Ulcer	E-3309	I
Elan	Crohn's disease	Natalizumab	III
Enzo Biochem	Crohn's disease	Alequel™	II
	Hepatitis B	EHT-899	II
	Hepatitis C	EHC-18	I/II
Epimmune	Hepatitis B	Hepatitis B vaccine	I
Forest	Irritable bowel syndrome	Dexloxiglumide[3]	Discontinued (U.S.)
Fujisawa	Ulcerative colitis	Tacrolimus[1,3]	Prereg.
Genentech	Crohn's disease	MLN-02	II
	Ulcerative colitis	MLN-02	II
Genzyme	Diarrhea	Tolevamer sodium	II
	Crohn's disease	RDP-58[3]	II
	Ulcerative colitis	RDP-58[3]	II
Gilead	Hepatitis B	Emtricitabine[1,3]	III
GlaxoSmithKline	Bowel dysfunction, opioid-induced	Alvimopan hydrate[3]	II
	Constipation	Alvimopan hydrate[3]	II
	Diarrhea	Rotavirus vaccine	III
	Dyspepsia	GW-597599	II
	Hepatitis B	Hepatitis B vaccine	Prereg.
		MIV-210 (204937)	I
	Hepatitis E	Hepatitis E vaccine	II
	Inflammatory bowel disease	270384	I
		683699 (T-0047)	I
	Irritable bowel syndrome	Alvimopan hydrate[3]	I
		Talnetant	II
	Nausea/vomiting prophylaxis, chemotherapy-induced	GW-597599	II
	Postoperative ileus	Alvimopan hydrate[3]	Prereg.
Guangdong Medical Group	Hepatitis C	Interferon alfa-n3[1]	II/III
GW Pharmaceuticals	Inflammatory bowel disease	Dronabinol/cannabidiol	I
H3 Pharma (Debiopharm)	Crohn's disease	Vapreotide acetate[3]	II/III
	Esophageal variceal bleeding	Vapreotide acetate[3]	Prereg.
Helsinn	Nausea/vomiting prophylaxis, chemotherapy-induced	Palonosetron hydrochloride[3]	L-2003
HemispheRx	Hepatitis C	Interferon alfa-n3[1]	II/III
Human Genome Sciences	Hepatitis C	Albumin interferon alfa	I/II
Idenix	Hepatitis B	Telbivudine[3]	III
		Valtorcitabine dihydrochloride	I/II
	Hepatitis C	NM-283	I/II
Idun	Hepatitis C	IDN-6556	II
	Steatohepatitis, nonalcoholic	IDN-6556	II
Il-Yang	Gastroesophageal reflux disease	Ilaprazole[3]	II
InDex Pharmaceuticals	Ulcerative colitis	Kappaproct®	II
InKine	Constipation	INKP-100[1]	II
	Crohn's disease	CBP-1011	II
	Ulcerative colitis	CBP-1011	II
Innogenetics	Hepatitis B	Hepatitis B vaccine	I
	Hepatitis C	Hepatitis C vaccine, therapeutic	II
Intercell	Hepatitis C	Hepatitis C vaccine, therapeutic	II
InterMune	Hepatitis C	PEG-interferon alfacon-1	I
Iomai	Diarrhea	ETEC vaccine	II
	Ulcer	*H. pylori* vaccine	I
Isis Pharmaceuticals	Crohn's disease	Alicaforsen sodium[3]	III
	Hepatitis C	ISIS-14803	II
	Ulcerative colitis	Alicaforsen sodium[3]	II

Continuation

Treatment of Gastrointestinal Disorders by Source

Source	Condition	Drug	Phase
Italfarmaco	Nausea/vomiting prophylaxis, chemotherapy-induced	Palonosetron hydrochloride[3]	L-2003
Ivax	Crohn's disease	Etiprednol dicloacetate[3]	II
	Ulcerative colitis	Etiprednol dicloacetate[3]	II
Japan Tobacco	Hepatitis C	JTK-003	II
		JTK-109	Discontinued
Jerini	Cirrhosis	Icatibant	II
Johnson & Johnson	Crohn's disease, fistulizing	Infliximab[1]	L-2003
	Ulcerative colitis	Infliximab[1]	III
Kemin Pharma	Hepatitis C	KPE-02003002	II
Kirin Brewery	Hepatitis B	KRN-7000[3]	I/II
	Hepatitis C	KRN-7000[3]	I/II
Kyorin	Nausea/vomiting prophylaxis, chemotherapy-induced	Indisetron hydrochlride[3]	R-2004
LG Life Sciences	Hepatitis B	LB-80380[3]	II
Lilly	Hepatitis B	Alamifovir	I/II
Maxim	Hepatitis C	Histamine dihydrochloride	II
Medivir	Hepatitis B	MIV-210 (204937)	I
Meiji Seika	Liver diseases	ME-3738	II
Menarini	Irritable bowel syndrome	Nepadutant	II
Merck & Co.	Diarrhea	Rotavirus vaccine	III
	Nausea/vomiting prophylaxis, chemotherapy-induced	Aprepitant[3]	L-2003
Merck KGaA	Irritable bowel syndrome	Asimadoline	II
Metabasis Therapeutics	Hepatitis B	Remofovir mesilate	I/II
MGI Pharma	Nausea/vomiting prophylaxis, chemotherapy-induced	Palonosetron hydrochloride[3]	L-2003
Micrologix Biotech	Hepatitis C	Celgosivir	I/II
Millennium	Crohn's disease	MLN-02	II
	Ulcerative colitis	MLN-02	II
Mitsubishi Pharma	Gastroesophageal reflux disease	Tenatoprazole[3]	I
	Hemorrhoids	OC-108	Prereg.
	Hepatitis C	Ursodiol[1]	III
	Ulcer	Tenatoprazole[3]	I
Nabi Biopharmaceuticals	Hepatitis C	Hepatitis C immune globulin	I/II
Nektar Therapeutics	Hepatitis C	PEG-interferon alfacon-1	I
Negma	Gastroesophageal reflux disease	Tenatoprazole[3]	I
	Ulcer	Tenatoprazole[3]	I
NIH	Hepatitis E	Hepatitis E vaccine	II
Nisshin Flour Milling	Nausea/vomiting prophylaxis, chemotherapy-induced	Indisetron hydrochloride[3]	R-2004
Nobex	Inflammatory bowel disease	NAA-004	I/II
Novartis	Constipation	Tegaserod maleate[1,3]	Prereg.
	Dyspepsia	Tegaserod maleate[1,3]	II
		CS-526	I
		Tegaserod maleate[1,3]	II
	Hepatitis B	Telbivudine[3]	III
		Valtorcitabine dihydrochloride	I/II
	Hepatitis C	NM-283	I/II
	Ulcer	CS-526	I
Novavax	Hepatitis E	Hepatitis E vaccine	II
NPS Pharmaceuticals	Crohn's disease	Teduglutide	II
	Diarrhea	Teduglutide	II
	Short bowel syndrome	Teduglutide	III
Ono Pharmaceutical	Inflammatory bowel disease	Ono-4817	I
Optimer Pharmaceuticals	Diarrhea	OPT-80	I
Oscient Pharmaceuticals	Diarrhea	Ramoplanin[3]	II
OSI Pharmaceuticals	Crohn's disease	OSI-461	II
Otsuka	Ulcerative colitis	OPC-6535	III
Oxis (Axonyx)	Ulcerative colitis	BXT-51072	II
Oxxon Pharmaccines	Hepatitis B	Hepatitis B pharmaccine	II
Pain Therapeutics	Irritable bowel syndrome	PTI-901	III
Pliva	Ulcerative colitis	PLD-116	II
Procter & Gamble	Crohn's disease	RDP-58[3]	II

Continuation

Treatment of Gastrointestinal Disorders by Source

Source	Condition	Drug	Phase
	Ulcerative colitis	RDP-58[3]	II
Progenics	Constipation, opioid-induced	Methylnaltrexone bromide	III
	Postoperative ileus	Methylnaltrexone bromide	II
Protein Design Labs	Crohn's disease	Fontolizumab	II
	Ulcerative colitis	Daclizumab[1]	Discontinued
		Visilizumab[3]	I/II
Rigel	Hepatitis C	R-803	I
Roche	Crohn's disease	Tocilizumab[3]	II
	Hepatitis B	Peginterferon alfa-2a[1]	III
	Hepatitis C	R-1479	I
		Levovirin	Discontinued
Rotta	Gastroesophageal reflux disease	Itriglumide[3]	I
	Irritable bowel syndrome	Dexloxiglumide[3]	III
	Ulcer	Itriglumide[3]	I
Salix	Crohn's disease	Rifaximin[1,3]	II
	Irritable bowel syndrome	Rifaximin[1,3]	II
Sankyo	Gastroesophageal reflux disease	CS-526	I
	Ulcer	CS-526	I
Sanofi-Synthélabo	Ascites, cirrhotic	SR-121463	II
	Irritable bowel syndrome	Saredutant[3]	II
	Ulcerative colitis	Nolpitantium besilate	II
Santarus	Bleeding, gastrointestinal upper	Omeprazole[2,3]	Prereg.
	Esophagitis, erosive	Omeprazole[2,3]	Prereg.
	Gastroesophageal reflux disease	Omeprazole[2,3]	Prereg.
	Ulcer	Omeprazole[2,3]	Prereg.
Schering AG	Crohn's disease	Sargramostim[1,3]	II/III
Schering-Plough	Crohn's disease, fistulizing	Infliximab[1]	L-2003
	Ulcerative colitis	Infliximab[1]	III
SciClone	Hepatitis B	Thymalfasin	III
	Hepatitis C	Thymalfasin	III
Seikagaku	Crohn's disease	Vapaliximib	I
	Ulcerative colitis	Vapaliximib	I
Serono	Hepatitis C	Interferon beta-1a[1]	III
	Short bowel syndrome	Somatropin[1]	L-2004
	Ulcerative colitis	Kappaproct®	II
Shionogi	Inflammatory bowel disease	S-3013	II
Shire	Ulcerative colitis	SPD-476	III
		SPD-480	II
SLA Pharma	Anal fissures	SLV-324	II
	Fecal incontinence	SLV-325	II
Solvay	Anal fissures	SLV-324	II
	Fecal incontinence	SLV-325	II
	Irritable bowel syndrome	Cilansetron[3]	III
		SLV-317	I
Sucampo Pharmaceuticals	Bowel dysfunction, opioid-induced	Lubiprostone[3]	I/II
	Constipation	Lubiprostone[3]	III
	Irritable bowel syndrome	Lubiprostone[3]	II
	Postoperative ileus	Lubiprostone[3]	II
	Steatohepatitis, nonalcoholic	SPI-8811	I/II
Sumitomo Pharmaceuticals	Cirrhosis	Interferon alfa-n1[1]	II
Synta Pharmaceuticals	Crohn's disease	STA-5326	II
Takeda	Postgastrectomy syndrome	Mosapride citrate[1,3]	II
Tanabe AAI	Ulcerative colitis	Ecabet sodium[1,3]	II/III
Tanabe Seiyaku	Inflammatory bowel disease	683699 (T-0047)	I
	Ulcerative colitis	Ecabet sodium[1,3]	II/III
Targacept	Ulcerative colitis	TC-2403	II
Toray	Cirrhosis	Interferon beta[1]	II/III
Tsumura	Hemorrhoids	TJN-219	II
Ube	Gastroesophageal reflux disease	CS-526	I
	Ulcer	CS-526	I
United Therapeutics	Hepatitis C	UT-231B	II
Valeant	Hepatitis B	Remofovir mesilate	I/II
	Hepatitis C	Viramidine hydrochloride	III
		Levovirin	Discontinued by Roche
Vela Pharmaceuticals	Irritable bowel syndrome	Dextofisopam	II

Continuation

Treatment of Gastrointestinal Disorders by Source

Source	Condition	Drug	Phase
Vertex	Hepatitis C	Merimepodib[3]	II
ViroPharma	Hepatitis C	HCV-086	I
Walter Reed Army Institute	Hepatitis E	Hepatitis E vaccine	II
WellSpring Pharmaceutical	Hyperbilirubinemia	Stannsoporfin	III
West Pharmaceutical Services	Inflammatory bowel disease	Budesonide[1] (oral)	I
Wyeth	Hepatitis C	HCV-086	I
XTL Biopharmaceuticals	Hepatitis B	HepeX-B™	II
	Hepatitis C	HepeX-C™	II
Yamanouchi	Dyspepsia	Z-338 (YM-443)[3]	II
	Irritable bowel syndrome	Ramosetron hydrochloride[1,3]	III
Yuhan	Ulcer	Revaprazan hydrochloride[3]	III
Zeria	Dyspepsia	Z-338 (YM-443)[3]	II
	Gastritis	Polaprezinc[1,3]	Prereg.
	Gastroesophageal reflux disease	Z-360	I
	Ulcer	Z-360	I

[1]Launched for another indication. [2]New formulation. [3]Monograph previously published in Drugs of the Future.

Treatment of Gastrointestinal Disorders

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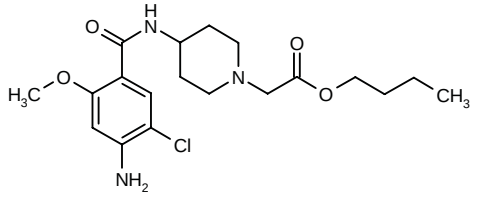
270384

An endothelial cell adhesion molecule designated 270384 is in early clinical development at GlaxoSmithKline for use in inflammatory bowel disease (IBD).

683699

GlaxoSmithKline is developing a compound designated 683699, a cell adhesion inhibitor that acts as an $\alpha_4\beta_7/\alpha_4\beta_1$ integrin antagonist, as a potential new treatment for multiple sclerosis and inflammatory bowel disease. The compound was licensed from Tanabe Seiyaku (T-0047) and is currently in phase I clinical testing.

ABT-224



ABT-224 (formerly AU-224) is an ester-type oral prodrug of a known prokinetic agent which is being tested in phase II clinical trials at Abbott for the treatment of constipation.

ABT-874

ABT-874 (formerly J695) is a fully human anti-IL-12 monoclonal antibody codeveloped by Cambridge Antibody Technology, Abbott and the former Genetics Institute (Wyeth). Abbott is responsible for development and is currently engaged in phase II clinical trials of the antibody in Crohn's disease and expects to begin phase II studies in multiple sclerosis soon.

The IL-12 in Crohn's Disease Study was a multicenter, double-blind, randomized, placebo-controlled clinical trial that assessed the efficacy and safety of ABT-874 in the treatment of Crohn's disease. A total of 79 patients with active disease were treated with 7 injections of placebo or ABT-874 (1 or 3 mg/kg s.c. once weekly), with either a 4-week treatment-free period between the first and second injections or no interruption. The greatest therapeutic effects were found in patients receiving 3 mg/kg of ABT-874 and no interruption. Compared with placebo, these patients showed a higher clinical response rate both at the end of the treatment (75% *vs.* 25%) and after follow-up for 12 weeks (69% *vs*. 13%). No placebo-treated patients achieved clinical remission, in contrast to 38% and 50% of these patients, respectively, at the end of the treatment and follow-up periods. ABT-874 was well tolerated and did not increase the incidence of antibody-related adverse events compared to placebo (1).

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

Adalimumab

Abbott has expanded the clinical trial program for adalimumab (Humira®, D2E7) to include an additional phase III study in Crohn's disease. The newly commenced phase III study will evaluate the safety and efficacy of adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active Crohn's disease. Patients will be randomized to receive adalimumab or placebo and responses will be

measured by the Crohn's Disease Activity Index (CDAI) score. Another phase III Crohn's disease study was previously initiated in 2002. Adalimumab, which acts by spec ifically blocking TNF-α and was discovered through a broad scientific collaboration between Abbott and Cambridge Antibody Technology (CAT), is the first human monoclonal antibody approved by the FDA (December 2002) for reducing the signs and symptoms and inhibiting the progression of structural damage in adults with moderately to severely active rheumatoid arthritis who have had insufficient response to one or more traditional disease-modifying antirheumatic drugs (DMARDs), and can be used alone or in combination with methotrexate or other DMARDs. European approval was also granted in September of last year for this indication, Abbott submitted a supplemental BLA to the FDA in the fall of 2003 seeking approval for improving physical function in patients with moderately to severely active rheumatoid arthritis, and the drug is additionally being evaluated for juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis and early rheumatoid arthritis. Eisai is developing the antibody in Japan in conjunction with Abbott Japan for the treatment of rheumatoid arthritis (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 the chimeric anti-TNF-α antibody infliximab were given s.c. adalimumab (80 mg at the beginning of the study and 50 mg 2 weeks later). At 4 weeks, 46% of the patients had a clinical response and 8% had achieved complete remission. Four of the 6 patients with perianal and/or rectovaginal fistula at baseline showed fistula 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).

1. *Humira approved in E.U. for rheumatoid arthritis*. DailyDrugNews.com (Daily Essentials) Sept 15, 2003.

2. *New phase III trial evaluates Humira for Crohn's disease*. DailyDrugNews.com (Daily Essentials) Oct 1, 2003.

3. *New phase III trial of Humira in psoriatic arthritis*. DailyDrugNews.com (Daily Essentials) Oct 9, 2003.

4. *A year of milestones for Humira*. DailyDrugNews.com (Daily Essentials) Jan 8, 2004.

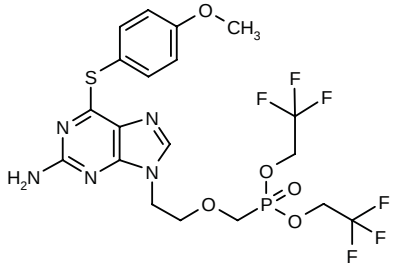
5. *Eisai reports Q3 R&D highlights*. Eisai Press Release 2004, Jan 30.

6. *Abbott seeks approval for Humira for improvement of physical function in RA*. DailyDrugNews.com (Daily Essentials) Oct 6, 2003.

7. Sandborn, W.J., Hanauer, S.B., Loftus, E.V. Jr. et al. *An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease.* Gastroenterology 2004, 126(4, Suppl. 2): Abst 435).

Original monograph – Drugs Fut 2001, 26(7): 639.

Alamifovir



Lilly is developing alamifovir (MCC-478, LY-582563) worldwide outside Japan under license from Mitsubishi Pharma. The purine nucleotide is in early clinical (I/II) development as a potential therapy for hepatitis B virus (HBV) infection.

Albumin Interferon Alfa

Albumin interferon alfa (Albuferon™), a novel long-acting form of interferon alfa, is a recombinant fusion protein comprised of human interferon alfa and human albumin, and is in development at Human Genome Sciences for the treatment of chronic hepatitis C. Interim results from an ongoing phase I/II trial demonstrated that the drug is well tolerated, has a prolonged half-life and is biologically active in adults with chronic hepatitis C who have failed previous interferon alfa treatments. Higher doses in both single- and repeat-dose cohorts, are being evaluated under an amended protocol designed to seek the maximum biological response that can be achieved at a tolerable dose. During this year, the company intends to complete the ongoing phase I/II clinical trial and complete enrollment for a phase II clinical study of albumin interferon alfa in patients with chronic hepatitis C who have not received treatment with interferon alfa (1-3).

The dose-finding phase I/II clinical trial enrolled 81 patients with chronic hepatitis C who received albumin interferon alfa (600 μg s.c.) either as single injections or as double injections on days 1 and 14. Overall, 62.5% of the 40 patients who received single doses of albumin interferon alfa showed antiviral response. Peak plasma concentrations after single doses increased with dose, and albumin interferon alfa had a terminal half-life of 143 h with single doses of 500 and 600 μg. Most adverse events were transient, mild to moderate and the incidence did not increase with dose (4).

1. *Human Genome Sciences reports Q3 R&D highlights*. Human Genome Sciences Press Release 2003, Oct 28.

2. Moore, P. et al. *Albuferon - A novel therapeutic agent with potent in vitro activity against RNA viral agents of bioterrorism*. 2004 ASM Biodefense Meet (March 7-10, Baltimore) 2004, Abst 171 (G).

3. *Human Genome Sciences reports 2003 year-end R&D highlights*. Human Genome Sciences Press Release 2004, Feb 10.

4. Balan, V., Sulkowski, M., Nelson, D. et al. *Safety, pharmacokinetics and pharmacodynamic results of higher doses of albuferon in a phase 1/2 single and double dose-escalation study in treatment experienced subjects with chronic hepatitis C*. J Hepatol 2004, 40(Suppl. 1): Abst 456.

Additional References

Balan, V. et al. *A phase 1/2 study to evaluate the pharmacokinetics, safety, tolerability, immunogenicity, and pharmacodynamics of Albuferon™ in treatment experienced subjects with chronic hepatitis C*. 54th Annu Meet Am Assoc Study Liver Dis (Oct 24-28, Boston) 2003, Abst 313.

Balan, V. et al. *Molecular profiles of drug response in HCV infected patients during the first 4 weeks of therapy for chronic hepatitis C virus with pegylated interferon containing regimens or Albuferon™*. 54th Annu Meet Am Assoc Study Liver Dis (Oct 24-28, Boston) 2003, Abst 984.

Alequel™

Enzo Biochem recently announced early interim results from a phase II study of Alequel™, the company's investigational therapeutic modality for the treatment of Crohn's disease. Alequel™ is a complex of autologous colon-derived antigens administered orally and is based on Enzo's immune regulation platform. In this double-blind, randomized study, patients with Crohn's disease and a CDAI score at baseline of 220-400 were randomized to receive the study drug or a placebo. To date, of subjects completing the 15-week treatment period with or without concomitant antiinflammatory medication, 7 evaluable patients received Alequel™ and 12 placebo. Clinical remission (CDAI score below 150 at 9, 12 and 15 weeks after initiation of treatment) was achieved in 71% of the treated subjects compared to 25%of those receiving placebo. The same percentage of Alequel™-treated subjects had a clinical response (CDAI score decrease of at least 70 points at 9, 12 and 15 weeks), versus only 42% of those on placebo. Quality of life was improved by a mean of 45% on Alequel™ compared to a mean improvement of 9% on placebo. Based on these results, Enzo plans to expand the study by increasing the number of subjects and the diversity of the patient population, as well as to determine the duration of the effects of the therapy (1).

1. *Enzo Biochem reports interim results for clinial trial of Alequel™, its investigational treatment for management of Crohn's disease. Company plans expanded study based on results.* Enzo Biochem Inc. Press Release 2004, March 11.

Alicaforsen Sodium

Nonadecasodium salt of 20-mer phosphorothioate oligodeoxynucleotide whose sequence is 5'-GCCCAAGCTGGCATCCGTCA-3'

Alicaforsen sodium is an antisense inhibitor of ICAM-1 that is being investigated by Isis Pharmaceuticals for Crohn's disease, ulcerative colitis and pouchitis. Results from phase II studies in Crohn's disease showed alicaforsen doses of 300 and 350 mg to be well tolerated and to induce clinical remissions. Isis plans to complete enrollment of 2 double-blind, placebo-controlled phase III Crohn's disease studies in the first half of 2004. The company will refine its NDA strategy in mid-2004. Phase II studies of alicaforsen in ulcerative colitis showed 73% reductions in the CDAI compared to placebo (1).

An open clinical trial determined the efficacy of an enema containing alicaforsen in patients with chronic unremitting pouchitis, the most common long-term complication from ileal pouch-anal anastomosis for ulcerative colitis. Each patient received 240 mg of alicaforsen once every night for 6 weeks. At the end of the treatment period, the mean Pouchitis Disease Activity Index (PDAI) had decreased from 11.4 to 6.8. The improvements in the PDAI and endoscopy scores of the patients were maintained for up to 9 months, although no response was obtained in 25% of the subjects. The percentage of patients who achieved remission (defined as PDAI score lower than 7) was 58% and 50% at 6 and 10 weeks from baseline, respectively. No serious or significant drug-related adverse events were reported. Additional studies are needed in order to confirm the promising effects of alicaforsen in the treatment of chronic unremitting pouchitis (2-4).

1. *R&D highlights from the Rodman & Renshaw Techvest Healthcare Conference: Isis Pharmaceuticals*. DailyDrugNews.com (Daily Essentials) Nov 24, 2003.

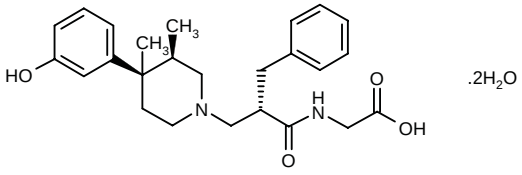
2. Miner, P.B. Jr., Bane, B., Bradley, J.D., Wedel, M.K. *ICAM-1 antisense inhibition by enema improves pouchitis and suggests long-term mucosal healing in patients with chronic, unremitting disease*. 68th Annu Sci Meet Am Coll Gastroenterol (Oct 13-15, Baltimore) 2003, Abst 52.

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

4. Miner, P., Wedel, M., Bane, B., Bradley, J. *An enema formulation of alicaforsen, an antisense inhibitor of intercellular adhesion molecule-1, in the treatment of chronic, unremitting pouchitis*. Aliment Pharmacol Ther 2004, 19(3): 281.

Original monograph – Drugs Fut 2002, 27(5): 439.

Alvimopan Hydrate



Adolor's lead product candidate, alvimopan hydrate (ADL-8-2698, Entereg™), a peripheral mu opioid agonist, is being developed for the treatment of postoperative ileus, bowel dysfunction affecting patients using opioid analgesics and chronic constipation in subjects not using opioids. The company is collaborating with GlaxoSmithKline for the development and commercialization of alvimopan. The first part of the NDA for alvimopan for use in postoperative ileus was submitted just recently by Adolor (1). The FDA has granted fast track designation to alvimopan for this indication (2).

Twenty-three adult patients with chronic constipation for at least 6 months were enrolled in a double-blind, crossover 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 (3).

Results from a phase III clinical study (14CL313) of alvimopan for the management of postoperative ileus in 510 patients undergoing small bowel resection, large bowel resection or radical hysterectomy showed that a statistically significant difference was achieved in the primary endpoint of time to recovery of gastrointestinal function in the alvimopan (6 and 12 mg) groups compared to placebo. The mean time to recovery of gastrointestinal function was 120, 105 and 98 h for placebo, 6 mg alvimopan and 12 mg alvimopan, respectively. A difference in favor of alvimopan was also observed for all secondary endpoints, including time to hospital discharge order. Alvimopan was generally well tolerated in the study, with nausea, vomiting and hypotension being the most frequently observed adverse events. The phase III program for alvimopan in postoperative ileus comprises 3 additional studies: 14CL302, 14CL308 and 14CL306 (4).

Adolor reported topline results from its 519-patient phase III safety study (14CL306) of alvimopan in postoperative ileus. The multicenter, double-blind, placebo-controlled study randomized patients undergoing total abdominal simple hysterectomy to receive either alvimopan 12 mg or placebo at least 2 h prior to surgery, and then twice a day beginning in the hospital on the first postoperative day. Dosing continued on an outpatient basis following hospital discharge, with medication administered for a total of 7 days postsurgery. Safety was the primary objective, with efficacy a secondary objective. Alvimopan was generally well tolerated in this study, with 93% of alvimopan patients completing treatment compared to 92% of placebo patients. Topline results from the first study, 14CL302, in 451 patients undergoing large bowel resection, simple or radical hysterectomy showed a statistically significant difference in the primary endpoint of time to recovery of gastrointestinal function in the low-dose alvimopan group compared to placebo. A positive trend was observed in the primary endpoint for alvimopan 12 mg (5).

Adolor recently presented the results of its fourth phase III study (14CL308) of alvimopan in the management of postoperative ileus. Study 14CL308 was a double-blind, placebo-controlled trial in 666 patients scheduled to undergo surgery for partial small/large bowel resection or simple or radical hysterectomy. Subjects were randomized to receive either 6 or 12 mg of alvimopan or placebo 2 h prior to surgery, then twice daily until hospital discharge or for a maximum of 7 days. Patients treated with 6 and 12 mg of alvimopan recovered normal gastrointestinal function approximately 8 and 10 h sooner, respectively, and were discharged from hospital about 14 and 15 h earlier, respectively, than placebo-treated patients. The percentage of patients who responded to the treatment was 69.9% with the 12-mg dose of alvimopan and 59.9% with placebo. The most common adverse events found in the study groups were nausea, vomiting and pruritus. Alvimopan was well tolerated and the percentage of patients who withdrew from the study due to adverse events was lower with the 6-mg dose (7.7%) and the 12-mg dose (7.7 mg) than with placebo (12.9%). The 14CL308 clinical trial confirms the favorable efficacy and safety results found for alvimopan in previous phase III clinical trials. Overall, the drug has been tested in more than 2,000 patients (6-8).

1. *Adolor submits first portion of NDA for Entereg™ (alvimopan) in postoperative ileus*. Adolor Corp. Press Release 2004, May 7.

2. *Entereg receives fast track status for postoperative ileus*. DailyDrugNews.com (Daily Essentials) Feb 26, 2004.

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

4. *Adolor announces positive results in phase III alvimopan study for postoperative ileus*. DailyDrugNews.com (Daily Essentials) Sept 29, 2003.

5. *Top-line results from third phase III study of Entereg for postoperative ileus*. DailyDrugNews.com (Daily Essentials) Oct 27, 2003.

6. *Enrollment completed in final phase III trial for Entereg in postoperative ileus*. DailyDrugNews.com (Daily Essentials) Nov 17, 2003.

7. *Additional favorable phase III results reported for Entereg™ in postoperative ileus*. DailyDrugNews.com (Daily Essentials) Jan 23, 2004.

8. *Adolor Corporation announces top-line results in Entereg™ phase 3 clinical study 308 in postoperative ileus*. Adolor Corp. Press Release 2004, Jan 13.

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

ANA-971

Anadys has initiated a clinical trial of ANA-971, an orally administered prodrug of isatoribine (see below). The trial aims to assess safety and pharmacokinetics in healthy volunteers following oral administration. ANA-971 is designed to improve the oral bioavailability of isatoribine. In preclinical animal studies, oral administration of ANA-971 resulted in higher levels of isatoribine in the blood than were present after oral administration of isatoribine itself. Anadys has exclusive worldwide rights to market and commercialize both ANA-971 and isatoribine. Isatoribine is a nucleoside analogue in development for the treatment of chronic hepatitis C virus (HCV) infection. Anadys believes isatoribine interacts with toll-like receptor 7 (TLR7), 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}. Anadys is enrolling patients for an isatoribine phase I/II study (1).

1. *Clinical trial of ANA-971, oral prodrug of isatoribine*. DailyDrugNews.com (Daily Essentials) Feb 23, 2004.

Antigastrin Therapeutic Vaccine

Aphton's antigastrin therapeutic vaccine (anti-G17 immunogen, G17DT) is being evaluated in phase III trials in advanced pancreatic cancer and phase II trials in advanced stomach and esophageal cancers under a collaboration with Aventis Pasteur, as well as phase II trials in gastrointestinal reflux disease (GERD).

