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Annual Update 2004/2005 - Treatment of Musculoskeletal Disorders

As in previous issues, the goal of this section is to present a balanced picture of the current status of therapies for musculoskeletal disorders in the clinical stage, summarizing in a few pages the most important advances in this area over the last year or so. A table of oncolytic drugs for the treatment of sarcoma has been included at the end of this review.

J.R. Prous
Editor

Treatment of Musculoskeletal Disorders by Condition

Condition	Phase	Drug	Source
Amyloidosis, amyloid A	II/III	Fibrillex™	Neurochem/Centocor (Johnson & Johnson)
Ankylosing spondylitis	L-2003 (EU)	Infliximab[1]	Schering-Plough
	R-2004 (US)	Infliximab[1]	Centocor (Johnson & Johnson)
	Prereg.	Etoricoxib[1,2]	Merck & Co.
	III	Adalimumab[1,2]	Abbott
Arthritis	R-2004	BSP-201	BSP Pharma
	II	CS-706	Sankyo
	I-II	Cimicoxib[2]	Uriach
	I	ERB-196	Wyeth
	I	MX-1094	Medinox
	Discontinued	S-3013	Shionogi/Lilly
Gout	Prereg. (US, JP)	Febuxostat[2]	TAP Pharmaceutical/Teijin
	III (EU)	Febuxostat[2]	Ipsen/Teijin
	II	PEG-Rasburicase	Savient Pharmaceuticals
	Discontinued	Oxypurinol	Cardiome
Lupus nephritis	III	Tacrolimus[1,2]	Fujisawa
	Clinical	Mycophenolate mofetil[1,2]	Aspreva
	Clinical	Rituximab[1]	Genentech/Biogen Idec/Roche
Osteoarthritis	III	Licofelone[2]	Merckle/EuroAlliance
	III	Lumiracoxib[2]	Novartis
	III	Zucapsaicin	Winston Laboratories
	II/III	LAS-34475	Almirall Prodesfarma
	II	AMG-108	Amgen
	II	Anakinra[1]	Amgen
	II	AZD-9056	AstraZeneca
	II	Clodronate disodium[1,2]	Abiogen
	II	CPA-926	Kureha
	II	CRx-102	CombinatoRx
	II	Efipladib	Wyeth
	II	HCT-3012[2]	NicOx
	II	SD-6010	Pfizer
	I	462795	GlaxoSmithKline
	I	AD-827	Arakis
	I	AZD-8955	AstraZeneca
	I	Ono-4817	Ono Pharmaceutical
	Suspended	Pralnacasan	Vertex
	Discontinued	S-3536	Shionogi

Continuation

Treatment of Musculoskeletal Disorders by Condition

Condition	Phase	Drug	Source
Psoriatic arthritis	L-2004 (EU)	Infliximab[1]	Schering-Plough
	L-2004	Leflunomide[1,2]	Aventis Pharma (Sanofi-Aventis)
	Prereg.	Adalimumab[1,2]	Abbott
	Prereg. (US)	Infliximab[1]	Centocor (Johnson & Johnson)
	II	Alefacept[1,2]	Biogen Idec
	Discontinued	Efalizumab[1,2]	Xoma/Genentech
Rheumatoid arthritis	Prereg.	Abatacept	Bristol-Myers Squibb
	Prereg.	Iguratimod[2]	Toyama/Eisai
	Prereg. (JP)	Tacrolimus[1,2]	Fujisawa
	III	Certolizumab pegol	UCB Pharma/Nektar Therapeutics
	III	CPH-82	Meda/Conpharm
	III	Lumiracoxib[2]	Novartis
	III (US)	Tacrolimus[1,2]	Fujisawa
	III	Tocilizumab[2]	Chugai/Roche
	II/III	Rituximab[1]	Genentech/Biogen Idec/Roche
	II	274150	GlaxoSmithKline
	II	AD-452	Arakis
	II	AMG-162	Amgen
	II	AMG-714	Amgen
	II	Apratastat	Wyeth
	II	AT-001	Androclus Therapeutics
	II	AZD-9056	AstraZeneca
	II	Belimumab	Human Genome Sciences
	II	C-4462	Merck & Co.
	II	CF-101[2]	Can-Fite Biopharma
	II	CRx-102	CombinatoRx
	II	CRx-119	CombinatoRx
	II	CRx-150	CombinatoRx
	II	Doramapimod	Boehringer Ingelheim
	II	Dronabinol/cannabidiol	GW Pharmaceuticals
	II	Eculizumab[2]	Alexion
	II	Efipladib	Wyeth
	II	Golimumab	Centocor (Johnson & Johnson)
	II	IL-1 Trap	Regeneron
	II	K-832	Kowa
	II	MLN-1202	Millennium
	II	MM-093	Merrimack
	II	Natalizumab[1,2]	Elan/Biogen Idec
	II	Paclitaxel[1,2]	Angiotech
	II	PMX-53	Promics
	II	PRO-70769 (R-1594)	Genentech/Roche/Biogen Idec
	II	Rosiglitazone maleate[1,2]	GlaxoSmithKline
	II	SCIO-469	Scios
	II	SMP-114	Sumitomo Pharmaceuticals
	II (EU)	Tacrolimus[1,2]	Fujisawa
	II (?)	Tadekinig alfa	Serono
	II	TAK-715	Takeda
	II	Temsirolimus[2]	Wyeth
	II	Zoledronic acid monohydrate[1,2]	Novartis
	I/II	AVE-9940	Aventis Pharma (Sanofi-Aventis)
	I/II	CDP-484	UCB Pharma/Nektar Therapeutics
	I/II	CRx-139	CombinatoRx
	I/II	HuMax™-CD20	Genmab
	I/II	YS-IL-6	Y's Therapeutics
	I	681323	GlaxoSmithKline
	I	ACZ-885	Novartis
	I	AZD-8309	AstraZeneca
	I	C-7198	Merck & Co.
	I	C-9101	Merck & Co.
	I	C-9787	Merck & Co.
	I	CDP-323	UCB Pharma
	I	DE-096	Santen
	I	ERB-041	Wyeth
	I	INCB-3284	Incyte
	I	LTβR-Ig	Biogen Idec

Continuation

Treatment of Musculoskeletal Disorders by Condition

Condition	Phase	Drug	Source
Rheumatoid arthritis	I	M-40419	MetaPhore
	I	MLN-3897 (AVE-9897)	Millennium/Aventis Pharma (Sanofi-Aventis)
	I	R-1295	Roche
	I	R-1503	Roche
	I	R-1594	Roche
	I	R-406	Rigel
	I	SC-12267	4SC/Serono
	I	STA-5326	Synta Pharmaceuticals
	I	TACI-Ig	Serono/ZymoGenetics
	I	tgAAC-94	Targeted Genetics
	I	TRU-015	Trubion Pharmaceuticals
	I	VX-702	Vertex
	Suspended	Pralnacasan	Vertex
	Discontinued	AGIX-4207	AtheroGenics
	Discontinued	APT-070	Inflazyme
	Discontinued	ISIS-104838	Isis Pharmaceuticals
	Discontinued	Ismomultin alfa	Organon
	Discontinued	MEDI-522	MedImmune
	Discontinued	NGD-2000-1	Neurogen
	Discontinued	Org-37663	Organon
	Discontinued	SIM-916	Wyeth/ArQule
Rheumatoid arthritis, juvenile	III	Adalimumab[1,2]	Abbott
	III	Infliximab[1]	Schering-Plough/Centocor (Johnson & Johnson)
	III	Tocilizumab[2]	Chugai/Roche
Sclerosis, systemic	I/II	Metelimumab[2]	Cambridge Antibody Technology/Genzyme
Sjögren's syndrome	III	Interferon alfa[1], low-dose oral	Amarillo Biosciences
	I/II	Epratuzumab	Immunomedics
Systemic lupus erythematosus	Prereg.	Abetimus sodium[2]	La Jolla Pharmaceutical
	Prereg.	Prasterone[2]	Watson/Genelabs Technologies
	II	Belimumab	Human Genome Sciences
	II	Epratuzumab	Immunomedics
	I/II	ET-201	EluSys
	I	ABR-215757	Active Biotech
	I	AMG-623	Amgen
	I	Edratide	Teva
	I	Interferon alfa kinoid	Neovacs
	I	TACI-Ig	Serono/ZymoGenetics
	I	Tocilizumab[2]	Chugai
	Clinical	Rituximab[1]	Genentech/Biogen Idec/Roche

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

Treatment of Musculoskeletal Disorders by Source

Source	Condition	Drug	Phase
4SC	Rheumatoid arthritis	SC-12267	I
Abbott	Ankylosing spondylitis	Adalimumab[1,2]	III
	Psoriatic arthritis	Adalimumab[1,2]	Prereg.
	Rheumatoid arthritis, juvenile	Adalimumab[1,2]	III
Abiogen	Osteoarthritis	Clodronate disodium[1,2]	II
Active Biotech	Systemic lupus erythematosus	ABR-215757	I
Alexion	Rheumatoid arthritis	Eculizumab[2]	II
Almirall Prodesfarma	Osteoarthritis	LAS-34475	II/III
Amarillo Biosciences	Sjögren's syndrome	Interferon alfa[1], low-dose oral	III
Amgen	Osteoarthritis	AMG-108	II
		Anakinra[1]	II
	Rheumatoid arthritis	AMG-162	II
		AMG-714	II
	Systemic lupus erythematosus	AMG-623	I
Androclus Therapeutics	Rheumatoid arthritis	AT-001	II
Angiotech	Rheumatoid arthritis	Paclitaxel[1,2]	II
Arakis	Osteoarthritis	AD-827	I
	Rheumatoid arthritis	AD-452	II
ArQule	Rheumatoid arthritis	SIM-916	Discontinued
Aspreva	Lupus nephritis	Mycophenolate mofetil[1,2]	Clinical
AstraZeneca	Osteoarthritis	AZD-8955	I
		AZD-9056	II
	Rheumatoid arthritis	AZD-8309	I
		AZD-9056	II
AtheroGenics	Rheumatoid arthritis	AGIX-4207	Discontinued
Aventis Pharma (Sanofi-Aventis)	Psoriatic arthritis	Leflunomide[1,2]	L-2004
	Rheumatoid arthritis	AVE-9940	I/II
		MLN-3897 (AVE-9897)	I
Biogen Idec	Lupus nephritis	Rituximab[1]	Clinical
	Psoriatic arthritis	Alefacept[1,2]	II
	Rheumatoid arthritis	LTβR-Ig	I
		Natalizumab[1,2]	II
		PRO-70769 (R-1594)	II
		Rituximab[1]	II/III
	Systemic lupus erythematosus	Rituximab[1]	Clinical
Boehringer Ingelheim	Rheumatoid arthritis	Doramapimod	II
Bristol-Myers Squibb	Rheumatoid arthritis	Abatacept	Prereg.
BSP Pharma	Arthritis	BSP-201	R-2004
Cambridge Antibody Technology	Sclerosis, systemic	Metelimumab[2]	I/II
Can-Fite Biopharma	Rheumatoid arthritis	CF-101[2]	II
Cardiome	Gout	Oxypurinol	Discontinued
Centocor (Johnson & Johnson)	Amyloidosis, amyloid A	Fibrillex™	II/III
	Ankylosing spondylitis	Infliximab[1]	R-2004 (US)
	Psoriatic arthritis	Infliximab[1]	Prereg. (US)
	Rheumatoid arthritis	Golimumab	II
	Rheumatoid arthritis, juvenile	Infliximab[1]	III
Chugai	Rheumatoid arthritis	Tocilizumab[2]	III
	Rheumatoid arthritis, juvenile	Tocilizumab[2]	III
	Systemic lupus erythematosus	Tocilizumab[2]	I
CombinatoRx	Osteoarthritis	CRx-102	II
	Rheumatoid arthritis	CRx-102	II
		CRx-119	II
		CRx-139	I/II
		CRx-150	II
Conpharm	Rheumatoid arthritis	CPH-82	III
Eisai	Rheumatoid Arthritis	Iguratimod[2]	Prereg.
Elan	Rheumatoid arthritis	Natalizumab[1,2]	II
EluSys	Systemic lupus erythematosus	ET-201	I/II
EuroAlliance	Osteoarthritis	Licofelone[2]	III
Fujisawa	Lupus nephritis	Tacrolimus[1,2]	III
	Rheumatoid arthritis	Tacrolimus[1,2]	Prereg. (JP)
		Tacrolimus[1,2]	III (US)
		Tacrolimus[1,2]	II (EU)
Genelabs Technologies	Systemic lupus erythematosus	Prasterone[2]	Prereg.

Continuation

Treatment of Musculoskeletal Disorders by Source

Source	Condition	Drug	Phase
Genentech	Lupus nephritis	Rituximab[1]	Clinical
	Psoriatic arthritis	Efalizumab[1,2]	Discontinued
	Rheumatoid arthritis	PRO-70769 (R-1594)	II
		Rituximab[1]	II/III
	Systemic lupus erythematosus	Rituximab[1]	Clinical
Genmab	Rheumatoid arthritis	HuMax™-CD20	I/II
Genzyme	Sclerosis, systemic	Metelimumab[2]	I/II
GlaxoSmithKline	Osteoarthritis	462795	I
	Rheumatoid arthritis	274150	II
		681323	I
		Rosiglitazone maleate[1,2]	II
GW Pharmaceuticals	Rheumatoid arthritis	Dronabinol/cannabidiol	II
Human Genome Sciences	Rheumatoid arthritis	Belimumab	II
	Systemic lupus erythematosus	Belimumab	II
Immunomedics	Sjögren's syndrome	Epratuzumab	I/II
	Systemic lupus erythematosus	Epratuzumab	II
Incyte	Rheumatoid arthritis	INCB-3284	I
Inflazyme	Rheumatoid arthritis	APT-070	Discontinued
Ipsen	Gout	Febuxostat[2]	III (EU)
Isis Pharmaceuticals	Rheumatoid arthritis	ISIS-104838	Discontinued
Kowa	Rheumatoid arthritis	K-832	II
Kureha	Osteoarthritis	CPA-926	II
La Jolla Pharmaceutical	Systemic lupus erythematosus	Abetimus sodium[2]	Prereg.
Lilly	Arthritis	S-3013	Discontinued
Meda	Rheumatoid arthritis	CPH-82	III
MedImmune	Rheumatoid arthritis	MEDI-522	Discontinued
Medinox	Arthritis	MX-1094	I
Merck & Co.	Ankylosing spondylitis	Etoricoxib[1,2]	Prereg.
	Rheumatoid arthritis	C-4462	II
		C-7198	I
		C-9101	I
		C-9787	I
Merckle	Osteoarthritis	Licofelone[2]	III
Merrimack	Rheumatoid arthritis	MM-093	II
MetaPhore	Rheumatoid arthritis	M-40419	I
Millennium	Rheumatoid arthritis	MLN-1202	II
		MLN-3897 (AVE-9897)	I
Nektar Therapeutics	Rheumatoid arthritis	CDP-484	I/II
		Certolizumab pegol	III
Neovacs	Systemic lupus erythematosus	Interferon alfa kinoid	I
Neurochem	Amyloidosis, amyloid A	Fibrillex™	II/III
Neurogen	Rheumatoid arthritis	NGD-2000-1	Discontinued
NicOx	Osteoarthritis	HCT-3012[2]	II
Novartis	Osteoarthritis	Lumiracoxib[2]	III
	Rheumatoid arthritis	ACZ-885	I
		Lumiracoxib[2]	III
		Zoledronic acid monohydrate[1,2]	II
Ono Pharmaceutical	Osteoarthritis	Ono-4817	I
Organon	Rheumatoid arthritis	Ismomultin alfa	Discontinued
		Org-37663	Discontinued
Pfizer	Osteoarthritis	SD-6010	II
Promics	Rheumatoid arthritis	PMX-53	II
Regeneron	Rheumatoid arthritis	IL-1 Trap	II
Rigel	Rheumatoid arthritis	R-406	I
Roche	Lupus nephritis	Rituximab[1]	Clinical
	Rheumatoid arthritis	PRO-70769 (R-1594)	II
		R-1295	I
		R-1503	I
		R-1594	I
		Rituximab[1]	II/III
		Tocilizumab[2]	III
	Rheumatoid arthritis, juvenile	Tocilizumab[2]	III
	Systemic lupus erythematosus	Rituximab[1]	Clinical