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

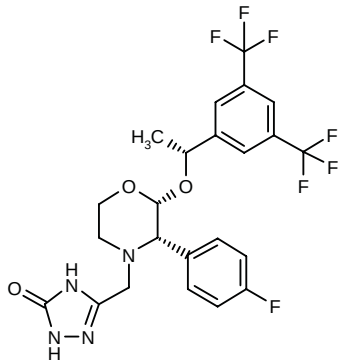
APF-530

Following the completion of preclinical studies, A.P. Pharma initiated phase I clinical evaluation of APF-530 in the U.K. earlier this year for the treatment of chemotherapy-induced nausea and vomiting (CINV). APF-530 contains the antiemetic agent granisetron and uses the company's proprietary Biochronomer™ bioerodible drug delivery system to provide 3-5 days of continuous relief from CINV following a single s.c. injection (1, 2).

1. *A.P. Pharma reports first quarter results; human clinical trials underway with two product candidates*. A.P. Pharma Press Release 2004, April 28.

2. *A.P. Pharma initiates phase I clinical trial with APF530, a potential treatment for chemotherapy-induced nausea and vomiting.* A.P. Pharma Press Release 2004, April 16.

Aprepitant



Aprepitant (MK-0869, Emend®) is an NK_1 antagonist developed at Merck & Co. for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting (CINV) and for the treatment of depression. The drug was launched last year for the former indication in the U.S., and European-wide approval was obtained later in the year. However, the company discontinued the phase III clinical development program for aprepitant for the treatment of depression after the compound failed to demonstrate efficacy (1-4).

In 2 randomized, double-blind phase III trials, over 1,000 patients undergoing cisplatin chemotherapy were given either ondansetron (32 mg i.v. on day 1) and dexamethasone (20 mg p.o. on day 1, 8 mg p.o. b.i.d. on days 2-4) or these agents plus aprepitant (125 mg p.o. on day 1, 80 mg once daily on days 2-3). Pooled analysis of data from the trials showed that aprepitant was well tolerated and significantly reduced the incidence of nausea and vomiting compared to standard therapy throughout the study period. Aprepitant reduced the incidence of delayed vomiting both in patients experiencing and those not experiencing acute vomiting. Complete response, which was defined as no emesis and no need for rescue therapy for 5 days after chemotherapy, was significantly more frequent among aprepitant-treated patients (66% *vs.* 41% for women, 69% *vs.* 53% for men). The improved antiemetic efficacy associated with aprepitant was similar in both gender groups during the acute and delayed phases of emesis (5-7).

Two multicenter, double-blind, randomized, placebo-controlled phase III clinical trials evaluated the antiemetic efficacy of aprepitant combined with a standard therapy of dexamethasone and a 5-HT_3 receptor antagonist in the prevention of CINV. A total of 1,099 adult cisplatin-naïve patients with histologically confirmed tumors and

scheduled to receive their first cisplatin dose were included in the studies. Each patient received either a standard regimen of ondansetron (32 mg i.v.) and dexamethasone (20 mg p.o.) on day 1 of each cycle, followed by dexamethasone (8 mg p.o. b.i.d.) on days 2-4, or a similar ondansetron/dexamethasone regimen that also included aprepitant (125 mg p.o. on day 1, 80 mg p.o. once daily on days 2-3). The probability of experiencing no emesis and no significant nausea on days 1-5 of the first chemotherapy cycle was 61% in the aprepitant group and 46% in the standard therapy group. After 6 chemotherapy cycles, this parameter decreased from 61% to 59% with aprepitant and from 46% to 40% with the standard regimen. These protection rates were consistently higher in the aprepitant group throughout the study. No significant differences were found between groups in the incidences of serious adverse events, drug-related adverse events, and adverse events causing discontinuation (8).

The Aprepitant Protocol 052 Study was a multinational, double-blind, randomized, placebo-controlled phase III clinical trial that assessed the antiemetic effects of aprepitant in the prevention of CINV. The study included 530 adult patients with histologically confirmed solid tumors who had been scheduled to receive their first chemotherapy cycle with a dose of at least 70 mg/m^2 of cisplatin. Before the chemotherapy regimen was administered on day 1, 266 patients were given a standard antiemetic therapy with ondansetron (32 mg i.v. on day 1) and dexamethasone (20 mg p.o. on day 1, followed by 8 mg p.o. b.i.d. on days 2-4), while another 264 patients received aprepitant (125 mg p.o.) plus ondansetron (32 mg i.v.) and dexamethasone (12 mg p.o.) on day 1, followed by aprepitant (80 mg p.o. once daily) on days 2 and 3, and dexamethasone (8 mg p.o. once daily) on days 2-4. The percentage of patients free from emetic episodes or who required no antiemetic rescue drugs was higher with aprepitant during the first 5 days after chemotherapy (72.7% *vs*. 52.3%). The antiemetic efficacy of the aprepitant regimen was also greater during day 1 (89.2% *vs*. 78.1%) and days 2-5 (75.4% *vs*. 55.8%) after chemotherapy. No significant differences were found between the safety profiles of the regimens, and none of the 16 deaths reported during the study was considered by the investigators to be caused by drug-related adverse events (9).

1. *MK-0869 phase III program discontinued*. DailyDrugNews.com (Daily Essentials) Nov 14, 2003.

2. *FDA committee reviews Emend data*. DailyDrugNews.com (Daily Essentials) March 11, 2003.

3. *Emend approved by FDA for chemotherapy-induced nausea and vomiting*. DailyDrugNews.com (Daily Essentials) March 31, 2003.

4. *Emend receives positive opinion from European CPMP*. DailyDrugNews.com (Daily Essentials) July 30, 2003.

5. Gralla, R., Hesketh, P., Grunberg, S. et al. *The oral NK$_1$ antagonist aprepitant for the prevention of chemotherapy induced nausea and vomiting: Pooled data from 2 randomized, double-blind, placebo controlled trials*. Eur J Cancer - Suppl 2003, 1(Suppl. 5): Abst 687.

6. Horgan, K., Grunberg, S., Hesketh, P., Guoguang-Ma, J., Ianus, J., Evans, J., Carides, A. *Analysis of pooled data from two phase III studies of the NK-1 antagonist aprepitant to assess relationships between the incidence and control of cisplatin-induced acute vomiting and delayed vomiting*. Eur J Cancer - Suppl 2003, 1(Suppl. 5): Abst 945.

7. Gralla, R.J., Carides, A.D., Ianes, J., Elmer, M., Evans, J.K., Horgan, K.J. *The oral neurokinin-1 antagonist aprepitant added to standard antiemetics provided equal efficacy in female and male patients receiving highly emetogenic chemotherapy: Combined data from 2 phase III clinical trials*. 26th Annu San Antonio Breast Cancer Symp (Dec 3-6, San Antonio) 2003, Abst 636.

8. de Wit, R., Herrstedt, R., Rapoport, B. et al. *The oral NK$_1$ antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: A combined analysis of two randomised, placebo-controlled phase III clinical trials*. Eur J Cancer 2004, 40(3): 403.

9. Hesketh, P.J., Grunberg, S.M., Gralla, R.J. et al. *The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin - The Aprepitant Protocol 052 Study Group*. J Clin Oncol 2003, 21(22): 4112.

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de Wit, R. et al. *Addition of the oral NK$_1$ antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy*. J Clin Oncol 2003, 21(22): 4105.

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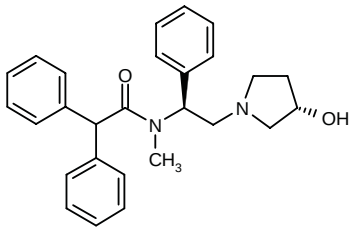
Asimadoline



A kappa opioid agonist from Merck KGaA, asimadoline is in phase II clinical trials for the treatment of pain associated with irritable bowel syndrome (IBS). The company is looking for licensing partners for this product.

A randomized, double-blind, placebo-controlled study was conducted to assess the effect of single oral doses of asimadoline (0.5 or 1.5 mg) on satiation volume, postprandial symptoms and gastric volumes in 39 healthy volunteers after a standard nutrient drink test. Both doses of the active treatment reduced postprandial fullness and the higher dose reduced satiation during the meal, despite an increase in ingested meal volume (1).

1. Delgado-Aros, S., Chial, H.J., Cremonini, F., Ferber, I., McKinzie, S., Burton, D.D., Camilleri, M. *Effects of asimadoline, a kappa-opioid agonist, on satiation and postprandial symptoms in health*. Aliment Pharmacol Ther 2003, 18(5): 507.

ATI-7505

ARYx Therapeutics' ATI-7505 just recently commenced phase I clinical testing in the U.S. A potent prokinetic agent for the treatment of GERD and diabetic gastroparesis, the cisapride analogue is designed to have similar efficacy to cisapride but with key improvements and changes in the metabolism and cardiac safety profile of the drug. ATI-7505 is expected to fill the void left when cisapride was withdrawn due to safety problems despite its high efficacy in the treatment of GERD and gastroparesis (1).

1. *ARYx Therapeutics launches phase 1 trial for ATI-7505. ATI-7505 preclinical pharmacology data to be featured during Digestive Disease Week in May*. ARYx Therapeutics Inc. Press Release 2004, April 29.

AZD-0865/AZD-3355/AZD-7371

AZD-0865 (formerly AR-H044277) is a compound from a new class –the potassium-competitive acid blockers– with potential for faster, more effective and reliable inhibition of gastric acid secretion than the proton pump inhibitors. It is in phase II trials at AstraZeneca for the treatment of acid-related gastrointestinal disorders such as GERD. The *in vitro, in vivo* gastric antisecretory and pharmacokinetic profile of AZD-0865 was discussed at the recent Digestive Disease Week meeting (1-4).

Two other potential gastrointestinal drugs are also in early clinical testing at AstraZeneca. The company has commenced human trials with AZD-3355, expected to be useful in the treatment of GERD due to its ability to inhibit transient lower esophageal sphincter relaxations, and AZD-7371 is in early clinical development for functional gastrointestinal disorders.

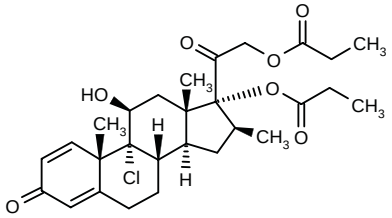
1. Andersson, K. et al. *Preclinical profile of AZD90865, a novel, selective, potassium-competitive acid blocker.* Gastroenterology 2004, 126(4, Suppl. 2): Abst 448.

2. Briving, C., Svensson, K., Maxvall, I. et al. *Mechanism of action of AZD0865, an H^+K-ATPase selective, potassium-competitive acid blocker.* Gastroenterology 2004, 126(4, Suppl. 2): Abst M1436.

3. Holstein, B. , Holmberg, A., Florentzson, M. et al. *Pharmacokinetic and pharmacodynamic profiles of AZD0865, a novel, potassium-competitive acid blocker.* Gastroenterology 2004, 126(4, Suppl. 2): Abst M1440.

4. Holstein, B., Holmberg, A., Florentzson, M. et al. *AZD0865 - a new potassium-competitive acid blocker - exhibits maximal gastric antisecretory effects from first dose.* Gastroenterology 2004, 126(4, Suppl. 2): Abst M1437.

Beclometasone Dipropionate



Two oral formulations of beclometasone dipropionate are in development by DOR BioPharma and Chiesi for use in gastrointestinal disorders. DOR BioPharma's OrBec™ is being evaluated in a pivotal phase III trial for use in the treatment of moderate to severe intestinal graft-versus-host disease (iGVHD), and may also have potential for use in other intestinal diseases, *i.e.,* IBD and IBS. Chiesi has completed phase III clinical evaluation of its own product CHF-1514, being developed in both oral and enema formulations for the treatment of ulcerative colitis.

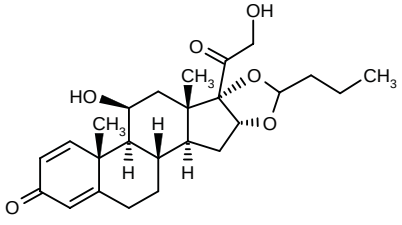
Bile Salt-Stimulated Lipase

Arexis has acquired from PPL Therapeutics and licensee AstraZeneca a project for the use of recombinant human bile salt-stimulated lipase (BSSL) in the development of a new type of substitution therapy for patients with pancreatic dysfunction, including those with

cystic fibrosis and preterm infants. BSSL is a naturally occurring lipid-degrading enzyme with the ability to degrade a large spectrum of lipids in food. It is present in the mature pancreas and breast milk, but is largely lacking in subjects with cystic fibrosis. The acquisition includes transfer of intellectual property and know-how within the BSSL project to Arexis. Arexis has also acquired an exclusive license to the patents covering BSSL held by the Oklahoma Medical Research Foundation. Arexis is now continuing the project for the treatment of cystic fibrosis and is planning clinical development of a product for preterm infants. In a completed phase II study in Belgium, the addition of BSSL to ordinary enzyme treatment for patients with cystic fibrosis showed good effects on fat uptake. Arexis has initiated an additional phase II study in Sweden to more specifically monitor the qualitative effects on lipid uptake (1).

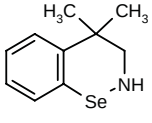
1. *Arexis acquires BSSL project from AstraZeneca*. DailyDrugNews.com (Daily Essentials) Feb 20, 2004.

Budesonide



A colon-targeting oral budesonide formulation for the treatment of IBD, *i.e.*, ulcerative colitis and Crohn's disease, has been developed by West Pharmaceutical Services. Currently in phase I clinical evaluation, the product is available for licensing.

BXT-51072



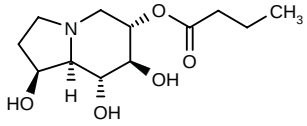
Axonyx has entered into agreements to acquire 53% of the outstanding voting stock of Oxis International. Oxis's lead drug candidate, BXT-51072, has completed a phase IIa clinical trial in IBD (ulcerative colitis), with further studies being reviewed (1). BXT-51072 is a low-molecular-weight organoselenium glutathione peroxidase mimic with antioxidant activity. It is the first in a class of potent catalytic antioxidants and possesses both free radical-neutralizing activity and the ability to downregulate gene transcription leading to the production of a number of inflammatory mediators. Oxis is seeking licensees for this product.

1. *Axonyx acquires interest in Oxis International*. DailyDrugNews.com (Daily Essentials) Jan 27, 2004.

CBP-1011

InKine Pharmaceutical has completed phase II trials in ulcerative colitis and is conducting a phase IIb trial in Crohn's disease with CBP-1011 (medroxyprogesterone, Colirest™), a steroid molecule acting on inflammatory macrophages.

Celgosivir



Micrologix Biotech has acquired from Virogen the global rights to celgosivir (MBI-3253, VIR-222), a phase I/II oral antiviral agent under development for the treatment of chronic hepatitis C virus (HCV) infections. Micrologix plans to initiate phase II development this year. Celgosivir is an oral prodrug of castanospermine, a natural product derived from the Australian black bean chestnut tree, *Castanospermum australe*. Celgosivir is a potent inhibitor of α-glucosidase. Because it inhibits a mammalian enzyme rather than a viral target, it is less likely to lead to drug-resistant viral mutants and has the potential to be used in combination with current HCV therapies (1).

1. *Micrologix Biotech acquires celgosivir rights*. DailyDrugNews.com (Daily Essentials) Feb 10, 2004.

Certolizumab Pegol

A pegylated anti-TNF-α antibody fragment, certolizumab pegol (CDP-870) is in phase III clinical trials for Crohn's disease and rheumatoid arthritis. CDP-870, which is administered by subcutaneous injection, is an Fab' fragment of a humanized anti-TNF-α antibody in which polyethylene glycol (PEG) is site-specifically attached to increase circulating half-life while maintaining binding activity. Late last year, Celltech Group announced that it would regain full rights to the product from Pfizer during early 2004. The company also intends to explore further indications where TNF inhibitors show promise, such as psoriasis, psoriatic arthritis and ankylosing spondylitis, indications for which Celltech did not

previously have rights. Celltech is in advanced discussions with potential partners to outlicense rights in rheumatoid arthritis. Two international pivotal phase III studies –PRECISE-1 and PRECISE-2 (Pegylated anibody Fragment Evaluation in Crohn's dIsease: Safety and Efficacy)– were initiated earlier this year in over 1,300 patients with moderate to severe Crohn's disease, with regulatory submissions planned for 2005. Celltech plans to market the drug in the U.S. and Europe itself (1-3).

A double-blind phase II clinical trial randomized 292 adult patients with active Crohn's disease (defined as a CDAI score of 220-450) to receive 3 subcutaneous doses of placebo or certolizumab pegol (100, 200 or 400 mg) at weeks 0, 4 and 8. Response to the treatment was assessed after dividing the patients into 2 groups: those with baseline serum C-reactive protein (CRP) levels of 10 mg/l or more and those with baseline serum CRP levels below 10 mg/l. The 400-mg dose was the most effective in inducing clinical response among patients with high CRP levels (53.1% *vs.* 17.9% with placebo at week 12); this was confirmed by the assessment of the CDAI scores and the CRP levels of the patients. No patients with baseline CRP levels below 10 mg/l responded to the drug, suggesting that conducting routine CRP measurements may be useful for determining which patients may benefit from anti-TNF treatments (4-6).

The results from the above study and another phase II study in which placebo or a single dose of certolizumab pegol (1.25, 5, 10 or 20 mg/kg i.v.) was administered to 92 adult Crohn's disease patients were used to assess the safety and pharmacokinetics of the drug. The pharmacokinetic profile in both studies suggested a median half-life of 2 weeks. No significant differences were found between the safety profile of subcutaneous and intravenous certolizumab pegol. Most adverse events were mild or moderate, and the most common were headache, aggravated Crohn's disease, nausea and nasopharyngitis. Neither route of administration was associated with an increase in the incidence of opportunistic infections, tuberculosis, deaths, lupus or malignancies (7, 8).

1. *Celltech to regain rights to CDP-870 from Pfizer*. DailyDrugNews.com (Daily Essentials) Dec 3, 2003.

2. *First phase III trial of CDP-870 in rheumatoid arthritis meets primary endpoint*. DailyDrugNews.com (Daily Essentials) April 6, 2004.

3. *Dosing commences in pivotal PRECIS-1 study of CDP-870 for Crohn's disease*. DailyDrugNews.com (Daily Essentials) Jan 9, 2004.

4. Schreiber, S., Fedorak, R., Rutgeerts, P., Innes, A., Patel, J. *CDP870, a pegylated humanised anti-TNF antibody fragment, offers particular benefit to Crohn's disease patients with elevated C-reactive reaction*. 11th United Eur Gastroenterol Week (Nov 1-5, Madrid) 2003, Abst OP-G-18.

5. Schreiber, S., Rutgeerts, P., Innes, A., Patel, J. *CDP870, a pegylated humanized anti-TNF antibody fragment, offers particular benefit to Crohn's disease patients with elevated C-reactive protein*. 68th Annu Sci Meet Am Coll Gastroenterol (Oct 13-15, Baltimore) 2003, Abst 299.

6. Rutgeerts, P. et al. *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.

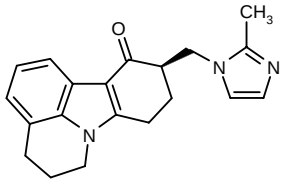
7. Schreiber, S., Winter, T., Innes, A., Patel, J. *Safety of CDP870, a pegylated human anti-TNF antibody fragment, in Crohn's disease*. 68th Annu Sci Meet Am Coll Gastroenterol (Oct 13-15, Baltimore) 2003, Abst 300.

8. Schreiber, S., Winter, T., Innes, A., Patel, J. *Safety of CDP870, a pegylated humanised anti-TNF antibody fragment, in Crohn's disease*. 11th United Eur Gastroenterol Week (Nov 1-5, Madrid) 2003, Abst WED-G-196.

CH-100

CH-100 is a Chinese herbal medicine preparation from Cathay Herbal for the management of chronic hepatitis C infection. Classified as a liver tonic and available in Australia, it has been shown to reduce and even normalize alanine aminotransferase (ALT) levels in patients with hepatitis C.

Cilansetron



Topline results from the first 2 large placebo-controlled phase III studies of Solvay's cilansetron (Calmactin®), a 5-HT_3 antagonist, demonstrated patient benefits associated with the drug for diarrhea-predominant IBS. Based on the encouraging results, Solvay plans to compile registration dossiers for major territories, beginning with submissions in Europe and the U.S. in the first quarter of 2004. Solvay and Quintiles have enrolled over 4,000 patients in the phase III clinical program for cilansetron. The 5-HT_3 antagonist has afforded clinical benefits in male and female IBS patients in 2 phase II and 2 phase III studies conducted in the U.S., Europe and other countries (1, 2). Launch of cilansetron is expected later this year.

A total of 792 patients suffering from diarrhea-predominant IBS were included in a double-blind, randomized, placebo-controlled clinical trial to assess the efficacy and safety of cilansetron (2 mg t.i.d.) in this indication. Cilansetron was more effective than placebo in improving the symptoms of IBS after 6 months of treatment. At 3 months, patients receiving cilansetron were more likely to report significant improvements in the incidence

of abdominal pain and discomfort (56% *vs.* 42%) and abnormal bowel habits (61% *vs.* 42%) than placebo-treated patients. The percentage of patients who completed the study was similar in both study groups (79% with cilansetron and 77% with placebo). The most common adverse event causing withdrawal was constipation, and although 3 patients experienced suspected ischemic colitis events, these resolved without sequelae (3).

Data from 2 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 diarrhea-predominant IBS 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, abdominal pain/discomfort and bowel habits. Patients receiving cilansetron showed a greater incidence of constipation compared to placebo patients, but no cases of ischemic colitis were reported (4).

1. *Encouraging topline results from phase III trials of cilansetron*. DailyDrugNews.com (Daily Essentials) Oct 31, 2003.

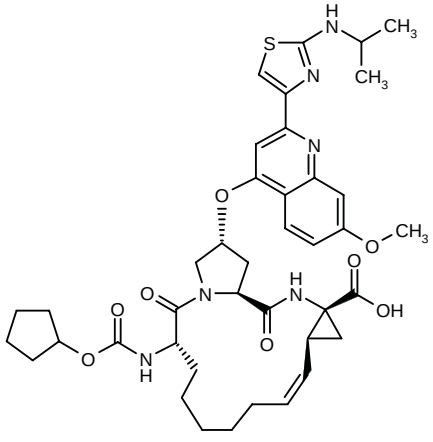
2. *Solvay reports Q3 R&D highlights*. Solvay Press Release 2003, Oct 31.

3. Bradette, M., Moennikes, H., Carter, F. et al. *Cilansetron in irritable bowel syndrome with diarrhea predominance (IBS-D): Efficacy and safety in 6 month global study.* Gastroenterology 2004, 126(4, Suppl. 2): Abst 351.

4. Coremans, G., Clouse, R.E., Carter, F. et al. *Cilansetron, a novel 5-HT$_3$ antagonist, demonstrated efficacy in males with irritable bowel syndrome with diarrhea-predominance (IBS-D).* Gastroenterology 2004, 126(4, Suppl. 2): Abst W1471.

Original monograph – Drugs Fut 1999, 24(5): 475.

Ciluprevir



Ciluprevir (BILN-2061) is a potent, selective, orally active, small-molecule, active-site inhibitor of hepatitis C virus (HCV) NS3 serine protease developed by Boehringer Ingelheim, the first member of this new drug class to be tested in humans.

Ten patients infected with HCV genotype 1 who also had liver cirrhosis were included in a double-blind clinical trial and randomized to receive placebo or 200 mg of ciluprevir orally twice daily for 2 days. All drug-treated patients but none of the placebo-treated patients showed reductions of at least 2 $\log_{10}$ units in their viral load. No significant differences were found between placebo and ciluprevir in the incidence of adverse events, vital signs, laboratory parameters and ECG of the patients. All patients completed the study and only 1 patient showed a significant increase in ALT levels after 2 days of drug administration (1).

A clinical trial randomized 10 patients infected with HCV genotypes 2 or 3 and minimal liver fibrosis to receive placebo or ciluprevir (500 mg twice daily) orally for 2 days. At the end of the treatment, 50% of the patients treated with ciluprevir showed a reduction of at least 2 $\log_{10}$ units in their viral load, whereas 1 patient showed a weak response to drug and no viral load reduction was found in 3 drug-treated patients and the 2 placebo-treated patients. The drug was well tolerated and no significant differences were found between the safety profiles of ciluprevir and placebo (2).

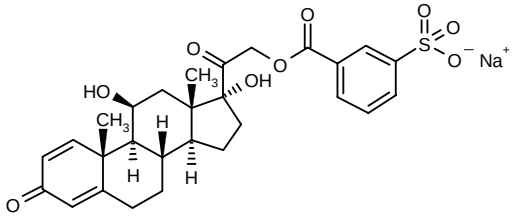
1. Wedemeyer, H. et al. *Safety and antiviral effect of BILN 2061, a novel HCV serine protease inhibitor, after oral treatment over 2 days in patients with chronic hepatitis C, genotype 1, and liver cirrhosis*. 54th Annu Meet Am Assoc Study Liver Dis (Oct 24-28, Boston) 2003, Abst 294.

2. Reiser, M. et al. *Antiviral effect of BILN 2061, a novel HCV serine protease inhibitor, after oral treatment over 2 days in patients with chronic hepatitis C, non-genotype 1*. 54th Annu Meet Am Assoc Study Liver Dis (Oct 24-28, Boston) 2003, Abst 136.

Clostridium difficile Toxoid Vaccine

Acambis has conducted phase I/II trials in its *Clostridium difficile* antibiotic-induced diarrhea (CDAD) project. The company is developing both passive and active toxoid vaccines using inactivated *C. difficile* toxins. In the passive immunization program aimed particularly at already immunocompromised subjects, the toxoid vaccine is used to vaccinate plasma donors; the antibodies generated in the form of hyperimmune globulin and purified are used to create a passive vaccine for the treatment of CDAD patients. The active vaccine is aimed especially at populations at risk.

COLAL-PRED™



Alizyme is developing COLAL-PRED™ as an improved treatment for ulcerative colitis incorporating the company's colon-specific drug delivery system (COLAL™) to release the steroid prednisolone metasulfobenzoate (ATL-2502) directly to the site of action to avoid side effects. A phase III trial has been approved by the U.K. authorities for the maintenance of remission and pivotal phase III trials for the treatment of active ulcerative colitis are also in preparation in Europe.

CpG-10101

Coley Pharmaceuticals has advanced CpG-10101 (Actilon™), a novel synthetic toll-like receptor 9 (TLR9) agonist identified through internal discovery efforts, for chronic hepatitis C virus (HCV) infection, into phase I trials. Two blinded, placebo-controlled, dose-escalation studies will examine the safety, tolerability, immunological and antiviral activity of subcutaneous CpG-10101, first in 40 healthy volunteers and then in 40 HCV-positive patients. The studies are expected to conclude in the first half of 2004. CpG-10101 acts through TLR9, found in dendritic cells and B-cells, to induce a durable and natural immune response against HCV. Firstly, it stimulates the production of polyclonal natural interferons by dendritic cells to reduce viral load, and secondly, it drives these dendritic cells to promote virus-specific immunity to help clear the viral infection (1).

1. *Actilon enters phase I for chronic HCV*. DailyDrugNews.com (Daily Essentials) Jan 16, 2004.

CS-526

Novartis has signed an agreement with Sankyo to codevelop and commercialize a treatment for GERD and peptic ulcer. The agreement focuses on Sankyo's CS-526 (formerly R-105266, known as AKU-517 at Novartis) oral acid pump antagonist and also includes 4 alternative potential drug candidates. The new reversible acid pump antagonist class may offer therapeutic advantages over existing antacid therapies, with faster acid reduction and more durable activity. Novartis will have exclusive worldwide rights to commercialize CS-526, or an alternative product, except in Japan and certain Middle East countries. Novartis and Sankyo will copromote the product in the U.S. and in most E.U. countries. Sankyo will receive a signing fee and development and sales milestone payments, in addition to royalties on sales in countries other than copromotion countries. Novartis and Sankyo will share equally all development costs, as well as costs and profits of cocommercialization. Ube, which together with Sankyo discovered CS-526, will manufacture the drug substance. CS-526 is entering phase I trials (1).

1. *Novartis and Sankyo to codevelop and commercialize new GERD treatment*. DailyDrugNews.com (Daily Essentials) Oct 10, 2003.

DA-9601

DA-9601 is a mucoprotective antiulcer phytopharmaceutical derived from the ethanol extract of *Artemisia asiatica* by researchers at Dong-A Pharmaceutical and currently in phase III clinical trials for acute and chronic gastritis and alcoholic gastritis.

Daclizumab

Daclizumab (Zenapax®) is a biosynthetic anti-CD25 monoclonal antibody designed at Protein Design Labs to inhibit the IL-2 receptor (IL-2R), thereby blocking human T-lymphocytes. It is currently marketed by licensee Roche for the prophylactic treatment of acute kidney transplant rejection in conjunction with a standard immunosuppressive regimen.

Disappointing results were reported earlier this month from a phase II clinical trial of daclizumab in patients with moderate or severe ulcerative colitis, and the company does not plan to develop the antibody further for this indication. However, phase II clinical studies in asthma are under way, and preparations for a clinical trial in multiple sclerosis continue (1).

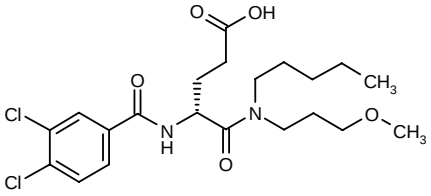
Protein Design Labs recently obtained exclusive worldwide rights to market, develop and sell daclizumab in all disease indications other than organ transplantation under a new agreement with Roche. Roche will continue to market daclizumab in transplantation indications until 2007. The agreement is a restructuring of an alliance between PDL and Roche dating back to 1989, when Roche acquired the rights to commercialize daclizumab worldwide. PDL will immediately assume worldwide responsibility for the development and future sales and marketing of daclizumab in all indications other than transplantation, for the sum of USD 80 million. PDL will also pay Roche an additional sum if the company chooses to acquire daclizumab in the transplantation indication (2, 3).

1. *Protein Design Labs reports negative results in phase II clinical trial of daclizumab in ulcerative colitis*. Protein Design Labs Press Release 2004, May 16.

2. *Roche and Protein Design Labs restructure Zenapax alliance*. DailyDrugNews.com (Daily Essentials) Oct 3, 2003.

3. *Protein Design Labs reports Q3 R&D highlights*. Protein Design Labs Press Release 2003, Nov 3.

Dexloxiglumide

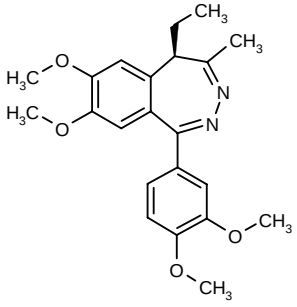


Forest has discontinued development of the cholecystokinin CCK_1 antagonist dexloxiglumide for the treatment of constipation-predominant IBS in the U.S. This decision stems from the results of 2 placebo-controlled phase III studies in over 1,400 women treated for 12 weeks. Although there was a numeric trend in favor of dexloxiglumide, the difference was not statistically significant. The primary endpoint was the Subject Global Assessment. Both trials suggested that dexloxiglumide had limited side effects and no effect on gallstone formation. Rotta, the originator of dexloxiglumide, is continuing a separate placebo-controlled phase III trial in Europe of different design in constipation-predominant IBS. Forest, the U.S. licensee, and Rotta will also continue to evaluate the potential of dexloxiglumide in other indications (1).

1. *Forest discontinues development of dexloxiglumide for constipation-predominant IBS*. DailyDrugNews.com (Daily Essentials) Oct 6, 2003.

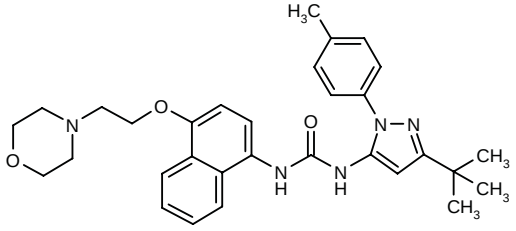
Original monograph – Drugs Fut 1999, 24(7): 725.

Dextofisopam



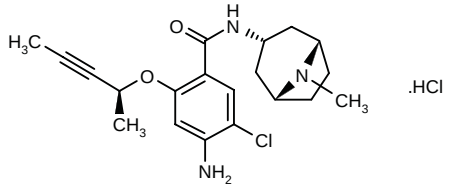
The *R*-isomer of tofisopam, dextofisopam, is in phase II studies at Vela Pharmaceuticals for the treatment of IBS in men and women. Dextofisopam has demonstrated significant activity in animal models of stress and gastrointestinal dysfunction, reducing stress-induced ulcer formation, normalizing stretch-induced colonic contractions and reducing visceral hypersensitivity, while having little or no effect on basal colonic motility. Phase I studies also demonstrated its safety and good tolerability.

Doramapimod



Boehringer Ingelheim is conducting phase IIb/III trials with the p38 MAP (mitogen-activated protein) kinase inhibitor doramapimod (BIBR-796) for the treatment of psoriasis, as well as phase IIa trials for rheumatoid arthritis and Crohn's disease.

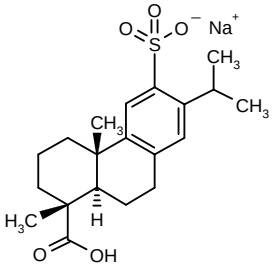
E-3309/E-3620



E-3620

Eisai has two gastrointestinal products in clinical trials: the gastroprokinetic agent E-3620, a dual 5-HT_3 receptor antagonist and 5-HT_4 receptor agonist, in phase II trials in Japan and E-3309 in phase I trials in Europe for the eradication of *Helicobacter pylori*.

Ecabet Sodium



A new enema formulation of the gastrointestinal mucoprotective agent ecabet sodium (TA-2711E,

Gastrom®) is being prepared for phase III clinical trials for the treatment of ulcerative colitis by Tanabe Seiyaku in Japan and Tanabe AAI, the company's joint venture with aai Pharma, in Europe and the U.S. Tanabe currently markets the drug for gastritis and peptic ulcers.

Original monograph – Drugs Fut 1988, 13(11): 966).

EHC-18

A phase I trial of EHC-18, Enzo Biochem's proprietary treatment for hepatitis C-associated chronic active hepatitis, met its endpoints and further studies are being planned (1).

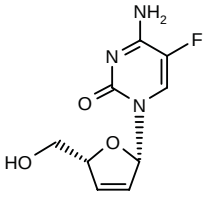
1. *Enzo Biochem acquires OraGen*. DailyDrugNews.com (Daily Essentials) March 2, 2004.

EHT-899

Enzo Biochem's oral hepatitis B virus (HBV) protein product EHT-899 has successfully completed an open-label phase II study for hepatitis B-associated chronic hepatitis and plans are under way for a multicenter, double-blind phase II study (1).

1. Enzo Biochem acquires OraGen. DailyDrugNews.com (Daily Essentials) March 2, 2004.

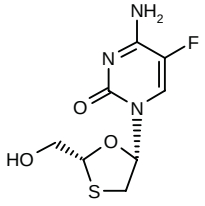
Elvucitabine



Elvucitabine (ACH-126443, β-L-Fd4C) is an L-cytosine nucleoside analogue with potent *in vitro* activity against wild-type strains of HIV and hepatitis B (HBV), as well as strains of HIV and HBV resistant to currently used therapies. Its antiviral activity has been shown to result from inhibition of the HIV reverse transcriptase enzyme and HBV DNA polymerase. Achillion has completed 2 phase II studies evaluating the use of elvucitabine in patients chronically infected with HIV and HBV. In these studies, elvucitabine demonstrated potent anti-HIV activity in patients whose virus carries the M184V mutation, a mutation associated with lamivudine (3TC) resistance, and potent anti-HBV activity in chronically infected HBV patients. Achillion is currently planning further longer term clinical studies to determine the optimal use of elvucitabine for the treatment of HIV and HBV.

Original monograph – Drugs Fut 2002, 27(12): 1131.

Emtricitabine



The newest nucleoside reverse transcriptase inhibitor (NRTI), emtricitabine (Emtriva™), was launched by Gilead last year in the U.S. and several European countries for the treatment of HIV infection in adults in combination with other antiretroviral medications, and it is also currently being tested in phase III clinical studies for the treatment of hepatitis B virus (HBV) infection. Gilead added emtricitabine to its portfolio upon its acquisition of Triangle Pharmaceuticals in October 2003, which in turn had licensed the product from Emory University in 1996. Gilead has also developed a fixed-dose coformulation of emtricitabine and tenofovir disoproxil fumarate (Viread®), which was recently submitted for regulatory review in the U.S. and the E.U. (1-4).

Preliminary results from Gilead's phase III trial (study FTCB-301) of emtricitabine in patients with chronic hepatitis B showed that 48 weeks of treatment with the drug resulted in improvements in liver histology. The 48-week, double-blind, placebo-controlled trial conducted at 34 sites in 7 countries in North America, Europe and Asia was designed to compare the efficacy and safety of emtricitabine 200 mg once daily *versus* placebo in 248 patients with chronic hepatitis B who had not previously received therapy with a nucleoside analogue. Prior to study entry, all patients were hepatitis B surface antigen (HBsAg)-positive for at least 6 months. Both hepatitis B e antigen (HBeAg)-negative and HBeAg-positive patients were enrolled in the study. After 48 weeks of treatment, 62% of patients treated with emtricitabine exhibited significant improvements in liver histology compared with 25% of patients receiving placebo. At baseline, emtricitabine and placebo patients had, respectively, median HBV DNA levels of 7.67 $\log_{10}$ copies/ml and 7.42 $\log_{10}$ copies/ml, respectively, and median alanine aminotransferase (ALT) levels of 81 IU/l and 92 IU/l, respectively. Treatment with emtricitabine resulted in a median reduction in HBV DNA from baseline of 3.00 $\log_{10}$ copies/ml compared with a median reduction in the placebo group of 0.44 $\log_{10}$ copies/ml. After 48 weeks, 56% of emtricitabine patients had HBV DNA below the lower limit of detection compared to 7% in the placebo arm. Of emtricitabine patients, 13% had virus with the YMDD mutation,

known to confer resistance to emtricitabine and lamivudine, at week 48. Emtricitabine patients achieved a median ALT reduction of 52 IU/l, compared to a median reduction of 25 IU/l for patients receiving placebo. In the subset of patients who were HBeAg-positive at baseline, there was no significant difference between the treatment and placebo arms in the percentage of patients who achieved seroconversion (5).

The potential use of emtricitabine in the treatment of hepatitis infection in HIV patients was evaluated in 3 clinical trials that administered emtricitabine as part of a triple drug therapy to a total of 1,084 patients for 48 weeks. At baseline, 39 of these patients were positive for HBsAg, 24 of whom had HBV DNA levels higher than 4,700 copies/ml. Overall, 82% of the 17 patients who were available for evaluation showed a reduction of at least 5 $\log_{10}$ in their HBV DNA levels compared to baseline. The incidence of resistance mutations in the HBV polymerase gene was low (12%) after 1 year (6).

1. *European approval announced for Emtriva*. DailyDrugNews.com (Daily Essentials) Oct 31, 2003.

2. *Gilead reports Q3 R&D highlights*. Gilead Sciences Press Release 2003, Oct 28.

3. *Gilead Sciences reports 2003 year-end R&D highlights*. Gilead Sciences Press Release 2004, Jan 29.

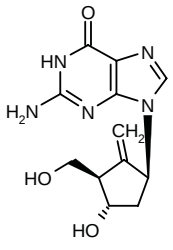
4. *Gilead submits applications to U.S. and European regulatory authorities for fixed-dose co-formulation of Viread® and Emtriva™*. Gilead Sciences Press Release 2004, March 15.

5. *Liver histology improvements in phase III study of emtricitabine for hepatitis B*. DailyDrugNews.com (Daily Essentials) Nov 28, 2003.

6. Snow, A., Harris, J., Borroto-Esoda, K., Mondou, E., Sorbel, J., Dalton, M., Rousseau, F. *Emtricitabine therapy for hepatitis infection in HIV+ patients co-infected with hepatitis B virus: Efficacy and genotypic findings in antiretroviral treatment-naïve patients*. 11th Conf Retroviruses Opportunistic Infect (Feb 8-11, San Francisco) 2004, Abst 836.

Original monograph – Drugs Fut 1995, 20(8): 761.

Entecavir



Bristol-Myers Squibb is conducting phase III trials with the investigational hepatitis B virus (HBV) nucleoside analogue entecavir.

A total of 181 hepatitis B patients unresponsive to lamivudine were randomized to continue receiving lamivudine (100 mg/day) or switch to entecavir (0.1, 0.5 and 1.0 mg once daily) for up to 85 weeks. Four patients treated with 0.5 or 1.0 mg/day of entecavir showed ALT flares that resolved while receiving blinded entecavir therapy. Two patients treated with 0.1 mg of entecavir and 5 of those receiving lamivudine had ALT flares that did not resolve during the blinded study period and were associated with increasing HBV levels. The low incidence of ALT flares suggested that no overlapping lamivudine administration was required when switching to entecavir in the treatment of hepatitis B (1).

A dose-finding phase II clinical trial compared the effects of entecavir (0.1, 0.5 and 1.0 mg) and continued lamivudine therapy given for 48 weeks to patients with hepatitis B unresponsive to lamivudine. The analysis of the changes in the HBV DNA levels of the patients during the study revealed that a dose of 1 mg of entecavir was significantly more potent as an antiviral drug than lamivudine. Greater antiviral efficacy was found for entecavir regardless of hepatitis B antigen status, ALT levels and HBV genotype. The percentage of patients who discontinued the study due to lack of efficacy was greater with lamivudine than with entecavir (2).

The safety results from 6 phase II clinical studies in a total of 409 patients with HBV infection who received entecavir alone, lamivudine alone, entecavir combined with lamivudine or placebo were reported at the European Association for the Study of the Liver Meeting last year in Geneva. Most adverse events were mild to moderate, and the most common were headache, rhinitis, fatigue and abdominal pain. No significant differences were found among treatments in the frequency of serious adverse events (7% with entecavir, 9% with lamivudine and 4% with the combination) or in the percentage of patients who discontinued the treatment due to adverse events (3% with entecavir and 5% with lamivudine) (3).

1. Gish, R.G., Chang, T.T., Hadziyannis, S. et al. *Lamivudine-refractory hepatitis B patients can be safely switched directly to entecavir 1 mg daily therapy*. J Hepatol 2004, 40(Suppl. 1): Abst 428.

2. Schiff, E.R., Chang, T.T., Gish, R.G. et al. *Entecavir 10 mg is consistently superior to lamivudine at 48 weeks across multiple baseline HBV disease characteristics in lamivudine-refractory patients*. J Hepatol 2004, 40(Suppl. 1): Abst 442.

3. Schiff, E.R., Hindes, R., O'Donnell, A. et al. *Summary of phase II clinical and laboratory safety experience with entecavir.* J Hepatol 2003, 38(Suppl. 2): Abst 585.

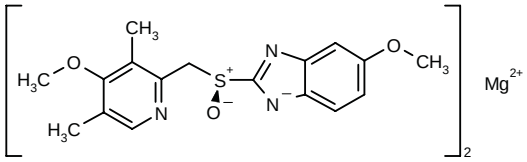
Original monograph – Drugs Fut 1999, 24(11): 1173.

Additional References

Buti, M., Esteban, R. *Entecavir, FTC, L-FMAU, LdT and others*. J Hepatol 2003, 39(Suppl. 1): 139.

Colonno, R. et al. *Absence of entecavir resistance emergence in lamivudine-refractory patients treated for at least one year with entecavir in study A1463-014*. J Hepatol 2004, 40(Suppl. 1): Abst 43.

Esomeprazole Magnesium



AstraZeneca's proton pump inhibitor esomeprazole magnesium (Nexium®) is currently marketed for the treatment of gastroesophageal reflux disease (GERD)/erosive esophagitis. Within the last year, the company has submitted regulatory applications in the U.S., the E.U. and other global markets for the healing of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcers and the prevention of NSAID-associated gastric and duodenal ulcers in patients at risk and in patients requiring continued NSAID therapy. Esomeprazole has been shown to provide more effective acid suppression compared with all other proton pump inhibitors. In clinical trials, it was effective in preventing the development of gastric and duodenal ulcers in long-term users of NSAIDs, including COX-2-selective NSAIDs, who are at risk of ulcer development. It was also effective in healing gastric ulcers in patients who require continuous NSAID treatment, including COX-2 selective NSAIDs (1, 2).

1. *AstraZeneca seeks approval for Nexium in NSAID-associated upper GI symptoms*. DailyDrugNews.com (Daily Essentials) 2003, April 3.

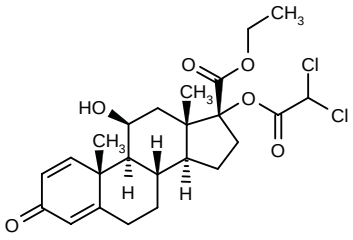
2. *New regulatory submissions for Nexium*. DailyDrugNews.com (Daily Essentials) 2004, Feb 2.

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

ETEC Vaccine

Iomai's ETEC vaccine for travelers' diarrhea is presently in early phase II clinical studies. This vaccine is based on the company's transcutaneous immunization (TCI) technology that effectively stimulates the body's immune system by delivering potent immune stimulants (adjuvants) to the Langerhans cells, a major component of the immune system, at the skin surface using patches.

Etiprednol Dicloacetate



Ivax is testing the soft corticosteroid etiprednol dicloacetate (BNP-166, Cronaze™) in phase II clinical studies as a potential new treatment for Crohn's disease and ulcerative colitis.

Fontolizumab

Two phase II trials of the anti-interferon gamma antibody fontolizumab (HuZAF™) are under way at Protein Design Labs for Crohn's disease. Last year, the company decided not to pursue its development for psoriasis and its plans to concentrate on the development of the antibody as a treatment for Crohn's disease (1).

The company more recently reported encouraging findings from a clinical study of the humanized antibody. The phase II HARMONY II study, a double-blind, randomized, placebo-controlled trial, evaluated an initial intravenous dose of fontolizumab of 4.0 or 10.0 mg/kg, followed by an additional i.v. dose at study day 28. Data from 133 evaluable patients indicated that the antibody was well tolerated and that all adverse events attributed to the drug were mild to moderate. A clinical response was defined as a 100-point drop in the CDAI score. The primary endpoint was the response to the initial dose, evaluated at day 28. At the 4.0 mg/kg dose, 38% of patients achieved a clinical response, while at the 10.0 mg/kg dose, 44% of patients responded. With 33% of placebo patients responding, the trial failed to meet the primary endpoint. Subsequently, 91 patients received a second i.v. dose of fontolizumab or placebo. However, significant differences in response rates compared to placebo were observed at a number of subsequent time points. Of patients receiving the second 4.0 mg/kg dose, 69% of the patients achieved a clinical response at study day 56, a statistically significant improvement compared with placebo. At the higher dose, 67% of the patients responded at day 56, again a statistically significant improvement compared with placebo. In the placebo group, 35% of the patients responded at day 56. The activity of fontolizumab in Crohn's disease suggests that blockade of interferon γ may be a potential therapy for other autoimmune diseases such as rheumatoid arthritis and lupus. In an additional 196-patient phase II study in Crohn's disease (HARMONY I) evaluating lower doses of fontolizumab (1.0 or 4.0 mg/kg), followed by additional

subcutaneous doses, at study day 28 there were no statistical differences in response between either of the fontolizumab treatment groups and the placebo group. This was the primary endpoint in the study. At the lower dose, 39% of the patients achieved a clinical response, and at the higher dose 33% of patients responded. In the placebo group, 38% of the patients responded. Analysis is ongoing (2).

Forty-five patients were enrolled in a double-blind, randomized, placebo-controlled study evaluating fontolizumab in Crohn's disease. Each patient 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 rerandomized to receive placebo or fontolizumab (50% of initial dose.) once every 3 months. The analysis of serum samples collected at different times after administration indicated a 2-compartment pharmacokinetic profile for fontolizumab, with peak plasma concentrations of 1.0-73.3 μg/ml and average elimination half-lives of 9-23 days. Fontolizumab was minimally immunogenic, dose-dependently improved the CDAI scores and reduced the serum levels of interferon gamma-inducible protein 10 (IP-10) of the patients (3).

1. *Protein Design Labs reports Q3 R&D highlights*. Protein Design Labs Press Release 2003, Nov 3.

2. *Protein Design Labs reports clinical data for visilizumab and fontolizumab*. DailyDrugNews.com (Daily Essentials) March 24, 2004.

3. Ding, H., Maia, M., Keller, S. et al. *Fontolizumab (HuZAF™) pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity and exposure/response relationship in patients (pts) with moderate and severe Crohn's disease (CD).* Gastroenterology 2004, 126(4, Suppl. 2): Abst T1302.

GW-597599

An NK_1 antagonist from GlaxoSmithKline, GW-597599 is under evaluation for its potential therapeutic use in several disorders. The company is conducting phase II studies in functional dyspepsia and chemotherapy-induced nausea and vomiting, as well as depression and anxiety.

HCV-086

HCV-086, a hepatitis C antiviral compound under development by ViroPharma and Wyeth, has entered a phase I clinical trial program. Initially, a placebo-controlled study will assess the safety, tolerability and pharmacokinetics of single ascending doses of HCV-086 administered orally to healthy volunteers. A successful outcome will lead to a multiple-dose study in patients with chronic HCV infection to assess the antiviral activity, safety, tolerability and pharmacokinetic profile of HCV-086. Proof-of-concept antiviral data from the second study are expected in the fall of 2004. The companies continue to advance an additional HCV antiviral compound through preclinical testing (1).

1. *Phase I program commences for HCV-086*. DailyDrugNews.com (Daily Essentials) Feb 26, 2004.

Helizide™

The FDA has determined that Axcan's resubmitted NDA for Helizide™ (formerly Helicide™), its single-capsule formulation of metronidazole, tetracycline and colloidal bismuth citrate, continues to be not approvable for the eradication of *H. pylori*. The FDA's decision was based on certain inspection-related issues previously raised for one of the five manufacturing sites, which remain unresolved. Axcan has been working closely with the manufacturer of one of Helizide™'s ingredients, biskalcitrate potassium, but the present financial status of the manufacturer has limited its ability to correct the identified problems. Helizide™ was approved in Canada in the second quarter of fiscal 2003 (1).

1. *Resubmitted NDA for Helicide deemed not approvable*. DailyDrugNews.com (Daily Essentials) Oct 8, 2003.

H. pylori Vaccine

Iomai's proprietary transcutaneous immunization (TCI) technology allows the successful delivery of vaccines and immunostimulants to the skin using patches. This technology combines the safe use of powerful immune stimulants (adjuvants) that target Langerhans cells, an important set of immune cells found in the outermost layer of the skin, resulting in robust immune responses. A TCI-based *H. pylori* vaccine is in phase I clinical development.

Hepatitis B Immune Globulin

Developed for postexposure prevention of hepatitis B infection, Cangene's hepatitis B immune globulin is a hyperimmune product comprised of a highly purified antibody specific for HBV. The product has been submitted for regulatory review in the U.S. and Canada.

Hepatitis B Pharmaccine

Oxxon Pharmaccines' hepatitis B pharmaccine is undergoing phase II trials, following a placebo-controlled,

randomized phase I study in 24 healthy volunteers which found the pharmaccine to be safe and well tolerated when used alone and in combination. The phase II dose-escalation study will carry out a randomized comparison of the immunotherapeutic alone and in combination with lamivudine.

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

Hepatitis B Vaccines

Several companies are investigating new hepatitis B vaccines.

Dynavax's prophylactic hepatitis B vaccine consists of recombinant hepatitis B surface antigen (rHBsAg) combined with the company's potent immunostimulatory DNA sequences (ISS-1018). Unlike conventional vaccines, this candidate appears to require only 2 immunizations over 2 months to achieve protective antibody responses due to the incorporation of ISS-1018. The company intends to commence international phase III clinical trials of the vaccine candidate outside the U.S. this year following the results of phase I and II studies demonstrating good tolerance and the induction of more rapid immunity with fewer injections compared to currently available vaccines. A second phase II trial is also under way in patients not responding to a full course of Engerix-B®.

Corixa's partner GlaxoSmithKline Biologicals filed for regulatory approval of an extrastrength hepatitis B vaccine (Fendrix®) in May of last year with the European Agency for the Evaluation of Medicinal Products (EMEA). This novel vaccine is designed to prevent infection from hepatitis B in high-risk groups such as prehemodialysis and hemodialysis patients. It includes GSK's hepatitis B antigen and Corixa's MPL® (monophosphoryl lipid A) adjuvant. Under their agreement, Corixa has granted GSK exclusive worldwide rights to use the MPL7 adjuvant in vaccines in a number of infectious disease fields, including hepatitis B (1).

Berna Biotech reported in September 2003 that its prophylatic hepatitis B vaccine Supervax had been approved for marketing in Argentina, with launch anticipated for this year. This vaccine was developed based on a hepatitis B antigen produced using the company's *Hanensula polymorpha* expression system and combined with Corixa's synthetic adjuvant RC-529 (2, 3).

Earlier this year, Innogenetics acquired the therapeutic vaccine programs of Genencor, gaining access to a broad technology platform, intellectual property rights, and licenses with respect to therapeutic and prophylactic vaccine applications for hepatitis B virus (HBV), human papillomavirus (HPV) and hepatitis C virus (HCV). Innogenetics will be responsible for the clinical development and worldwide commercialization of all products arising from these programs. The portfolio consists of a clinical vaccine candidate for HBV, a preclinical viral boost candidate for HBV, a research-stage lead compound for HPV and a complementary discovery platform for future HCV vaccine products. The HBV vaccine candidate recently entered a phase I study in the U.S. to investigate its safety and immunogenicity. Innogenetics will take over this trial from Genencor. Innogenetics also acquired exclusive access to a broad portfolio of patented cytotoxic T-lymphocyte (CTL) epitopes, complementary rights (including PADRE technology) and licenses in the fields of HBV, HPV, HCV and associated technologies. These immunotherapeutic tools were developed by Genencor's partner Epimmune and will now be further developed together with Innogenetics. Innogenetics and Epimmune have agreed to collaborate through September 2005. The DNA-based therapeutic vaccine also incorporates a Valentis polymer delivery system, DNAVax™, which was nonexclusively licensed by Genencor in July 2002 on a worldwide basis for DNA-based vaccines to treat or prevent HBV and HPV infections (4-6).

1. *Regulatory approval sought for Fendrix*. DailyDrugNews.com (Daily Essentials) May 15, 2003.

2. *Berna Biotech announces the registration of the hepatitis B vaccine SUPERVAX in Argentina.* Berna Biotech Press Release 2003, Sept 8.

3. *Corixa announces first approval of an infectious disease vaccine containing the company's RC-529™ adjuvant. Berna Bitoech's SUPERVAX approved for sale in Argentina*. Corixa Press Release 2003, Sept 8.

4. *Genencor hepatitis B vaccine to enter phase I this month*. DailyDrugNews.com (Daily Essentials) Feb 4, 2004.

5. *Dosing under way in Genencor's phase I hepatitis B study*. DailyDrugNews.com (Daily Essentials) March 22, 2004.

6. *Innogenetics acquires Genencor's therapeutic vaccine programs*. DailyDrugNews.com (Daily Essentials) April 1, 2004.

Hepatitis C Immune Globulin

Nabi Biopharmaceuticals has reported preliminary results of its phase I/II trial of Civacir™ (hepatitis C immune globulin [human]), an antibody-based therapeutic being developed to prevent HCV reinfection of transplanted livers in patients with chronic hepatitis C. The randomized, controlled, multicenter study was designed to evaluate the safety and pharmacokinetics of 2 dose levels of Civacir™ *versus* a control in 18 patients who underwent liver transplantation due to hepatitis C-induced end-stage liver failure. Civacir™ was well tolerated in both the high- and low-dose treatment arms. The study was not powered to detect significant differences in effect but there was a trend towards a reduction in serum ALT, as well as a trend for lower hepatitis C viral levels in liver tissue 1 month after beginning Civacir™ administration.

The study was sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) (1).

1. *Nabi reports preliminary results from phase I/II Cicavir study*. DailyDrugNews.com (Daily Essentials) Feb 25, 2004.

Hepatitis C Vaccines

Several companies have therapeutic hepatitis C vaccines in the clinic.

Intercell's hepatitis C vaccine proved very promising in phase I clinical trials and was advanced in 2002 to European phase II trials in patients not responding to interferon + ribavirin. The synthetic vaccine is based on 5 HCV peptides and poly-L-arginine, and specifically targets T-cells. Following administration of the vaccine, the stimulated immune system learns to recognize and destroy the 5 peptides.

Innogenetics announced the histological results achieved in 24 hepatitis C patients who were included in an ongoing phase IIa clinical trial and received 4 courses of a hepatitis C virus (HCV) E1-based therapeutic vaccine over 3 years. Compared with baseline, the liver biopsy conducted at 3 years showed significant improvements in liver fibrosis. The Ishak liver fibrosis score of at least 87% of the patients improved or remained stable throughout the study. These results confirmed the findings of a previous interim analysis conducted at 2 years from the beginning of the study, and suggested that the vaccine not only stopped disease progression, but also induced fibrosis regression over the long term and was well tolerated. The results of a large-scale, placebo-controlled phase IIb clinical trial with this vaccine are expected during the second quarter of 2005 (1).

Chiron and CSL are collaborating to develop a therapeutic hepatitis C vaccine comrising Chiron's novel HCV antigens and CSL's proprietary ISCOMATRIX® adjuvant technology. The adjuvant t echnology is based on ISCOM® particles, which provide both adjuvant and antigen delivery properties. The particles comprise Quillaia saponins, cholesterol and phospholipids, and particles without an incorporated or associated antigenare known as ISCOMATRIX®. The vaccine has completed a phase I trial demonstrating good safety and the generation of appropriate immune responses (2). Chiron also has an HCV program in early clinical trials in collaboration with St. Louis University.

1. *Innogenetics reports significantly improved liver fibrosis in hepatitis C patients after 3 years of therapeutic vaccination*. Innogenetics Press Release 2004, March 25.

2. *Chiron advances hepatitis C vaccine development program.* Chiron Corp. Press Release 2004, Jan 14.

Additional References

Nevens, F., Roskams, T., Van Vlierberghe, H. et al. *A pilot study of therapeutic vaccination with envelope protein E1 in 35 patients with chronic hepatitis C*. Hepatology 2003, 38(5): 1289.

Hepatitis E Vaccine

GlaxoSmithKline is developing a hepatitis E vaccine in collaboration with the National Institutes of Health (NIH), Novavax and the Walter Reed Army Institute. The vaccine was invented by investigators at Novavax and the NIH/National Institute of Allergy and Infectious Diseases, and the former SmithKline Beecham was granted a nonexclusive license to the recombinant HEV ORF2 capsid genes for commercial development, manufacturing and marketing of HEV vaccines. The recombinant HEV ORF2 subunit protein vaccine is in phase II clinical development.

HepeX-B™

As part of a review of recent clinical progress and corporate developments, XTL Biopharmaceuticals announced that dosing has commenced in a phase IIb trial with HepeX-B™ (formerly XTL-001) for the prevention of reinfection in hepatitis B patients following liver transplant. The trial will involve 45 patients in the U.S., Europe and Israel. Patients receiving the current first-line preventive treatment, blood-derived polyclonal hepatitis B immune globulin (HBIg) solution together with lamivudine, will be randomized to 3 cohorts, 1 cohort continuing on the standard preventive treatment and 2 receiving different doses of HepeX-B™ plus lamivudine. The study aims to demonstrate that replacement of HBIg with HepeX-B™ in the current prophylaxis protocol in HBV liver transplant patients is effective in preventing HBV reinfection. Patients will be treated for 6 months, with a 12-month follow-on observation period. Primary endpoints will be HBV DNA and HBV antigen levels, while secondary endpoints will be anti-HBV antibody blood levels and the safety of HepeX-B™ compared to the current drug. HepeX-B™ is a combination of 2 fully human monoclonal antibodies acting on the HBV surface antigen. In a recent study, HepeX-B™ maintained serum levels similar to or higher than the current first-line treatment (HBIg), while using 1,000 times less drug. HepeX-B™ holds orphan drug designation from both the FDA and the EMEA for the prevention of hepatitis B intransplant patients (1-3).

The viral dynamics of HepeX-B™ were recently evaluated in 27 patients with chronic HBV infection, 15 of whom received a single infusion of the mixture at doses of 0.26-40 mg and 12 of whom received 4 weekly infusions at doses of 10-80 mg. In 11 patients receiving single infusions at doses below 9 mg, no significant viral decline was seen, whereas the 4 patients receiving higher single doses (30-40 mg) showed a decrease of 1.3-3.2 log cp/ml in HBV DNA at 8 h after infusion. Also, 11 of 12 patients receiving multiple infusions had a significant decline in HBV DNA of 1.5-4.1 log cp/ml at 4 h after each infusion. Viral dynamics modeling indicated that its

efficacy against HBV is mainly due to acceleration of free virus clearance (4).

1. *XTL Biopharmaceuticals reviews recent developments*. DailyDrugNews.com (Daily Essentials) Dec 22, 2003.

2. *XTLbio's HepeX-B receives orphan drug designation from the European Agency for the Evaluation of Medicinal Products (EMEA).* XTL Biopharmaceuticals Ltd. Press Release 2004, March 1.

3. *XTLbio's HepeX-B receives orphan drug designation from the FDA.* XTL Biopharmaceuticals Ltd. Press Release 2003, Aug 4.

4. Neumann, A.U., Feldberg, I., Eren, R., Dagan, S. *Viral dynamics modeling indicates that the major mechanism of action of HepeX-B against hepatitis B virus is acceleration of the free virus clearance*. 54th Annu Meet Am Assoc Study Liver Dis (Oct 24-28, Boston) 2003, Abst 1148.

HepeX-C™

XTL Biopharmaceuticals' anti-HCV therapeutic HepeX-C™ (formerly XTL-002), a fully human high-affinity monoclonal antibody against the HCV envelope protein E2, is in phase II clinical evaluation for preventing HCV reinfection in transplant patients.