Continuation

Treatment of Musculoskeletal Disorders by Source

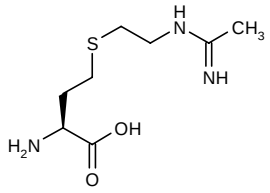
Source	Condition	Drug	Phase
Sankyo	Arthritis	CS-706	II
Santen	Rheumatoid arthritis	DE-096	I
Savient Pharmaceuticals	Gout	PEG-Rasburicase	II
Schering-Plough	Ankylosing spondylitis	Infliximab[1]	L-2003 (EU)
	Psoriatic arthritis	Infliximab[1]	L-2004 (EU)
	Rheumatoid arthritis, juvenile	Infliximab[1]	III
Scios	Rheumatoid arthritis	SCIO-469	II
Serono	Rheumatoid arthritis	SC-12267	I
		Tadekinig alfa	II (?)
		TACI-Ig	I
	Systemic lupus erythematosus	TACI-Ig	I
Shionogi	Arthritis	S-3013	Discontinued
	Osteoarthritis	S-3536	Discontinued
Sumitomo Pharmaceuticals	Rheumatoid arthritis	SMP-114	II
Synta Pharmaceuticals	Rheumatoid arthritis	STA-5326	I
Takeda	Rheumatoid arthritis	TAK-715	II
TAP Pharmaceutical	Gout	Febuxostat[2]	Prereg. (US, JP)
Targeted Genetics	Rheumatoid arthritis	tgAAC-94	I
Teijin	Gout	Febuxostat[2]	Prereg. (US, JP)
		Febuxostat[2]	III (EU)
Teva	Systemic lupus erythematosus	Edratide	I
Toyama	Rheumatoid arthritis	Iguratimod[2]	Prereg.
Trubion Pharmaceuticals	Rheumatoid arthritis	TRU-015	I
UCB Pharma	Rheumatoid arthritis	CDP-323	I
		CDP-484	I/II
		Certolizumab pegol	III
Uriach	Arthritis	Cimicoxib[2]	I-II
Vertex	Osteoarthritis	Pralnacasan	Suspended
	Rheumatoid arthritis	Pralnacasan	Suspended
	Rheumatoid arthritis	VX-702	I
Watson	Systemic lupus erythematosus	Prasterone[2]	Prereg.
Winston Laboratories	Osteoarthritis	Zucapsaicin	III
Wyeth	Arthritis	ERB-196	I
	Osteoarthritis	Efipladib	II
	Rheumatoid arthritis	Apratastat	II
		Efipladib	II
		ERB-041	I
		SIM-916	Discontinued
		Temsirolimus[2]	II
Xoma	Psoriatic arthritis	Efalizumab[1,2]	Discontinued
Y's Therapeutics	Rheumatoid arthritis	YS-IL-6	I/II
ZymoGenetics	Rheumatoid arthritis	TACI-Ig	I
	Systemic lupus erythematosus	TACI-Ig	I

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

Treatment of Musculoskeletal Disorders

N.E. Mealy, M. Bayés
Prous Science, P.O. Box 540, 08080 Barcelona, Spain

274150



Compound 274150 (GW-274150) is a potent and selective inhibitor of inducible nitric oxide synthase (iNOS) discovered at GlaxoSmithKline. Phase II clinical evaluation is under way for a number of indications, including rheumatoid arthritis, asthma, allergic rhinitis and chronic obstructive pulmonary disease (COPD), and phase I trials are being conducted in migraine.

462795

A cathepsin K inhibitor, 462795 (SB-462795) is undergoing early clinical testing at GlaxoSmithKline for the treatment of osteoarthritis and osteoporosis. 462795 was developed as part of an agreement signed by GSK and Human Genome Sciences in 1993 under which the former was granted rights to use HGS's technology and intellectual property in exchange for clinical development milestone payments and royalties on discovered compounds.

681323

GlaxoSmithKline has discovered a new p38 mitogen-activated protein (MAP) kinase inhibitor, 681323, which the company is evaluating in phase I for its potential in the treatment of rheumatoid arthritis, atherosclerosis and COPD.

Abatacept

Bristol-Myers Squibb recently submitted the complete nonclinical and clinical sections of its rolling BLA for abatacept (BMS-188667, CTLA4Ig), a fast track investigational treatment for rheumatoid arthritis; the submission is expected to be completed early this year. Abatacept is BMS's first internally discovered biologic and would be the first in the selective T-cell costimulation modulator class for the treatment of rheumatoid arthritis. Data presented in October 2004 showed that abatacept demonstrated clinical activity in patients who had inadequately responded to other treatment regimens, including methotrexate and anti-TNF therapies. As with other agents that modulate the immune system, a somewhat increased rate of infection was seen with abatacept (1, 2).

A double-blind, placebo-controlled clinical trial randomized 234 patients with rheumatoid arthritis to receive methotrexate (10-30 mg/week) alone or combined with abatacept (10 mg/kg) for 12 months. The combination of the drugs was more effective than methotrexate alone in inducing clinical response. The American College of Rheumatology ACR20, ACR50 and ACR70 response rates at 12 months were, respectively, 63%, 42% and 21% with the combination and 36%, 20% and 8% with methotrexate alone. The effects of abatacept on the physical function of the patients were also assessed using the modified Health Assessment Questionnaire (mHAQ). All 8 physical function domains included in the questionnaire significantly improved with combination therapy compared to methotrexate alone after 6 and 12 months. The percentage of patients with no disability at the end of the study was 50% with abatacept plus methotrexate and 28% with methotrexate alone. Clinical remission was more common with the combination than with methotrexate alone (34.8% *vs.* 10.1%). The serum levels of the proinflammatory markers C-reactive protein (CRP), rheumatoid factor, soluble IL-2 receptor (sIL-2r), IL-6 and E-selectin decreased significantly in patients treated with the combination but showed minimal changes (except for sIL-2r, which increased) in placebo-treated patients. Both

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

Indication	Design	Treatments	n	Conclusions	Ref.
Arthritis, rheumatoid	Randomized Double-blind	Abatacept, 10 mg/kg + Methotrexate, 10-30 mg/wk x 12 mo (n=115) Placebo + Methotrexate, 10-30 mg/wk x 12 mo (n=119)	234	Compared with methotrexate alone, the combination of abatacept and methotrexate was more effective in inducing clinical remission, sustained reductions in inflammatory marker levels, and improvement in physical function and quality of life in patients with active rheumatoid arthritis	3,4,6,7
Arthritis, rheumatoid	Randomized Double-blind	Abatacept, 10 mg/kg i.v. + Methotrexate x 1 y (n=90) Placebo + Methotrexate x 1 y (n=71)	161	The addition of abatacept to baseline methotrexate therapy was well tolerated and increased response for up to 1 year in patients with active rheumatoid arthritis	9

study treatments were well tolerated (3-8). The results from this and the following study are summarized in Table I.

The dynamics of response to abatacept were evaluated in a randomized, placebo-controlled phase II clinical trial in which 161 active rheumatoid arthritis patients were treated with methotrexate alone or combined with abatacept (10 mg/kg) for 1 year. The percentage of patients who responded to treatment was greater with the combination therapy throughout the study. Compared with methotrexate alone, the addition of abatacept to the therapy resulted in significantly higher ACR20, ACR50 and ACR70 response rates, which were sustained for up to 1 year in patients completing the study (9).

Patients participating in a 1-year double-blind phase II trial were randomized to abatacept 10 mg/kg i.v. per month or placebo in addition to methotrexate therapy. This was followed by a 1-year, open, long-term extension phase, which was completed by 75 abatacept-treated patients. Almost half of the patients given abatacept achieved remission (DAS28 < 2.6) at 1 year, and this rate was similar after 2 years. The ACR20, ACR50 and ACR70 response rates did not significantly change between the end of 1 and 2 years of treatment with abatacept. ACR20 response rates were 76% and 77.3% at 1 and 2 years, respectively, in abatacept-treated patients. At 2 years, an ACR70 response was maintained for 6 consecutive months by 25% of patients taking abatacept. The safety of the abatacept/methotrexate combination was comparable to placebo at 1 year and did not decline at 2 years in this study. The incidence of serious adverse events at 1 year was 16% with placebo and 12.2% with abatacept, and the incidence at 2 years with abatacept was 14.3%. The good tolerability of the drug was maintained through 2 years, supporting its long-term use in combination with methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate (10-12).

The ATTAIN (Abatacept Trial in Treatment of Anti-TNF inadequate responders) trial was a 24-week, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of abatacept 10 mg *vs.* placebo in 391 patients with active rheumatoid arthritis with inadequate responses to at least 3 months of anti-TNF-α therapy. The ACR20 response rate (the primary efficacy endpoint) at 24 weeks was 50.4% in the abatacept group and 19.5% in the placebo group, and ACR50 and ACR70 responses and remission rates were also significantly higher in the abatacept-treated group. The incidence of adverse events or serious infections were similar between the groups (13).

The 1-year AIM (Abatacept in Inadequate responders to Methotrexate) trial enrolled 652 rheumatoid arthritis patients who were randomized to abatacept 10 mg/kg i.v. per month or placebo in addition to methotrexate therapy. Significant differences in ACR responses were seen at 6 months and 1 year between the abatacept and placebo groups. ACR20 response rates for abatacept and placebo at 6 months were 67.9% and 39.7%, respectively, and these rates at 1 year were 73.1% and 39.7%, respectively. The rates of remission at 1 year were 23.8% and 1.9%, respectively, and abatacept was also associated with significant improvements in radiographic evaluations (14).

A randomized, placebo-controlled phase II study investigated the efficacy of abatacept 10 mg/kg in patients with active rheumatoid arthritis completing 1 year of double-blind treatment, as assessed by ACR scores. Results showed that the number of patients with ACR responses of 20%, 50% and 70% was consistently higher in the group taking abatacept plus methotrexate than in those taking placebo plus methotrexate from day 30 onward, suggesting that abatacept may have sustained efficacy in treating rheumatoid arthritis. The safety profile of abatacept was similar to placebo (15).

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

2. *Rolling BLA for abatacept to be completed in early 2005*. DailyDrugNews.com (Daily Essentials) Dec 28, 2004.

3. Sibilia, J., Steinfeld, S., Nuamah, I., Aranda, R., Becker, J., Keystone, E. *Efficacy of abatacept (CTLA4Ig; BMS-188667) in combination with methotrexate in the treatment of early and established rheumatoid arthritis*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst OP0104.

4. Tugwell, P., Bombardier, C., Emery, P. et al. *Treatment with abatacept (CTLA4Ig; BMS-188667) in combination with methotrexate significantly improves physical function over 1 year in patients with active rheumatoid arthritis compared with methotrexate alone*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst SAT0457.

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10. Dougados, M., Westhovens, R., St. Clair, E.E. et al. *Sustained remission and major clinical response at 2 years shown with abatacept (CTLA4Ig) in combination with methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 359.

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Abetimus Sodium

La Jolla Pharmaceutical has received an approvable letter from the FDA for its lupus drug candidate abetimus sodium (LJP-394, Riquent®), a toleragen designed using the company's Tolerance Technology® platform with orphan drug status in the U.S. and the E.U. The FDA has requested an additional randomized, double-blind study demonstrating the clinical benefit of abetimus prior to approval. The FDA letter indicated that the ongoing clinical trial initiated in August 2004 would appear to satisfy this requirement. If approved, abetimus, designed to reduce the levels of antibodies to double-stranded DNA (dsDNA) believed to be responsible for lupus renal disease, would be the first drug developed specifically for this indication in more than 30 years. The company has also met with the European Agency for the Evaluation of Medicinal Products (EMEA), which has designated 2 countries to lead the review of the company's European regulatory filing. Because of the efforts involved in its ongoing discussions with the FDA, the company anticipates a delay in filing its marketing authorization application (MAA) in Europe. Data from La Jolla's phase III and phase II/III trials of abetimus showed that after 1 year of treatment, the number of lupus patients with a reduction in proteinuria of at least 50% from baseline was greater in the abetimus-treated group than in the placebo group. In patients who had 24-h urine protein measured at both baseline and at week 52 during the phase III trial, 41% of patients in the abetimus-treated group with high-affinity antibodies to abetimus achieved a 50% or greater reduction from baseline in the amount of protein in their urine at week 52, compared with 28% of placebo patients with high-affinity antibodies. In patients who had 24-h urine protein measured at both baseline and at approximately week 52 during the phase II/III trial, 44% of patients in the abetimus group with high-affinity antibodies had a 50% or greater reduction from baseline in the amount of protein in their urine at approximately week 52, compared with 18% of placebo patients with high-affinity antibodies. These data were included in the company's NDA for the drug (1-5).

A retrospective analysis of data pooled from a phase II/III trial and a phase III trial reviewed the latest information available on the effects of abetimus in patients with

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

Indication	Design	Treatments	n	Conclusions	Ref.
Lupus erythematosus, systemic	Randomized Pooled/meta-analysis	Abetimus, 100 mg 1x/wk x 16 wks → 50 mg 1x/wk x 12 wks 1x/20 wks x 76 wks (n=114) Abetimus, 100 mg 1x/wk x 92 wks (n=158) Placebo (n=275)	547	Abetimus was well tolerated in both trials and significantly reduced anti-dsDNA antibody levels, which were inversely correlated with C3 levels, and improved health-related quality of life by the Medical Outcomes Survey-Short Form-36 in patients with systemic lupus erythematosus	7, 8

systemic lupus erythematosus (SLE). Both trials enrolled SLE patients with renal disease and at least 15 IU/ml of anti-dsDNA antibodies at baseline. A total of 230 patients participated in the phase II/III trial and received placebo or abetimus (100 mg once weekly for 16 weeks, followed by three cycles of 8 weeks' drug holiday and 12 weeks of 50 mg once weekly) for a total study period of 18 months. The 317 patients included in the phase III trial were given placebo or abetimus (100 mg) once weekly for up to 22 months. The baseline levels of anti-dsDNA antibodies decreased significantly in patients treated with abetimus; these changes were associated with a lower risk of SLE renal flares and were inversely correlated with C3 levels in both trials. A weekly dose of 100 mg of abetimus was well tolerated and showed similar rates of adverse events (88% *vs*. 89%), serious adverse events (15% *vs.* 16%) and patient withdrawals (4.8% *vs*. 4.7%) compared to placebo. In the phase II/III trial, abetimus also significantly improved health-related quality of life. The treatment may be used along with corticosteroids and immunosuppression as induction or maintenance therapy in patients with elevated anti-dsDNA antibodies (6-8). The results from these studies are summarized in Table II.

Data from a randomized, placebo-controlled phase III clinical trial were used to evaluate the effects of abetimus combined with other immunosuppressive agents on the levels of anti-dsDNA antibodies in 298 patients with SLE, renal disease and high levels of anti-dsDNA antibodies. Compared with placebo, abetimus (100 mg once weekly) given for up to 22 months significantly decreased the levels of anti-dsDNA antibodies. This effect was also detected in patients who at baseline were also receiving mycophenolate mofetil (MMF) or azathioprine. At 24 weeks, abetimus decreased the levels of anti-dsDNA antibodies by 55% in MMF-treated patients and by 28% in azathioprine-treated patients, whereas placebo reduced them by 6% and 1%, respectively (9).