Preliminary results have been reported from a 24-patient randomized, placebo-controlled, dose-escalating phase IIa safety study of HepeX-C™. Interim results involved 12 HCV-associated liver transplant patients who received low-dose regimens of HepeX-C™ for 3 months after transplant. The FDA has allowed a higher dosing regimen and studies are now being completed. The continuation of the study in 12 additional patients is designed to determine the minimum dose necessary to achieve antibody excess while demonstrating safety. HepeX-C™ was previously reported to reduce levels of the HCV virus in chronic HCV patients in a phase Ib study (1). Early in May, the phsae IIa study was placed on partial clinical hold by the company, in agreement with the FDA, when a patient suffering complications associated with both HCV and hepatocellular carcinoma did not survive the transplant procedure. Recruitment and dosing in the highest dose cohort have been halted, although patients in all other cohorts will continue to receive drug. No drug-related severe adverse events have been reported to date in other cohorts of liver transplant patients treated with HepeX-C™, and the product has been administered to 40 chronic HCV patients without drug-related severe adverse events (2).

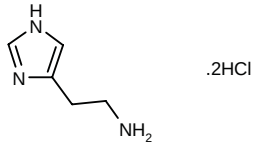
A phase Ia clinical trial that administered single doses of HepeX-C™ (0.25-40 mg i.v.) to 15 patients with chronic HCV infection revealed that HepeX-C™ was well tolerated and effective in reducing HCV RNA levels. In a phase Ib study, 25 patients with chronic HCV infection were treated with HepeX-C™ (10, 20, 40, 80 and 120 mg i.v.) once weekly for 3 weeks, and then 3 times weekly for 1 week. Overall, 72% and 32% of the patients achieved at least 0.75 log and 1 log reductions in their baseline HCV RNA levels, respectively (3).

1. *XTL Biopharmaceuticals reviews recent developments*. DailyDrugNews.com (Daily Essentials) Dec 22, 2003.

2. *XTLbio reports on dose ranging study of HepeX-C in liver transplant patients*. XTL Biopharmaceuticals Press Release 2004, May 10.

3. Dagan, S., Eren, R., Graham, N. et al. *Clinical evaluation of a human monoclonal antibody against the envelope protein (E2) of HCV for prevention of HCV infection.* J Hepatol 2004, 40(Suppl. 1): Abst 65.

Histamine Dihydrochloride



Ceplene™, Maxim's lead drug candidate containing histamine dihydrochloride, was filed for regulatory approval in the E.U. in the first quarter of fiscal 2004, for use in combination with IL-2 in the treatment of patients with advanced malignant melanoma. The product is also undergoing phase III evaluation in acute myeloid leukemia and phase II studies for the treatment of hepatitis C and advanced renal cell carcinoma. Additionally, Maxim is developing an oral formulation of histamine for the potential treatment of chronic liver diseases. A confirmatory phase III trial of Ceplene™/IL-2 is under way in the U.S. in patients with advanced malignant melanoma and is expected to conclude in late 2004. Ceplene™ has been shown to reduce oxidative stress and may therefore prevent the production and release of oxygen free radicals, protecting NK cells and T-cells and facilitating their activation by cytokines such as IL-2, interferon or other immunomodulators and protecting other critical cells and tissues (1-3).

The company has completed a phase Ia pharmacokinetic trial of a new orally dosed histamine dihydrochloride drug candidate, designated HD-O for initial research purposes. The trial, in which 23 normal volunteers received escalating doses of HD-O, evaluated the absorption, pharmacokinetics and maximum tolerated dose. The trial provides the basis for further clinical trials in the treatment of chronic liver diseases, including hepatitis C, alcoholic liver disease (ALD) and nonalcoholic steatohepatitis (NASH). Preclinical research suggests that histamine can protect and promote the healing of the liver in models of ALD, NASH and partial surgical resection (4).

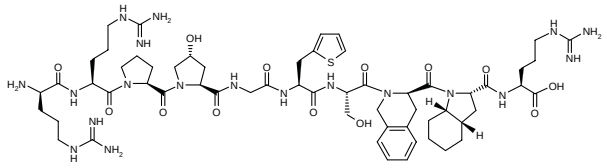
1. *Maxim seeks European approval for Ceplene treatment*. DailyDrugNews.com (Daily Essentials) Nov 11, 2003.

2. *Maxim Pharmaceuticals reports Q1 R&D highlights*. Maxim Pharmaceuticals Press Release 2004, Feb 3.

3. *Approval for treatment protocol for Ceplene plus IL-2 in malignant melanoma*. DailyDrugNews.com (Daily Essentials) April 16, 2004.

4. *Phase I pharmacokinetic trial of orally dosed histamine completed*. DailyDrugNews.com (Daily Essentials) March 24, 2004.

Icatibant



Jerini's selective bradykinin B_2 receptor antagonist icatibant (JE-049) is the first in its class to demonstrate positive results in a phase IIa study in patients with refractory ascites associated with liver cirrhosis. In the randomized, crossover, placebo-controlled trial, patients with decompensation were challenged with a water/sodium load and the capacity of the patients to deal with the increased sodium load was assessed. Icatibant improved all parameters in a statistically significant and clinically relevant manner. Icatibant met all primary endpoints of improved sodium and potassium excretion, urine flow and body weight. Further analysis of other parameters is ongoing. Icatibant, a synthetic decapeptide, has virtually the same affinity for bradykinin receptors as bradykinin itself, and shows good stability after *in vivo* administration. It has been successfully tested in several pharmacological models where elevated bradykinin potentially plays a significant role, such as neuropathic pain, postoperative pain and diseases associated with vascular leakage. In an animal model of liver cirrhosis, icatibant was shown to prevent sodium retention, improve diuresis and correct microvascular leakage. Pivotal registration studies of a subcutaneous formulation are also expected to begin in 2004 in patients with hereditary angioedema, for which the drug has orphan drug designation in the U.S. and the E.U. (1-3).

Jerini has reported positive results from a bioavailability study of icatibant asessing the pharmacokinetics, safety and local tolerability of a subcutaneous formulation in comparison with intravenous infusion. In the randomized study, 24 healthy subjects were treated with an s.c. injection of icatibant. It demonstrated very good bioavailability of about 90% combined with low variability, and the maximum concentration was reached after about 30 min (4).

A randomized, double-blind clinical trial enrolled 8 healthy volunteers and 8 patients with liver cirrhosis (defined as having a Child-Pugh score of 5-8), who were treated with placebo or icatibant (0.15 mg/kg/day i.v. for 3 days). Following intravenous injection of 2 l of a sodium chloride 0.9% solution on day 2 of the study, compared to placebo, icatibant increased sodium excretion, potassium excretion, urine osmolarity and urine flow in liver cirrhosis patients. In healthy subjects, the response to sodium load was similar with icatibant and placebo. Both study treatments were well tolerated (5).

Eighteen healthy male volunteers participated in a double-blind, placebo-controlled clinical trial that evaluated the pharmacodynamics and safety of icatibant (single doses of 0.005-3.2 mg/kg i.v. over 1 and 4 h, 3 doses of 0.5 mg/kg i.v. over 1 h once every 8 h, and a continuous 24-h infusion of 0.15 mg/kg/day). All doses tested completely blocked the effects of an intravenous bradykinin dose selected for reducing blood pressure by 10-15 mmHg and inducing reflex tachycardia. The intensity and duration of the antagonistic effects of icatibant increased with dose, and evidence of competitive inhibition was found. Doses up to 1.6 mg/kg were well tolerated, but the 3.2 mg/kg dose was associated with head/trunk flushing, itching and 1 case of orthostatic hypotension (6).

1. *Icatibant awarded orphan drug status for angioedema*. DailyDrugNews.com (Daily Essentials) Nov 20, 2003.

2. *Positive results for icatibant in treatment of refractory ascites in liver cirrhosis*. DailyDrugNews.com (Daily Essentials) Dec 4, 2003.

3. *Phase II trial confirms icatibant utility in hereditary angioedema*. DailyDrugNews.com (Daily Essentials) Jan 15, 2004.

4. *Subcutaneous icatibant produces positive results in bioavailability study*. DailyDrugNews.com (Daily Essentials) April 16, 2004.

5. Russmann, S., Decosterd, L., Buclin, T. et al. *The bradykinin antagonist icatibant increases electrolyte and water excretion after sodium challenge in patients with liver cirrhosis*. Clin Pharmacol Ther 2004, 75(2): Abst PI-33.

6. Perrin, Y., Nguyen, M.T., Rousso, P. et al. *Pharmacokinetic and pharmacodynamic profile of icatibant*. Clin Pharmacol Ther 2004, 75(2): Abst PII-16.

IDN-6556

The FDA has granted orphan drug designation for the use of IDN-6556 (Idun Pharmaceuticals) to treat patients undergoing liver transplantation and other solid organ transplants. A caspase inhibitor, IDN-6556 is intended to protect liver cells (hepatocytes) from excessive programmed cell death, or apoptosis. Excessive apoptosis has been implicated in many different liver diseases and conditions. Oral IDN-6556 is currently in phase II clinical trials for the treatment of a number of hepatic diseases including hepatitis C treatment failures and fatty liver disease, or nonalcoholic steatohepatitis (NASH). There is also preclinical evidence that the drug will be useful in treating many other diseases of the liver. The company recently initiated a phase II trial of IDN-6556 in patients

undergoing liver transplantation. The study will evaluate whether IDN-6556 can decrease the cellular liver damage that can occur during transport and transplantation. IDN-6556 will be administered to the donor liver during transport to the transplant center, as well as to the liver recipient. The study, which was initiated at the Mayo Clinic, will enroll approximately 100 patients at 12 transplant hospitals (1, 2).

A multicenter, double-blind, randomized, placebo-controlled clinical trial evaluated the effects of IDN-6556 administered once daily (25, 100 and 200 mg p.o.) or twice daily (5, 50 and 100 mg p.o.) for 14 days to 49 patients with chronic hepatitis C or NASH. All IDN-6556 doses significantly reduced the serum levels of ALT and aspartate aminotransferase (AST) of the patients. The greatest ALT reductions were found with 100 mg of IDN-6556 given twice daily, which also normalized the ALT and AST levels of all patients. Most adverse events were mild and transient. The clinical trial is still ongoing and will also determine the effects of IDN-6556 in patients with other liver diseases such as hepatitis B (3, 4).

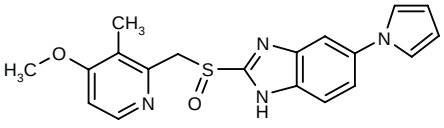
1. *FDA grants orphan drug designation for IDN-6556 in liver transplantation*. DailyDrugNews.com (Daily Essentials) Sept 29, 2003.

2. *IDN-6556 evaluated in liver transplant patients in new phase II trial*. DailyDrugNews.com (Daily Essentials) Oct 10, 2003.

3. Schiff, E.R., Pockros, P., Schiffman, M.L. et al. *Oral IDN-6556, an anti-apoptotic caspase inhibitor, lowers aminotransferases in HCV patients*. J Hepatol 2004, 40(Suppl. 1): Abst 66.

4. 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.

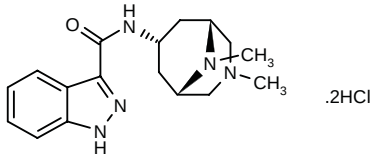
Ilaprazole



The Korean pharmaceutical company Il-Yang continues to study the proton pump inhibitor ilaprazole (IY-81149) in phase II studies for the treatment of GERD.

Original monograph – Drugs Fut 1999, 24(6): 618.

Indisetron Hydrochloride



The antiemetic agent indisetron hydrochloride (N-3389), under joint development by Kyorin and Nisshin Flour Milling, was filed in 2002 with the Japanese regulatory authorities as a treatment for chemotherapy-induced nausea and vomiting. Indisetron acts as a dual antagonist of 5-HT_3 and 5-HT_4 receptors and has proven efficacy against the nausea/vomiting appearing 12-24 h after the administration of anticancer agents.

Original monograph – Drugs Fut 1995, 20(8): 780.

Infliximab

Schering-Plough's infliximab (Remicade®) was approved last fall in the E.U. for maintenance dosing for sustaining clinical response in patients with fistulizing Crohn's disease who have responded to initial infliximab therapy. Approval was based on data from the 1-year ACCENT II trial (A Crohn's disease Clinical trial Evaluating infliximab in a New long-term Treatment regimen in patients with fistulizing Crohn's disease; see below), which demonstrated the ability of infliximab to induce and maintain closure of draining fistulas. In those patients demonstrating benefit after a 3-dose induction regimen, infliximab is now indicated for maintenance treatment every 8 weeks or when signs and symptoms recur. In May, the E.U. approved infliximab for maintenance dosing for the treatment of patients with severe, active Crohn's disease who have responded to initial infliximab therapy. Infliximab is also approved for the treatment of rheumatoid arthritis and ankylosing spondylitis, and studies are under way in a wide range of immune-mediated inflammatory disorders, including early rheumatoid arthritis, psoriatic arthritis and psoriasis. Infliximab is a monoclonal antibody that specifically targets and irreversibly binds to TNF-α. Developed by Johnson & Johnson's Centocor subsidiary, it is marketed by Schering-Plough in all countries outside the U.S., except Japan and parts of the Far East where Tanabe Seiyaku holds marketing rights. Centocor, a wholly owned subsidiary of Johnson & Johnson, has exclusive marketing rights in the U.S. Centocor recently reported that over half a million patients have been treated with infliximab worldwide since it was introduced in the U.S. 5 years ago (1-5). The product is also in late-stage clinical development for the treatment of ulcerative colitis.

The ACCENT II trial was a multicenter, double-blind, randomized, placebo-controlled clinical study that evaluated the benefits of administering infliximab as long-term maintenance therapy to 306 adult patients with Crohn's disease and abdominal or perianal fistulas. At week 14, 195 patients showed a reduction of at least 50% in the number of draining fistulas after receiving infliximab (5 mg/kg i.v. at weeks 0, 2 and 6) and were randomized to receive maintenance therapy with placebo or infliximab (5 mg/kg i.v.) once every 8 weeks for another 40 weeks. Infliximab was associated with a longer median time to loss of response (40 weeks *vs*. 14 weeks), a lower percentage of patients losing response (40% *vs*. 61%), a lower need for changing therapy for Crohn's disease (25% *vs*. 38%) and a lower recrudescence of fistulas

(16% *vs.* 22%) compared with placebo. Another 87 patients who did not respond to open-label infliximab were also randomized to receive long-term therapy with placebo or infliximab; subsequent response was found in 16% of placebo patients and 21% of infliximab patients. Most adverse events reported in both study groups were associated with the gastrointestinal system and similar to those commonly found in patients with Crohn's disease (6).

1. *Remicade approved in E.U. for maintenance dosing in fistulizing Crohn's disease*. DailyDrugNews.com (Daily Essentials) Oct 27, 2003.

2. *Remicade reduces signs and symptoms of anklyosing spondylitis in ASSERT trial*. DailyDrugNews.com (Daily Essentials) Oct 29, 2003.

3. *Remicade sBLA accepted for first-line use in early RA*. DailyDrugNews.com (Daily Essentials) April 8, 2004.

4. *FDA accepts sBLA for Remicade in treatment of ankylosing spondylitis*. DailyDrugNews.com (Daily Essentials) April 21, 2004.

5. *European CPMP recommends broader indication for Remicade in early RA*. DailyDrugNews.com (Daily Essentials) April 28, 2004.

6. Sands, B.E., Anderson, F.H., Bernstein, C.N. et al. *Infliximab maintenance therapy for fistulizing Crohn's disease*. New Engl J Med 2004, 350(9): 876.

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INKP-100

InKine has agreed on the design of a phase II study for a new generation of colon-cleansing tablets with the FDA. The study is expected to begin in the first half of 2004 and will compare InKine's marketed purgative Visicol® (sodium phosphate, INKP-100) tablets against several dosing regimens of the new product in patients undergoing colonoscopy. These regimens will include one similar to the approved regimen for Visicol®, as well as several lower dose regimens, including dosing regimens completed by patients entirely the evening before the colonoscopy procedure. If the phase II study results are supportive, the FDA has said it only requires one pivotal study for approval. The new tablets are smaller and contain no microcrystalline cellulose. They are covered by InKine's provisional U.S. patent application filed late in 2003, which if issued, would provide protection through 2024. Worldwide patent applications will be filed in 2004 (1).

InKine has completed enrollment in its phase IV study using Visicol® tablets as a laxative in patients with constipation. The multicenter, open-label, randomized, dose-ranging trial involves some 40 patients with either chronic functional constipation or constipation-predominant IBS. Patients are treated for up to 28 days, with the last patient scheduled to complete treatment in the first quarter of 2004. Data are expected shortly thereafter (2).

1. *Phase II trial design agreed for InKine's new generation purgative product*. DailyDrugNews.com (Daily Essentials) Jan 19, 2004.

2. *Enrollment complete in phase IV Visicol constipation study*. DailyDrugNews.com (Daily Essentials) March 3, 2004.

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 inteferon 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.

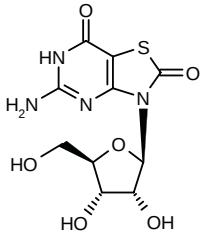
Interferon Beta-1a

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.

Interferon Omega

Interferon omega is a novel genetically engineered biological product for which BioMedicines acquired rights from Boehringer Ingelheim in 1998. Phase I testing has been successfully completed in Germany, demonstrating biological activity, and interferon omega has begun phase II clinical testing in patients with chronic hepatitis C at the Scripps Clinic, as well as at multiple centers in Europe. BioMedicines intends to develop interferon omega for use in both hepatitis B and C and various cancers. The company also has an R&D initiative in collaboration with Alza (Johnson & Johnson) to develop a new multimonth formulation of interferon omega (Omega Duros®) that will be targeted to the liver only, to simplify administration and improve tolerance compared to existing hepatitis therapies.

Isatoribine



Isatoribine (ANA-245) is a patent-protected nucleoside analogue currently entering phase II clinical trials at Anadys in HCV patients.

Interim results from the ongoing open-label, dose-escalating phase Ib trial of isatoribine demonstrate that the drug is safe and well tolerated. Although efficacy is not an objective of the study and the patient population is small, results also showed that isatoribine is biologically active in adults with chronic HCV infection, as indicated by statistically significant changes in biological markers, including levels of 2',5'-oligoadenylate synthetase (OAS). A trend toward a reduction in viral load over the course of treatment was also seen. In the study, isatoribine is administered at doses of 200, 400, 600 and 800 mg i.v. once daily over 7 days to 13 adults with chronic HCV infection in order to determine the safety, tolerability and pharmacokinetics of the drug. The latest data were taken from the first 3 of 4 cohorts, and support previous data generated after single doses in healthy volunteers. Isatoribine is being developed to regulate innate immunity, combat HCV infection and overcome limitations of current therapies. The drug is believed to interact with toll-like receptor 7 (TLR7) (1).

Researchers from Anadys presented new data from this trial during the HEP DART 2003 Meeting on Frontiers in Drug Development for Viral Hepatitis, held in Kauai, Hawaii, in December 2003. The results presented at the meeting corroborate and extend previously disclosed safety, tolerability and pharmacokinetic data. The treatment has been well tolerated by patients in this study, with a low frequency of mild to moderate adverse events and no serious side effects. Reductions in viral load have been observed in all 6 patients treated to date at the highest dose tested. Viral load decreased significantly at the 800-mg dose, with a median change from baseline of -0.94 $\log_{10}$ units. This reduction confirmed the favorable trend seen at lower doses, and was accompanied by changes in biological markers of antiviral immune response, similar to results seen at lower doses (2).

1. *Isatoribine biologically active in HCV patients in phase Ib trial*. DailyDrugNews.com (Daily Essentials) Dec 10, 2003.

2. *HEP DART 2003 meeting highlights: Phase Ib data presented for isatoribine*. DailyDrugNews.com (Daily Essentials) Jan 5, 2004.

ISIS-14803

20-Mer antisense phosphorothioate oligodeoxynucleotide whose sequence is:
5'-GTGCmTCmATGGTGCmACmGGTCmT-3' where Cm represents 5-methylcytidine

ISIS-14803, an antisense oligonucleotide targeting HCV RNA and protein expression designed by Isis Pharmaceuticals, is in phase II testing for HCV infection. Following the promising results of a phase II trial in HCV patients who had failed previous therapy and were treated with ISIS-14803 as a single agent, an ongoing phase II study in combination with standard therapy was initiated, with results expected in the second half of 2004 (1, 2).

A recent phase II clinical trial evaluated the safety and efficacy of ISIS-14803 (initial dose of 2.5 mg/kg i.v. 3 times weekly for 2 weeks, increased to higher doses once or twice weekly for 10 weeks) in 43 noncirrhotic chronic HCV patients, most of whom had genotype 1 HCV and had failed interferon therapy. Significant reductions in the HCV viral load were found in some patients treated with 6 mg of ISIS-14803 once or twice weekly; these

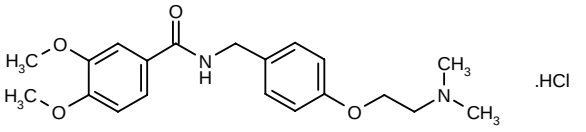
reductions were associated with transient increases in the levels of ALT in plasma. Other common adverse events were mild to moderate headache, fever, chills, fatigue, nausea and myalgia. Only 2 serious adverse events were considered to be related to ISIS-14803. The use of a 6 mg/kg i.v. dose twice weekly was recommended in future clinical trials on ISIS-14803 in the treatment of chronic hepatitis C (3).

1. *R&D highlights from the Rodman & Renshaw Techvest Healthcare Conference: Isis Pharmaceuticals*. DailyDrugNews.com (Daily Essentials) Nov 24, 2003.

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

3. Gordon, S.C., Bacon, B.R., Jacobson, I.M. et al. *Treatment of chronic hepatitis C with ISIS 14803, an antisense inhibitor of HCV, given for 12 weeks*. 54th Annu Meet Am Assoc Study Liver Dis (Oct 24-28, Boston) 2003, Abst 312.

Itopride Hydrochloride



Axcan has reported results from a phase II study of itopride hydrochloride (Itax™). The double-blind, placebo-controlled, dose-response study was designed to confirm the safety and efficacy of itopride in a Caucasian population and to identify the appropriate dose for use in pivotal phase III studies. Doses of 50, 100 and 200 mg of itopride administered 3 times a day were compared to placebo. The study involved 554 patients with functional nonulcer dyspepsia or functional dyspepsia, 424 of whom were included in the study analysis. 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. 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. The pain and fullness response 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. The cardiac safety of itopride was shown by resting 12-lead standard electrocardiograms recorded at 4 and 8 weeks after initiation of treatment. Results confirmed that no cardiac side effects occurred and that there was no significant Q-T prolongation in patients treated with itopride. The phase II results confirm data from a postmarketing study in some 5,000 Japanese patients who received the drug following the 1995 launch of itopride in Japan (Ganaton®; comarketed by Fujisawa). Itax™, a patented oral gastroprokinetic drug with antiemetic properties, was recently acquired by Axcan from Abbott. The drug is indicated for the treatment of gastrointestinal symptoms caused by reduced gastrointestinal motility (1, 2).

At a pre-IND meeting for itopride, the FDA endorsed Axcan's proposal to conduct 2 pivotal, double-blind, placebo-controlled phase III studies to demonstrate the safety and efficacy of itopride in the treatment of functional dyspepsia. The FDA agreed that no additional phase II studies were required. Axcan plans to commence the phase III studies in the second half of fiscal 2004 after filing an IND application. An NDA for the treatment of functional dyspepsia is anticipated for the latter part of 2005. Axcan plans to conduct 2 phase III studies testing the efficacy of itopride 100-mg tablets in the treatment of functional dyspepsia in a total of 600 patients. The primary endpoint will be the assessment of abdominal symptom relief, while the secondary endpoint will consist of changes in the clinical condition of patients. Axcan 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 observed in the phase I and II studies (3).

Patients with symptoms of gastroesophageal reflux disease, total acid exposure time > 5% at baseline and mild esophagitis were included in an open-label clinical trial evaluating the effects of itopride on esophageal acid exposure. The 26 patients were randomized to receive 150 or 300 mg of the drug t.i.d. for 30 days. Both dose levels were effective in reducing the total symptom scores of the patients, although the greatest improvements were found with the 300-mg dose. No serious adverse events were reported during the study (4).

1. *Phase II results for Itax confirm earlier safety and efficacy findings*. DailyDrugNews.com (Daily Essentials) Dec 17, 2003.

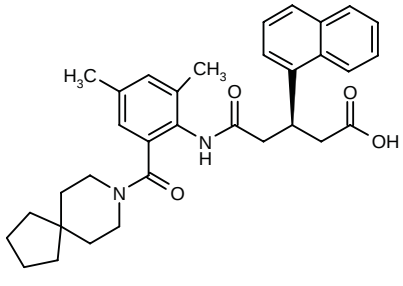
2. *Axcan Pharma reports Q1 R&D highlights*. Axcan Pharma Press Release 2004, Feb 5.

3. *Successful pre-IND meeting for Itax leads to phase III studies*. DailyDrugNews.com (Daily Essentials) Jan 27, 2004.

4. Choi, S., Yeom, J., Kim, Y. et al. *The effect of itopride, a new prokinetic, on acid reflux symptoms and variables in patients with GERD*. 11th United Eur Gastroenterol Week (Nov 1-5, Madrid) 2003, Abst TUE-G-050.

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

Itriglumide



The gastric antisecretory agent itriglumide (CR-2945) is in phase I clinical studies at Rotta as a potential new

drug for the treatment of gastric ulcer and GERD. The compound acts by antagonizing cholecystokinin CCK_2 receptors.

Original monograph – Drugs Fut 1999, 24(5): 483.

JTK-003/JTK-109

A hepatitis C virus (HCV) RNA polymerase inhibitor, oral JTK-003 is being tested by Japan Tobacco in phase II trials in Japan and phase I trials overseas as a potential new therapy for HCV-infected patients. Another HCV RNA polymerase inhibitor, JTK-109, was discontinued last year after it had reached phase I clinical trials in Japan and overseas.

Kappaproct®

The first RNA-blocking drug from InDex Pharmaceuticals, Kappaproct®, has advanced to phase II trials in patients with active ulcerative colitis. An antisense inhibitor of the p65 protein, it was recently licensed to Serono on an exclusive worldwide basis for the treatment of ulcerative colitis and potentially other inflammatory diseases. In an earlier proof-of-concept study in patients with therapy-resistant inflammatory bowel disease, the majority of patients responded positively to a single dose of Kappaproct® (1).

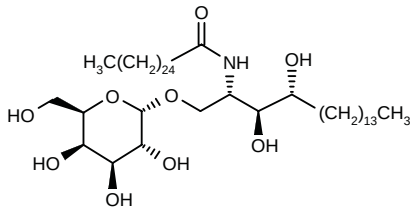
1. *Serono receives rights to InDex's Kappaproct.* DailyDrugNews.com (Daily Essentials) 2004, Feb 27.

KPE-02003002

Kemin Pharma has developed a molecule with apparent biological effects against the hepatitis C virus (HCV). KPE-02003002, a synthetic derivative of a phytochemical with several chiral centers, was discovered in October 2002 through Kemin's collaborative effort with the National Institutes of Health (NIH) and the Rega Institute for Medical Research, Belgium. The molecule showed very good biological activity against HCV in several *in vitro* screening assays. In December 2003, KPE-02003002 completed a first phase II trial, in which the majority of patients were infected with HCV genotype 1 and had not previously responded to treatment with pegylated interferon and ribavirin. Encouraging results led to a second phase II trial in the first quarter of 2004 (1).

1. *Kemin Pharma develops two new molecules for HCV*. DailyDrugNews.com (Daily Essentials) Jan 15, 2004.

KRN-7000

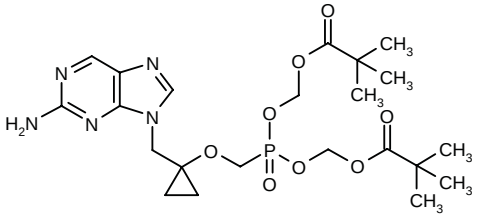


Kirin Brewery reported recently that its immunostimulant KRN-7000 (AGL-582, α-galactosylceramide), under development for the treatment of cancer and hepatitis C, is also now being developed for the treatment of hepatitis B. In Europe, the product is in phase I/II clinical trials for the treatment of hepatitis B and C, and in phase I for cancer (1).

1. *Kirin announces phase I clinical trial of KRN-125 and other recent developments*. DailyDrugNews.com (Daily Essentials) March 3, 2004.

Original monograph – Drugs Fut 1996, 21(2): 152.

LB-80380

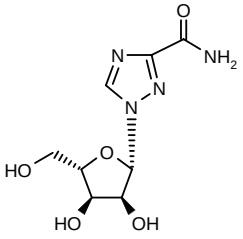


The nucleotide analogue LB-80380, the orally active double prodrug of LB-80317, is currently in phase II clinical development at Anadys in conjunction with LG Life Sciences as a potential new therapy for hepatitis B virus (HBV) infection. The analogue has exhibited *in vitro* activity against virus typically found in untreated patients, as well as HBV variants resistant to lamivudine. In phase I studies in healthy volunteers, it was shown to be safe and well tolerated, and pharmacokinetic data indicated the feasibility of once-daily dosing. Anadys's license covers the development and marketing of the product for chronic HBV infection in North America, Europe, Japan and most other countries, other than China, Korea, India and countries in Southeast Asia.

Twenty-eight patients infected with HBV were included in a dose-finding, placebo-controlled clinical trial that determined the antiviral effects and the safety of LB-80380. Each patient received placebo or escalating doses of LB-80380 (30, 60, 120 and 240 mg) daily for 4 weeks. Effective reduction of HBV DNA levels was detected at doses of 60 mg/day or more. No serious adverse events were found (1).

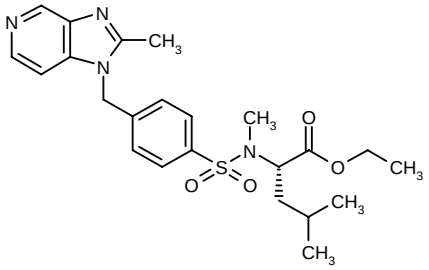
1. Yuen, M.F., Kim, J., Wong, D.K.H., Ngai, V.W.S., Yuen, J.C.H., Lai, C.L. *Interim report on a phase I/IIA, double-blind, randomized, placebo-controlled trial of a novel antiviral agent, LB80380 in Chinese patients with chronic hepatitis B infection*. J Hepatol 2004, 40(Suppl. 1): Abst 450.

Levovirin



Levovirin, the L-enantiomer of ribavirin, was licensed by Roche from the former ICN, now Valeant, in 2001 as a promising agent for hepatitis C. The compound had reached phase I trials before Roche decided last year to abandon development.