1. *FDA accepts for review Riquent NDA*. DailyDrugNews.com (Daily Essentials) Feb 18, 2004.

2. *Presentation of new Riquent data*. DailyDrugNews.com (Daily Essentials) March 15, 2004.

3. *Approvable letter for Riquent*. DailyDrugNews.com (Daily Essentials) Oct 19, 2004.

4. *Update on Riquent development program*. DailyDrugNews.com (Daily Essentials) Nov 29, 2004.

5. *La Jolla reaches agreement for phase IV Riquent study*. DailyDrugNews.com (Daily Essentials) Aug 5, 2004.

6. Hu, J.Z., Heilbrunn, K.R., Hurley, F.L., Joh, T., Linnik, M.D. *Anti-dsDNA antibodies and exacerbation of renal disease in patients with systemic lupus erythematosus: Results from 2 randomized controlled trials (RCTs) with LJP 394*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst THU0364.

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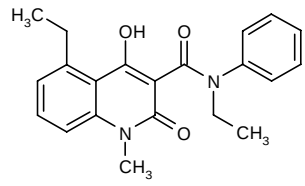
ABR-215757



Following approval by the Swedish Medical Products Agency and Swedish Science Council's Ethics Committee, Active Biotech has initiated phase I trials of oral

ABR-215757 for SLE. A dose-escalation study will evaluate the safety of increasing doses of ABR-215757 in parallel groups of healthy volunteers. A small number of healthy volunteers will take part in the study at the Karolinska Institute hospital. The trial is scheduled for completion during the first half of 2005. The next step will be a phase I trial which will test tolerability of the agent in SLE patients (1-5).

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

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

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

4. *ABR-215757 enters phase I trials in Sweden*. DailyDrugNews.com (Daily Essentials) Nov 5, 2004.

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

ACZ-885

ACZ-885, a fully human monoclonal antibody to IL-1β, is in early clinical studies at Novartis for treating rheumatoid arthritis (1).

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

AD-452

Arakis has initiated a phase IIa trial in 96 rheumatoid arthritis patients to study the pharmacokinetics, safety and tolerability of a range of doses of AD-452, a novel, once-daily, oral disease-modifying treatment for early-stage rheumatoid arthritis. The multicenter, double-blind, placebo-controlled, parallel-group study will involve patients who are receiving stable background therapy. It will be a conducted under U.S. IND and E.U. CTA regulatory authorizations. A cytokine modulator, AD-452 is the single isomer of a drug that is marketed for a different indication and unsuitable for chronic dosing. AD-452 has a broad spectrum of activity inhibiting joint damage. Single- and multiple-dose phase I trials in 74 subjects have been successfully completed with no significant adverse events (1).

1. *AD-452 enters phase IIa study for rheumatoid arthritis*. DailyDrugNews.com (Daily Essentials) June 14, 2004.

AD-827

AD-827 is an oral, once-daily disease-modifying antirheumatic drug (DMARD) in early clinical development at Arakis for the treatment of osteoarthritis. AD-827 is the optimized single isomer of a currently marketed racemic drug indicated for an entirely different disease.

Adalimumab

The development of adalimumab (D2E7, Humira®), a human monoclonal antibody targeting TNF-α, continues to make positive progress since its approval by the FDA in December 2002 and subsequent launch in the U.S. in January 2003 for the treatment of rheumatoid arthritis; European approval followed in September 2003 and it is also available in Canada. Adalimumab, discovered through a scientific collaboration between Abbott and Cambridge Antibody Technology, was the first fully human monoclonal antibody approved by the FDA for reducing the signs and symptoms and inhibiting the progression of structural damage in rheumatoid arthritis. Further clinical trials are also under way in juvenile rheumatoid arthritis (phase III), ankylosing spondylitis (phase III), psoriasis (phase II) and Crohn's disease (phase III), and it has been submitted in the U.S. and the E.U. for the treatment of psoriatic arthritis and early arthritis. In Japan, where it is in phase II trials for rheumatoid arthritis, adalimumab is being developed jointly by Abbott Japan and Eisai (1-6).

The filings for psoriatic arthritis were based on 2 placebo-controlled studies, including data from the phase III ADEPT (Adalimumab Effectiveness in Psoriatic Arthritis Trial) study showing patients on adalimumab achieved significant improvement in both arthritic and psoriatic signs and symptoms. The placebo-controlled, double-blind ADEPT study assessed adalimumab in 313 adults with active psoriatic arthritis (defined as 3 or more swollen joints and 3 or more tender joints) who had an inadequate response to therapy with nonsteroidal antiinflammatory drugs (NSAIDs). Patients received placebo or 40 mg of adalimumab administered subcutaneously every other week. The study found that patients' psoriatic arthritis skin symptoms showed a significant response to adalimumab. Of the 69 patients with > 3% body surface involvement who were treated with adalimumab, 42% achieved a 90% Psoriasis Area and Severity Index (PASI90) response at 24 weeks. Nearly one-third of patients achieved a PASI90 by week 12, which was maintained throughout the study. Patients' arthritic symptoms exhibited a rapid response to adalimumab, with nearly 60% of patients achieving ACR20 at week 12, one of the study's primary endpoints, and sustaining response through week 24. At the 24-week follow-up, nearly one-fourth of these patients achieved ACR70 (7).

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

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

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

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

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

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

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

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

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Emery, P. et al. *Adalimumab (Humira®) plus methotrexate induces sustained remission in both early and long-standing rheumatoid arthritis*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 355.

Haibel, H., Brandt, H., Rudwaleit, M., Listing, J., Braun, J., Kupper, H., Sieper, J. *Efficacy of adalimumab, a fully human anti-TNF monoclonal antibody, in the treatment of patients with active ankylosing spondylitis*. 4th Int Congr Spondyloarthropathies (Oct 7-9, Gent) 2004, Abst P 4.16.

Haibel, H. et al. *Efficacy and safety of adalimumab in the treatment of active ankylosing spondylitis: Preliminary results of an open-label, 20-week trial*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 454.

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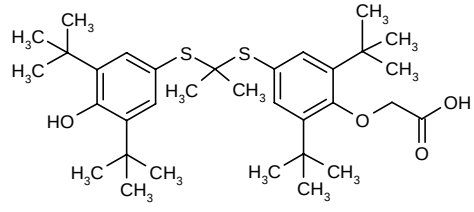
Mease, P.J. et al. *Adalimumab therapy in patients with psoriatic arthritis: 24-week results of a phase III study*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst L6.

Ritchlin, C., Anandarajaha, A., Totterman, S., Shao, T., Kemshetti, W., Durham, R. *Preliminary data from a study of adalimumab in the treatment of psoriatic arthritis*. 4th Int Congr Spondyloarthropathies (Oct 7-9, Gent) 2004, Abst P 4.21.

Ritchlin, C. et al. *Preliminary data from a study of adalimumab in the treatment of psoriatic arthritis*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst SAT0054.

AGIX-4207



Results of AtheroGenics' European OSCAR phase II trial of AGIX-4207 in patients with rheumatoid arthritis showed that none of the 3 dosing arms of AGIX-4207 produced a statistically significant improvement in ACR20 scores when compared to placebo, the primary efficacy endpoint of the trial. In the analysis of all randomized patients, 25% of placebo-treated patients achieved an ACR20 response at week 12 compared with 20%, 15% and 23%, respectively, of those treated with AGIX-4207 doses of 75, 150 and 225 mg. Two of the prespecified secondary endpoints, tender joint count and morning stiffness, did show statistically significant improvement compared to placebo. The 12-week, double-blind, placebo-controlled study involved 275 patients with mild to severe rheumatoid arthritis. Subjects were randomized into 4 groups receiving either placebo or 1 of 3 single daily oral doses of AGIX-4207: 75, 150 or 225 mg. Subjects who were previously treated with biological DMARDs were not enrolled in the study, nor were subjects who were taking nonbiological DMARDs at the commencement of the study. Study subjects on NSAIDs, including aspirin, cyclooxygenase type 2 (COX-2) inhibitors and analgesics, were allowed to remain on their drug regimens. Based on the overall findings of the study, AtheroGenics is discontinuing clinical development of AGIX-4207 in rheumatoid arthritis. AtheroGenics believes that the disappointing results of the study are compound-specific and that its v-protectant™ technology still offers promise for rheumatoid arthritis. Other compounds have been identified with enhanced therapeutic potential within the company's rheumatoid arthritis preclinical models (1).

1. *AGIX-4207 discontinued for rheumatoid arthritis after disappointing results*. DailyDrugNews.com (Daily Essentials) Oct 18, 2004.

Alefacept

Alefacept is a fusion protein developed by the former Biogen, now Biogen Idec, that combines human leukocyte function-associated antigen LFA-3 with IgG_1. A novel biological agent that selectively targets the memory T-cells that stimulate hyperproliferation in psoriasis, alefacept was approved and launched in 2003 in the U.S. under the brand name Amevive® for the treatment of adults with moderate to severe psoriasis. It is also being evaluated for its potential in the treatment of psoriatic arthritis (phase II).

Original monograph – Drugs Fut 2001, 26(6): 527.

AMG-108

Amgen's AMG-108 is an anti-IL-1β monoclonal antibody in phase II development for the treatment of osteoarthritis.

AMG-162

A fully human monoclonal antibody targeting receptor activator of NF-κB ligand (RANKL) and created using Abgenix's proprietary XenoMouse® technology, AMG-162 has advanced to phase III development at Amgen for the treatment of osteoporosis in postmenopausal women and is also in phase II trials for the treatment of rheumatoid arthritis and for the suppression of bone loss in patients with cancer that has metastasized to the bone. AMG-162 is a biological response modifier intended for administration every 6 months by s.c. injection. Amgen licensed the antibody generation technology from Abgenix in 1999 and is responsible for product development and commercialization (1).

1. *AMG-162 pivotal study triggers milestone payment to Abgenix*. DailyDrugNews.com (Daily Essentials) Aug 18, 2004.

AMG-623

AMG-623 is a B-cell-activating factor (BAFF) antagonist in early clinical development at Amgen for the treatment of SLE. According to the company, candidates from the BBAF program may also have potential for the treatment of rheumatoid arthritis.

AMG-714

A fully human monoclonal antibody directed against IL-15, AMG-714 (formerly HuMax™-IL-15) is in phase II clinical development by Amgen for the treatment of rheumatoid arthritis. By blocking IL-15, AMG-714 may have therapeutic potential in a wide variety of inflammatory diseases in addition to rheumatoid arthritis, such as psoriasis, inflammatory bowel disease (IBD), lupus, multiple sclerosis and others. Genmab obtained exclusive worldwide rights to Amgen's patents relating to anti-IL-15 antibodies and the IL-15 receptor as a result of several licensing arrangements beginning in 1999. In 2001, Amgen replaced the sublicenses with direct licenses and retained an exclusive commercialization option for the products through phase II. In 2003, Amgen exercised its commercialization options for both the AMG-714 antibody program and the IL-15 receptor program and is now responsible for further development of AMG-714 (1, 2).

Amgen has reported positive interim data from the ongoing AMG-714 phase II study in rheumatoid arthritis. Patients in the study received AMG-714 40, 80, 160 or 280 mg or placebo by s.c. infusion every other week for 12 weeks. Responses were measured at weeks 4, 8, 12 and 14, with the primary endpoint at week 14. The interim analysis covered 110 patients and showed a significant difference between treated patients and those in the placebo group. Current pharmacokinetic data support dosing every other week. The incidence of adverse events was similar in the AMG-714 and placebo groups. American College of Rheumatology ACR20 responses were seen more often in AMG-714-treated patients, with ACR20 responses achieved by 62% and 26% of patients given AMG-714 280 mg and placebo, respectively. Greater reductions in CRP were seen at weeks 4 and 14 with AMG-714, and disease worsening was observed more often in the placebo group. The highest AMG-714 dose appeared to be the most effective, with the lowest flare frequency and an incidence of adverse events very similar to that seen in placebo-treated patients (57.1% *vs.* 56.5%) (2-4).

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

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

3. *Interim data from HuMax-IL-15 phase II study in RA*. DailyDrugNews.com (Daily Essentials) March 26, 2004.

4. McInnes, I., Martin, R., Zimmerman-Gorska, I., Nayiager, S., Sun, G., Patel, A., Appleton, B. *Safety and efficacy of a human monoclonal antibody to IL-15 (AMG 714) in patients with rheumatoid arthritis (RA): Results from a multicenter, randomized, double-blind, placebo-controlled trial*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 527.

Anakinra

Anakinra (Kineret®) is a recombinant, nonglycosylated form of the human IL-1 receptor antagonist (IL-1ra) that blocks the biological activity of IL-1 by competitively inhibiting IL-1 binding to the IL-1 type I receptor. It was first introduced by Amgen in the U.S. in 2001, and subsequently in the E.U. in 2002, for the treatment of rheumatoid arthritis. In August 2004, Amgen signed an agreement with NPS Pharmaceuticals to promote anakinra in the U.S. (1). Anakinra is also in phase II clinical trials for the treatment of osteoarthritis.

1. *NPS to promote Amgen's Kineret to rheumatologists*. DailyDrugNews.com (Daily Essentials) Aug 11, 2004.

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Aelion, J.A., Odhav, S.K. *Prompt response to treatment with anakinra in adult onset Still's disease*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst FRI0109.

Haibel, H., Rudwaleit, M., Braun, J., Listing, J., Sieper, J. *Results of an open label study with anakinra in active ankylosing spondylitis*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst SAT0048.

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systemic lupus erythematosus (SLE) and arthritis of the finger joints. Ann Rheum Dis 2004, 63(Suppl. 1): Abst THU0404.

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Tan, A.L. et al. *Efficacy of anakinra in active ankylosing spondylitis: A clinical and magnetic resonance imaging study*. Ann Rheum Dis 2004, 63(9): 1041.

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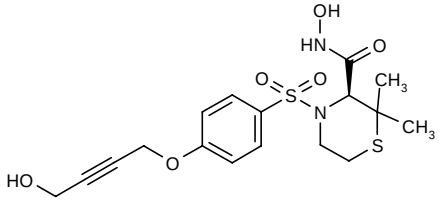
Apratastat



Apratastat (TMI-005), an orally active inhibitor of TNF-α-converting enzyme (TACE) and matrix metalloproteinases (MMPs), is in phase II development at Wyeth for the treatment of rheumatoid arthritis.

APT-070

During the summer of 2004, Inflazyme ceased recruitment of patients in its phase I/II rheumatoid arthritis trial of APT-070 (now Mirococept®), its lead Prodaptin™-linked molecule which it added to its pipeline through the acquisition of Adprotech. APT-070 is a truncated form of the human complement CR1 receptor which regulates the overproduction of complement at the cell surface. The company stopped the rheumatoid arthritis trial as it believed that the design and protocol would not generate sufficient data to support future clinical trials. The product is now undergoing preclinical evaluation for a number of indications, *i.e.,* as an acute care treatment for hypovolemic shock (1-4).

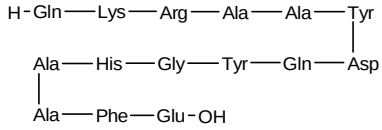
1. *Inflazyme to acquire Adprotech*. DailyDrugNews.com (Daily Essentials) April 14, 2004.

2. *Inflazyme completes acquisition of Adprotech*. DailyDrugNews.com (Daily Essentials) April 23, 2004.

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

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

AT-001



Phase II clinical trials sponsored by the National Institutes of Health (NIH) are in progress for AT-001 (dnaJP1), an engineered oral peptide therapeutic for the treatment of rheumatoid arthritis. The peptide was discovered at the University of California, San Diego, and exclusively licensed to Androclus Therapeutics for the development of immunomodulation therapies for rheumatoid arthritis and other indications. Designed to induce tolerization of the autoimmune process in patients with rheumatoid arthritis, AT-001 halts disease-related inflammation while having no affect on the patient's immunity to infection or cancer. AT-001 may hold advantages over other current antiinflammatory biologics in that it is administered orally, was designed to have specific and not broadly immunosuppressive action, and has shown a favorable side effect profile to date. AT-001 may have potential for the treatment of a broad range of autoimmune diseases. Androclus is developing AT-001 in collaboration with an undisclosed biotechnology company for the treatment of rheumatoid arthritis.

In a recent phase I/IIa clinical trial, a group of 15 patients with early rheumatoid arthritis were treated with AT-001 for 6 months. Immunological analysis showed a significant increase in AT-001-induced T-cell production of IL-4 and IL-10 at the end of treatment. Conversely, the production of IL-2, interferon gamma and TNF-α, as well as T-cell proliferation, were reduced by the peptide. As the number of AT-001-specific cells remained unchanged and foxP3 expression by $CD4^+CD25$ cells was increased, the change in T-cell immune reactivity to AT-001 appeared to be due to a functional switch from proinflammatory to tolerogenic responses (1) (Table III).

1. Prakken, B.J., Samodal, R., Le, T.D. et al. *Epitope-specific immunotherapy induces immune deviation of proinflammatory T cells in rheumatoid arthritis*. Proc Natl Acad Sci USA 2004, 101(12): 4228.

Additional References

Prakken, B., Yung, G.P., Samodal, R., Giannoni, F., Teklenburg, O., Jearanai, S., Amox, D., Roord, S., De Kleer, I., Massa, M., Billetta, R., Bonnin, D., Albani, S. *Peptide-specific oral tolerance induces immune deviation of T cells in rheumatoid arthritis*. Clin Invest Med 2004, 27(4, Suppl.): Abst W51.174.

Table III: Clinical studies of AT-001 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Arthritis, rheumatoid	Open	AT-001, 0.25 mg/d p.o. x 6 mo AT-001, 2.5 mg/d p.o. x 6 mo AT-001, 25 mg/d p.o. x 6 mo	15	Epitope-specific immunotherapy with AT-001 affected regulatory T-cell function in rheumatoid arthritis by inducing immune deviation of proinflammatory T-cells	1

AVE-9940

AVE-9940 is a p38 MAP kinase inhibitor last reported to be in phase I/II clinical evaluation by the former Aventis Pharma, now part of Sanofi-Aventis, for the treatment of rheumatoid arthritis.

AZD-8309/AZD-8955/AZD-9056

AstraZeneca's pipeline includes several compounds in clinical development for rheumatoid arthritis/ osteoarthritis. The most advanced is AZD-9056, an ion channel blocker which is in phase II studies for both rheumatoid arthritis and osteoarthritis, in addition to phase I trials for chronic obstructive pulmonary disease (COPD). The collagenase inhibitor AZD-8955 is undergoing phase I trials for the treatment of osteoarthritis. Another phase I compound is AZD-8309, a chemokine receptor antagonist being developed for both rheumatoid arthritis and COPD.

Belimumab

Belimumab (anti-BLyS, LymphoStat-B™) is a specific human monoclonal antibody developed by Human Genome Sciences in collaboration with Cambridge Antibody Technology that prevents the stimulation of B-cell maturation by binding to the B-lymphocyte stimulator (BLyS), and thereby restores the potential of mature plasma B-cells to undergo apoptosis. Previous preclinical and clinical studies showed that belimumab was well tolerated and reduced the levels of antigen-producing B-cells, thus suggesting a potential role in autoimmune diseases. Based on these results, an ongoing phase II clinical trial is evaluating the efficacy and safety of belimumab in patients with SLE, and another phase II trial is under way in patients with rheumatoid arthritis. Results for the rheumatoid arthritis study are expected in the spring of 2005, and those for the SLE study in the fall of this year. Assuming that the data from the phase II study in rheumatoid arthritis are positive, HGS plans to initiate a phase III trial of belimumab in the second half of 2005. The FDA has selected belimumab for SLE for inclusion in the Continuous Marketing Application (CMA) Pilot 2 program and the product also has fast track status for this indication. Phase I results show that belimumab is well tolerated and biologically active in patients with SLE, with no clinically significant differences from placebo in adverse events or laboratory abnormalities. The half-life was consistent with that of other human monoclonal antibodies, and a dose-proportional pharmacokinetic profile was observed. Belimumab significantly reduced the levels of circulating B (CD20)-cells (1-8).

1. *LymphoStat-B enters phase II evaluation for active rheumatoid arthritis*. DailyDrugNews.com (Daily Essentials) Jan 13, 2004.

2. *CAT continues progress in 2004*. DailyDrugNews.com (Daily Essentials) Feb 4, 2004.

3. *LymphoStat-B selected for CMA Pilot 2 program*. DailyDrugNews.com (Daily Essentials) March 9, 2004.

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

5. *Enrollment completed in phase II LymphoStat-B studies in RA and SLE*. DailyDrugNews.com (Daily Essentials) Aug 2, 2004.

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

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

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

BSP-201

The FDA has accepted the new dietary notification of dietary supplements containing BSP-201 for sale in the U.S. BSP Pharma now plans to team up with partners in 2004 for the launch of the product for arthritis. In 2003, BSP Pharma conducted a clinical study on BSP-201 in order to evaluate its pain-relieving effects, safety and tolerability. The study was based on a postexercise muscle soreness model, whereby muscle soreness was experimentally induced in the subjects using an eccentric exercise of the first dorsal interosseous hand muscle. The daily intake of BSP-201 resulted in a fast, statistically significant and clinically relevant reduction of the soreness experienced by the subjects (1).

1. *BSP-201 dietary supplements for arthritis approved for sale in U.S.* DailyDrugNews.com (Daily Essentials) March 2, 2004.

C-4462/C-7198/C-9101/C-9787

Merck & Co. has several compounds in clinical development for the treatment of rheumatoid arthritis. The most advanced is C-4462, in phase II clinical trials, and C-7198, C-9101 and C-9787 are in early clinical development.

CDP-323

UCB Pharma (through its acquisition of Celltech Group) has successfully completed a second phase I study with CDP-323, a small-molecule inhibitor of α_4 integrins that has demonstrated potent antiinflammatory activity in preclinical models of disease. The multiple-dose study in healthy volunteers demonstrated good plasma exposure and potent and prolonged inhibition of ligand binding to α_4 integrins in an *in vitro* whole blood assay. The first phase II study with CDP-323 is planned in rheumatoid arthritis patients. The company is currently evaluating the optimum development strategy for further indications (1-3).

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

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

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

CDP-484

CDP-484, a PEGylated humanized monoclonal antibody fragment targeting the proinflammatory cytokine IL-1β, entered a large placebo-controlled phase I/II study in rheumatoid arthritis patients last year at Celltech Group, prior to its acquisition by UCB Pharma. This study will assess the safety and efficacy of ascending doses of CDP-484. The product uses Nektar Therapeutics' Advanced PEGylation technology (1-3).

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

2. *Nektar Therapeutics reports Q1 R&D highlights*. Nektar Therapeutics Press Release 2004, May 5.

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

Certolizumab Pegol

Certolizumab pegol (CDP-870) is a 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. Developed by the former Celltech Group, now part of UCB Pharma, using Nektar Therapeutics' Advanced PEGylation technology, it is in phase III clinical evaluation for the treatment of rheumatoid arthritis and Crohn's disease. Certolizumab may also be studied for other disease indications, such as psoriasis, psoriatic arthritis and ankylosing spondylitis. According to preliminary results, both phase III trials in rheumatoid arthritis (Study 014 and 011) met their primary endpoint. These studies were designed to assess the safety and efficacy of certolizumab as monotherapy (011) or in combination with methotrexate (014) over a 6-month period in refractory patients who had active moderate to severe disease despite treatment with methotrexate and other DMARDs. The studies met the primary endpoint, as assessed by the number of patients achieving a 20% reduction in the American College of Rheumatology score at 24 weeks. A significant ACR20 response was seen at week 1 and was maintained for the duration of the study (1-8).

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

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

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

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

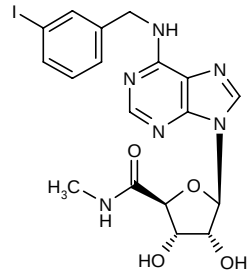
5. *Nektar Therapeutics reports Q1R&D highlights*. Nektar Therapeutics Press Release 2004, May 5.

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

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

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

CF-101



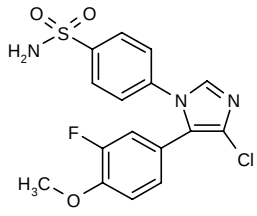
Can-Fite Biopharma's lead drug CF-101 (RPR-113090, IB-MECA), an adenosine A_3 receptor agonist, is currently being studied in a phase II trial in Israel as monotherapy for colorectal cancer. The company recent-

ly initiated a phase I study of CF-101 in the U.S. in patients with solid tumors. The trial will take place at Harvard Medical School affiliate hospitals and will investigate combinations of CF-101 with 3 different standard chemotherapeutic regimens. The primary objective of this open-label, dose-escalation study will be to determine the safety, tolerability and clinical effects of the oral administration of CF-101 in combination with 1 of 3 different cytotoxic chemotherapy (1, 2). Phase II trials are also under way in rheumatoid arthritis.

1. *CF-101 enters phase I study in solid tumor patients*. DailyDrugNews.com (Daily Essentials) July 5, 2004.

2. Fishman, P., Cohn, I., Bar-Yehuda, S. et al. *A_3 adenosine receptor as a new target for colorectal cancer treatment: A phase II, multi-center study in metastatic colorectal cancer patients with the specific receptor agonist CF101*. Proc Am Assoc Cancer Res 2004, 45: Abst LB-335.

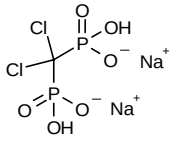
Cimicoxib



The imidazole derivative cimicoxib (UR-8880) is a selective COX-2 inhibitor last reported to be in phase I-II development by Uriach for the treatment of rheumatoid arthritis and pain.

Original monograph – Drugs Fut 2004, 29(4): 325.

Clodronate Disodium



Clodronate disodium is an oral bisphosphonate originally launched in 1985 by Leiras as Bonefos® capsules and injectables for i.v. infusion for the treatment of malignant osteolytic bone diseases. The drug was launched again in 1988 by Abiogen for the treatment of cancer-related hypercalcemia and postmenopausal osteoporosis. At present, clodronate is approved in 60 countries for the treatment of tumor-induced osteolysis and hypercalcemia. Berlex, a U.S. affiliate of Schering AG, has filed a regulatory application seeking approval for the drug in the U.S. for reducing the occurrence of bone metastases in the postsurgical (adjuvant) treatment of breast cancer patients, and the FDA just recently issued an approvable letter for clodronate for this indication. Abiogen is also currently evaluating clodronate in phase II trials for the treatment of osteoarthritis. Clodronate is a potent inhibitor of osteoclast-mediated bone resorption and is able to inhibit cancer cell-stimulated osteolytic activity, thereby helping to preserve the structure of the bone. For the treatment of osteoarthritis, clodronate, like other bisphosphonates, has high affinity for hydroxyapatite, which appears to play an important role in the progression of inflammatory damage.

Original monograph – Drugs Fut 1982, 7(9): 615.

CPA-926

A novel inhibitor of MMP-3 (stromelysin 1) production synthesized at Kureha, CPA-926 is being tested in phase II trials for the treatment of osteoarthritis.

CPH-82

The DMARD CPH-82 is currently in phase III trials at Meda for the treatment of rheumatoid arthritis. The product, known commercially as Reumacon®, is available in several countries for the treatment of rheumatoid arthritis on a named-patient basis. In 2000, Conpharm, originator of CPH-82, established an alliance with Meda pursuant to which Meda would market CPH-82, once approved, in the Nordic region and the Baltic states. A second alliance gave Meda responsibility to direct the clinical development of CPH-82 and ultimately to file for regulatory approval of the product in Sweden, the basis for registration in the other European countries. In exchange, Meda obtained exclusive rights to the product in the rest of the world, with the exception of a few Asian countries, including China. CPH-82 is a semisynthetic derivative of two lignan glucosides from the plant *Podophyllum emodi* found growing over most of the Himalayan Range.

CRx-102/CRx-119/CRx-139/ CRx-150

CombinatoRx is developing a portfolio of selective steroid amplifier product candidates for the treatment of immunoinflammatory disorders. Each of these drug candidates consists of a reduced-dose steroid and a different enhancing agent. The result is a synergistic increase in the immunomodulatory activity of the steroid without a comparable increase in adverse events. CRx-102 is comprised of the steroid prednisolone and the antiplatelet agent dipyridamole and is presently being tested in phase

IIa clinical trials in rheumatoid arthritis, osteoarthritis and severe adult periodontitis. CRx-119 is a combination of the antidepressant amoxapine and low-dose prednisolone that is being investigated in phase IIa clinical trials in rheumatoid arthritis and severe adult periodontitis. Another product, CRx-139, combines prednisolone and a selective serotonin reuptake inhibitor (SSRI) and is expected to enter phase IIa clinical trials in rheumatoid arthritis and severe adult periodontitis this year.

The company has also designed a series of synergistic cytokine modulator product candidates combining approved drugs not currently indicated for immunoinflammatory diseases. CRx-150 combines two undisclosed pharmaceutical ingredients shown in preclinical studies to synergistically inhibit cytokines, including TNF-α, when administered together. A phase IIa clinical trial is under way in the U.K. in rheumatoid arthritis and another in severe adult periodontitis.

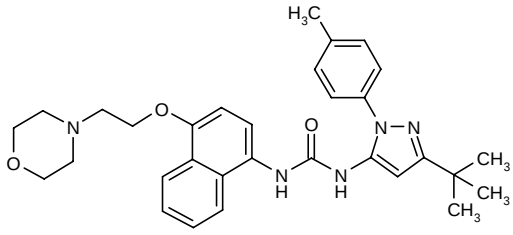
CS-706

Sankyo is conducting phase II clinical trials in the U.S. and Europe with CS-706 (R-109339), a COX-2 inhibitor, for arthritis.

DE-096

DE-096 is a TNF-α production inhibitor in early clinical development by Santen for the treatment of rheumatoid arthritis and edema due to diabetes mellitus. The company is making preparations to advance DE-096 to phase II trials for both indications.

Doramapimod



A p38 MAP kinase and TNF-α production inhibitor, doramapimod (BIBR-796) was last reported to be in phase II studies at Boehringer Ingelheim for the oral treatment of rheumatoid arthritis and Crohn's disease, and phase IIb/III trials for psoriasis.

Dronabinol/Cannabidiol

GW Pharmaceuticals is developing its cannabis-based medicinal product extract Sativex® (dronabinol/cannabidiol) for a number of indications, principally for the treatment of the debilitating symptoms and severe neuropathic pain of multiple sclerosis. It has been submitted for approval for this indication in the U.K., and also in Canada where it will be marketed by licensee Bayer. The oral spray product is a whole-plant extract containing dronabinol (tetrahydrocannabinol, THC, Tetranabinex™) and cannabidiol (CBD, Nabidiolex™). Phase II or III trials are also under way for various types of pain and the product is being tested in phase II studies for its potential in rheumatoid arthritis, inflammatory bowel disease and neurogenic symptoms (1-3).