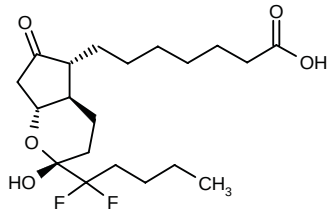
Lexipafant



The virtual pharmaceutical company DevCo has successfully completed a confirmatory safety clinical trial of lexipafant in 24 subjects in the U.K. In the double-blind, placebo-controlled, safety, tolerability, pharmacokinetic and pharmacodynamic study, subjects tolerated intravenous infusions of 400 and 800 mg per 24 h over 72 h. The pharmacokinetics were dose-proportional and the plasma levels achieved resulted in 70% inhibition of platelet-activating factor (PAF)-activated neutrophil function during the entire infusion period. Protocols and clinical trial material are ready for an immediate start of phase III. Lexipafant is under late-stage development for protection from organ dysfunction associated with coronary artery bypass graft (CABG), the treatment of HIV-associated cognitive/motor dysfunction and as a treatment for patients with acute pancreatitis. The highly potent and selective PAF antagonist has been developed for both intravenous and oral administration. DevCo has engaged The Sage Group to search for development and marketing alliances for lexipafant. Originally discovered by British Biotech (now Vernalis), it has since been investigated by GlaxoSmithKline (then Glaxo Wellcome) as an oral drug to treat asthma and by Vernalis as an intravenous treatment for acute pancreatitis (1).

1. *DevCo completes lexipafant safety study, seeks commercialization partner*. DailyDrugNews.com (Daily Essentials) March 17, 2004.

Lubiprostone



Lubiprostone (SPI-0211, RU-0211) activates specific chloride channels on cells lining the gut, thereby naturally increasing intestinal fluid secretion. The increased fluid level softens the stool, facilitates intestinal motility and promotes spontaneous bowel movements Sucampo is developing lubiprostone for various bowel dysfunctions, including constipation (phase III), constipation-predominant IBS (phase II), postoperative ileus (phase II) and opioid-induced bowel dysfunction (phase I/II).

The clinical efficacy of lubiprostone was evaluated in a randomized withdrawal trial involving administration at a dose of 24 μg b.i.d. 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 drug-related serious adverse events were reported (1).

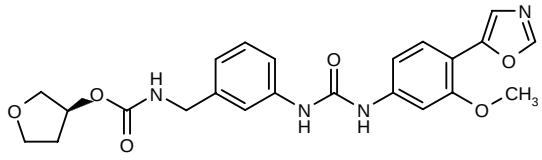
1. Johanson, J.F. et al. *Phase III, randomized withdrawal study of RU-0211, a novel chloride channel activator for the treatment of constipation.* Gastroenterology 2004, 126(4, Suppl. 2): Abst 749.

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

ME-3738

The hepatoprotective agent ME-3738 (Meiji Seika) is in phase II clinical evaluation for its potential in the treatment of liver diseases. The compound appears to act via an IL-6-dependent mechanism.

Merimepodib



Merimepodib (VX-497), Vertex's lead product candidate for the treatment of HCV infection, is a small-molecule, orally administered inhibitor of the enzyme IMP dehydrogenase (IMPDH), inhibition of which leads to a reduction in intracellular guanosine triphosphate (GTP). Recent reports in the medical literature suggest that IMPDH inhibitors such as merimepodib may enhance the antiviral activity of ribavirin *in vitro* by depleting GTP and increasing the rate of incorporation of ribavirin into viral RNA, rendering the virus nonfunctional. The product has successfully completed phase II studies and the first pivotal trial is expected to begin soon; preparations are also under way to meet with the FDA to discuss study results and the company's development plan. Vertex believes that merimepodib holds promise as an adjunctive therapy for HCV patients who have failed a previous course of combination therapy and thus have very limited treatment options (1).

Vertex reported encouraging results from a 6-month interim analysis of a phase II trial with merimepodib for the treatment of HCV infection. The double-blind, placebo-controlled, randomized, 31-patient study was designed to evaluate the safety, tolerability and clinical activity of merimepodib (25 or 50 mg b.i.d.) administered in combination with pegylated interferon (peginterferon) and ribavirin in patients with HCV genotype 1 who were nonresponsive to treatment with a previous course of interferon and ribavirin. At 6 months, merimepodib met its primary endpoint of safety and tolerability, as well as its secondary endpoint of clinical activity, demonstrating a statistically significant antiviral response in combination with pegylated interferon and ribavirin. At 24 weeks, 86% of patients treated with the 50-mg dose of merimepodib had undetectable levels of HCV RNA, as compared to 33% of those receiving 25 mg merimepodib and 33% of those treated with placebo. The European study enrolled patients who had previously received a minimum of 12 weeks of interferon and ribavirin treatment without achieving undetectable viral RNA (vRNA). After the initial 6 months of the trial, patients had the option to extend treatment for an additional 6 months. In a previous 28-day phase II study in treatment-naïve HCV patients, viral load data showed a trend toward enhanced antiviral activity in patients treated with merimepodib combined with interferon alfa as compared to patients receiving interferon alone. In another 28-day phase II study of merimepodib administered as monotherapy to HCV patients who were nonresponsive to prior treatment with interferon alfa, merimepodib appeared to reduce levels of serum ALT (2, 3).

1. *Vertex reports Q3 financial results and product pipeline update*. DailyDrugNews.com (Daily Essentials) Nov 12, 2003.

2. *Encouraging six-month results from phase II study of merimepodib in HCV*. DailyDrugNews.com (Daily Essentials) Oct 21, 2003.

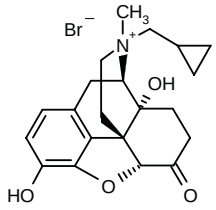
3. *Merimepodib enhances the anti-HCV activity of PEG-IFN and ribavirin*. DailyDrugNews.com (Daily Essentials) Jan 5, 2004.

Original monograph – Drugs Fut 2000, 25(8): 809.

Additional References

Marcellin, P. et al. *A phase II, placebo-controlled study of merimepodib (XV-497), in combination with pegylated interferon-alfa, and ribavirin in patients with chronic hepatitis C non-responsive to previous therapy with interferon-alfa and ribavirin*. J Hepatol 2004, 40(Suppl. 1): Abst 492.

Methylnaltrexone Bromide



Progenics has begun dosing in a double-blind, randomized, placebo-controlled phase I study of a new oral tablet formulation of methylnaltrexone (MNTX) bromide, designed to treat the debilitating side effects of opioid pain therapy and to prevent or reverse postoperative ileus. The study in 35 healthy volunteers is designed to further characterize the tolerability and pharmacokinetics of oral MNTX at 3 dose levels. Phase II studies of oral MNTX are expected to begin in 2004 in chronic pain patients who experience opioid-induced constipation. In addition to this program for oral MNTX, two other clinical programs are ongoing for different dosage formats of MNTX. Subcutaneous MNTX is the subject of a phase III trial in opioid-induced constipation in advanced medical illness (AMI) at 20 hospice centers. Enrollment is scheduled for completion in early 2004, and a second phase III study in AMI was subsequently initiated. The double-blind, randomized, placebo-controlled study will measure the ability of MNTX to induce laxation within 4 h in patients with AMI and opioid-induced constipation. The ability of MNTX to restore patients to a normal bowel schedule of 3 or more laxations per week will also be monitored. Patients will receive MNTX every other day for 2 weeks at sites in the U.S. and Canada. A 3-month open-label extension study will then follow. Phase II results showed that subcutaneous MNTX induced laxation in approximately 60% of patients in a median time of 1 h, and restored AMI patients to normal bowel status of greater than 3 bowel movements per week. Simultaneously, intravenous MNTX is being studied in a phase II trial for the treatment of postoperative ileus. The study,

in 60 colectomy patients, is scheduled for completion in the first half of 2004 (1, 2).

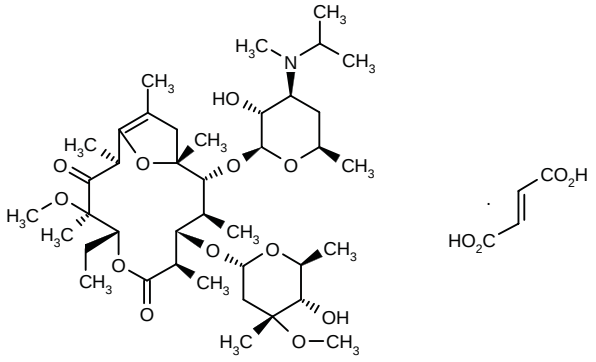
1. *Phase I study of oral methylnaltrexone commences dosing*. DailyDrugNews.com (Daily Essentials) Nov 25, 2003.

2. *Second pivotal trial of methylnaltrexone for opioid-induced constipation*. DailyDrugNews.com (Daily Essentials) Jan 15, 2004.

Additional References

Thomas, J., Portenoy, R., Moehl, M., Von Gunten, C., Thielemann, P., Stambler, N., Tran, D., Galasso, F., Israel, R. *A phase II randomized dose-finding trial of methylnaltrexone for the relief of opioid-induced constipation in hospice patients*. Proc Am Soc Clin Oncol 2003, 22: Abst 2933.

Mitemcinal Fumarate



The gastroprokinetic motilin agonist mitemcinal fumarate (GM-611; Chugai) has completed phase I clinical trials in Japan and is in phase II trials in the U.S. for diabetic/idiopathic gastroparesis.

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

MIV-210 (204937)

Medivir's nucleoside reverse transcriptase inhibitor (NRTI) MIV-210 (known as 204937 at GlaxoSmithKline) is currently in phase I clinical development as a potential therapy for HIV and hepatitis B virus (HBV). The global licensing agreement between Medivir and GSK is primarily focusing on its development for HIV. MIV-210 is a prodrug of the nucleoside analogue FLG (3'-fluoro-2',3'-dideoxyguanosine). Under their licensing agreement, GSK is responsible for development and has exclusive worldwide marketing rights, except for the Nordic countries where Medivir has retained rights (1, 2).

1. *MIV-210 effective in vitro against resistant viruses*. DailyDrugNews.com (Daily Essentials) Dec 11, 2003.

2. *Medivir interim report 1 January B 31 March 2004*. Medivir Press Release 2004, April 22.

MLN-02

MLN-02 (formerly LDP-02), a humanized monoclonal antibody that binds specifically to the T-cell integrin $\alpha_4\beta_7$ and blocks the recruitment of lymphocytes in the gut, has been tested in phase II clinical trials in Crohn's disease and ulcerative colitis. Following a review of the phase II results for ulcerative colitis, Genentech and Millennium have decided not to pursue a phase III study with MLN-02 at this time. The companies are currently in discussions regarding the next steps for the MLN-02 program (1).

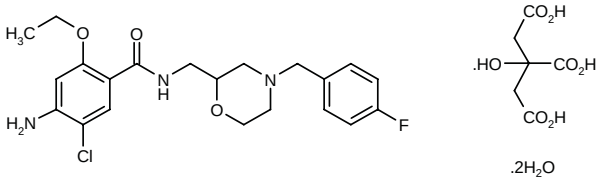
A clinical trial randomized 181 patients with moderately active ulcerative colitis to receive placebo or MLN-02 (0.5 or 2.0 mg/kg) intravenously on days 1 and 29 after randomization. At 43 days, the remission rates were 15% with placebo, 33% with the 0.5 mg/kg dose and 34% with the 2.0 mg/kg dose. The percentage of patients in each group who showed a reduction of 3 or more points in their Ulcerative Colitis Clinical Score was, respectively, 33%, 66% and 57%. Most serious adverse events were associated with ulcerative colitis and were slightly more common with MLN-02 than placebo (8% *vs.* 5%) (2, 3).

1. *2003 Third quarter report*. Genentech Press Release 2003, Oct 20.

2. Feagan, B.G., Greenberg, G., Wild, G. et al. *A randomized controlled trial of a humanized $\alpha_4\beta_7$ antibody in ulcerative colitis (UC)*. 11th United Eur Gastroenterol Week (Nov 1-5, Madrid) 2003, Abst OP-G-17.

3. Feagan, B., Greenberg, G., Wild, G. et al. *A randomized controlled trial of a humanized $\alpha_4\beta_7$ antibody in ulcerative colitis (UC)*. 68th Annu Sci Meet Am Coll Gastroenterol (Oct 13-15, Baltimore) 2003, Abst 9.

Mosapride Citrate

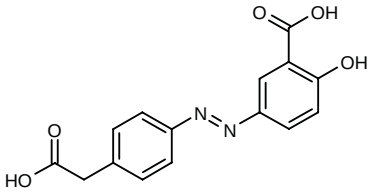


Dainippon's prokinetic 5-HT_4 receptor agonist mosapride citrate (Gasmotin®) was first introduced in Japan in 1998 for the treatment of GERD and subsequently in China and Korea by licensees. Takeda, the licensee for markets outside Asia, is conducting phase II trials in the U.S. (TAK-370). Dainippon is also developing

mosapride for use in postgastrectomy syndrome and phase II trials are under way in Japan.

Original monograph – Drugs Fut 1993, 18(6): 513.

NAA-004



Currently in phase I/II trials at Nobex, NAA-004 (APAZA™) is a dual-acting drug for the treatment of IBD, *i.e.*, Crohn's disease and ulcerative colitis. This novel compound is designed to target the lower gastrointestinal tract and combines antiinflammatory and immunomodulating properties. NAA-004 is comprised of 5-aminosalicylic acid (5-ASA, mesalamine) and an immunomodulator, 4-aminophenylacetic acid (4-APAA), limiting the absorption of the drug across the stomach and small intestine and focusing delivery on the target area of the colon. Upon reaching the colon, bacteria cleave the azo bond, thereby releasing the two active compounds, to act locally to reduce inflammation in ulcerative colitis and Crohn's disease limited to the colon.

The first phase I trial of NAA-004, assessing the tolerance, safety and pharmacokinetics of the drug and its metabolites in 16 healthy volunteers has been completed. The randomized, single-blind, placebo-controlled, dose-escalating study assessed 4 dose levels (0.5-4 g). In each dose group, 3 subjects were given the active drug and 1 subject was given a placebo. NAA-004 was safe at the doses studied. There was evidence of minimal absorption into the body of the intact molecule, with the chemical bond between the two drugs being broken in the colon, thereby releasing each drug. Blood and urine levels of the antiinflammatory and the immunomodulator and their metabolites were low. NAA-004 is expected to enter phase II trials in IBD patients in 2004. Nobex is seeking commercialization partners (1).

1. *APAZA completes first phase I trial*. DailyDrugNews.com (Daily Essentials) Oct 3, 2003.

Natalizumab

Elan and Biogen Idec are collaborating on the development, manufacturing and marketing of natalizumab (Antegren®), a humanized monoclonal antibody with a novel mechanism of action. It is the first α_4 antagonist in the new selective adhesion molecule (SAM) inhibitor class and is designed to selectively prevent immune cells from leaving the bloodstream and prevent them from migrating into tissue where they may cause or maintain inflammation. Natalizumab is in phase III trials for multiple sclerosis and Crohn's disease, and phase II trials in rheumatoid arthritis are scheduled to commenced in the first half of this year. The companies anticipate filing for regulatory approval in the U.S. and Europe for the treatment of multiple sclerosis around mid-year (1-4).

Positive data were reported last year from a phase III trial of natalizumab in the treatment of Crohn's disease, where statistical significance was reached in the primary endpoint of maintenance of response following 6 months' treatment. At the beginning of this year, Elan and Biogen Idec announced results from a second Crohn's disease study. In this study, the primary endpoint of maintenance of response, as defined by a sustained CDAI score of < 220 and no use of rescue intervention throughout 6 months of the study, was met. The companies plan to initiate an additional phase III study of natalizumab in Crohn's disease in 2004 (5).

ENACT-1 (Evaluation of Natalizumab as Continuous Therapy) was a multicenter, double-blind, randomized, placebo-controlled phase III clinical trial that evaluated the efficacy and safety of natalizumab as a novel therapeutic option for Crohn's disease. A total of 905 adult patients with active disease (defined as a CDAI of 220-450) were randomized to receive 3 i.v. infusions of placebo or natalizumab (300 mg) once every 4 weeks. The drug was significantly more effective than placebo in reducing the baseline CDAI scores of the patients, even in those receiving concomitant treatment with immunosuppressants or anti-TNF drugs, or in patients showing active inflammation at baseline. Clinical response was defined as a reduction of at least 70 points in the CDAI score, and clinical remission was defined as a reduction of > 150 points in the CDAI score, both measured at 10 weeks after the first dose. Natalizumab was associated with a greater clinical response rate (54.3% *vs.* 34.8%) and clinical remission rate (33.3% *vs.* 21.7%) in patients previously treated with anti-TNF-α therapy. Patients treated with anti-TNF-α therapy who also showed evidence of active inflammation achieved a clinical response rate of 53.6% (30.9% with placebo) and a clinical remission rate of 35.5% (20.0% with placebo) (6). A large placebo effect was found, however, and the percentages of patients showing clinical response and remission at 12 weeks were, respectively, 62% and 40% with natalizumab and 53% and 31% with placebo. The drug was well tolerated, and no patients suffered from opportunistic infections or lymphomas during the study. The most common events were headache, nausea and abdominal pain, and the rates of infusion reactions and development of antibodies against natalizumab were low (7, 8). The mean total circulating lymphocyte count of patients given natalizumab increased from 1690 cells/mm^3 at baseline to 2857 cells/mm^3 at week 10, but returned to baseline values within 12 weeks after the last dose. These effects were correlated with significant reductions in the serum levels of C-reactive protein, a marker of inflammation,

suggesting that natalizumab effectively inhibited leukocyte migration into surrounding tissues and suppressed active inflammation in Crohn's disease (9). A subanalysis conducted in 53 patients included in the ENACT-1 study determined the effects of natalizumab on gut healing. Colonoscopies performed at week 10 revealed that the baseline Crohn's Disease Endoscopic Index of Severity (CDEIS) score of the patients decreased by 50% with natalizumab and by 7% with placebo. The percentage of patients with ulcers at baseline who were ulcer-free at week 10 was 22% with natalizumab and 8% with placebo. These improvements were correlated with greater rates of histological remission (80% *vs.* 57%) and histological healing (64% *vs.* 29%) with natalizumab compared to placebo (10). The histochemical analysis of colonoscopy biopsy samples from 40 patients showed that the number of mononuclear cells within the colonic lamina propria decreased by 60% from baseline with natalizumab and by 30% with placebo. Reductions of at least 50% in the number of macrophages, T-cells and B-cells were more common among natalizumab-treated patients than among placebo-treated patients (11).

ENACT-2, a multicenter, double-blind, randomized, placebo-controlled phase III clinical trial, also determined the efficacy of natalizumab in Crohn's disease. A total of 428 patients who had been included in the previous ENACT-1 trial and had responded to treatment were randomized to receive placebo or natalizumab (300 mg) once monthly for 12 months. An interim analysis conducted after 6 months of treatment confirmed that natalizumab was more effective than placebo in maintaining response, defined as a CDAI lower than 220 and no need for rescue medication. Natalizumab was also well tolerated, and the most common adverse events were headache, nausea and abdominal pain (12).

The good safety profile of natalizumab was confirmed by the results of a randomized, double-blind, placebo-controlled phase II clinical trial. A total of 79 adult patients with active Crohn's disease previously treated with infliximab were given 3 infusions of natalizumab (300 mg i.v. once every 4 weeks) or placebo combined with 2 infusions of their baseline infliximab therapy (5 mg/kg i.v. every 8 weeks). At the end of the study, no significant differences were found between the incidence of adverse events and serious adverse events in each study group. The lack of serious infusion reactions and the low incidence of serious adverse events and patients developing anti-natalizumab antibodies were consistent with the safety results of the ENACT-1 study (13).

Data from 2 multicenter, double-blind, randomized, placebo-controlled clinical trials were used to compare the pharmacokinetics and pharmacodynamics of natalizumab administered as a fixed dose (300 mg i.v. once every 4 weeks) or as a weight-dependent dose (3 or 6 mg/kg i.v. once every 4 weeks) in patients with moderately or severely active Crohn's disease. Pharmacokinetic parameters increased with dose and were only weakly related to body weight. The levels of α_4 integrin receptor saturation achieved with each natalizumab regimen were similar, and the CDAI scores of the patients decreased by 182, 191 and 196 points after receiving 3 mg/kg, 6 mg/kg and 300 mg of natalizumab, respectively, for 8 weeks. The authors concluded that these results supported the use of a fixed i.v. dose of 300 mg once every 4 weeks in Crohn's disease (14).

A method has been claimed for the long-term alleviation of pathological inflammation, comprising the chronic administration of a pharmaceutical composition containing a compound with selective inhibitory affinity for α_4 integrin or an integrin dimer comprising α_4 integrin, such as $\alpha_4\beta_1$ or $\alpha_4\beta_7$, both implicated in the inflammatory responses associated with IBD and multiple sclerosis, among others. Candidate agents include the anti-CD49d (VLA-4) humanized monoclonal antibody natalizumab (15).

1. *Idec and Biogen complete merger*. DailyDrugNews.com (Daily Essentials) Nov 17, 2003.

2. *IND filing to study Antegren for rheumatoid arthritis*. DailyDrugNews.com (Daily Essentials) Feb 6, 2004.

3. *Mid-year BLA filing planned for Antegren in MS*. DailyDrugNews.com (Daily Essentials) Feb 20, 2004.

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

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

6. Sandborn, W.J., Colombel, J.-F., Enns, R. et al. *Efficacy assessment of natalizumab in patients with Crohn's disease and prior history of anti-TNF therapy: Results from ENACT-2.* Gastroenterology 2004, 126(4, Suppl. 2): Abst 583.

7. Rutgeerts, P., Colombel, J., Enns, R. et al. *Subanalyses from a phase 3 study on the evaluation of natalizumab in active Crohn's disease therapy-1 (ENACT-1)*. 11th United Eur Gastroenterol Week (Nov 1-5, Madrid) 2003, Abst OP-G-297.

8. Enns, R., Colombel, J.-F., Feagan, B. et al. *Safety, tolerability and immunogenicity of natalizumab in a phase III study of active Crohn's disease therapy (ENACT-1).* Gastroenterology 2004, 126(4, Suppl. 2): Abst T1287.

9. Lawrance, I., Colombel, J.-F., Enns, R. et al. *Pharmacodynamic effects from a phase 3 study evaluating natalizumab therapy in Crohn's disease (ENACT-1).* Gastroenterology 2004, 126(4, Suppl. 2): Abst S1403.

10. Rutgeerts, P., Allison, M.C., Cortot, A. et al. *Effects of natalizumab on gut healing in a phase 3 study of active Crohn's disease therapy (ENACT-1).* Gastroenterology 2004, 126(4, Suppl. 2): Abst S1387.

11. Gehoes, K., Allison, M.C., Cortot, A. et al. *Natalizumab decreases inflammatory cells within the colonic lamina propria of patients with active Crohn's disease. Results from ENACT-1.* Gastroenterology 2004, 126(4, Suppl. 2): Abst S1415.

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

13. Sands, B.E., Kozarek, R.A., Spainhour, J. et al. *Safety and tolerability of natalizumab in patients concurrently receiving*

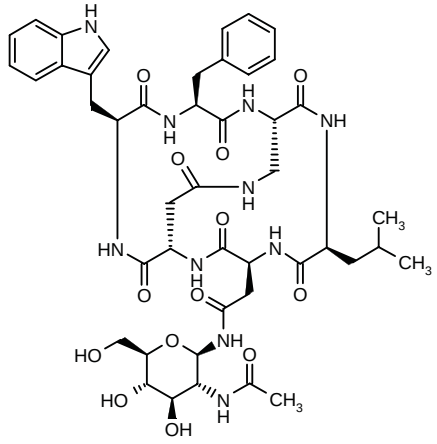
infliximab in a phase 2 study of active Crohn's disease. Gastroenterology 2004, 126(4, Suppl. 2): Abst T1292.

14. Panaccione, R., Colombel, J.-F., Enns, R. et al. *Comparability of natalizumab pharmacokinetics (PK), α_4-integrin receptor saturation and clinical response in patients with Crohn's disease (CD) treated once monthly iv witheither a fixed dose of 300 mg (ENACT-1) or doses of 3 or 6 mg/kg.* Gastroenterology 2004, 126(4, Suppl. 2): Abst 584.

15. Taylor, J. and Yednock, T.A. (Elan Pharmaceuticals, Inc.). *Administration of agents for the treatment of inflammation.* WO 0372040.

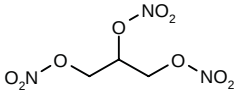
Original monograph – Drugs Fut 2000, 25(9): 917.

Nepadutant



Nepadutant is a glycosylated bicyclic peptide that acts as a tachykinin NK_2 receptor antagonist. In animal models of IBS, nepadutant was found to correct colonic visceral hyperalgesia, the main pathophysiological event underlying IBS symptoms, and the compound has been advanced to phase IIa clinical evaluation at Menarini.

Nitroglycerin Ointment



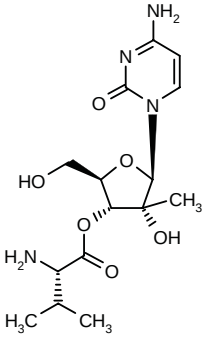
Cellegy's Cellegesic™ (nitroglycerin 0.4%) ointment has completed phase III clinical trials in the U.S. and Europe for reducing pain associated with chronic anal fissures. This product is similar to the company's Rectogesic™ (nitroglycerin 0.2%) ointment product which is available in Australia and several other markets for anal fissure therapy. Cellegesic™ is also being assessed in phase II trials in the U.S. for the treatment of hemorrhoids and is expected to enter phase I/II trials in the U.S. in the near future for dyspareunia pain. The phase III chronic anal fissure study, which commenced in June 2003, had as a primary endpoint the reduction in pain over a 21-day period. In total, 193 subjects completed testing, more than the 150 originally planned. The NDA should be resubmitted during the second quarter of 2004 (1).

Cellegy announced the results of a preliminary analysis of this double-blind, placebo-controlled phase III clinical trial on the efficacy and safety of Cellegesic™ given for 8 weeks to patients with chronic anal fissures. The nitroglycerin ointment significantly reduced the average pain intensity of the patients during the first 21 days of treatment. Other endpoints, such as time to 50% pain reduction, reduction of average pain during the study period and reduction of pain upon defecation improved significantly with Cellegesic™ compared to placebo. The most common adverse event was mild to moderate headache, which caused 3 patients to discontinue Cellegesic™. The trial was conducted following a Special Protocol Assessment agreed by Cellegy and the FDA to accelerate approval of the product for commercial sale if the primary endpoint of the study was achieved and no unexpected side effects were found (2).

1. *Patient testing completed in phase III Cellegesic trial.* DailyDrugNews.com (Daily Essentials) Jan 13, 2004.

2. *Cellegy announces positive results of phase 3 study using Cellegesic™ to treat chronic anal fissure pain.* Cellegy Pharmaceuticals, Inc. Press Release 2004, Jan 27.

NM-283



Idenix's drug candidate for hepatitis C virus (HCV) infection, NM-283, an oral, once-daily nucleoside, is in phase I/II clinical development. Novartis obtained rights last year to jointly develop this compound, in addition to two agents for HBV: telbivudine and valtorcitabine (see below) (1-3).

The antiviral effects of NM-283 (50-800 mg/day p.o. once daily) were evaluated in a placebo-controlled phase I/II clinical trial that included adult patients with chronic hepatitis C genotype 1 infection and baseline serum HCV RNA levels higher than 5 $\log_{10}$. A preliminary analysis evaluating the results obtained from the first 48 patients who received doses of 50-400 mg/day for 15 days revealed that NM-283 induced dose-dependent

reductions in serum HCV RNA levels and was well tolerated. No serious adverse events were found, and although some patients suffered from transient mild nausea or vomiting on the first day of receiving 400 mg/day of NM-283, all patients completed the study and none of them required dose changes (4, 5).

1. *Novartis and Idenix Pharmaceuticals, Inc. announce successful closing of strategic alliance. Innovative collaboration to advance antiviral therapeutic franchise.* Idenix Pharmaceuticals, Inc. Press Release 2003, May 9.

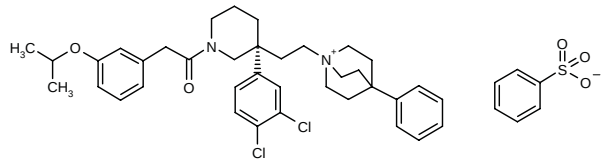
2. *Novartis closes two strategic acquisitions in pharmaceuticals.* Novartis Press Release 2003, May 9.

3. *Novartis set for strategic expansion into antiviral medicines through acquisition of 51% of Idenix, a Cambridge MA-based biotech company.* Novartis Press Release 2003, March 26.

4. Godofsky, E., Afdhal, N., Rustgi, V. et al. *First clinical results for a novel antiviral treatment for hepatitis C: A phase I/II dose escalation trial assessing tolerance, pharmacokinetics, and antiviral activity of NM283.* J Hepatol 2004, 40(Suppl. 1): Abst 96.

5. Godofsky, E. et al. *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.

Nolpitantium Besilate



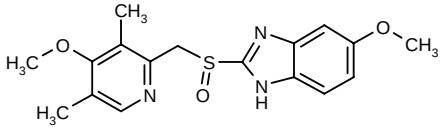
Preclinical and clinical studies have shown that nolpitantium besilate (SR-140333; Sanofi-Synthélabo), a neurokinin NK_1 antagonist in phase II a clinical trials, is effective in reducing neurogenic inflammation in the colon and is well tolerated in healthy volunteers. These results led researchers to conduct an open-label clinical trial to assess the efficacy and safety of this drug in 9 patients with mild to moderate active ulcerative colitis. An oral dose of 125 mg administered twice daily for 4 weeks significantly reduced the clinical disease activity index or induced remission in 5 patients. The drug was especially effective in reducing both abdominal pain and fecal blood loss. These effects were associated with improvements in the quality of life of the patients who responded to the treatment. Nolpitantium was well tolerated, 2 patients reporting transient increases in ALT levels (1).

1. Van Assche, G., Noman, M., Asnong, K., Rutgeerts, P. *The use of neurokinin-1 receptor antagonist, SR-140333B, nolpitantium besilate, in mild to moderate active ulcerative colitis.* Gastroenterology 2003, 124(4, Suppl. 1): Abst T1377.

OC-108

Mitsubishi Pharma's OC-108 (Zione®) is awaiting approval in Japan for the treatment of hemorrhoids.

Omeprazole

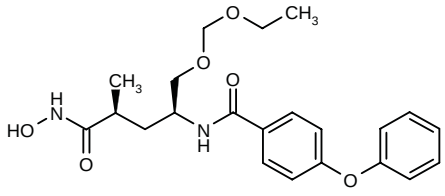


The FDA has accepted for filing Santarus's NDA for Rapinex™ powder for suspension 40 mg, an immediate-release formulation of the proton pump inhibitor (PPI) omeprazole. The NDA, submitted in February 2004, seeks approval for the treatment of gastric ulcers and the prevention of upper gastrointestinal (GI) bleeding in critically ill patients. An action date has been set for December 26, 2004. An NDA for Rapinex™ powder for suspension 20 mg was filed in August 2003 for the treatment of heartburn and other symptoms related to GERD, the treatment and maintenance of healing of erosive esophagitis and the treatment of duodenal ulcer. An FDA response is expected by June 15, 2004. The NDA for Rapinex™ 40 mg contained data from a pivotal phase III trial in 359 critically ill patients. The blinded trial compared Rapinex™ 40 mg, administered through a nasogastric tube, with the approved intravenous cimetidine. The primary endpoint, the occurrence of clinically significant bleeding, was the same as that seen in the intravenous cimetidine trial that led to its approval. Santarus also conducted an open-label trial treating 243 patients, including 97 patients with gastric ulcers, to collect safety data over an 8-week treatment period (1). The Rapinex™ product candidates, unlike currently available delayed-release PPIs which use an enteric coating to protect the drug from acid degradation, utilize an antacid instead of the enteric coating, which rapidly neutralizes acid in the esophagus and stomach, allowing the immediate release of omeprazole into the bloodstream. Rapinex™ thereby provides a rapid reduction in gastric acidity while maintaining a similar therapeutic effect and duration to delayed-release PPIs. Also in development are capsule and chewable tablet formulations of immediate-release omeprezole. The Rapinex™ products are based on patents licensed from the University of Missouri.