The company reported positive preliminary results from a phase II trial of dronabinol/cannabidiol in patients with pain caused by rheumatoid arthritis. The multicenter, double-blind, randomized, parallel-group study assessed the efficacy, safety and tolerability of the extract compared with placebo in 58 patients with pain caused by rheumatoid arthritis. Study medication was administered by spray into the mouth as an evening dose only and measures were assessed the following day. Statistically significant improvements were seen in a range of outcome measures, including morning pain at rest, quality of sleep, disease activity score and Short Form McGill Pain Questionnaire-pain at present. Analysis of morning pain on movement approached statistical significance in favor of dronabinol/cannabidiol. The safety profile was consistent with earlier studies. Future research in rheumatoid arthritis will examine the optimal cannabinoid ratios in this indication prior to selecting the product candidate to enter into a pivotal phase III program (4).

1. *GW Pharmaceuticals to submit more information for U.K. review of Sativex*. DailyDrugNews.com (Daily Essentials) May 4, 2004.

2. *NDS submission for Sativex in Canada*. DailyDrugNews.com (Daily Essentials) May 13, 2004.

3. *GW receives Qualifying Notice for Sativex in Canada*. DailyDrugNews.com (Daily Essentials) Dec 28, 2004.

4. *Sativex produces positive results in phase II rheumatoid arthritis study*. DailyDrugNews.com (Daily Essentials) June 11, 2004.

Eculizumab

Alexion's humanized anti-C5 monoclonal antibody eculizumab (5G1.1) could become the first of a new class of antiinflammatory therapeutics called terminal complement inhibitors. The lead indication for eculizumab is paroxysmal nocturnal hemoglobinuria (PNH), for which it is in phase III clinical trials, and phase II trials are also under way in rheumatoid arthritis and nephritis. Early clinical trials have also been conducted for dermatomyositis.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Arthritis, rheumatoid	Randomized Double-blind Multicenter	Eculizumab, 600 mg 1x/wk x 5 wks → 600 mg 1x/4 wks Eculizumab, 600 mg 1x/wk x 5 wks → 600 mg 1x/2 wks Placebo	368	At 6 months, the percentage of patients with rheumatoid arthritis who achieved an ACR20 response was greater with eculizumab every 4 weeks compared with eculizumab every 2 weeks or placebo. All study treatments were safe, although the incidence of adverse events was slightly higher with eculizumab every 2 weeks	2

The antibody was assigned orphan drug designation by the FDA in 2001 for idiopathic membranous glomerular nephropathy, and in 2003 it was granted orphan drug status by the FDA and the EMEA for PNH.

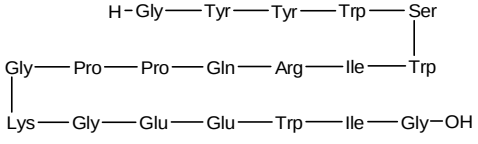
A double-blind, randomized, placebo-controlled phase IIb clinical trial evaluated the efficacy and safety of eculizumab in 368 adult patients with active rheumatoid arthritis unresponsive to methotrexate and/or leflunomide. Each patient was randomized to receive placebo or eculizumab (600 mg once weekly for 5 weeks, followed by 600 mg once every 2 weeks or once monthly). At 6 months, the percentage of patients who achieved an ACR20 response was greater with monthly eculizumab (34% *vs*. 24% with eculizumab every 2 weeks and 22% with placebo). The incidence of adverse events was slightly higher among patients given eculizumab every 2 weeks, although the incidence of injection-site reactions remained low. These results confirmed previous findings on the efficacy of once-monthly eculizumab in rheumatoid arthritis (1, 2) (see Table IV).

1. *Preliminary results of phase IIb eculizumab show improvement in ACR20*. DailyDrugNews.com (Daily Essentials) Feb 2, 2004.

2. Mojcik, C.F., Kremer, J., Bingham, C., Burch, F., Vitiello, S., McCroskery, E., Bookbinder, S. *Results of a phase 2B study of the humanized anti-C5 antibody eculizumab in patients with rheumatoid arthritis*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst FRI0170.

Original monograph – Drugs Fut 2004, 29(7): 673.

Edratide



Edratide (TV-4710), a CDR1-based peptide derived from a human anti-DNA antibody, is currently in early clinical development at Teva for the treatment of SLE.

Efalizumab

Efalizumab (Raptiva®) is a humanized therapeutic antibody designed to selectively and reversibly block the activation, reactivation and trafficking of T-cells that lead to the development of psoriasis symptoms. The antibody has been available in the U.S. since November 2003 for the treatment of moderate to severe chronic plaque psoriasis in adults who are candidates for systemic therapy or phototherapy, and it was subsequently approved in Switzerland, the E.U., Australia, Argentina, Mexico and Brazil. Genentech and Xoma codeveloped efalizumab and hold U.S. development and marketing rights. Serono was granted development and marketing rights worldwide outside the U.S. and Japan. Genentech and Xoma were also evaluating efaluzimab for use in rheumatoid arthritis and psoriatic arthritis. Clinical studies for the former condition were discontinued in 2003 and for the latter condition in 2004 (see below), due to lack of significant efficacy (1-11).

Preliminary results from a randomized, placebo-controlled phase II study with efalizumab in 107 patients with psoriatic arthritis indicated that the study did not reach statistical significance at 12 weeks (84 days) for the primary endpoint of ACR20 response. After 12 weeks of therapy, 28% of patients receiving efalizumab achieved an ACR20 response compared to 19% of those receiving placebo. In the subgroup of patients with moderate to severe plaque psoriasis, PASI scores for patients receiving efalizumab were similar to the statistically significant results demonstrated in phase III studies in psoriasis. There was no worsening in the signs and symptoms of psoriatic arthritis with efalizumab and the treatment was well tolerated (12, 13).

1. *Genentech reports R&D highlights*. DailyDrugNews.com (Daily Essentials) Jan 26, 2004.

2. *Raptiva receives Swiss approval*. DailyDrugNews.com (Daily Essentials) March 18, 2004.

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

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

5. *European approval for Raptiva for psoriasis*. DailyDrugNews.com (Daily Essentials) Sept 30, 2004.

6. *Xoma restructures Raptiva agreement with Genentech*. DailyDrugNews.com (Daily Essentials) Jan 17, 2005.

7. *Germany marks first European launch of Raptiva*. DailyDrugNews.com (Daily Essentials) Oct 7, 2004.

8. *Xoma reports Q2 R&D highlights*. Xoma Press Release 2004, Aug 9.

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

10. *Xoma reviews recent pipeline progress*. DailyDrugNews.com (Daily Essentials) July 12, 2004.

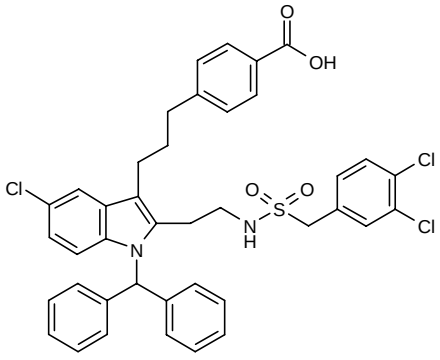
11. *Positive opinion for Raptiva for psoriasis in Europe*. DailyDrugNews.com (Daily Essentials) June 30, 2004.

12. *Genentech reports Q1 R&D highlights*. Genentech Press Release 2004, April 7.

13. *Genentech and XOMA announce results of phase II study of Raptiva in psoriatic arthritis patients*. Genentech Press Release 2004, March 21.

Original monograph – Drugs Fut 2001, 26(3): 232.

Efipladib



Efipladib (PLA-902) blocks the release of arachidonic acid associated with the pain and inflammation of rheumatoid arthritis and osteoarthritis and is in phase II clinical studies at Wyeth for these indications. It may also have potential in the treatment of asthma.

Epratuzumab

Immunomedics has received fast track designation for epratuzumab (IMMU-1903) for the treatment of patients with moderate to severe systemic lupus erythematosus (SLE). Epratuzumab is a versatile humanized anti-CD22 monoclonal antibody targeting B-cell-mediated autoimmune diseases and non-Hodgkin's lymphoma (NHL). Following recent phase II studies in Europe, phase III trials are set to begin in the first half of 2005. Epratuzumab appears to show activity in SLE patients without a drastic drop in their circulating B-lymphocytes, indicating that the CD22-targeting molecule may work by modulating B-cell function. Immunomedics regained all rights to epratuzumab from Amgen last year. Phase II trials have demonstrated its activity against NHL and registration trials in this indication are planned. Epratuzumab is also in phase I/II clinical evaluation for the treatment of Sjögren's syndrome (1-4).

The clinical benefits of epratuzumab in SLE were determined in an open-label, nonrandomized clinical trial that enrolled adult patients with a moderately active form of the disease. A preliminary analysis of the first 9 patients who completed the study showed that epratuzumab (360 mg/m^2 i.v. over 23-86 min once every 2 weeks for 8 weeks) reduced their baseline global disease activity scores for at least 1 month after the beginning of the treatment. Evidence suggested that epratuzumab decreased B-cell counts without having any effect on T-cell counts or immunoglobulin levels. Adverse events included sleepiness (associated with previous administration of antihistamines) and herpes zoster that responded to antivirals (5) (Table V).

1. *Immunomedics reports Q2 R&D highlights*. Immunomedics Press Release 2004, Feb 9.

2. *Amgen returns epratuzumab rights to Immunomedics*. DailyDrugNews.com (Daily Essentials) April 15, 2004.

3. *Immunomedics plans registration trials of epratuzumab in lupus*. DailyDrugNews.com (Daily Essentials) Oct 25, 2004.

4. *Fast track designation for epratuzumab in lupus*. DailyDrugNews.com (Daily Essentials) Jan 12, 2005.

5. Kaufmann, J., Wegener, W.A., Horak, I.D. et al. *Pilot clinical trial of epratuzumab (humanized anti-CD22 antibody) for immunotherapy in systemic lupus erythematosus (SLE)*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst THU0443.

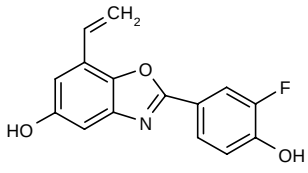
Additional References

Kaufmann, J. et al. *Initial clinical study of immunotherapy in SLE using epratuzumab (humanized anti-CD22 antibody)*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1127.

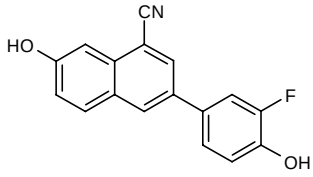
Table V: Clinical studies of epratuzumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Lupus erythematosus, systemic	Open	Epratuzumab, 360 mg/m^2 i.v. infusion over 23-86 min 1x/2 wks x 4	9	Epratuzumab once every 2 weeks was well tolerated and was associated with clinical benefits for at least 1 month in patients with moderate systemic lupus erythematosus	5

ERB-041/ERB-196



ERB-041



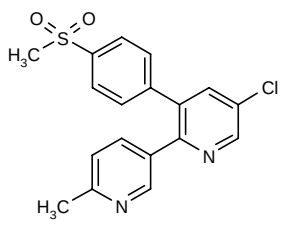
ERB-196

Wyeth is conducting early clinical evaluation of ERB-041 and ERB-196 (WAY-202196), two potent and selective estrogen receptor ERβ agonists, as potential new therapies for rheumatoid arthritis.

ET-201

EluSys's ET-201 is a first-in-class heteropolymer (HP) antibody product consisting of a humanized monoclonal antibody to CR1, a receptor on red blood cells, crosslinked to double-stranded DNA (dsDNA) and designed to remove pathogenic autoantibodies to dsDNA in patients with SLE. ET-201 is currently in phase I/II development for the treatment of SLE. Preliminary studies in humans demonstrated good safety and the ability to reduce dsDNA autoantibody titers in lupus patients. The company's HP System is a monoclonal antibody-based technology that enables the body to use its own red blood cells to efficiently remove and destroy a wide variety of blood-borne pathogens, toxins and autoantibodies. The company is seeking a partner for the further development of this product.

Etoricoxib



Etoricoxib (Arcoxia®; Merck & Co.) is a selective inhibitor of COX-2, an enzyme involved in pain and inflammation. It is a member of the COX-2-selective (coxib) class of NSAIDs. Extensive clinical trials have confirmed its analgesic and antiinflammatory efficacy to be at least as good as, and in some cases superior to, nonselective NSAIDs in a number of disease and patient treatment settings. Etoricoxib displays improved gastrointestinal safety compared with nonselective NSAIDs and has a favorable overall safety and tolerability profile. It is rapidly and completely absorbed following oral administration, providing a rapid onset of action. Its long plasma half-life allows for once-daily dosing. Etoricoxib is currently approved in a number of countries for various indications, including the treatment of acute pain, acute gouty arthritis, chronic low back pain, primary dysmenorrhea and the chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis. In countries where it is approved, the highest recommended daily dose for chronic use is 90 mg for rheumatoid arthritis and 60 mg for osteoarthritis and chronic low back pain. The recommended daily dose for acute pain relief from primary dysmenorrhea and acute gouty arthritis is 120 mg. This review summarizes the published preclinical and clinical data relevant to the use of etoricoxib in clinical practice (1).

As part of the ongoing review of COX-2 inhibitors, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has held hearings with Pfizer (for celecoxib, parecoxib and valdecoxib), Merck Sharp & Dohme (for etoricoxib) and Novartis (for lumiracoxib). Data are being assessed and discussions continue (2).

Late last year, Merck & Co. received an approvable letter from the FDA for the company's NDA for etoricoxib. The letter requests additional safety and efficacy data prior to approval of the drug. In the NDA, Merck is seeking approval of etoricoxib for the treatment of osteoarthritis, rheumatoid arthritis, chronic low back pain, acute pain, dysmenorrhea, acute gouty arthritis and ankylosing spondylitis. A revised NDA was submitted in December 2003 to include efficacy data for ankylosing spondylitis and to provide additional cardiovascular safety data. Etoricoxib has been launched in 48 countries worldwide in Europe, Latin America and the Asia-Pacific region. It was also introduced last year in India by Zydus Cadila as Nucoxia (3-9).

1. Matsumoto, A.K., Cavanaugh, P.F. *Etoricoxib*. Drugs Today 2004, 40(5): 395.

2. *Merck & Co., Inc. reports Q2 R&D highlights*. Merck & Co., Inc. Press Release 2004, July 21.

3. *European CHMP reviews COX-2 inhibitors*. DailyDrugNews.com (Daily Essentials) Jan 25, 2005.

4. *NDA filing for Arcoxia*. DailyDrugNews.com (Daily Essentials) Jan 7, 2004.

5. *Zydus Cadila launches Nucoxia in India*. DailyDrugNews.com (Daily Essentials) March 18, 2004.

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

7. *Merck & Co. reports Q1 R&D highlights*. Merck & Co., Inc. Press Release 2004, April 22.

8. *Merck & Co.: pipeline review*. DailyDrugNews.com (Daily Essentials) Dec 20, 2004.

9. *Approvable letter for Arcoxia*. DailyDrugNews.com (Daily Essentials) Nov 3, 2004.

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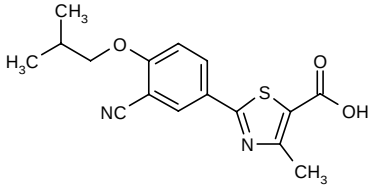
Febuxostat



An oral, once-daily, selective, nonpurine inhibitor of xanthine oxidase, febuxostat (TMX-67) was developed at Teijin and is currently undergoing review by the U.S. and Japanese authorities for the management of hyperuricemia in patients with chronic gout. The product is licensed to TAP Pharmaceutical for North America, to Ipsen for Europe and to SK Pharma for South Korea. Phase III clinical evaluation is under way in the E.U.