1. *Latest Rapinex NDA filing accepted for review*. DailyDrugNews.com (Daily Essentials) May 3, 2004.

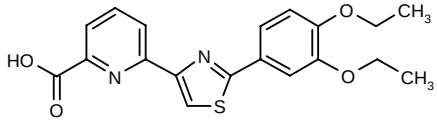
Original monograph – Drugs Fut 1983, 8(2): 129.

Ono-4817



Ono-4817 is a third-generation, broad-spectrum matrix metalloproteinase inhibitor from Ono Pharmaceutical in development as an oral treatment for inflammatory bowel disease and osteoarthritis. Phase I clinical testing is ongoing in Japan and phase I trials have been concluded overseas. Ono-4817 has been reported to selectively inhibit MMP-2 (gelatinase A), MMP-8 (neutrophil collagenase), MMP-9 (gelatinase B), MMP-12 (metalloelastase) and MMP-13 (collagenase 3), but not MMP-1 (interstitial collagenase) or MMP-7 (matrilysin).

OPC-6535



The phosphodiesterase type 4 (PDE4) inhibitor OPC-6535 (Otsuka) was advanced to phase III clinical trials for the treatment of ulcerative colitis last year. Two pivotal trials in the U.S., Canada and Australia will enroll 750 patients to investigate the therapeutic efficacy of OPC-6535 (1).

A double-blind, randomized, placebo-controlled trial determined the efficacy and safety of OPC-6535 (25 and 50 mg p.o.) given once daily for 8 weeks to 186 patients with active ulcerative colitis. Clinical improvement, which was defined as a 3-point reduction in the Disease Activity Index score, was achieved by 55% and 48% of patients, respectively, receiving 25 and 50 mg of OPC-6535 and by 40% of placebo-treated patients. OPC-6535 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 OPC-6535 was greater among patients with more severe disease scores at baseline (2).

1. *Ostuka initiates phase III clinical trials of compound for ulcerative colitis.* Otsuka Maryland Research Institute, Inc. Press Release 2003, July 22.

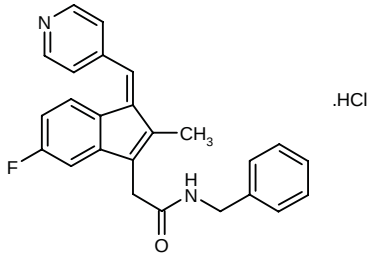
2. Hanauer, S.B. et al. *Randomized, double-blind, placebo-controlled, parallel arm, safety and efficacy trial of once-daily, oral OPC-6335 in the treatment of active ulcerative colitis (UC).* Gastroenterology 2004, 126(4, Suppl. 2): Abst 814.

OPT-80

OPT-80 is a new narrow-spectrum antibiotic with activity against *Clostridium difficile*, which recently entered phase I clinical studies at Optimer Pharmaceuticals to evaluate its potential in antibiotic-induced colitis, or *C. difficile*-associated diarrhea. OPT-80 remains in the gut and is not absorbed systemically. It demonstrated high activity against all clinical isolates of *C. difficile* tested; for comparison, all strains were also inhibited by vancomycin, metronidazole and fusidic acid, but 2% of strains were resistant to linezolid and 13% to moxifloxacin (1).

1. Ackermann, G., Loffler, B., Adler, D., Rodloff, A.C. *In vitro activity of OPT-80 against Clostridium difficile.* 43rd Intersci Conf Antimicrob Agents Chemother (Sept 14-17, Chicago) 2003, Abst F-2158.

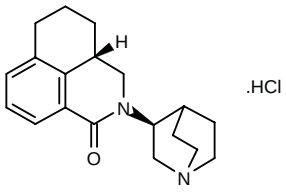
OSI-461



OSI-461 is a cGMP phosphodiesterase (cGMP-PDE) inhibitor designed to lead to sustained activation of the intracellular signaling molecule protein kinase G (PKG), and subsequent stimulation of apoptosis through the c-Jun kinase pathway. OSI-461 is part of the SAANDs (selective apoptotic antineoplastic drugs) technology platform acquired by OSI Pharmaceuticals from Cell Pathways in June 2003. OSI-461 is a second-generation molecule from the selective SAANDs class and has demonstrated superior potency compared to the prototype clinical candidate Aptosyn® (exisulind) in preclinical studies. Although development is being focused on oncology indications, with phase II trials under way in chronic lymphocytic leukemia, prostate cancer and renal cell carcinoma, OSI-461 is also being evaluated in phase II clinical studies in moderate to severe Crohn's disease, from which topline data are expected in mid-2004 (1). According to the company's web site, OSI will most likely seek a partner to copromote the drug for IBD.

1. *OSI expands ongoing phase I study of OSI-461*. DailyDrugNews.com (Daily Essentials) March 1, 2004.

Palonosetron Hydrochloride



MGI Pharma began marketing palonosetron hydrochloride (Aloxi™ for injection) in the U.S. in September 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. Palonosetron was approved by the FDA in late July 2003 as a fixed dose of 0.25 mg and is the first and only 5-HT_3 receptor antagonist indicated for the prevention of delayed CINV caused by moderately emetogenic cancer chemotherapy; the compound is a selective, high-affinity antagonist with an extended 40-h half-life. In phase III trials in over 2,800 patients, a single i.v.dose of palonosetron was effective in preventing both acute and delayed CINV in patients receiving modertely emetogenic chemotherapy. MGI licensed the U.S. and Canadian rights for the drug from Helsinn. Schering-Plough has acquired exclusive rights to the drug from Helsinn for Latin America, Australia, New Zealand and the Caribbean, and Taiho has been granted exclusive rights to develop and commercialize palonostetron in Japan for CINV. MGI Pharma and Helsinn more recently expanded their agreement for palonosetron to include rights for the postoperative nausea and vomiting (PONV) application and an oral formulation. Pivotal trials for PONV and the CINV oral formulation are expected to begin this year. Palonosetron is under regulatory review in Europe and will be marketed by Italfarmaco in Italy and Spain as Onicit® (1-5).

Palonosetron has been incorporated into the 2004 National Comprehensive Cancer Network® (NCCN®) antiemetic guidelines for the prevention of CINV following moderately and highly emetogenic chemotherapy. The revised guidelines identified palonosetron injection as the preferred agent for the prevention of CINV following moderately emetogenic (levels 3-4) chemotherapy. The drug is also recommended by the NCCN® for day 1 administration to protect patients receiving highly emetogenic (level 5) chemotherapy (6).

A multicenter, double-blind, randomized phase III clinical trial compared the efficacy of palonosetron and ondansetron in the prevention of CINV. A total of 570 adult cancer patients received a single dose of palonosetron (0.25 or 0.75 mg i.v.) or ondansetron (32 mg i.v.) 30 min before the first dose of moderately emetogenic chemotherapy. The percentage of patients who showed complete response (*i.e.*, no emetic episodes and no use of rescue medication) during the first 24 h after administration was 81.0% with palonosetron 0.25 mg, 73.5% with palonosetron 0.75 mg and 68.6% with ondansetron. These percentages were, respectively, 74.1%, 64.6% and 55.1% for the period of time ranging from 24 h to 120 h after administration, and 69.3%, 58.7% and 50.3% for the whole 120-h study period. The time to treatment failure was significantly longer with palonosetron 0.25 mg compared with ondansetron. All study treatments were well tolerated. Most adverse events were mild and few were related to study medications (16% in each palonosetron group and 13.9% with ondansetron). Only 2 patients withdrew from the study due to adverse events (7).

A multicenter, randomized, double-blind, dose-ranging clinical trial evaluated the efficacy, safety and pharmacokinetics of palonosetron in 161 adult patients with histologically proven cancer who were scheduled to receive their first dose of highly emetogenic cisplatin-based chemotherapy. Each patient received a single dose of palonosetron (0.3, 1, 3, 10, 30 and 90 μg/kg by i.v. bolus) at 30 min before the first chemotherapy dose and was followed up for 14 days. Complete response to palonosetron (defined as no emetic episodes and no need for rescue medication during the first 24 h after chemotherapy) was achieved by 24% of patients treated at doses of 0.3-1 mg/kg and by 40-50% of those treated with higher doses. Between 29% and 57% of the patients showed no emetic episodes and had only mild or no nausea. The four highest dose levels were associated with longer median times to first emetic episode, rescue medication and treatment failure. Palonosetron was also effective in preventing delayed emesis, and approximately one-third of the patients treated with 10 or 30 μg/kg of the drug maintained complete response for up to 7 days after chemotherapy. The most common drug-related adverse events were headache and constipation. Overall, 15.5% of the patients had serious adverse events but none were related to palonosetron. The pharmacokinetic parameters of palonosetron increased with dose, and the drug was detected in plasma up to 168 h after administration (8).

1. *Market launch announced for Aloxi*. DailyDrugNews.com (Daily Essentials) Sept 16, 2003.

2. *Schering-Plough acquires rights to palonosetron*. DailyDrugNews.com (Daily Essentials) Oct 3, 2003.

3. *MGI and Helsinn expand North American Aloxi agreement*. DailyDrugNews.com (Daily Essentials) Nov 19, 2003.

4. *Helsinn and Taiho sign an agreement for palonosetron*. DailyDrugNews.com (Daily Essentials) Jan 20, 2004.

5. *Italfarmaco gains Spanish license and distribution rights to palonosetron*. DailyDrugNews.com (Daily Essentials) March 16, 2004.

6. *Aloxi incorporated in NCCN antiemetic guidelines for CINV*. DailyDrugNews.com (Daily Essentials) March 18, 2004.

7. Gralla, R., Lichinitser, M., Vander Vegt, S. et al. *Palonosetron improves prevention of chemotherapy-induced nausea and*

vomiting following moderately emetogenic chemotherapy: Results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol 2003, 14(10): 1570.

8. Eisenberg, P., MacKintosh, F.R., Ritch, P., Cornett, P.A., Macciocchi, A. *Efficacy, safety and pharmacokinetics of palonosetron in patients receiving highly emetogenic cisplatin-based chemotherapy: A dose-ranging clinical study*. Ann Oncol 2004, 15(2): 330.

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

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PEG-Interferon Alfacon-1

InterMune has developed a pegylated form of interferon –PEG-interferon alfacon-1 (PEG-Infergen®)– for the treatment of hepatitis C infections. Designed as an alternative with less frequent dosing, PEG-interferon alfacon-1, which uses Nektar Therapeutics' pegylation technology, entered clinical evaluation in 2003.

Peginterferon Alfa-2a

Peginterferon alfa-2a (Pegasys®), developed by Roche, is a new-generation hepatitis therapy that was first approved in Switzerland in July 2001 for the treatment of chronic hepatitis C. Approval was subsequently obtained in the E.U. and the U.S. and the drug is now available in 86 countries for the treatment of HCV. The polyethylene glycol (PEG) in Pegasys® allows for constant viral suppression for a full week and also results in improved distribution to the liver compared to conventional interferon. The product is available as a premixed solution in vials and was also recently approved in the form of prefilled syringes. The phase III program for peginterferon alfa-2a in hepatitis B was just recently completed. Additional studies are under way for peginterferon alfa-2a in combination with Copegus® (ribavirin) for the treatment of African-Americans, who have a substantially higher prevalence of HCV infection and typically have lower response rates to therapy than Caucasian Americans. Trials are also evaluating this combination in patients coinfected with HCV and HIV and in patients with HCV who failed to achieve a sustained virological response on standard interferon and ribavirin (1-6).

The first study reporting on the use of peginterferon alfa-2a for the treatment of chronic HBV demonstrated its superiority to conventional interferon. This phase II study enrolled 194 patients to receive treatment with either conventional interferon 3 times weekly or peginterferon alfa-2a (90, 180 or 240 μg) once weekly for 24 weeks, with follow-up for another 24 weeks. The study assessed the combined response of the patients, *i.e.*, loss of viral protein, suppression of HBV DNA levels and normalization of liver function. Overall, 28% of the patients treated with peginterferon alfa-2a at the dose of 180 μg achieved a combined response compared to only 12% of those receiving conventional interferon. The effects of peginterferon alfa-2a were also observed in difficult-to-treat patients, such as those with cirrhosis, low ALT or high baseline HBV DNA levels, and those with HBV genotype C (4).

An international phase III study, the first large-scale head-to-head comparison of peginterferon alfa-2a and lamivudine, the most commonly used therapy for HBV, included 537 patients with the most difficult-to-treat form of HBV (HBeAg-negative, also known as precore or variant HBV) and raised blood levels of ALT. The patients were treated for 48 weeks with either peginterferon alfa-2a (180 μg once weekly) plus placebo, lamuvidine (100 mg once daily) or combination of the two, followed by 24 weeks of observation. Peginterferon alfa-2a was more effective than lamivudine and the combination did not improve the treatment outcome. At the end of the follow-up period, 42.9% of those treated with peginterferon alfa-2a had their HBV DNA reduced to < 20,000 copies/ml compared to only 29.3% of those treated with lamivudine; the combination reduced HBV DNA in 44.1% of patients. Peginterferon alfa-2a also had a better impact on ALT than lamivudine, with normalization of ALT levels in 59.3% of patients on peginterferon alfa-2a *versus* only 44.2% of those on lamivudine; combination of the two drugs led to normalization in 59.8% of patients (5).

The last trial in Roche's registration profram for peginterferon alfa-2a in HBV was recently completed. The multinational phase III study compared the efficacy and safety of peginterferon alfa-2a with or without lamivudine *versus* lamivudine alone in 820 patients with HBeAg-positive HBV. Similar to the above trial, peginterferon alfa-2a was superior to lamivudine monotherapy and the combination did not improve response rates compared to peginterferon alfa-2a alone. In this study, the patients received peginterferon alfa-2a (180 μg once weekly) plus placebo, lamivudine (100 mg once daily) or a combination of the two for 48 weeks, followed by 24 weeks without treatment. The primary endpoints were HBeAg seroconversion at the end of follow-up and HBV DNA levels < 100,000 copies/ml (6).

The APRICOT (AIDS Pegasys Ribavirin International CO-infection Trial) was a multicenter, randomized, placebo-controlled clinical trial that evaluated the antiviral efficacy of a combination of peginterferon alfa-2a and ribavirin in patients coinfected with HIV and HCV. A total of 868 patients with HIV/HCV coinfection, compensated liver disease and stable HIV disease were treated with interferon alfa-2a (300 MIU 3 times weekly) plus ribavirin (800 mg once daily), peginterferon alfa-2a (180 μg once weekly) alone, or peginterferon alfa-2a (190 μg once weekly) combined with ribavirin (800 mg once daily) for 48 weeks. At the end of the study, the percentage of patients who achieved a sustained HCV virological response was higher with peginterferon alfa-2a and ribavirin (40%) compared with peginterferon alfa-2a alone (20%) and ribavirin plus interferon (12%). The percentage of patients with undetectable serum HCV levels at the end of the study was, respectively, 47%, 31% and 14%; after 24 weeks of drug-free follow-up, these values were 35%, 17% and 11% (7). Analysis of the data from 289 patients included in the APRICOT study and treated with peginterferon alfa-2a plus ribavirin showed that 71% achieved an early virological response after 12 or 24 weeks, and that 56% of these had a sustained virological response at the end of the study. These results suggested that the absence of an early virological response at 12 weeks was predictive of a low probability of achieving sustained virological response at 48 weeks (8).

1. *Pegasys approved in Japan*. DailyDrugNews.com (Daily Essentials) Oct 21, 2003.

2. *Chugai launches Pegasys in Japan*. DailyDrugNews.com (Daily Essentials) Dec 17, 2003.

3. *Prefilled Pegasys syringes approved by FDA*. DailyDrugNews.com (Daily Essentials) Jan 13, 2004.

4. *Pegasys twice as effective as current standard therapy for hepatitis B patients. Published study achieves two firsts*. Roche Press Release 2003, June 30.

5. *Pegasys found superior to current hepatitis B treatments. New study shows Pegasys more effective than lamivudine in most difficult-to-treat form of hepatitis B disease*. Roche Press Release 2003, Oct 28.

6. *Pegasys shows promising results in HBeAg-positive chronic hepatitis B*. Roche Press Release 2004, May 4.

7. Torriani, F.J., Rockstroh, J., Rodriguez-Torres, M. et al. *Final week-72 results of the AIDS Pegasys Ribavirin International Co-infection Trial (APRICOT): A randomized, partially blinded, multinational comparative trial of peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (RBV) (Copegus®) vs interferon alfa-2a (IFN)*. J Hepatol 2004, 40(Suppl. 1): Abst 92.

8. Rodriguez-Torres, M., Torriani, F.J., Lissen, E. et al. *Early prediction of sustained virological response (SVR) during treatment with peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (RBV) (Copegus®) in patients with HCV/HIV co-infection: Results from the AIDS Pegasys Ribavirin International Co-infection*. J Hepatol 2004, 40(Suppl. 1): Abst 507.

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Colombatto, P. et al. *A new bio-mathematical model to describe the dynamics of HBV-DNA and infected hepatocytes in HBeAg-negative/anti-Hbe-positive chronic hepatitis B patients treated with peginterferon alfa-2a (40KD) (Pegasys®), lamivudine, or Pegasys® plus lamivudine combination*. J Hepatol 2004, 40(Suppl. 1): Abst 421.

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Marcellin, P. et al. *Peginterferon alfa-2a (40KD) (Pegasys®) monotherapy is more effective than lamivudine monotherapy in the treatment of HBeAg-negative chronic hepatitis B: 72-week results from a phase III, partially double-blind study of Pegasys® alone vs Pegasys® plus lamivudine vs lamivudine*. J Hepatol 2004, 40(Suppl. 1): Abst 95.

Nuñez, M. et al. *The PRESCO study: Peginterferon-alfa2a plus ribavirin for treatment of chronic hepatitis C in HIV-coinfected patients in Spain*. 9th Eur AIDS Conf (Oct 25-29, Warsaw) 2003, Abst 13.2/16.

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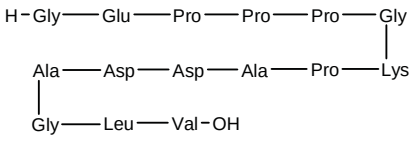
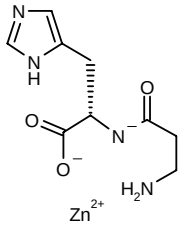
PLD-116



In 2003, the first phase II safety and efficacy study of the gastric pentapeptide PLD-116 (PLD-10, PLD-14736, PL-10, BPC-157; Pliva) was completed in patients with left-sided mild to moderate ulcerative colitis. Preliminary results from the placebo-controlled study suggest that the compound is likely to be safe in these patients. A statistically significant decrease in disease activity at the end of treatment was seen in patients who received PLD-116. Although the response was greater than that observed in placebo patients, due to a small sample size it failed to reach statistical significance. PLD-116 is also in preclinical evaluation for the treatment of wound healing (4).

1. *Pliva updates pipeline progress*. DailyDrugNews.com (Daily Essentials) Dec 1, 2003.

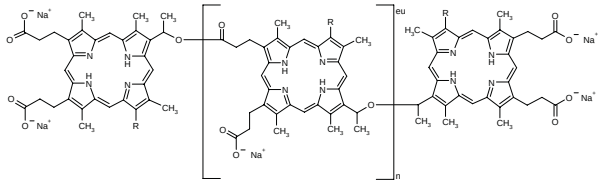
Polaprezinc



Polaprezinc (Z-103, Promac®) is a complex of carnosine and zinc with chelating properties, introduced a number of years ago by Zeria in Japan for the treatment of gastric ulcers. It is now awaiting approval in Japan for additional use in gastritis.

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

Porfimer Sodium



Photodynamic therapy (PDT) with porfimer sodium (Photobarr® in the E.U., Photofrin® in the U.S.) received approval from U.S. and Canadian regulatory authorities last year and was recently launched for the treatment of high-grade dysplasia associated with Barrett's esophagus, and CPMP approval was granted early this year. Axcan's marketing authorization applications were based on a 208-patient multicenter, controlled, partially blinded, 2-arm trial, in which 138 patients were randomized to Photobarr® PDT + omeprazole and 70 patients to omeprazole only as a control. Patients were followed every 3 months until 4 consecutive endoscopic results were negative for high-grade dysplasia and then semi-annually until the last enrolled patient had completed at least 24 months of follow-up evaluation. Photobarr® PDT resulted in the complete ablation of high-grade dysplasia, the primary endpoint, in 77% of treated patients, while omeprazole alone resulted in 39%. According to secondary efficacy endpoint analyses, the median duration of the ablation of high-grade dysplasia was 987 days for Photobarr® PDT and 98 days in the omeprazole-only group. The proportion of patients who progressed to esophageal cancer was about twice as high in the omeprazole-only group compared to the Photobarr® PDT group (1, 2). Photodynamic therapy with porfimer has been available for some time for use in late-stage lung cancer and advanced esophageal cancer. Axcan is also supporting phase II studies of its use in the treatment of cholangiocarcinoma.

1. *Photobarr PDT recommended for approval in E.U.* DailyDrugNews.com (Daily Essentials) Dec 23, 2003.

2. *Axcan receives European marketing approval for Photobarr PDT*. DailyDrugNews.com (Daily Essentials) April 2, 2004.

Probactrix™

BioBalance, a wholly owned subsidiary of New York Health Care, has completed a safety trial at Bikur Cholim Hospital, Jerusalem, of the company's proprietary biotherapeutic agent Probactrix™. The study involved 125 healthy adult human volunteers and an intake level of the agent 10 times higher than normal for 8 weeks. Probactrix™ was well tolerated with no adverse events. A recent expert panel review of Probactrix™ determined that the product is generally recognized as safe under the conditions of its intended use for the dietary management of irritable bowel syndrome (IBS) and other gastrointestinal disorders. Probactrix™ is a patented strain of nonpathogenic *Escherichia coli* M-17 in a liquid suspension that helps restore the microbial balance in the digestive tract (1).

A recent randomized clinical study of a formulation containing Probactrix™ showed that the drug rapidly and effectively controlled antibiotic-associated diarrhea. Conducted at 2 Moscow hospitals, the trial enrolled 80 patients undergoing combination antibiotic therapy (including ampicillin) for acute pneumonia or prostatitis. Half received Probactrix™ and half acted as controls. Probactrix™ significantly reduced gastrointestinal complaints *versus* the control group within 5 days after initiation of treatment. In the Probactrix™ arm, there was significant improvement in relief of the average duration of diarrhea symptoms, as measured by stool frequency, at almost half the duration of the control group. After 10 days of treatment, the Probactrix™ group showed 90% complete recovery *versus* 58% for the control group. Those receiving Probactrix™ treatment also showed a measurable improvement in intestinal microflora composition *versus* the control, with total elimination of *Candida albicans* in the feces *versus* a 43% positive toll in the control group. Based on these results, BioBalance intends to explore over-the-counter (OTC) regulatory approval for the indication (2).

BioBalance has begun enrolling patients in a randomized, double-blind, placebo-controlled IBS trial of Probactrix™ at sites in Israel and Canada. Additional sites in the U.S. will also take part, enrolling a total of up to 240 IBS patients. The study aims to demonstrate the utility of Probactrix™ in the dietary management of IBS, in terms of improvement in symptoms and quality of life, and should be completed by mid-2004 (3, 4).

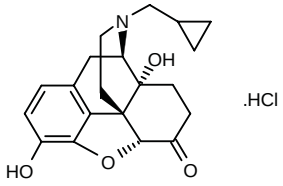
1. *Probactrix well tolerated and safe in safety study*. DailyDrugNews.com (Daily Essentials) Feb 3, 2004.

2. *Probactrix controls antibiotic-associated diarrhea in clinical study*. DailyDrugNews.com (Daily Essentials) Sept 15, 2003.

3. *BioBalance commences enrollment in IBS trial of Probactrix*. DailyDrugNews.com (Daily Essentials) Nov 21, 2003.

4. *Probactrix IBS trial commences enrollment*. DailyDrugNews.com (Daily Essentials) Feb 10, 2004.

PTI-901



PTI-901 is the first in a new class of drugs Pain Therapeutics is developing for the treatment of irritable bowel syndrome (IBS), recently advanced to phase III clinical development. PTI-901 is a low-dose version of the opioid antagonist naltrexone designed to restore the balance of opioid activity in the gut, thereby relieving abdominal pain and other symptoms seen in patients with IBS (1, 2).

PTI-901 was found to significantly improve all the common symptoms associated with IBS in an open-label, pilot study conducted in Israel in 50 patients who received a 0.5-mg dose daily over a 4-week period. The primary efficacy endpoint was the patients' observations of Global Assessment of Adequacy of Treatment. At the conclusion of the 4-week study, both male and female patients achieved a response rate of 76.2%, a response far greater than the study was designed to demonstrate. The study also met the secondary endpoints of improving daily abdominal pain, bowel habits and stool consistency. The improvements were observed in patients whose baseline symptoms were either diarrhea or constipation, or both. The male and female response rate was 76.5% and 75.0%, respectively. Patients on PTI-901 reported a 193% increase in the number of pain-free days at week 4 compared to baseline. Significant clinical improvements in bowel urgency, stool consistency and number of stools per day were also reported at week 4 in men and women (3, 4).

Based on these favorable results, the company initiated a large phase III clinical program with PTI-901. The program will enroll a total of 1,200 IBS patients at 80 U.S. sites. The program design,recently discussed and agreed upon with the FDA, comprises 2 studies that are identical in all respects except for gender. One study will enroll 600 men and the other will enroll 600 women. They will include patients with constipation-predominant, diarrhea-predominant or mixed-symptom IBS. Each randomized, double-blind, placebo-controlled study is designed to compare the clinical effects of PTI-901 against placebo during a 3-month treatment period. Patients will be

evaluated for abdominal pain, bowel habits and stool consistency at baseline and during the treatment period. Treatment consists of a single daily 0.5-mg oral dose of PTI-901 or matching placebo. The primary efficacy endpoint is relief of IBS symptoms, as measured by patients' observations of Subject Global Assessment of Relief. Secondary efficacy endpoints include improvements in abdominal pain, bloating, bowel habits and quality of life (5).

1. *Pain Therapeutics reports 2003 progress*. DailyDrugNews.com (Daily Essentials) 2004, Feb 6.

2. *Pain Therapeutics continues development of three drug candidates*. DailyDrugNews.com (Daily Essentials) 2004, May 13.

3. *Pilot study for PTI-901 in IBS completes enrollment*. DailyDrugNews.com (Daily Essentials) 2003, May 2.

4. *PTI-901 significantly improves common symptoms of IBS*. DailyDrugNews.com (Daily Essentials) 2003, June 2.

5. *Phase III program commences for PTI-901 in IBS*. DailyDrugNews.com (Daily Essentials) 2003, Nov 27.

R-803

Results from a phase I trial of Rigel's R-803, an experimental drug to treat HCV, showed that the drug is well tolerated with no notable adverse effects at the dose levels chosen for future development. The study compared an escalating dose regimen of R-803 to placebo in 42 volunteers. Results from the U.K. trial will be included in Rigel's IND package, which it plans to file in the first quarter of 2004. A U.S. phase I/II efficacy trial is planned for the second quarter of 2004 in HCV-infected patients. The trial will monitor viral clearance and safety over numerous days of drug administration. R-803 is an oral non-nucleoside HCV polymerase inhibitor with efficacy against various genotypes of HCV, including genotype 1. R-803 appears to act within days to reduce viral levels significantly. Given R-803's novel viral binding site, resistance may be slow to develop. Experiments indicate that R-803 directly, rapidly, selectively and potently targets HCV by interfering with a viral polymerase protein that is needed for replication. R-803 is extremely potent in inhibiting viral replication, with an EC_{50} in the low nanomolar range, and it does not appear to interfere with normal cellular functions (1, 2).

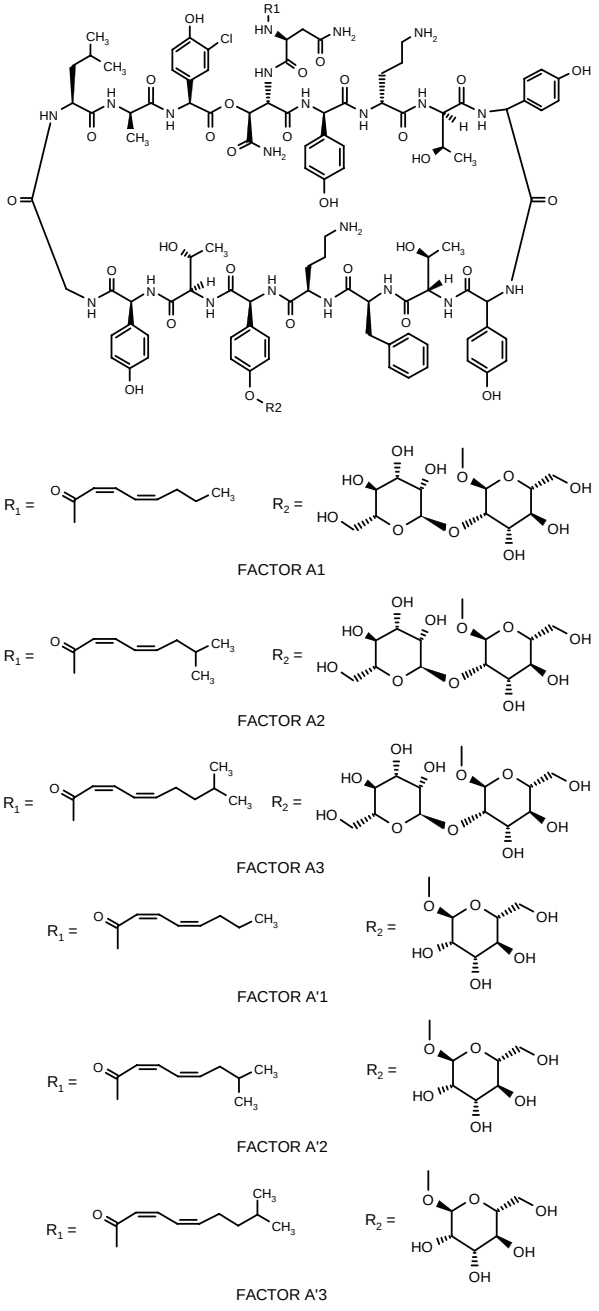
1. *New safety trial for HCV drug R-803*. DailyDrugNews.com (Daily Essentials) Nov 14, 2003.

2. *Rigel reports on the progress of R-803, R-406*. DailyDrugNews.com (Daily Essentials) Jan 30, 2004.

R-1479

R-1479 is a new polymerase inhibitor from Roche which has progressed to phase I clinical evaluation for HCV infection.

Ramoplanin



The antibiotic ramoplanin has received fast track status for the treatment of *Clostridium difficile*-associated diarrhea. Ramoplanin is being developed by Oscient Pharmaceuticals, the new name for Genome Therapeutics following its recent merger with GeneSoft. The phase II program in the above indication is nearing completion, and preliminary data are expected in the coming months. A phase III program for ramoplanin for the treatment of *C. difficile*-associated diarrhea is anticipated to commence later this year. Ramoplanin is also in phase III

development for the prevention of vancomycin-resistant enterococci bloodstream infections (1, 2).

A method has been claimed for the prevention and/or treatment of diseases related to prior antibiotic therapy comprising the administration of the glycolipodepsipeptide compound ramoplanin. Targeted conditions include those resulting from gastrointestinal infection by enterotoxin-releasing strains of *C. difficile, Clostridium perfringens* and *Staphylococcus aureus*, such as colitis, pseudomembranous colitis and antibiotic-related diarrhea. The claim further embodies the concurrent implementation of additional therapies (3).

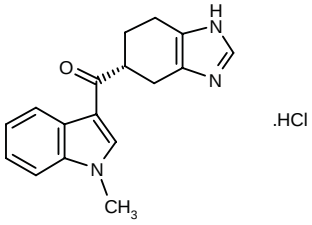
1. *Genome Therapeutics changes name to Oscient Pharmaceuticals Corporation to reflect focus on drug development and commercialization*. Oscient Pharmaceuticals Corp. Press Release 2004, April 13.

2. *Fast track status for ramoplanin in C. difficile-associated diarrhea*. DailyDrugNews.com (Daily Essentials) Feb 20, 2004.

3. Leach, T.S. et al. (Vicuron Pharmaceuticals Inc.). *Use of ramoplanin to treat diseases associated with the use of antibiotics*. WO 03103699.

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

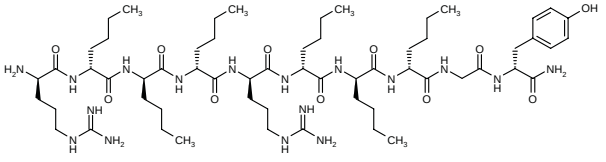
Ramosetron Hydrochloride



Currently available as an antiemetic under the brand name Nasea®, the 5-HT_3 receptor antagonist ramosetron hydrochloride (YM-060) is also being evaluated by Yamanouchi in phase III clinical trials for diarrhea-predominant irritable bowel syndrome.

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

RDP-58



RDP-58 (Allotrap-1258) is an antiinflammatory peptide being investigated for various immune-mediated diseases, including ulcerative colitis and Crohn's disease, which was acquired by Genzyme along with its acquisition of SangStat last year. Under a recent agreement, Procter & Gamble is to develop and market Genzyme's RDP-58 for the treatment of gastrointestinal and other disorders. Procter & Gamble will begin to evaluate RDP-58 for the treatment of inflammatory bowel disease (IBD), with initial clinical trials in ulcerative colitis. Genzyme will grant Procter & Gamble an exclusive worldwide license to develop, manufacture and commercialize RDP-58, in exchange for an upfront fee, milestone payments and royalties. Genzyme will retain development and commercialization rights to RDP-58 in pulmonary and other disorders. Genzyme will also retain copromotion rights in oncology-related disorders, such as chemotherapy-induced diarrhea. RDP-58 inhibits the inflammatory cytokines TNF-α, interferon gamma, IL-12 and IL-2. It was previously investigated by SangStat for IBD in 2 multicenter, randomized, blinded, placebo-controlled phase IIa trials (see below), which supported the potential use of RDP-58 in ulcerative colitis. Additional applications licensed to Procter & Gamble include periodontal, topical, ocular and urogenital disorders (1, 2).

The efficacy and safety of RDP-58 in the treatment of ulcerative colitis were evaluated in 2 multicenter, double-blind, randomized, placebo-controlled clinical trials. A total of 127 patients with mild to moderate ulcerative colitis were treated with placebo or RDP-58 (100, 200 or 300 mg p.o.) once daily for 28 days. At the end of treatment, the clinical remission rate was higher with the 200- and 300-mg doses (72% and 70%, respectively) compared to the 100-mg dose (29%) and placebo (40%). The response rates for these treatments were 77%, 72%, 33% and 44%, respectively. All study treatments were well tolerated and no significant differences were found among their safety profiles (3, 4).

A method for diminishing gastrointestinal toxicity and dysfunction resulting from cytoablative therapy, including diarrhea, mucositis and stomatitis, has been claimed comprising the administration of pharmaceutical compositions containing immunomodulatory peptides, such as the IL-2, IL-12 and TNF-α production inhibitor RDP-58, alone, or in conjunction with adjunctive therapies such as antidiarrheal and antiinflammatory agents. The claim further embodies the enhancement of cancer therapy using these peptides to facilitate the administration of elevated maximum tolerated doses of cytoablative agents in order to accentuate efficacy and tumor response (5).

1. *Genzyme completes acquisition of SangStat*. DailyDrugNews.com (Daily Essentials) Sept 19, 2003.

2. *P&G to develop Genzyme's RDP-58 for IBD*. DailyDrugNews.com (Daily Essentials) April 6, 2004.

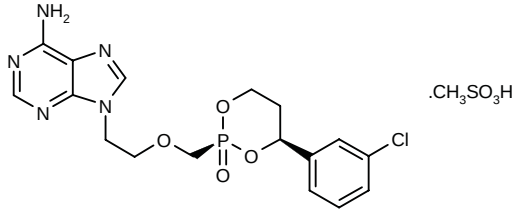
3. Travis, S.P.L., Yap, L., Hawkey, C.J. et al. *RDP58 - A novel and effective oral therapy for ulcerative colitis (UC): Results of parallel prospective, multicentre, placebo-controlled trials*. 11th United Eur Gastroenterol Week (Nov 1-5, Madrid) 2003, Abst OP-G-21.

4. Travis, S.P.L., Yap, L.M., Hawkey, C.J., Warren, B.F., Lazarov, M., Fong, T., Tesi, R.J. *RDP-58: Novel and effective therapy for ulcerative colitis. Results of parallel, prospective, placebo-controlled trials*. 68th Annu Sci Meet Am Coll Gastroenterol (Oct 13-15, Baltimore) 2003, Abst 50.

5. Buelow, R. (SangStat Medical Corp.). *Methods and compns. for treating gastrointestinal toxicity induced by cytoablative therapy*. WO 0372061.

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

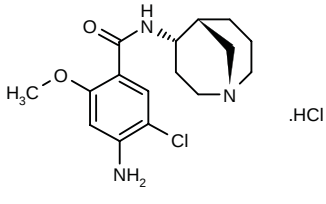
Remofovir Mesilate



The recent decision to initiate a phase II trial of remofovir mesilate (formerly known as Hepavir B™) in patients with chronic hepatitis B infection has triggered a USD 1 million milestone payment to Metabasis Therapeutics from Valeant, the former ICN Pharmaceuticals. Valeant licensed remofovir, an orally active prodrug of the antiviral agent adefovir, from Metabasis in October 2001 and is primarily responsible for the clinical development of the drug. Progression into the phase II trial follows results from the first clinical evaluation of remofovir in HBV-infected patients (1).

1. *Clinical progression of remofovir earns Metabasis milestone*. DailyDrugNews.com (Daily Essentials) April 21, 2004.

Renzapride Hydrochloride



Renzapride is a novel benzamide derivative and a potent full 5-HT_4 receptor agonist that also acts as a 5-HT_3 receptor antagonist. It was discovered and initially investigated for the treatment of GERD by Beecham Research Laboratories. Following a collaborative agreement, Alizyme obtained full ownership of the rights to renzapride from the former SmithKline Beecham (now GlaxoSmithKline). The product has now completed phase II clinical evaluation for IBS.

Alizyme reported positive preliminary results from its phase IIb trial of renzapride in patients with mixed-symptom irritable bowel syndrome (m-IBS). The double-blind, placebo-controlled, parallel-group, dose-ranging study randomized patients to 1 of 3 doses of renzapride (1, 2 and 4 mg/day) or placebo, administered once daily for 8 weeks following a 2-week run-in period. The trial enrolled 168 evaluable patients with m-IBS in the U.K. and several other European countries. At the optimum dose of 2 mg/day, up to 14% more patients at any one time were classified as responders (satisfactory relief of IBS on more than 50% of days during treatment) compared to placebo. The proportion of responders was increased to 18% in female patients. The proportion of female patients in this dose group classified as responders also showed an increase over placebo. The daily responder rate during the 2-week run-in period was approximately 30% for all groups, increasing to up to 57% in the 2-mg group, compared to up to 43% on placebo. An additional analysis of the preliminary results of the constipation-predominant IBS (c-IBS) phase IIb trial (also see below) reported previously indicates that the response rate is improved by analyzing data from female patients only, increasing the average weekly response rate by up to 4.6%, from 7.7% to 12.3%. Alizyme also announced that it has filed a new patent application which could provide protection for renzapride manufactured by commercial process until 2023 (1, 2).

The therapeutic benefits of renzapride in the treatment of c-IBS were evaluated in a recent double-blind, placebo-controlled clinical trial conducted at the Mayo Clinic. Forty-eight patients with c-IBS and a slow to normal colonic transit were randomized to receive placebo or renzapride (1, 2 or 4 mg) once daily for 11-14 days. Patients treated with renzapride showed dose-dependent improvements in colonic motility, bowel function scores and relief of IBS symptoms. The effects of renzapride were correlated with the blood levels of the drug. All study regimens were well tolerated and no significant adverse events were found (3, 4).

A randomized, double-blind, placebo-controlled, phase IIb study evaluated the efficacy and safety of renzapride (1, 2 and 4 mg/day) and placebo administered once daily over a 12-week treatment period in 510 evaluable patients with c-IBS. The primary endpoint was the patient's weekly assessment of adequate relief of abdominal pain and discomfort during weeks 5-12 of treatment. Renzapride increased the response rates for the primary endpoint by up to 8.2% over placebo. Treatment with renzapride also increased both the frequency of bowel movements and improved stool consistency. Statistical significance was recorded in frequency of bowel movements at 2 and 4 mg/day, and on stool consistency at 4 mg/day (5, 6).

1. *Positive preliminary findings emerge from phase IIb trial of renzapride for mixed-symptom IBS*. DailyDrugNews.com (Daily Essentials) Oct 17, 2003.

2. 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.

3. *Significant improvements induced by renzapride in IBS*. DailyDrugNews.com (Daily Essentials) Jan 19, 2004.

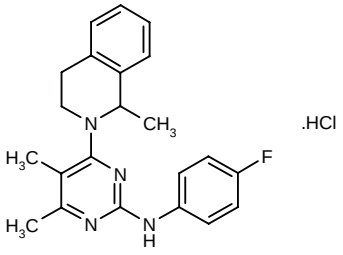
4. Camilleri, M. , McKinzie, S. Fox, J. et al. *Renzapride accelerates colonic transit and improves bowel function in constipation-predominant irritable bowel syndrome (C-IBS)*. Gastroenterology 2004, 126(4, Suppl. 2): Abst W1466.

5. George, A., Meyers, N.L., Palmer, R.M.J. *Efficacy and safety of renzapride in patients with constipation-predominant IBS: A phase IIB study in the UK primary healthcare setting*. 11th United Eur Gastroenterol Week (Nov 1-5, Madrid) 2003, Abst MON-G-161.

6. 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.

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

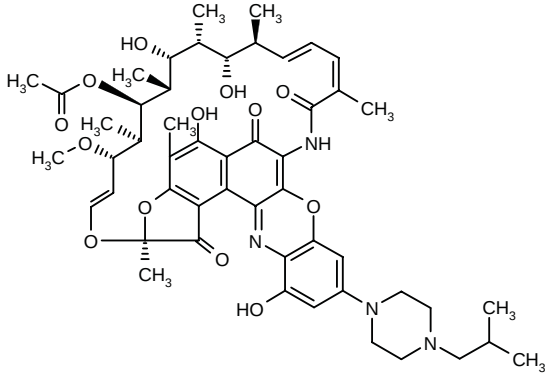
Revazapran Hydrochloride



Yuhan expects to launch its antiulcer agent revazapran hydrochloride (YH-1885; see monograph this issue) this year in Japan for the treatment of peptic ulcer. Phase III clinical studies with this new reversible proton pump inhibitor are under way.

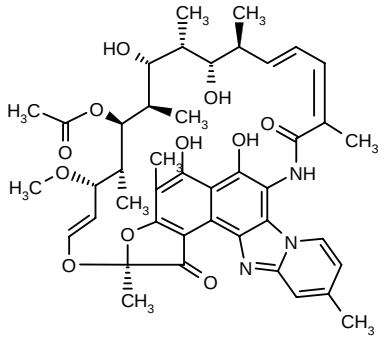
Original monograph – Drugs Fut 2004, 29(5): 455.

Rifalazil



Under development at ActivBiotics, rifalazil is a potent rifamycin antibiotic which is in phase II trials for gastric and peptic ulcer disease caused by *H. pylori,* as well as for nongonococcal urethritis caused by *Chlamydia trachomatis*.

Rifaximin



Rifaximin is a nonsystemic gastrointestinal site-specific antibiotic marketed for a number of years by Alfa Wassermann for the treatment of travelers' diarrhea. Licensee Salix is currently seeking FDA approval for this indication. Salix is also developing the drug for additional potential applications, including Crohn's disease, pouchitis, small bowel overgrowth/irritable bowel syndrome and the prophylaxis of travelers' diarrhea (1-3).

The efficacy and safety of rifaximin in the treatment of active Crohn's disease were recently determined. A group of patients with active Crohn's disease for at least 3 months before inclusion and a CDAI score ranging from 220 to 400 received a dose of 200 mg of rifaximin 3 times daily for 16 weeks. The preliminary results obtained for 21 patients revealed that rifaximin was well tolerated and effective in reducing the CDAI score, improving the clinical status and inducing clinical remission in patients with active Crohn's disease (4).

1. *Salix reports Q3 R&D highlights*. Salix Pharmaceuticals Press Release 2003, Oct 28.

2. *Salix submits amendment to NDA for rifaximin*. DailyDrugNews.com (Daily Essentials) Nov 28, 2003.

3. *Rifaximin NDA amendment considered complete response*. DailyDrugNews.com (Daily Essentials) Dec 16, 2003.

4. Shafran, I., Johnson, L.K., Hamm, L., Murdock, R.H. Jr. *Efficacy and tolerability of rifaximin, a nonabsorbed oral antibiotic, in the treatment of active Crohn's disease: Results of an open-label study*. 68th Annu Sci Meet Am Coll Gastroenterol (Oct 13-15, Baltimore) 2003, Abst 281.

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

Rotavirus Vaccines

At least two different groups are have developed rotavirus vaccines.

GlaxoSmithKline and Avant Immunotherapeutics are collaborating on the development of Rotarix®, a live, attenuated rotavirus vaccine for preventing rotavirus gastroenteritis. Currently in phase III clinical evaluation, GSK anticipates filing for approval this year (1).

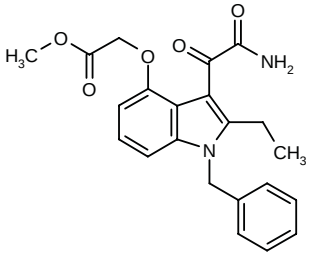
Merck & Co.'s late-stage pipeline candidates include RotaTeq™, a vaccine for rotavirus-induced infant diarrhea. Merck plans to make a regulatory submission with the FDA for this novel vaccine candidate in the second half of 2005.

The REST (Rotavirus Efficacy and Safety Trial) study is an ongoing large-scale study that will include more than 60,000 infants to determine the efficacy and safety of RotaTeq™. Special attention will be devoted to the incidence of intussusception, a condition sometimes found in children in which a segment of intestine invaginates into the adjoining intestinal lumen and causes bowel obstruction (2).

1. *Merck & Co. reports 2003 year-end R&D highlights*. Merck & Co., Inc. Press Release 2004, Jan 27.

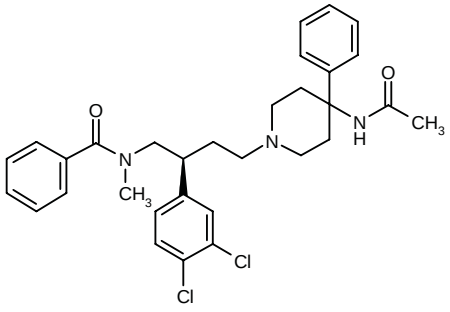
2. Heaton, P. *Rotavirus: Strategy for rotavirus vaccine development in the face of safety concerns about intussusception*. Int J Infect Dis 2004, 8(Suppl. 1): Abst 28.002.

S-3013



A secretory phospholipase A_2 ($sPLA_2$) inhibitor, Shionogi's S-3013 is in phase II clinical trials in Japan as a potential new drug for inflammatory bowel disease (ulcerative colitis, Crohn's disease).

Saredutant



Sanofi-Synthélabo is conducting phase IIb clinical trials with saredutant (SR-48968), a tachykinin NK_2 receptor antagonist, for two different indications: irritable bowel syndrome and depression.

Original monograph – Drugs Fut 1995, 20(7): 701.

Sargramostim

Results from a phase II clinical trial with sargramostim (rhuGM-CSF, Leukine®) in the treatment of Crohn's disease showed positive results and Schering AG plans to begin phase III clinical trials in the spring of 2004. The company has plans to seek U.S. and E.U. approval for this indication in the fourth quarter of 2006 (1, 2). Sargramostim is marketed by Schering AG and its subsidiary Berlex for use following induction chemotherapy in older adults with acute myelogenous leukemia (AML), after bone marrow transplantation and before and/or after peripheral blood stem cell transplantation.

In a double-blind clinical trial sponsored by Berlex, 124 patients with moderately to severely active Crohn's disease (defined as CDAI scores of 220-475) were randomized 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. Sargramostim was generally well tolerated, although it was associated with higher incidences of bone pain and mild to moderate injection site reactions (3).

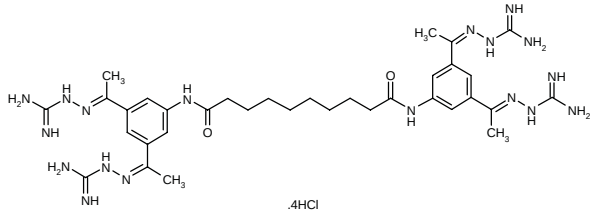
1. *Schering AG reports Q3 R&D highlights*. Schering AG Press Release 2003, Oct 27.

2. *Schering plans introduction of new drugs in coming years*. DailyDrugNews.com (Daily Essentials) March 11, 2004.

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 study.* Gastroenterology 2004, 126(4, Suppl. 2): Abst 582.

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

Semapimod Hydrochloride



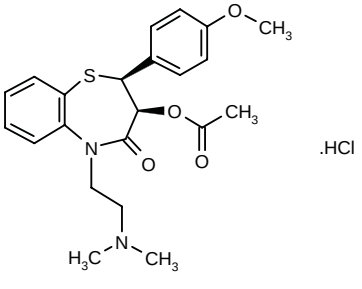
Semapimod hydrochloride (formerly CNI-1493) is a synthetic guanylhydrazone that inhibits signal

transduction pathways by preventing phosphorylation of p38 MAP (mitogen-activated protein) kinase and JNK (c-Jun *N*-terminal kinase), the production of the proinflammatory cytokines TNF-α, IL-1, IL-6, MIP-1α and MIP-1β, and the production of nitric oxide. As these signal transduction pathways and proinflammatory molecules are known to be active in various inflammatory and autoimmune diseases, semapimod may have broad application in these areas. Cytokine PharmaSciences has conducted successful proof-of-principle studies in psoriasis and Crohn's disease, leading to the initiation of phase II trials in the latter indication in the U.S., Europe and Israel. The company is also conducting a phase II study in the prophylaxis of ERCP (endoscope retrograde cholangiopancreatography)-induced pancreatitis in The Netherlands. Cytokine PharmaSciences is seeking licensing partners for semapimod in various indications and territories.

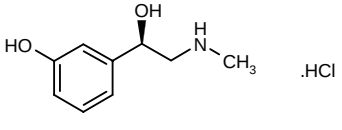
The potential of semapimod (30 and 60 mg i.v. once daily for 5 days) in the treatment of Crohn's disease was evaluated in a double-blind, randomized, placebo-controlled trial in 33 patients with CDAI scores of 250-400 at baseline. Both the CDAI and the Inflammatory Bowel Disease Questionnaire (IBDQ) scores 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).

1. Buchman, A.L., Katz, S., Barish, C. et al. *Semapimod treatment of Crohn's disease.* Gastroenterology 2004, 126(4, Suppl. 2): Abst T1299.

SLV-317/SLV-324/SLV-325



SLV-324



SLV-325

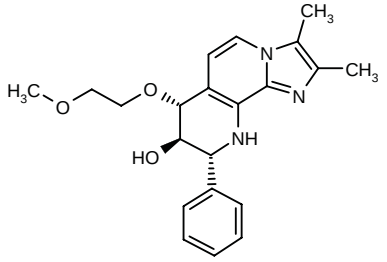
In addition to cilansetron (see above), three other products are in clinical development at Solvay for gastrointestinal indications. SLV-317, an NK_1 antagonist, is being evaluated in phase I clinical studies for irritable bowel syndrome. Two compounds licensed worldwide from SLA Pharma are in phase II clinical studies: SLV-324 (diltiazem cream, Anoheal®) for anal fissures and SLV-325 (phenylephrine cream, Incostop®) for fecal incontinence.

Somatropin

In December, Serono's Zorbtive™ (somatropin [rDNA origin]) received FDA approval for use in the treatment of short bowel syndrome, and the product was launched earlier this month. In a randomized double-blind, controlled, parallel-group phase III study, Serono's recombinant human growth hormone administered with specialized nutritional support was shown to significantly reduce patient dependence on total parenteral nutrition as measured by total volume, total calories and frequency of infusion. Serono's recombinant human growth hormone has orphan drug status for this indication. Previously, treatment of this condition involved management of dietary intake and hydration, or parenteral nutrition. On rare occasions, surgical transplant of the intestine may be necessary (1).

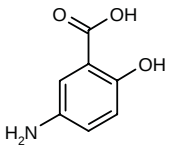
1. *Zorbtive receives FDA approval for short bowel syndrome*. DailyDrugNews.com (Daily Essentials) Dec 5, 2003.

Soraprazan



The acid pump antagonist soraprazan is progressing through the clinical pipeline at Altana Pharma. Phase II trials have been completed demonstrating efficacy and safety, and further studies are under way to determine the optimal dose. Acid pump antagonists differ from proton pump inhibitors in their very rapid onset of pump inhibition, which should translate into fast relief of acid-related symptoms.

SPD-476/SPD-480

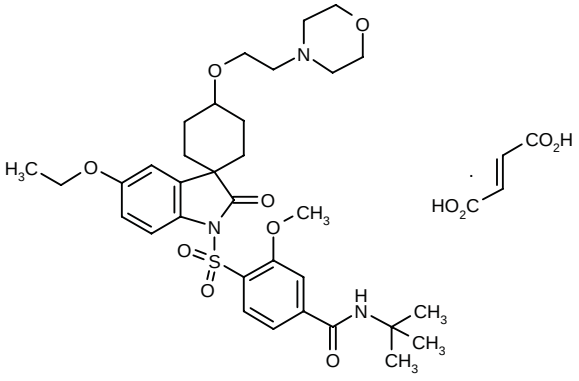


Shire licensed two 5-aminosalicyclic acid (5-ASA, mesalamine) products from Giuliani in 2002. SPD-476 is a high-strength (1200 mg) product using a unique formulation and delivery platform. It was advanced last year to phase III clinical trials in ulcerative colitis. SPD-480 is a single-dose (2 and 4 g) foam for rectal delivery in the treatment of ulcerative colitis, presently in phase II clinical evaluation.

SPI-8811

Sucampo Pharmaceuticals' SPI-8811 (RU-8811) is an ion transport modulator that facilitates the transport of chloride ions across cell membranes. It is therefore expected to reduce mucus viscosity and increase mucus clearance from the lungs, pancreas and liver. The product is in early clinical evaluation as a potential treatment for nonalcoholic steatohepatitis, also known as nonalcoholic fatty liver, as well as in phase II evaluation for cystic fibrosis.

SR-121463



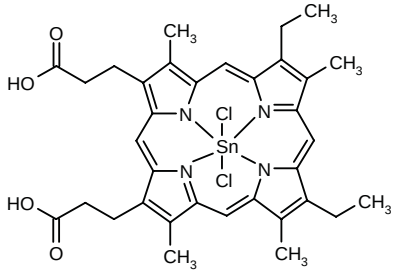
SR-121463 (Sanofi-Synthélabo) is a selective vasopressin V_2 receptor antagonist with aquaretic properties. In phase II trials, it has demonstrated positive results and good efficacy in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). This year it is expected to enter phase III trials for SIADH and hyponatremia, as well as phase IIb trials for cirrhotic ascites.

STA-5326

The oral IL-12 inhibitor STA-5326 is being evaluated by Synta Pharmaceuticals in a phase IIa trial for Crohn's disease. Trials for additional indications are planned for 2004 (1).

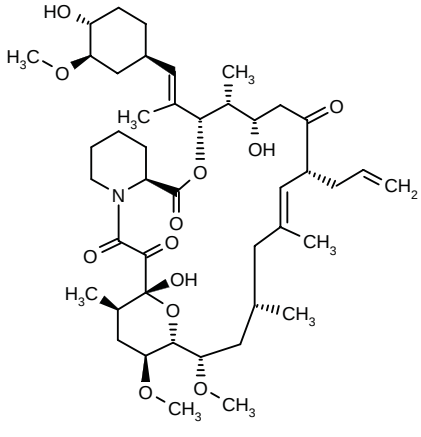
1. *Synta Pharmaceuticals gives update on clinical status of its products.* DailyDrugNews.com (Daily Essentials) Jan 27, 2004.

Stannsoporfin



Stannsoporfin is a synthetic heme analogue which can inhibit the catabolism of heme and therefore bilirubin in a wide variety of naturally occurring forms of jaundice in humans. It is especially useful in reducing plasma bilirubin in newborns shortly after birth. WellSpring Pharmaceutical is currently progressing to phase III trials to study stannsoporfin in this indication, with hopes of filing an NDA this year.

Tacrolimus



Fujisawa's immunosuppressant tacrolimus (FK-506, Prograf®, Protopic®) continues to be investigated and launched for different indications. It was recently filed for regulatory review in Japan for the treatment of ulcerative colitis.

An open-label clinical trial assessed the effects of tacrolimus hydrate (0.1 mg/kg p.o. once daily) in 19 patients with refractory inflammatory bowel disease. Administration of the agent for an average of 9.6 months induced complete or partial response in 77% of patients with pouchitis/cuffitis and 100% of those with rectitis or perianal Crohn's disease. Tacrolimus was also associated with significant improvements in the quality of life of the patients. The adverse events observed during the study (hand tremor, hyperglycemia, increased creatinine, diarrhea, drowsiness) were mild and controlled after drug dose adjustment (1).

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 and partial responses in 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 (2).

1. de Oca, J., Vilar, J., Castellote, J. et al. *Immunomodulation with tacrolimus (FK506): Result of a prospective, open-label, non-controlled trial in patients with inflammatory bowel disease*. Rev Esp Enferm Dig 2003, 95(7): 465.

2. 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.

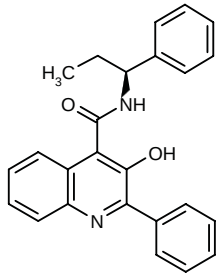
Original monograph – Drugs Fut 1989, 14(8): 746.

Additional References

Hogenauer, C. et al. *Effect of oral tacrolimus (FK 506) on steroid-refractory moderate/severe ulcerative colitis*. Aliment Pharmacol Ther 2003, 18(4): 415.

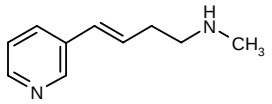
Lama, Y.G., Vera, M.I., Tabernero, S., Revilla, J., Fernandez, N., Abreu, L. *Long term oral tacrolimus therapy in refractory to infliximab fistulizing Crohn's disease*. 11th United Eur Gastroenterol Week (Nov 1-5, Madrid) 2003, Abst WED-G-166.

Talnetant



Talnetant (SB-223412) is an NK_3 antagonist in development at GlaxoSmithKline for use in several different disorders. Phase II trials are in progress in irritable bowel syndrome (IBS), as well as schizophrenia and overactive bladder.

TC-2403



The neuronal nicotinic receptor agonist TC-2403, the result of a collaboration between Targacept and Dr. Falk, has reached phase II clinical evaluation as an enema for the treatment of ulcerative colitis. An oral, delayed-release formulation is also in active development.

Teduglutide

[2-Glycine]-1-33-glucagon-like peptide II (human)

NPS Pharmaceuticals has initiated a proof-of-concept study of teduglutide (ALX-0600) for the treatment of patients with Crohn's disease. Following previous clinical tests showing that teduglutide produces a significant growth effect on cells that line the intestine, the new trial is aiming to duplicate the result in Crohn's patients. The multicenter, dose-ranging study will enroll approximately 100 patients with active Crohn's disease. Three groups will receive various doses of teduglutide, and a fourth group will receive a placebo, all administered by daily subcutaneous injections over 8 weeks. The primary endpoint will be a reduction in the CDAI. Results are anticipated by the end of 2004. Teduglutide is a derivative of the naturally occurring protein glucagon-like peptide-2 (GLP-2) involved in the regulation of various processes of the gastrointestinal tract (1).

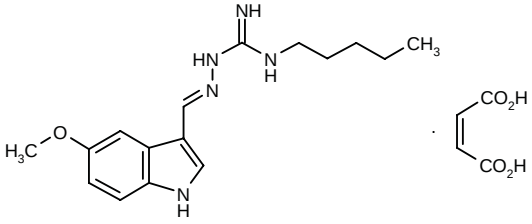
The company also initiated a pivotal phase III study of teduglutide in patients with short bowel syndrome. The multicenter, double-blind, international trial will randomize some 80 patients to receive daily subcutaneous injections of teduglutide (0.05 or 0.10 mg/kg) or placebo for 6 months. The primary endpoint is a reduction in the use of

intravenous feeding, often required to sustain life in patients with this disorder. Teduglutide has orphan drug status in the U.S. and E.U. for this indication (2).

1. *Proof-of-concept study of teduglutide for Crohn's disease*. DailyDrugNews.com (Daily Essentials) Oct 10, 2003.

2. *Pivotal phase III trial studies teduglutide for short bowel syndrome*. DailyDrugNews.com (Daily Essentials) April 8, 2004.

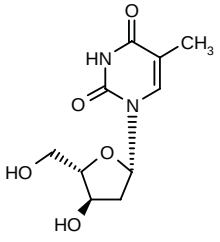
Tegaserod Maleate



Tegaserod maleate (Zelnorm™, Zelmac®) is the first compound in the class of 5-HT_4 receptor partial agonists developed to target the gastrointestinal tract. Launched in over 50 countries for use in women with constipation-predominant IBS, Novartis continues to investigate the drug for other uses. It is under review in the U.S. for the treatment of chronic constipation and phase II clinical studies are under way in functional dyspepsia and GERD.