The NDA submission includes a randomized, controlled, 52-week study in 760 patients with diagnosed gout and serum uric acid levels of 8.0 mg/dl or greater. Febuxostat 80 mg daily (53%) and 120 mg daily (62%) reached the study's primary endpoint of lowering serum uric acid levels to below 6 mg/dl for 3 consecutive months compared to treatment with allopurinol 300 mg daily (21%). The standard goal in the treatment of chronic gout is the reduction and maintenance of serum uric acid levels to < 6 mg/dl. Serum uric acid levels below 6 mg/dl were associated with a reduction in the incidence of gout flares and larger reductions in tophus area. Febuxostat was well tolerated, most adverse events being mild to moderate in all treatment groups (1, 2).

A pharmacokinetic/pharmacodynamic study concluded that febuxostat dose adjustments were not necessary in patients with renal impairment. The study included subjects with normal renal function and others with mild, moderate or severe renal impairment who were given 80 mg once daily for 7 days. Similar pharmacokinetic and pharmacodynamic parameters were measured in each group on day 7, and adverse events were mild or moderate (3).

Escalating doses of febuxostat (10, 20, 30, 40, 50, 70, 90, 120, 160, 180 and 240 mg) were administered once daily to groups of 12 healthy subjects in a phase I study. The drug was taken on day 1 and on days 3-14. The time to maximum concentration was approximately 1 h and the half-life was approximately 6 h. Dose-proportional pharmacokinetics were observed for doses ranging from 10 to 120 mg. Glucuronidation and oxidation accounted for most of the metabolism of the drug. Febuxostat was also found to significantly decrease serum uric acid and was safe, most adverse effects being mild to moderate in severity (4).

Hepatic impairment did not appear to alter the pharmacokinetics, pharmacodynamics or safety of febuxostat in a study in patients with normal, mild or moderate hepatic dysfunction given a dose of 80 mg once daily for 7 days. Although significant differences in mean serum uric acid levels were seen between patients with normal hepatic function and those with impairment, the differences were not deemed clinically significant (5).

Febuxostat did not prolong the Q-T interval in 41 healthy subjects given multiple doses in a randomized, crossover study. Subjects were given febuxostat 80 mg/day, febuxostat 300 mg/day, placebo or moxifloxacin 400 mg/day for 4 days each. Average maximum Q-T intervals on day 4 were 403.7, 405.1, 402.9 and 415.9 ms, respectively. The only significant difference in comparison to placebo was seen with moxifloxacin. Most adverse events were mild (6).

A multicenter, double-blind, randomized clinical trial determined the safety profile and the effects of febuxostat in the treatment of gout. A total of 136 male and 17 female patients with gout were randomized to receive placebo or febuxostat (40, 80 or 120 mg) once daily for 4 weeks. The serum urate levels of the patients, measured at the end of the study, showed significant reductions compared to baseline with all febuxostat doses. The average reductions in serum urate levels achieved with each study treatment were 2% with placebo and 37%, 44% and 59%, respectively, with 40, 80 and 120 mg of febuxostat. The percentages of patients who achieved serum urate levels below 6 mg/dl in these study groups were 0%, 56%, 76% and 94%, respectively. Most patients completed the study, and the incidence of adverse events was similar with febuxostat (54%) and placebo (50%). Most adverse events were mild and self-limiting, the most common being diarrhea, pain, back pain, headache and arthralgia (7).

The use of colchicine (0.6 mg b.i.d.) appeared to be safe and effective in reducing the incidence of gout flares in patients with gout and serum uric acid above 8 mg/dl treated with placebo or febuxostat in a double-blind study and in those continuing febuxostat treatment in an open-label extension study. The gout flare incidence decreased with colchicine administration compared with

either febuxostat or placebo given alone in the double-blind study. In the open trial, gout flares initially increased after withdrawal of colchicine but declined over the course of the study (8).

Of patients with gout and hyperuricemia enrolled in a double-blind, placebo-controlled trial and a long-term extension study of febuxostat, 11 were allopurinol-intolerant. A reduction in serum uric acid from 8.2-11.1 mg/dl to below 6 mg/dl was seen in the open-label trial in these patients, and long-term treatment was safe and well tolerated. Self-limiting respiratory infections were the most frequently seen adverse events (9).

A phase III trial was conducted in 103 Japanese patients with gout or hyperuricemia who were randomized to placebo or febuxostat (10 mg/day for 2 weeks, then 20 or 40 mg/day for 6 weeks). Serum uric acid fell below 6 mg/dl in 0%, 45.7% and 91.2% of patients given placebo, febuxostat 20 and febuxostat 40 mg, respectively. The efficacy of febuxostat was similar in patients with gout and those with hyperuricemia and in under-excretors and non-under-excretors. Most adverse events were mild (10).

In a multicenter, double-blind phase III trial, 256 patients with gout or hyperuricemia were randomized to allopurinol 100 mg/day or febuxostat 10 mg/day for 12 days; doses were increased to allopurinol 100 mg b.i.d. and febuxostat 40 mg/day for 44 days. Significantly greater serum uric acid reductions were seen with febuxostat (40.5% *versus* 33.9%), and more patients achieved serum uric acid below 6 mg/dl with febuxostat (82% *versus* 69%). The treatments were safe, with mostly mild and no serious adverse events reported (11).

Reductions in serum uric acid levels with febuxostat appeared to be associated with reductions in the size of gouty tophi in a study in 9 patients. Patients received treatment with febuxostat 80 mg/day, which was adjusted based on efficacy and tolerability. Magnetic resonance imaging showed that tophus volumes decreased when serum uric acid levels were below 6 mg/dl and increased when levels were above 6 mg/dl (12).

After a 4-week, double-blind, placebo-controlled trial, 116 patients with gout and hyperuricemia were enrolled in an open, long-term extension trial. A starting dose of febuxostat 80 mg/day could be titrated to either 40 or 120 mg/day after 4 weeks. Febuxostat treatment for up to 2 years was associated with reductions in serum uric acid of 45-48%, with most patients achieving levels below 6 mg/dl throughout the study. Long-term treatment was also safe and well tolerated (13).

1. *TAP submits febuxostat NDA for management of hyperuricemia in gout*. DailyDrugNews.com (Daily Essentials) Dec 20, 2004.

2. Becker, M.A., Schumacher, H.R., Wortmann, R.L., MacDonald, P.A., Palo, W., Eustace, D., Joseph-Ridge, N. *A phase 3 study comparing the safety and efficacy of oral febuxostat and allopurinol in subjects with hyperuricemia and gout*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst L18.

3. Mayer, M., Wu, J.-T., Joseph-Ridge, N., Vernillet, L., Khosravan, R. *Febuxostat, a novel non-purine selective inhibitor of xanthine oxidase - Effect of renal impairment on pharmacokinetics, pharmacodynamics and safety*. 33rd Annu Meet Am Coll Clin Pharmacol (Oct 3-5, Phoenix) 2004, Abst 45.

4. Khosravan, R., Vernillet, L., Wu, J.-T., Joseph-Ridge, N., Mulford, D., Grabowski, B. *Pharmacokinetics, pharmacodynamics, and safty of febuxostat (TMX-67), a non-purine selective inhibitor of xanthine oxidase, in healthy subjects*. 33rd Annu Meet Am Coll Clin Pharmacol (Oct 3-5, Phoenix) 2004, Abst 47.

5. Khosravan, R., Mayer, M., Grabowski, B., Vernillet, L., Wu, J.T., Joseph-Ridge, N. *Febuxostat, a non-purine selective inhibitor of xanthine oxidase - Effect of mild and moderate hepatic impairment on pharmacokinetics, pharmacodynamics, and safety*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 806.

6. Khosravan, R., MacDonald, P., Joseph-Ridge, N., Yu, P. *Effect of febuxostat, a novel non-purine, selective inhibitor of xanthine oxidase, on the QT interval in healthy subjects*. 33rd Annu Meet Am Coll Clin Pharmacol (Oct 3-5, Phoenix) 2004, Abst 46.

7. Becker, M.A., Schumacher, H. Jr., Wortmann, R.L., Joseph-Dridge, N., Lademacher, C. *A safety and efficacy clinical trial of a novel non-purine selective inhibitor of xanthine oxidase, febuxostat in subjects with gout*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst OP0007.

8. Wortmann, R., Becker, M.A., Schumacher, H.R., MacDonald, P., Palo, W.A., Joseph-Ridge, N. *Gout flare prophylaxis during management of chronic gout with febuxostat, a non-purine selective inhibitor of xanthine oxidase*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 801.

9. Becker, M.A., Schumacher, R., Wortmann, R., MacDonald, P., Palo, W., Joseph-Ridge, N. *Febuxostat, a novel non-purine selective inhibitor of xanthine oxidase, therapy in allopurinol intolerant patients*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 803.

10. Kamatani, N., Fujimori, S., Hada, T., Hosoya, T., Matsuzawa, Y., Ueda, T., Yamanaka, H., Kato, R. *Febuxostat, a novel non-purine selective inhibitor of xanthine oxidase, in a phase III placebo-controlled double-blind clinical trial in Japanese subjects with gout or hyperuricemia*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 805.

11. Kamatani, N., Fujimori, S., Hada, T., Hosoya, T., Matsuzawa, Y., Ueda, T., Yamanaka, H., Kato, R. *Febuxostat, a novel non-purine selective inhibitor of xanthine oxidase, in an allopurinol-controlled phase III clinical trial in Japanese subjects with gout or hyperuricemia*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 804.

12. Schumacher, H.R., Becker, M.A., Wortmann, R., MacDonald, P., Palo, W.A., Streit, J., Lademacher, C., Joseph-Ridge, N. *Magnetic resonance imaging of gouty tophi during treatment with febuxostat, a non-purine selective inhibitor of xanthine oxidase*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 802.

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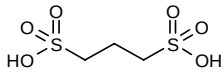
Fibrillex™



Neurochem has signed a definitive collaboration and distribution agreement granting Centocor, a wholly owned subsidiary of Johnson & Johnson, exclusive distribution rights for Neurochem's investigational product candidate 1,3-propanedisulfonate (1,3-PDS, Fibrillex™) for the prevention and treatment of amyloid A (AA) amyloidosis, formerly known as secondary amyloidosis. Distribution rights granted to Centocor are worldwide, with the exception of Canada, Switzerland, China, Japan, Taiwan and South Korea, which remain with Neurochem. Neurochem will be responsible for product approval activities in the U.S. and E.U., as well as for global manufacturing activities. Centocor and other affiliates will manage the marketing and sales of Fibrillex™ in the applicable territories. Centocor will also be responsible for worldwide safety surveillance. Neurochem recently completed the phase II/III trial FAST (Fibrillex Amyloidosis Secondary Trial) of this product candidate and anticipates filing for regulatory approval in 2005. The 2-year, international, randomized, double-blind, placebo-controlled, parallel-design trial was conducted to evaluate the efficacy and safety of the investigational product candidate in patients suffering from AA amyloidosis confirmed by biopsy and renal involvement. A total of 183 patients were enrolled at 27 sites across North America, Europe, North Africa and Israel. The most frequent underlying diseases in patients during the trial were rheumatoid arthritis and familial Mediterranean fever (49% and 19%, respectively). The mean time from onset of underlying disease until AA amyloidosis was 14.6 ± 10.6 years and nephrotic syndrome was present in 32% of the participating patients. The final study visits by the last patients enrolled in the trial were recently completed and data are expected to be reported during the second quarter of 2005. All patients who completed the trial have been invited to join the 2-year open-label phase II/III extension study (OLPES). Fibrillex™ holds orphan drug designation in both the U.S. and the E.U. and has been granted fast track status by the FDA (1-7).

1. *Pivotal Fibrillex study cleared to continue by DSMB*. DailyDrugNews.com (Daily Essentials) Jan 19, 2004.

2. *Fast track status for Fibrillex*. DailyDrugNews.com (Daily Essentials) Feb 13, 2004.

3. *Phase II/III trial of Fibrillex cleared to continue*. DailyDrugNews.com (Daily Essentials) April 28, 2004.

4. *Neurochem updates clinical pipeline progress*. DailyDrugNews.com (Daily Essentials) May 21, 2004.

5. *Neurochem reports Q1 R&D highlights*. Neurochem Press Release 2004, May 11.

6. *FAST phase II/III study completed for Fibrillex*. DailyDrugNews.com (Daily Essentials) Dec 13, 2004.

7. *Neurochem grants Centocor rights to Fibrillex*. DailyDrugNews.com (Daily Essentials) Dec 28, 2004.

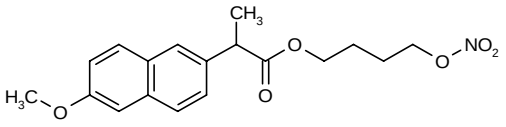
Golimumab

Golimumab (CNTO-148) is an anti-TNF-α human monoclonal antibody developed using Medarex's HuMAb-Mouse™ technology, in phase II development by Centocor (Johnson & Johnson) for the treatment of rheumatoid arthritis.

Encouraging results were recorded for golimumab in phase I trials in rheumatoid arthritis patients. In a single-dose study, 36 patients were randomized to placebo or golimumab 0.1-10 mg/kg given intravenously. In a second randomized, double-blind study, 52 patients received single s.c. doses of placebo or golimumab 0.3-3 mg/kg, or s.c. doses of placebo or golimumab 0.3 or 1 mg/kg given at weeks 0, 2 and 4. The active treatment was deemed safe and well tolerated upon both single and repeated administration. No serious adverse events were seen in the first study, and 1 (breast carcinoma) was reported in the second study. One withdrawal due to an allergic response occurred in the second trial. Linear, dose-proportional pharmacokinetics were measured and the antibody was also found to reduce markers of inflammation (1).

1. Fleischmann, R., Cohen, S., Caldwell, J.R. et al. *Phase I studies evaluating the safety, pharmacokinetics, and pharmacodynamics of intravenous and subcutaneous administration of a fully human monoclonal antibody to human THF-α (CNTO 148) in rheumatoid arthritis patients*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 341.

HCT-3012



NicOx has had a successful end-of-phase II meeting with the FDA for HCT-3012 (formerly AZD-3582, nitronaproxen, naproxen nitroxybutyl ester), the lead compound in the cyclooxygenase (COX)-inhibiting nitric oxide (NO) donor (CINOD) class. The company will now move forward with the U.S. clinical development program for the compound through phase III, planned to start in the second half of 2005, subject to a further meeting on manufacturing and formulation with the FDA in the first quarter of 2005. HCT-3012 is being developed as a new pain treatment for osteoarthritis patients with an improved cardiovascular and gastrointestinal safety profile. A broad phase II program in more than 2,700 patients has already demonstrated that HCT-3012 is a potent and safe antiinflammatory with the potential for improved cardiovascular safety over NSAIDs and COX-2-selective NSAIDs. Following a review of results from the full phase II clinical program, an independent U.S. Clinical Consultant Advisory Board (CAB) considered the overall results encouraging and recommended further development through to registration in the treatment of osteoarthritis. The CAB identified 375 mg b.i.d. as the minimum fully effective dose to be carried forward into further development and recommended a program of additional clinical studies to further define the product profile of HCT-3012. The company subsequently initiated a comparative clinical study of the effects of HCT-3012 and rofecoxib on arterial blood pressure in patients with mild essential hypertension, with the aim of providing definitive proof of data observed in analysis of the OASIS pivotal phase II trial in patients treated for osteoarthritis. This analysis suggested that HCT-3012 decreased systolic blood pressure on average by 3 mmHg, while rofecoxib tended to raise systolic blood pressure to a similar extent. HCT-3012 may potentially counteract the detrimental effects of COX inhibition on blood pressure through its unique mechanism of action and may prove to be beneficial in patients with osteoarthritis and concomitant cardiovascular risk factors (1-4). NicOx regained full rights to the product from AstraZeneca in 2003.

HCT-3012 was associated with less upper gastrointestinal tract mucosal injury than naproxen in a study in healthy volunteers. Healthy male subjects (n=75) were randomized to double-blind, crossover treatment with HCT-3012 750 mg/day and HCT-3012 375 mg b.i.d., HCT-3012 375 mg b.i.d. and HCT-3012 750 mg b.i.d., or naproxen 500 mg b.i.d. and naproxen 250 mg b.i.d. After 12 days of drug administration, significantly fewer erosions and ulcers were noted endoscopically in patients taking HCT-3012 than in patients taking equimolar doses of naproxen. The fewest erosions and ulcers were seen in patients taking HCT-3012 750 mg/day (mean = 0.92), and the most were seen in patients taking naproxen 500 mg b.i.d. (mean = 6.68). The treatments were safe and did not differ in terms of the most common adverse events, which were minor gastrointestinal effects (5).

Data from 2 double-blind, randomized clinical trials were used to determine the analgesic efficacy and cardiovascular safety profile of HCT-3012 in osteoarthritis. These trials randomized 672 and 543 patients with symptomatic knee/hip osteoarthritis to receive HCT-3012 (375 and 750 mg b.i.d.), naproxen (500 mg b.i.d.), rofecoxib (25 mg once daily) or placebo for 6 weeks. The analgesic activity of HCT-3012 was significantly greater than that of placebo and similar to that found with naproxen or rofecoxib. The average systolic blood pressure of the patients decreased with both HCT-3012 doses, but increased with naproxen or rofecoxib; the difference between the blood pressure effects of the study treatments was even greater in patients with hypertension. These results suggest that HCT-3012 may be especially useful for patients with osteoarthritis and concomitant cardiovascular risk factors (6, 7) (see Table VI).

1. *AZD-3582 recommended for further development based on phase II results*. DailyDrugNews.com (Daily Essentials) Jan 29, 2004.

2. *New study evaluates effects of HCT-3012 vs. rofecoxib on blood pressure*. DailyDrugNews.com (Daily Essentials) Sept 10, 2004.

3. *NicOx prepares for phase III program of HCT-3012*. DailyDrugNews.com (Daily Essentials) Dec 17, 2004.

Table VI: Clinical studies of HCT-3012 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Osteoarthritis, Osteoarthritis, localized	Double-blind Multicenter Pooled/meta-analysis	HCT-3012, 125 mg b.i.d. x 6 wks HCT-3012, 375 mg b.i.d. x 6 wks HCT-3012, 750 mg b.i.d. x 6 wks Rofecoxib, 25 mg o.d. x 6 wks Naproxen, 500 mg b.i.d. x 6 wks Placebo	672	HCT-3012 375 and 750 mg twice daily was well tolerated and as effective as rofecoxib or naproxen in inducing pain relief in patients with osteoarthritis of the knee. These doses of HCT-3012 also reduced the systolic and diastolic blood pressure values, suggesting that HCT-3012 may be associated with a good cardiovascular profile	6

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

5. Wilder-Smith, C.H., Robert, J., Schindler, D. *Upper gastrointestinal tract mucosal injury by AZD3582, a COX-inhibiting nitric oxide donor (CINOD), and naproxen: A randomised, double-blind, crossover study in healthy subjects*. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst OP-G-168.

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7. Schnitzer, T., Ballabio, M., Bonizzoni, E. *AZD3582, a CINOD, differs significantly from rofecoxib in having a neutral effect on blood pressure in patients with osteoarthritis: Results of a randomized controlled trial*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 833.

HuMax™-CD20

The FDA has accepted Genmab's IND for a phase I/II dose-escalation trial for HuMax™-CD20 to treat patients with active rheumatoid arthritis who have failed treatment with at least 1 DMARD. In the study, 60 patients will be randomized to 3 cohorts each containing 20 patients. In each cohort, 16 patients will receive 2 infusions of HuMax™-CD20 (300, 700 or 1000 mg) and 4 patients will receive placebo, given 14 days apart. All patients will also receive methotrexate. Patients will be followed for 24 weeks to evaluate safety and efficacy, and then every 12 weeks until B-cell counts return to baseline levels. Genmab plans to initiate the study during the early part of 2005. HuMax™-CD20 is also currenty in phase I/II studies in patients with chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma (NHL) and has received fast track designation for patients with CLL who have failed fludarabine therapy. This patient group includes those who are refractory to available treatment. HuMax™-CD20, developed using Medarex's UltiMAb® technology, is a human antibody that appears to bind to a unique site on CD20 target cells, and releases only very slowly from the target over time. Phase I/II data from patients with relapsed or refractory follicular lymphoma presented in December 2004 showed that 55% of patients treated with HuMax™-CD20 achieved a clinical response, including 2 complete responses and 1 unconfirmed complete response, for a 27% complete response rate. These responses were observed in 11 evaluable patients among the first 15 of the 40 patients included in this study at the week 11 evaluation point (1-5).

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

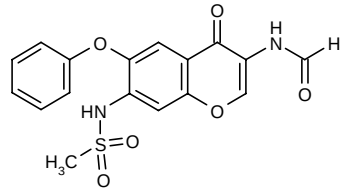
2. *Clinical responses seen in phase I/II study of Humax-CD20 in NHL*. DailyDrugNews.com (Daily Essentials) Dec 10, 2004.

3. *HuMax-CD20 receives fast track designation in CLL*. DailyDrugNews.com (Daily Essentials) Dec 20, 2004.

4. *HuMax-CD20 IND accepted for phase I/II study in RA*. DailyDrugNews.com (Daily Essentials) Dec 15, 2004.

5. *FDA accepts Genmab IND for phase I/II study of HuMax-CD20 in CLL*. DailyDrugNews.com (Daily Essentials) June 22, 2004.

Iguratimod



The DMARD iguratimod (T-614) has been filed for approval in Japan by Toyama and development partner Eisai for the treatment of rheumatoid arthritis. Iguratimod is an NF-κB activation inhibitor which suppresses immunoglobulin and inflammatory cytokine production. Toyama granted Dong-A Pharmaceuticals a license to iguratimod in Korea. Iguratimod will be launched and marketed by Taisho Toyama and Eisai following approval.

A multicenter, double-blind, randomized clinical trial determined the efficacy and safety of iguratimod. A total of 375 patients with active rheumatoid arthritis were given iguratimod (25 mg/day for 4 weeks, then increased to 50 mg/day), sulfasalazine (1000 mg/day) or placebo for a total of 28 weeks. The percentage of patients who achieved an ACR20 response at the end of the trial was significantly greater with iguratimod (62.5%) and sulfasalazine (58.1%) compared to placebo. No significant differences were found between the iguratimod and sulfasalazine study groups, although patients treated with iguratimod showed a greater incidence of transient elevations in liver enzymes that improved following discontinuation (1) (Table VII).

1. Hara, M., Abe, T., Sugawara, S. et al. *A phase III, double blind, comparative study to evaluate the efficacy and safety of*

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

Indication	Design	Treatments	n	Conclusions	Ref.
Arthritis, rheumatoid	Randomized Double-blind Multicenter	Iguratimod, 50 mg/d x 80 wks (n=146) Sulfasalazine, 1000 mg/d x 28 wks → Iguratimod, 50 mg/d x 52 wks (n=156) Placebo x 28 wks → Iguratimod, 50 mg/d x 52 wks (n=73)	375	Iguratimod was well tolerated and as effective as sulfasalazine in improving symptoms in patients with active rheumatoid arthritis, even in those refractory to methotrexate	1

T-614, a newly developed DMARD. Ann Rheum Dis 2004, 63(Suppl. 1): Abst OP0109.

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IL-1 Trap

Regeneron's IL-1 Trap is a fusion protein consisting of extracellular domains of the IL-1 receptor (IL-1RI and IL-1R accessory protein) linked to the Fc portion of human IgG_1. The company is developing IL-1 Trap for rheumatoid arthritis and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institutes of Health (NIH) are also evaluating IL-1 Trap in a phase II trial for the treatment of familial Mediterranean fever and Still's disease.

Regeneron announced plans last year to initiate a phase IIb study of its IL-1 Trap for the treatment of rheumatoid arthritis. The trial is being conducted on the recommendation of an advisory panel of independent medical experts who reviewed results from a phase II trial of IL-1 Trap in patients with rheumatoid arthritis. According to the panel, the trial may not have tested the maximally effective dose of IL-1 Trap, and the new phase IIb study should be conducted in a larger patient population, testing higher doses for a longer period of time. The trial is expected to begin following completion of development of a new formulation and patient tolerability studies. Regeneron also plans to study the IL-1 Trap in other inflammatory diseases. Novartis has forgone its rights under the parties' collaboration agreement to jointly develop and commercialize the IL-1 Trap. Novartis elected not to proceed with the joint development of the IL-1 Trap after Regeneron refused to revise the terms of the companies' original agreement in accordance with Novartis's suggestions. Each company retains rights to elect to collaborate on the development and commercialization of other IL-1 antagonists being developed independently by the other party that are in earlier stages of development (1, 2).

1. *Regeneron to test IL-1 Trap in phase IIb study*. DailyDrugNews.com (Daily Essentials) March 4, 2004.

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

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INCB-3284

Incyte has initiated a phase I study to assess the safety and tolerability of its most advanced oral chemokine CCR_2 antagonist, INCB-3284, in healthy volunteers. Both single and multiple doses will be tested in the U.S.-based single-site trial. The multiple-dose portion of the trial will also include a delayed-type hypersensitivity (DTH) test that is intended to serve as a pharmacological proof of principle for evaluating the potential antiinflammatory properties of the antagonist. CCR_2 ligands are potent chemoattractants for peripheral blood monocytes. CCR_2 knockout mice show a marked impairment of macrophage influx into sites of inflammation and are less susceptible to the development of inflammatory disease in a range of models, including experimental autoimmune encephalomyelitis, atherosclerosis, neuropathic pain and inflammatory bowel disease. In addition to INCB-3284, Incyte has other chemically distinct series of oral CCR_2 antagonists that are highly selective and have excellent pharmacokinetic properties. The company intends to secure a partner for its CCR_2 program. Phase II studies are anticipated to begin in the first quarter of 2005 in rheumatoid arthritis, and possibly one other potential indication (1, 2).

1. *Phase I trial commences for oral CCR2 antagonist INCB-3284*. DailyDrugNews.com (Daily Essentials) May 14, 2004.

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

Infliximab

Since the last annual review on this therapeutic class in 2003, infliximab, an anti-TNF-α monoclonal antibody marketed as Remicade® by the Johnson & Johnson subsidiary Centocor in the U.S. and by licensees Schering-Plough (worldwide except Japan) and Tanabe Seiyaku (Japan) for several years for the treatment of Crohn's disease and in combination with methotrexate for the treatment of rheumatoid arthritis, has also been introduced for the treatment of ankylosing spondylitis. Infliximab was the first biologic approved for the latter indication in the E.U., and it was approved for this indication by the FDA late in 2004. Schering-Plough received additional E.U. approval for infliximab in psoriatic arthritis, with launch following in 2004, and Centocor also filed with the FDA seeking permission to market the drug for this indication. In Japan, Tanabe Seiyaku has filed a regulatory application for infliximab for the treatment of Behçet's disease. A range of other potential indications are also under study in late-stage clinical trials, including ulcerative colitis, for which fast track status has been granted by the FDA, psoriasis and juvenile rheumatoid arthritis (1-8).

The approval of infliximab for the treatment of ankylosing spondylitis was based primarily on the results of

the ASSERT (Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy) trial. The multicenter, double-blind, randomized, placebo-controlled phase III trial in North America and Europe included 279 patients who received either placebo or infliximab as 5 mg/kg infusions at weeks 0, 2 and 6, followed by infusions every 6 weeks. At 24 weeks, 61% of the infliximab group achieved a 20% or greater improvement in signs and symptoms as measured by the Ankylosing Spondylitis Assessment (ASAS20), compared to only 19% of the placebo group. The benefit seen in the infliximab group was statistically significant compared to placebo. Also, the baseline activity score for spinal inflammation decreased at 24 weeks by a median of 72.9% on infliximab, whereas no significant change was observed on placebo. Minimal disease activity (defined as a value of < 20 on a scale of 0-100 mm in each of the 4 ASAS response parameters) was achieved in 22% of infliximab patients *versus* 1% in the placebo group, and patients receiving infliximab also showed significant improvement in individual measurements of disease activity, function and mobility, as well as improvement in chest expansion and patient global assessment (9-11).

The E.U. approval and the U.S. BLA submission for its use in combination with methotrexate for the treatment of active, progressive psoriatic arthritis in patients with an inadequate response to DMARDs were based on data from the multicenter, randomized, double-blind, placebo-controlled IMPACT (Infliximab Multinational Psoriatic Arthritis Controlled Trial) and IMPACT 2 studies in patients with active psoriatic arthritis who had failed at least 1 DMARD. In the IMPACT 2 study, treatment with infliximab 5 mg/kg resulted in marked improvement in patients with psoriatic arthritis, with significant improvement in both joint and skin disease evident as early as week 2. The data showed that at week 14, more than half of the patients in the infliximab treatment group achieved significant improvements in the signs and symptoms of psoriatic arthritis as measured by the proportion of patients achieving ACR20 (58% on infliximab *vs.* 11% on placebo) and 75% improvement in the PASI score (63.9% on infliximab *vs*. 2.3% on placebo). The ACR20 and PASI75 responses were achieved regardless of concomitant methotrexate use or level of joint involvement at baseline. Furthermore, compared to placebo, significantly more subjects in the infliximab treatment group achieved ACR70 or PASI90 as early as week 6 and improved or maintained these results at later points in the study. At week 24, results showed that 27% of patients treated with infliximab exhibited a 70% improvement in symptoms of arthritis (as measured by ACR70) compared with 2% in the placebo group. A total of 39% of patients showed a 90% improvement in psoriasis (as measured by PASI90) compared with 0% in the placebo group. In the IMPACT study, 104 subjects were randomized to infliximab (5 mg/kg) or placebo. At week 16, 65% of those on infliximab therapy achieved ACR20. Additionally, of the 38 subjects with evaluable psoriasis, 68% achieved a 75% or greater improvement from baseline (PASI75), indicating clinically meaningful improvement in psoriasis. Significant improvements were maintained through 1 year (12-17).

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

2. *Johnson & Johnson reports Q1 R&D highlights*. Johnson & Johnson Press Release 2004, April 13.

3. *Remicade approved in E.U. for early rheumatoid arthritis*. DailyDrugNews.com (Daily Essentials) June 25, 2004.

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

5. *Schering-Plough reports Q2 R&D highlights*. Schering-Plough Corp. Press Release 2004, July 21.

6. *Tanabe Seiyaku signs addendum to Remicade license agreement in Japan*. DailyDrugNews.com (Daily Essentials) Feb 1, 2005.

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

8. *FDA approves Remicade as first-line therapy in moderate to severe RA*. DailyDrugNews.com (Daily Essentials) Oct 5, 2004.

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

10. *Remicade receives FDA approval for ankylosing spondylitis*. DailyDrugNews.com (Daily Essentials) Dec 22, 2004.

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12. *Remicade receives European approval for psoriatic arthritis*. DailyDrugNews.com (Daily Essentials) Oct 19, 2004.

13. *Remicade sBLA for psoriatic arthritis accepted for filing*. DailyDrugNews.com (Daily Essentials) Dec 3, 2004.

14. *European CHMP recommends approval of Remicade for psoriatic arthritis*. DailyDrugNews.com (Daily Essentials) Aug 3, 2004.

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17. Gottlieb, A.B., Evans, R., Patel, K., Matheson, R. *Infliximab improves signs of plaque psoriasis in patients with psoriatic arthritis*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P612.