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

Telbivudine



Telbuvidine (LdT, L-deoxythymidine, LDT-600), presently in phase III clinical trials, is Idenix's first drug candidate for the treatment of HBV. Telbuvidine is the L-enantiomer of thymidine, a natural building block of DNA, and shows high selectivity for the hepatitis B virus. The nucleoside specifically targets the DNA polymerase enzyme responsible for the replication of HBV. Novartis licensed the rights to this compound along with Idenix's other anti-HBV agent valtorcitabine (see below) and the anti-HCV therapy NM-283 (see above) last year; under their agreement, Idenix retains copromotion rights for the U.S. and a number of European countries (1-3).

Six healthy volunteers and 18 patients with mild, moderate or severe hepatic impairment were given a single dose of 600 mg of telbivudine. Hepatic impairment had no significant effects on overall drug exposure, and therefore no dose adjustment is needed in these patients. Telbivudine is mainly eliminated by renal clearance and thus renal impairment may severely affect drug exposure. Twenty-nine patients with normal and impaired renal function received a single dose of telbivudine, adjusted according to renal impairment. A similar level of drug exposure was found for 600 mg of telbivudine in normal subjects and patients with mild renal impairment, 400 mg in patients with moderate renal impairment, and 200 mg in those with severe renal impairment (4).

A multicenter, randomized, phase IIb clinical trial evaluated the efficacy and safety of telbivudine in the treatment of chronic hepatitis B. A total of 104 adult patients were treated with telbivudine alone (400 or 600 mg p.o. once daily), lamivudine alone (100 mg p.o. once daily) or a combination of both drugs for 52 weeks. At the end of the study, the median reductions in serum HBV DNA levels were significantly higher with telbivudine (either alone or combined with lamivudine) compared to lamivudine alone. The percentage of patients who had achieved normal serum ALT levels at the end of the treatment period was 63% with lamivudine monotherapy, 86% with telbivudine monotherapy and 78% with the combination regimen (5).

1. *Novartis and Idenix Pharmaceuticals, Inc., announce successful closing of strategic alliance. Innovative collaboration to advance antiviral therapeutic franchise.* Idenix Pharmaceuticals, Inc. Press Release 2003, May 9.

2. *Novartis closes two strategic acquisitions in pharmaceuticals.* Novartis Press Release 2003, May 9.

3. *Novartis set for strategic expansion into antiviral medicines through acquisition of 51% of Idenix, a Cambridge MA-based biotech company.* Novartis Press Release 2003, March 26.

4. Zhou, X.J., Myers, M., Chao, G., Dubuc, G., Brown, N. *Clinical pharmacokinetics of telbivudine, a potent antiviral for hepatitis B, in subjects with impaired hepatic or renal function*. J Hepatol 2004, 40(Suppl. 1): Abst 452.

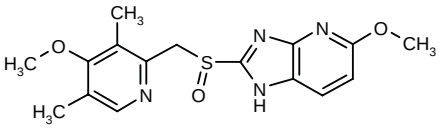
5. Han, S.H., Leung, N.W.Y., Teo, E.K. et al. *Results of a one-year international phase IIB trial of LDT, and LDT plus lamivudine, in patients with chronic hepatitis B*. J Hepatol 2004, 40(Suppl. 1): Abst 42.

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

Additional References

Lai, C.L. et al. *A phase IIb comparative trial of LdT, lamivudine, and the combination in hepatitis B patients: Greater antiviral effect with LdT*. 43rd Intersci Conf Antimicrob Agents Chemother (Sept 14-17, Chicago) 2003, Abst V-1723.

Tenatoprazole



Tenatoprazole (TU-199) is a proton pump inhibitor with a prolonged half-life in early clinical development at Negma, under license from Mitsubishi Pharma, for the treatment of peptic ulcer disease and GERD.

An open-label, randomized, crossover clinical trial administered tenatoprazole (20 and 40 mg p.o. once daily) or esomeprazole (40 mg p.o. once daily) for 7 days to 18 healthy volunteers. The median 24-h gastric pH values measured during each treatment period were 4.6 with tenatoprazole 40 mg, 4.0 with tenatoprazole 20 mg and 4.2 with esomeprazole. The respective nighttime median pH values were 4.7, 4.1 and 3.6. Tenatoprazole 40 mg/day was also associated with shorter nocturnal acid breakthroughs and a longer period of time with pH values > 4 at night compared to esomeprazole (1).

The early effects of tenatoprazole were evaluated in an open-label, crossover clinical trial in which 24 healthy volunteers were randomized to receive tenatoprazole (40 mg p.o. once daily) or esomeprazole (40 mg p.o. once daily) 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 during both the first night (4.24 *vs.* 2.92) and the second night (4.53 *vs.* 3.24) (2).

The maintenance of the effects induced by tenatoprazole and esomeprazole on gastric acid output was assessed in a single-blind, randomized, crossover trial in 30 healthy volunteers. Each patient received tenatoprazole (40 mg p.o. once daily) or esomeprazole (40 mg p.o. once daily) for 7 days, and gastric pH was measured at baseline, at the end of the treatment period, and 3 and 5 days after 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 (3).

1. Galmiche, J-P., Ducrotte, P., Bruley des Varannes, B. et al. *Tenatoprazole, a novel proton pump inhibitor with a porolonged 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.

2. Galmiche, J-P., Bruley des Varannes, B., 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. Chowdhury, S.K., James, C., Fiorentini, P. et al. *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.

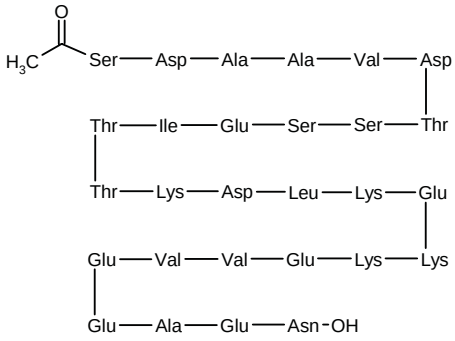
Original monograph – Drugs Fut 1994, 19(11): 1018.

TheraCLEC™

The FDA has designated Altus Biologics' TheraCLEC™ a fast track product for the treatment of malabsorption due to exocrine pancreatic insufficiency. TheraCLEC™ is a novel, orally delivered enzyme replacement therapy designed to replace digestive enzymes in patients suffering from pancreatic insufficiency. An international pivotal phase II trial was scheduled to begin in the first quarter of 2004 to determine the safety and efficacy of TheraCLEC™ in the treatment of malabsorption due to pancreatic insufficiency in patients with cystic fibrosis. TheraCLEC™, which also has orphan drug status, has previously been shown to be clinically active and well tolerated in cystic fibrosis patients with severe pancreatic insufficiency (1).

1. *Fast track designation for TheraCLEC*. DailyDrugNews.com (Daily Essentials) Dec 3, 2003.

Thymalfasin



SciClone has completed enrollment of 500 patients in the first of 2 phase III hepatitis C (HCV) clinical trials evaluating its lead immune system-enhancing drug thymalfasin (Zadaxin®), a pure synthetic preparation of thymosin α1 approved in over 30 countries and marketed in China and selected other countries for various viral and oncological indications. The company intends to complete enrollment of the second phase III trial by the end of the first quarter of 2004. The trials will include HCV patients who have failed to respond to prior FDA- approved HCV therapies. The trials are multicenter, randomized, double-blind studies. The first trial includes HCV patients without evidence of cirrhosis of the liver and the second trial includes HCV patients with mild cirrhosis of the liver. In each of the trials, patients are assigned to a 12-month

course of either thymalfasin and pegylated interferon alfa or placebo and pegylated interferon alfa. After completing treatment, the patients will be followed for a 6-month observation period. Primary endpoints are a sustained virological response (clearance of HCV from the blood) and an improvement in the liver histological activity index measured at the end of the 6-month observation period. The company also reported data from a pilot study showing that thymalfasin in combination with pegylated interferon alfa and ribavirin produced a virological response in 61% of HCV-infected nonresponders (1, 2). Thymalfasin is also being studied for use in other indications; a phase II study in malignant melanoma is under way in Europe, two phase II pilot liver cancer studies are being conducted in the U.S., as is a pilot hepatitis C triple therapy trial in Mexico, and a phase III hepatitis B trial has been completed in Japan, with filing for this indication in that country expected by the end of the year (3).

SciClone is exploring the possibility of increasing the efficacy of current treatment for chronic HBV infection in a randomized, placebo-controlled trial in Taiwan using a high dose of thymalfasin in combination with lamivudine. In the new combination study, one group of patients receives a high dose of thymalfasin (3.2 mg twice weekly) for 6 months plus a standard dose of lamivudine (100 mg once daily) for 12 months. The other group of patients receives the same dose of lamivudine for 12 months plus a placebo. Upon completing the 12 months of therapy, each patient will be followed for a 6-month observation period. The primary objective of this study is to demonstrate that patients receiving the thymalfasin/lamivudine combination therapy could achieve a significantly higher sustained response rate than patients receiving lamivudine monotherapy, while limiting the use of lamivudine to 1 year. Endpoints include the disappearance of HBV DNA and the achievement of sustained seroconversion. Some 120 patients with chronic HBV will be enrolled by the end of 2004. SciClone has a U.S. patent for the treatment of hepatitis B using thymalfasin in combination with lamivudine that does not expire until 2018. In a phase III trial in Japan, thymalfasin monotherapy demonstrated sustained seroconversion in 19% of patients receiving a low dose (0.8 mg twice weekly) and in 22% of patients receiving the standard dose (1.6 mg twice weekly (4).

The Triple Therapy Trial is an ongoing, open-label, pilot study that is evaluating the efficacy and safety of a combination of thymalfasin (1.6 mg every 2 weeks), pegylated interferon alfa-2a (Pegasys®; Roche; 180 μg once weekly) and ribavirin (800-1000 mg daily) to treat patients with HCV infection unresponsive to previous treatment with interferon alfa plus ribavirin. The trial will administer the triple regimen to 50 nonresponders for 12 months and will follow them for another 6 months after the end of therapy. An interim analysis of the first 22 patients to complete 24 weeks of triple therapy showed that 41% were negative for HCV RNA and 50% had a reduction of at least 2 $\log_{10}$ in the plasma levels of HCV RNA. No significant adverse events were associated with thymalfasin (5).

1. *Phase III hepatitis C trial of Zadaxin enrolled*. DailyDrugNews.com (Daily Essentials) Sept 29, 2003.

2. *SciClone reports Q3 R&D highlights*. SciClone Pharmaceuticals Press Release 2003, Oct 27.

3. *Zadaxin shows efficacy in preclinical invasive aspergillosis study*. DailyDrugNews.com (Daily Essentials) March 3, 2004.

4. *Zadaxin in combination with lamivudine investigated for hepatitis B*. DailyDrugNews.com (Daily Essentials) April 16, 2004.

5. *SciClone reports data: 41% of hepatitis C non-responder patients test HCV RNA negative after 24 weeks of Zadaxin triple therapy*. SciClone Pharmaceuticals Press Release 2004, Feb 18.

TJN-219

Tsumura continues to evaluate a potential new treatment for hemorrhoids, TJN-219 (MPEC), in phase II clinical studies.

Tocilizumab

Tocilizumab (atlizumab, MRA, R-1569) is a humanized anti-IL-6 receptor antibody that inhibits the function of the cytokine. It is being developed by Roche and Chugai in collaboration with Osaka University. The partnership was set up under the first licensing agreement between the two companies in 2003, whereby Roche will promote it in all countries except Japan, South Korea and Taiwan, and the parties will copromote the product in the U.K., France and Germany. Tocilizumab was submitted for regulatory approval in Japan last year for the orphan indication of Castleman's disease, and it is in phase II/III clinical development for rheumatoid arthritis, phase II clinical development for Crohn's disease, juvenile idiopathic arthritis and multiple myeloma, and phase I clinical trials for systemic lupus erythematosus (1).

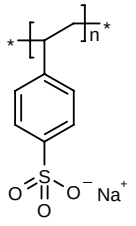
A multicenter, double-blind clinical trial randomized 36 patients with active Crohn's disease refractory to conventional therapies to supplement their baseline treatments with placebo or tocilizumab (8 mg/kg once every 2 or 4 weeks) for 12 weeks. Clinical response, which was defined as a reduction of at least 70 points in the baseline CDAI of the patients, was achieved in 80% of patients who received tocilizumab every 2 weeks, in 42% of those treated with tocilizumab every 4 weeks, and in 31% of placebo-treated patients. The administration of tocilizumab every 2 weeks was also associated with clinical remission in 20% of the patients, an increase in the mean Inflammatory Bowel Disease Questionnaire score, and normalization of erythrocyte sedimentation rates and serum C-reactive protein levels. The drug was safe and well tolerated, with a similar incidence of adverse events in all study groups (2).

1. *MRA potentially effective for adult rheumatoid arthritis*. DailyDrugNews.com (Daily Essentials) Nov 14, 2003.

2. Ito, H., Takazoe, M., Fukuda, Y. et al. *An exploratory randomized trial of a human anti-interleukin-6 receptor monoclonal antibody MRA in active Crohn's disease*. 11th United Eur Gastroenterol Week (Nov 1-5, Madrid) 2003, Abst OPG-19.

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

Tolevamer Sodium



Genzyme has reported positive results from a preliminary analysis of the phase II trial of tolevamer sodium (GT-160-246), an investigational polymer therapy for patients with *Clostridium difficile*-associated diarrhea (CDAD). The randomized, double blind, active-controlled study enrolled 289 patients at 58 sites in the U.S., Canada and the U.K. and compared the safety and efficacy of tolevamer sodium capsules at daily dose levels of 3 and 6 g, *versus* the standard prescribed oral dose of vancomycin (125 mg p.o. once daily). The study evaluated patients with mild to moderate disease, and included patients with a first episode of CDAD, as well as those with recurrent disease. The primary endpoint was the noninferiority of tolevamer to vancomycin with respect to time to resolution of diarrhea. Preliminary data show tolevamer met this endpoint at the 6-g dose level and was found to be similar to vancomycin in median days to resolution of diarrhea (2 days for vancomycin *versus* 2.5 days for tolevamer 6 g). There was also a similar frequency of recurrence of diarrhea after initial successful resolution of symptoms, with 22% of patients taking vancomycin experiencing a recurrence of CDAD compared to 19% of patients taking tolevamer 6 g (1). In the final analysis, the higher dose of tolevamer was associated with a lower rate of recurrence (10%) compared to vancomycin (19%) (2).

Tolevamer is being developed as a novel, nonabsorbed, nonantibiotic therapy for the treatment of CDAD under fast track designation. The drug acts in the gastrointestinal tract, binding to toxins that cause CDAD. Genzyme is also developing a liquid formulation of tolevamer and plans to partner the product for further development and commercialization (1).

1. *Positive preliminary results announced for tolevamer in C. difficile diarrhea*. DailyDrugNews.com (Daily Essentials) Oct 23, 2003.

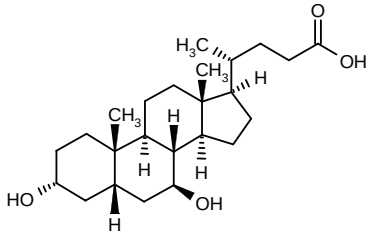
2. Louie, T., Peppe, J., Watte, C.K. et al. *A phase 2 study of the toxin binding polymer tolevamer in patients with C. difficile-associated diarrhea*. Gastroenterology 2004, 126(4, Suppl. 2): Abst T1785.

Traficet-EN™

Traficet-EN™ is a highly potent, specific, orally available, small-molecule antiinflammatory agent designed at ChemoCentryx as a treatment for IBD. The compound antagonizes a chemokine receptor implicated in both ulcerative colitis and Crohn's disease. By selectively binding to a chemokine receptor involved in the trafficking of lymphocytes to the bowel, Traficet-EN™ inhibits the migration of such cells to the intestinal mucosa in models of Crohn's disease and ulcerative colitis, alleviating inflammation in the large and small intestine. Efficacy has been achieved in both therapeutic and prophylactic models of IBD. Traficet-EN™ is designed to be taken orally once a day. In the last quarter of 2003, ChemoCentryx initiated phase I trials of Traficet-EN™ in healthy adult volunteers in the U.K. The trials will assess the safety and pharmacokinetic properties of Traficet-EN™, first in a single-dose regimen and subsequently as multiple doses. Both studies are expected to be completed in the second quarter of 2004 (1).

1. *New phase I trial for Traficet-EN*. DailyDrugNews.com (Daily Essentials) Jan 15, 2004.

Ursodiol



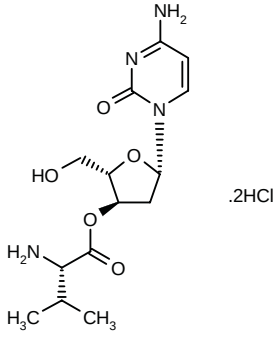
Ursodiol (ursodeoxycholic acid) is marketed by Axcan as URSO® and Delursan® as a treatment for cholestatic liver diseases, including primary biliary cirrhosis, sclerosing cholangitis and liver disorders related to cystic fibrosis. Mitsubishi Pharma is also evaluating its potential use in hepatitis C, for which it is now in phase III clinical studies.

UT-231B

United Therapeutics' lead iminosugar UT-231B, in phase II clinical testing for hepatitis C, appears to be able

to pass through cellular membranes and enter the endoplasmic reticulum, where it alters viral assembly and prevents the virus from infecting and replicating in other cells.

Valtorcitabine Dihydrochloride



Idenix is performing phase I/II clinical trials with the nucleoside analogue valtorcitabine dihydrochloride (val-LdC, LDC-300) as a second drug candidate for hepatitis B virus (HBV) infection after telbivudine (see above). A phase IIb trial evaluating valtorcitabine in combination with telbivudine in HBV is expected to begin this year. Both compounds have demonstrated potent and selective activity against HBV in laboratory studies and animal models, as well as synergistic effects when used in combination. The company entered into a licensing agreement with Novartis last year covering valtorcitabine, whereby Novartis will be responsible for worldwide development and marketing; Idenix and Novartis will copromote the drug in the U.S. and several European markets (1-3).

1. *Novartis and Idenix Pharmaceuticals, Inc. announce successful closing of strategic alliance. Innovative collaboration to advance antiviral therapeutic franchise*. Idenix Pharmaceuticals, Inc. Press Release 2003, May 9.

2. *Novartis closes two strategic acquisitions in pharmaceuticals*. Novartis Press Release 2003, May 9.

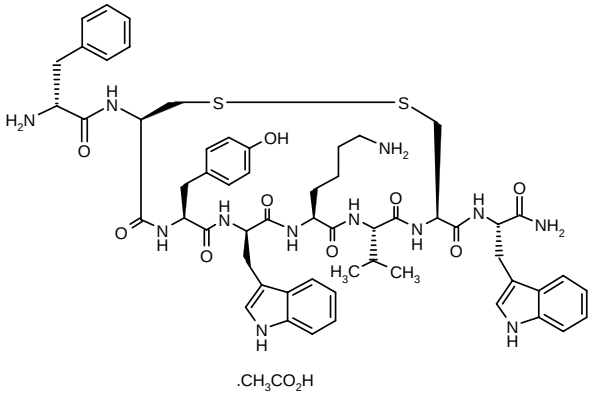
3. *Novartis set for strategic expansion into antiviral medicines through acquisition of 51% of Idenix, a Cambridge MA-based biotech company.* Novartis Press Release 2003, March 26.

Vapaliximab

BioTie Therapies completed the first phase I study of the chimeric anti-VAP-1 monoclonal antibody vapaliximab (BTT-1002, HUVAP7) in 2003 and, although it was well tolerated by healthy volunteers, the pharmacokinetics were not considered suitable for the treatment of chronic diseases for which the product is targeted (rheumatoid arthritis, asthma, hepatitis, psoriasis and inflammatory bowel diseases, including Crohn's disease and ulcerative colitis). The company and collaborators at Seikagaku therefore decided to modify its molecular structure and pursue the development of humanized (nonchimeric) and fully human VAP antibodies. Vapaliximab was developed in collaboration with Cambridge University, the University of Turku and Boehringer Ingelheim (1).

1. *BioTie Therapies reports 2003 year-end R&D highlights*. BioTie Therapies Press Release 2004, Jan 28.

Vapreotide Acetate

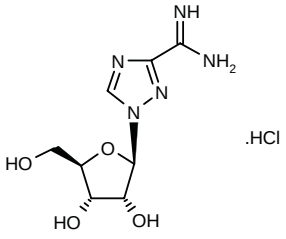


H3 Pharma, a Debiopharm subsidiary, has submitted an NDA for an immediate-release formulation of the somatostatin analogue vapreotide acetate (Sanvar® IR) for the acute treatment of esophageal variceal bleeding (EVB) to stop hemorrhage prior to endoscopic intervention and to prevent recurring bleeding during the critical 5 days following treatment. The company plans to conclude commercialization agreements with third parties in the Americas and Europe in 2004 and anticipates a launch in the U.S., where the product has orphan drug status, in 2005. The Sanvar® IR formulation was submitted for registration in Mexico in December 2003, and European submission is planned for late 2004. In a phase III study in 227 patients at 22 centers Sanvar® IR significantly reduced active bleeding. Survival with hemostasis at 5 days was achieved significantly more often with Sanvar® IR than with placebo. In patients with control of bleeding at day 5, Sanvar® IR significantly increased hemostasis and survival through day 42. H3 Pharma is also developing a 3-month sustained-release (SR) formulation of vapreotide for the management of life-long symptoms of carcinoid tumors and acromegaly, for which it has orphan drug designation. Sustained-release vapreotide has also demonstrated positive effects on the clinical symptoms of Crohn's disease, with phase III clinical trials expected to commence in the spring of 2004 (1). H3 Pharma obtained worldwide research, development and commercialization rights to vapreotide from Debiopharm, a shareholder in the company, last year.

1. *H3 Pharma submits Sanvar IR NDA*. DailyDrugNews.com (Daily Essentials) March 4, 2004.

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

Viramidine Hydrochloride



Following a meeting with the FDA, the former ICN, now Valeant, decided in the fall of 2003 to begin phase III clinical trials of its antiviral compound viramidine hydrochloride, a nucleoside analogue the company is developing for the oral treatment of HCV. Viramidine is converted to ribavirin by adenosine deaminase in the liver. The company will test viramidine's effect on the virus in combination with pegylated interferon. At the meeting, ICN presented interim analyses of 12 weeks of clinical data from a phase II trial in 180 patients. The trial was designed to treat patients for 48 weeks, take the patients off therapy for an additional 24 weeks, and then determine the percentage of patients with undetectable virus in the blood, as well as the incidence of hemolytic anemia at the end of the entire 72-week study period. Analysis of the 12-week data showed that viramidine, in combination with pegylated interferon, produced a clinically significant reduction in viral load. In addition, when compared with ribavirin, viramidine produced approximately half the drop in hemoglobin levels at week 4, which was maintained throughout week 12 and will compare viramidine and ribavirin in conjunction with pegylated interferon (1).

Valeant subsequently initiated the first of the global phase III studies for oral viramidine for the treatment of hepatitis C. The trials will be conducted at some 80 sites, enrolling around 1,000 patients in each study and will compare viramidine and ribavirin in conjunction with pegylated interferon. Enrollment in the first study, known as VISER1 (VIramidine's Safety and Efficacy vs. Ribavirin), has commenced and is expected to be completed in 2004. The second phase III study, known as VISER2, is scheduled to commence by mid-2004 with investigator meetings in the U.S., Europe and Australia. Enrollment will commence shortly thereafter. The studies will compare viramidine and ribavirin, each in conjunction with a pegylated interferon. The first study will use Schering-Plough's PegIntron (peginterferon alfa-2b), and the second will use Roche's Pegasys (peginterferon alfa-2a). Patients will be treated for either 24 or 48 weeks, depending on viral genotypes, and will then have an additional 24 weeks off therapy. The number of patients with undetectable virus in their blood and the incidence of anemia over the course of 72 weeks will be monitored (2).

The company also recently reported 24-week data from the above-mentioned phase II trial. The 24-week data show that viramidine demonstrated antiviral activity comparable to that of ribavirin when used in combination with peginterferon alfa-2a in treatment-naïve patients, but with a significantly lower incidence of hemolytic anemia (2% *vs*. 24%). Following 24 weeks of treatment, there was no significant difference between viramidine (800-1600 mg/day) and ribavirin in the proportion of patients with at least a 2 $\log_{10}$ reduction in or nondetectable HCV RNA. There were also significantly fewer patients in the viramidine groups with anemia when compared with the ribavirin arm. Among patients receiving viramidine doses of 400 and 600 mg b.i.d., there were no cases of defined anemia (3-6).

A placebo-controlled clinical trial was conducted to determine the safety and pharmacological profile of single doses of viramidine (200, 600 and 1200 mg p.o.) in 30 healthy volunteers. The area under the curve and the peak plasma concentration of viramidine increased with dose, although the latter was consistently reached at 2.5 h postdose at all doses. Viramidine was quickly converted to ribavirin, which showed an apparent half-life of 54-123 h. Peak plasma concentrations of ribavirin increased with dose and were reached at 1.5-3.0 h postdose. No dose effects were found in the renal clearance of viramidine or ribavirin. The most common adverse events during the study were headache, upper respiratory tract infections, sore throat, nasal congestion, nausea and cough, most of which were mild and none of which was serious. A substudy that included the 10 subjects receiving 600 mg of viramidine and 27 additional volunteers was conducted to determine the effects of food on the safety and pharmacokinetics of viramidine. Following a crossover study design, the volunteers received single doses of 600 mg of viramidine after an overnight fast or 1 h after eating a high-fat breakfast. Coadministration with a high-fat meal delayed absorption, increased the half-life, area under the curve and peak plasma concentration of both viramidine and ribavirin, and had no significant effects on the safety profile of viramidine (7).

1. *Viramidine heads for late-stage clinical testing*. DailyDrugNews.com (Daily Essentials) Nov 7, 2003.

2. *Phase III program underway for viramidine*. DailyDrugNews.com (Daily Essentials) Feb 2, 2004.

3. *Data reported from viramidine phase II trial*. DailyDrugNews.com (Daily Essentials) March 10, 2004.

4. Gish, R., Arora, S., Nelson, D., Fernandez, H., Lamon, K. *Safety and efficacy of viramidine in combination with pegylated interferon alfa-2a for treatment of hepatitis C in therapy-naïve patients*. J Hepatol 2004, 40(Suppl. 1): Abst 479.

5. Gish, R., Nelson, D., Arora, S. et al. *Hepatitis C combination therapy with viramidine and peginterferon alfa-2a reduces potential for ribavirin-related hemolytic anemia.* Gastroenterology 2004, 126(4, Suppl. 2): Abst 406.

6. Arora, S., Gish, R., Nelson, D. et al. *Clinical study of viramidine in treatment of hepatitis C supports RBC-sparing mechanism of action.* Gastroenterology 2004, 126(4, Suppl. 2): Abst 84.

7. Lin, C.-C., Philips, L., Xu, C., Yeh, L.-T. *Pharmacokinetics and safety of viramidine, a prodrug of ribavirin, in healthy volunteers*. J Clin Pharmacol 2004, 44(3): 265.

Visilizumab

Visilizumab (Nuvion®; Protein Design Labs) is a humanized non-FcR-binding monoclonal antibody directed at the CD3 antigen on activated T-cells, implicated as the primary immune cells mediating the induction and progression of certain autoimmune diseases. Although its mechanism of action is still being characterized, early research has demonstrated that visilizumab induces selective apoptosis of activated, but not resting, T-cells *in vitro*, which may provide therapeutic benefit in autoimmune diseases such as inflammatory bowel disease (IBD). It is presently in phase I/II clinical testing for the treatment of ulcerative colitis. Future studies of visilizumab in other autoimmune diseases, *i.e.,* Crohn's disease and multiple sclerosis, are being considered.

Protein Design Labs reported encouraging findings from a phase I clinical study of the humanized antibody for ulcerative colitis. The trial enrolled 32 patients with severe ulcerative colitis refractory to treatment with intravenous steroids. Eight patients were treated in the initial dose cohort (15 μg/kg), with all patients responding and 7 of the 8 achieving remission. Mild to moderate constitutional symptoms consistent with the cytokine release syndrome were observed in all 8 patients. The transient symptoms were associated primarily with the initial infusion, with T-cell recovery occurring over 2-6 weeks. In the second dose cohort (10 μg/kg), 24 patients were treated, with 20 evaluable for response at day 30. Clinical response was achieved in 17 patients, of whom 11 achieved remission. Endoscopic improvement was maintained for up to 16 months in 16 patients. Transient symptoms consistent with the cytokine release syndrome were observed in 13 of 18 evaluable patients, occurring primarily with the first infusion. T-cell recovery occurred over 2-8 weeks with a mean of 3.25 weeks for the 15 μg/kg group and 2.7 weeks for the 10 mcg/kg group. Activity in the phase I trial was evaluated as a reduction in the Modified Truelove and Witts Severity Index (MTWSI) score, with remission defined as achievement of an MTWSI score of < 4 at 30 days following treatment. A clinical response was defined as achievement of an MTWSI score of < 10 at 30 days. PDL is enrolling patients into an ongoing phase I/II trial of visilizumab in the severe ulcerative colitis setting. The study, initiated in the fourth quarter of 2003, is exploring 4 dose levels of visilizumab (5-12.5 μg/kg) given intravenously on days 1 and 2 as a bolus injection. Following the stage I portion of the study, up to an additional 20 patients will be treated at the optimal clinical dose in the stage II portion. If subsequent studies are allowed to serve as the basis for regulatory approval, a U.S. regulatory submission could occur by the end of 2006 (1-3).

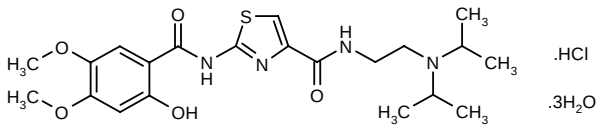
1. *Protein Design Labs reports Q3 R&D highlights*. Protein Design Labs Press Release 2003, Nov 3.

2. *Protein Design Labs reports clinical data for visilizumab and fontolizumab*. DailyDrugNews.com (Daily Essentials) March 24, 2004.

3. 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.

Original monograph – Drugs Fut 2002, 27(5): 469.

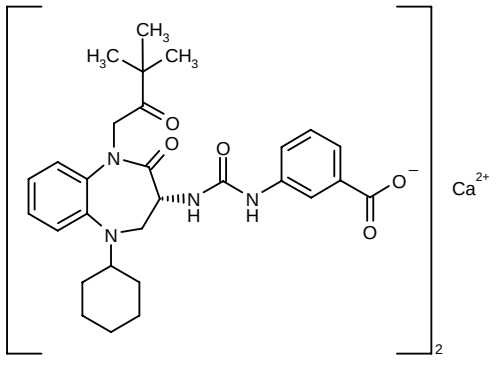
Z-338 (YM-443)



Zeria and Yamanouchi are collaborating on the development of Z-338 (YM-443) for the treatment of functional gastrointestinal disorders. A gastroprokinetic acetylcholine release enhancer, Z-338 is in phase II clinical trials in Europe and phase I studies in Japan for the treatment of functional dyspepsia.

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

Z-360



Phase I clinical trials are in progress at Zeria with Z-360, a selective cholecystokinin CCK_2 antagonist, for use in both GERD and gastric and duodenal ulcer.