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Interferon Alfa Kinoid

Interferon alfa kinoid (IFN-α kinoid, Antiferon™) is a chemically inactivated but immunogenic interferon alfa designed to trigger antibodies neutralizing overproduced interferon alfa. Developed by Neovacs, it has been licensed to Aventis Pasteur for the treatment of AIDS. Neovacs is also evaluating its potential for the treatment of systemic lupus erythematosus (SLE) in early clinical trials.

Interferon Alfa, Low-Dose Oral

Research conducted at Amarillo Biosciences indicates that the company's low-dose oral interferon alfa mimics normal immune system activation via interferon's attraction to receptors on the oral mucosal surface. Low-dose oral interferon has several advantages, including convenient administration, lack of severe adverse effects, ease of storage (room temperature) and low cost. A phase III trial was conducted several years ago in patients with Sjögren's syndrome, and it may also have potential in the treatment of Behçet's disease, essential thrombocythemia and polycythemia rubra vera. The FDA has granted orphan drug status for use in the treatment of oral warts in HIV-positive patients, Behçet's disease and polycythemia rubra vera.

ISIS-104838

As part of its reorganization and refocusing of resources, Isis Pharmaceuticals has terminated development of ISIS-104838, an antisense TNF-α inhibitor which had reached phase II development for the treatment of rheumatoid arthritis (1-4).

1. *ISIS-104838 gives statistically significant disease response in phase II RA study*. DailyDrugNews.com (Daily Essentials) Jan 8, 2004.

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

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

4. *Isis Pharmaceuticals reports Q2 R&D highlights*. Isis Pharmaceuticals Press Release 2004, Aug 5.

Ismomutilin Alfa

Organon has discontinued the development of the autoantigen ismomutilin alfa (Org-39141), which was being evaluated in phase II clinical trials as a potential new treatment for rheumatoid arthritis.

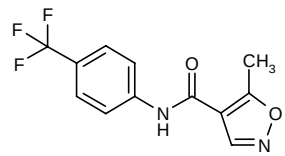
K-832

A cytokine production inhibitor synthesized at Kowa, K-832 is in phase II evaluation for the oral treatment of rheumatoid arthritis.

LAS-34475

LAS-34475 is a potent and highly selective COX-2 inhibitor which has reached phase II/III development at Almirall Prodesfarma for the treatment of osteoarthritis.

Leflunomide



Last year, the European Commission approved a new indication for the DMARD leflunomide (Arava®; Aventis Pharma): the treatment of adult patients with active psoriatic arthritis. It was subsequently introduced in the U.K. and France for this indication. In clinical studies, leflunomide demonstrated significant improvements com pared to placebo both in functional status and in skin-related quality of life. The Dermatological Life Quality Index in leflunomide-treated patients showed an improvement of skin-related quality of life of 24% as compared to the index for psoriatic patients in general. Leflunomide was previously approved for the treatment of adult patients with active rheumatoid arthritis. It reduces the signs and

symptoms of rheumatoid arthritis, improves physical function and retards structural damage, such as erosions and joint space narrowing as evidenced by X-ray. Leflunomide offers once-daily oral dosing and can be used in both early and late stages of the disease. It was launched in the U.S. in 1998 for the traetment of rheumatoid arthritis and is available in over 70 countries, including the E.U., Asia and parts of Latin America (1).

1. *Arava approved in Europe for active psoriatic arthritis*. DailyDrugNews.com (Daily Essentials) July 2, 2004.

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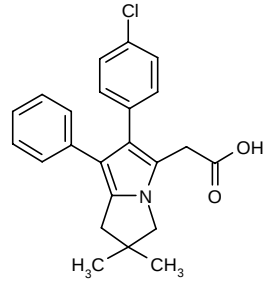
Licofelone



Sumitomo has concluded a license agreement with Merckle which grants Sumitomo Japanese development and marketing rights for the antiarthritic agent licofelone (ML-3000). Licofelone, a lipoxygenase/cyclooxygenase (LOX/COX) inhibitor discovered by Merckle, is being studied in phase III by the EuroAlliance (Merckle/Alfa Wassermann/Lacer) in Europe. Unlike NSAIDs, including COX-2-selective inhibitors, the compound has the ability to protect the arthrodial cartilage, which may make it suitable for osteoarthritis. Sumitomo will begin efficacy and safety trials for licofelone for a potential launch at the earliest possible date (1).

Data from a multicenter, double-blind, randomized phase III clinical trial were used to reassess the antiinflammatory effects of licofelone (200 mg b.i.d.) and celecoxib (200 mg once daily) given for 12 weeks to 302 and 306 patients, respectively, with symptomatic osteoarthritis of the knee. Reassessment of the improvement in pain, physical function and patient global assessment using the OARSI criteria and the OMERACT-OARSI criteria

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

Indication	Design	Treatments	n	Conclusions	Ref.
Osteoarthritis, localized	Randomized Double-blind Multicenter	Licofelone, 200 mg b.i.d. x 12 wks (n=302) Celecoxib, 200 mg o.d. x 12 wks (n=306)	608	Reassessment of efficacy using the OARSI and the OMERACT-OARSI response criteria confirmed that licofelone was as effective as celecoxib in the treatment of patients with osteoarthritis of the knee	2, 3
Osteoarthritis, localized	Randomized Double-blind Multicenter	Licofelone, 100 mg b.i.d. x 52 wks (n=235) Licofelone, 200 mg b.i.d. x 52 wks (n=240) Naproxen, 500 mg b.i.d. x 52 wks (n=229)	704	Compared with naproxen, licofelone was associated with a lower incidence of gastrointestinal adverse events and microbleeding in patients with symptomatic osteoarthritis of the knee	4

confirmed that licofelone was as effective as celecoxib in treating the signs and symptoms of osteoarthritis. At 12 weeks, the response rates for licofelone and celecoxib were, respectively, 60.9% and 62.8% according to the OARSI criteria A, 60.9% and 64.7% according to the OARSI criteria B, and 75.5% and 76.1% according to the OMERACT-OARSI criteria. Both study treatments were well tolerated and showed similar incidences of adverse events (31.9% with licofelone and 36.4% with celecoxib). No patients treated with licofelone for 12 weeks showed clinically relevant changes in their liver enzyme levels, confirming the good hepatic safety profile of licofelone suggested by previous studies (2, 3). The results from this and the following study are summarized in Table VIII.

Another multicenter, double-blind, randomized phase III clinical trial compared the safety profile of licofelone (100 or 200 mg b.i.d.) and naproxen (500 mg b.i.d.) given for 52 weeks to patients with symptomatic osteoarthritis of the knee. The incidence of gastrointestinal adverse events was lower with licofelone (20.6% for 100 mg and 22.5% for 200 mg) compared to naproxen (24.1%). The finding that licofelone-treated patients showed higher erythrocyte counts, hemoglobin levels and hematocrit values suggested that licofelone was also associated with less microbleeding in the upper and lower gastrointestinal tract (4).

1. *Sumitomo licenses licofelone for Japan*. DailyDrugNews.com (Daily Essentials) June 9, 2004.

2. Bias, P., Schulz, U., Buchner, A. *Licofelone, a 5-LOX, COX-1 and COX-2 inhibitor, is as effective as celecoxib over 12 weeks of treatment: OARSI/OMERACT-OARSI response criteria results*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst FRI0407.

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4. Bias, P., Buchner, A. *Potential for fewer cases of GI tract micro-bleeding following treatment with the LOX/COX inhibitor, licofelone, compared with the conventional NSAID, naproxen*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst FRI0409.

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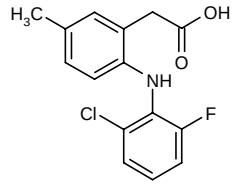
LtβR-Ig

LTβR-Ig is a lymphotoxin-β receptor-immunoglobulin fusion protein in early clinical development at Biogen Idec for the treatment of autoimmune diseases, including rheumatoid arthritis and inflammatory bowel disease. LTR-Ig blocks immunoglobulin production by interrupting the signaling between the surface lymphotoxin ligand and the receptor. As a consequence, follicular dendritic cells, which are antigen-presenting cells for B-cells, lose their cell-specific markers and also the capacity to deposit and maintain immune complexes on their surface.

Lumiracoxib



Novartis expects the E.U. mutual recognition procedure for lumiracoxib (COX-189, Prexige®), a novel antiinflammatory medicine being developed for osteoarthritis, to resume in mid-2005 after the European Medicines Agency (EMEA) completes a review of the COX-2 inhibitor class. The company has withdrawn its application and plans to further document the safety and efficacy profile by incorporating additional data. Data from the landmark TARGET (Therapeutic Arthritis Research & Gastrointestinal Event Trial of lumiracoxib) safety outcomes study demonstrated a significant 79% reduction in

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

Indication	Design	Treatments	n	Conclusions	Ref.
Osteoarthritis, localized	Randomized Double-blind Multicenter	Lumiracoxib, 100 mg o.d. x 13 wks (n=420) Lumiracoxib, 200 mg o.d. x 2 wks → 100 mg o.d. x 11 wks (n=420) Celecoxib, 200 mg o.d. x 13 wks (n=420) Placebo (n=424)	1684	Lumiracoxib was well tolerated and as effective as celecoxib in reducing pain intensity in target knee and improving disease activity and functional status in patients with osteoarthritis of the knee	10-12

the incidence of upper gastrointestinal ulcer complications without compromising cardiovascular safety. The TARGET study showed that lumiracoxib had a cardiovascular profile similar to conventional NSAIDs. Discussions are under way with the FDA on requirements for a new cardiovascular safety study. Additional studies are already in progress to support the 100-mg dose for treating osteoarthritis. Submissions for osteoarthritis, rheumatoid arthritis and pain are anticipated in 2007. Novartis has filed applications for regulatory approval throughout the world based on data from more than 40 preclinical and clinical studies in osteoarthritis, rheumatoid arthritis, acute pain and primary dysmenorrhea involving more than 31,000 adult patients. In addition to the U.K., where it was approved in 2003 for the treatment of moderate to severe acute pain associated with primary dysmenorrhea, the symptomatic relief of osteoarthritis and the treatment of pain, lumiracoxib has been approved in 21 countries to date, including Australia, New Zealand and several countries in Latin America, including Argentina, Brazil and Mexico (1-4).

The TARGET study was a multicenter, double-blind clinical trial that compared the safety profiles of lumiracoxib, ibuprofen and naproxen in 18,325 patients aged 50 years or older with osteoarthritis of the hip, knee or hand. Each patient was randomized to receive lumiracoxib (400 mg once daily), naproxen (500 mg b.i.d.) or ibuprofen (800 mg t.i.d.) for 52 weeks. All study treatments showed similar efficacy in improving disease activity and reducing target joint pain scores of the patients. The incidence of definite or probable upper gastrointestinal ulcer complications in the overall population during the study was significantly lower with lumiracoxib compared with either naproxen or ibuprofen (0.32% *vs.* 0.91% in the overall population, and 0.20% *vs.* 0.92% in patients not simultaneously treated with low-dose aspirin). Lumiracoxib was also associated with fewer symptomatic uncomplicated ulcers (0.64% *vs.* 1.13%). The most common gastrointestinal adverse events were dyspepsia and upper abdominal pain. A greater percentage of lumiracoxib-treated patients showed serious liver abnormalities (0.07% *vs.* 0.03%) and significant increases in transaminase concentrations (2.57% *vs.* 0.63%), although these effects disappeared after the end of treatment. No significant differences among the lumiracoxib group and the ibuprofen and naproxen groups were found for the incidence of a composite primary endpoint of nonfatal and silent myocardial infarction, stroke or cardiovascular death, either in the overall population or in patients receiving low-dose aspirin. Significantly fewer patients treated with lumiracoxib discontinued the study due to adverse events. The good cardiovascular safety associated with lumiracoxib confirmed the feasibility of using it to treat patients with osteoarthritis (5, 6).

The therapeutic effects of lumiracoxib were evaluated in a single-blind, placebo-controlled clinical trial in healthy Japanese volunteers. The pharmacokinetic profile after administration of single oral doses of lumiracoxib revealed that the plasma levels of the drug increased dose-dependently. The synthesis of prostaglandin E_2 (PGE_2, a marker of COX-2 activity) decreased with dose, whereas TxB_2 activity (a marker of COX-1 activity) remained unchanged. These effects were similar to those found in Western subjects and further support the idea that lumiracoxib may be better tolerated than other COX-2 inhibitors thanks to a lower incidence of upper gastrointestinal tract disorders caused by COX-1 inhibition (7).

The pharmacokinetic and pharmacodynamic profiles of lumiracoxib (400 mg as a single dose) were not altered to any clinically significant degree following coadministration with fluconazole (400 mg on day 1 and 200 mg on days 2-4) to 13 healthy individuals in a randomized, crossover trial. Results therefore verified the compatibility of coadministering cytochrome P-4502C9 and COX-2 inhibitors and precluded the need for any dose alterations (8).

Patients with osteoarthritis of the hand (n=594) were randomized to receive lumiracoxib 200 or 400 mg once daily or placebo in a multicenter, double-blind trial. Pain intensity in the target hand was reduced significantly in lumiracoxib-treated patients compared with placebo, and the pain intensity reduction did not differ according to lumiracoxib dose. The active treatment was well tolerated (9).

A large multicenter, randomized clinical trial enrolled patients with osteoarthritis of the knee to receive lumiracoxib (100 mg/day, with or without a loading dose of 200 mg/day for the first 2 weeks) or celecoxib (200 mg/day). Significant improvements in pain intensity in the target knee, functional status and global assessment of disease activity were observed after only 2 weeks of treatment. After 13 weeks of treatment, the percentage of patients who achieved response as established by the OMERACT-OARSI criteria was, respectively, 64.7% with lumiracoxib 100 mg/day, 66.8% with lumiracoxib 200/100 mg/day, 61.6% with celecoxib 200 mg/day and 49.3% with placebo. No significant differences were found in the safety profiles of the study treatments (10-12) (Table IX).

The incidence of gastroduodenal ulcers among 893 rheumatoid arthritis patients was 2.8%, 4.3%, 13.6% and 1.9% following treatment with lumiracoxib 400 mg once daily, lumiracoxib 800 mg once daily, ibuprofen 800 mg t.i.d. and celecoxib 200 mg b.i.d., respectively, in a 13-week, double-blind, randomized trial (13).

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

2. *European CHMP reviews COX-2 inhibitors*. DailyDrugNews.com (Daily Essentials) Jan 25, 2005.

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Table X: Clinical studies of metelimumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Sclerosis, systemic	Randomized Double-blind Multicenter	Metelimumab, 0.5 mg/kg i.v. 1x/6 wks x 4 Metelimumab, 5 mg/kg i.v. 1x/6 wks x 4 Metelimumab, 10 mg/kg i.v. 1x/6 wks x 4 Placebo	45	Metelimumab was well tolerated in patients with diffuse systemic sclerosis, but the small sample size and the finding that the skin score of placebo-treated patients did not deteriorate as much as expected prevented the establishment of final conclusions on the efficacy of metelimumab in the treatment of this disease	3, 4

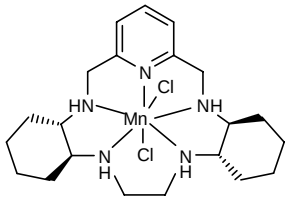
ibuprofen. 12th United Eur Gastroenterol Week (Sept 25-29, Prague) 2004, Abst OP-G-171.

Scott, G., Reynolds, C.V., Milosavljev, S., Langholff, W., Shenouda, M., Rordorf, C. *Lack of effect of omeprazole or of an aluminium hydroxide/magnesium hydroxide antacid on the pharmacokinetics of lumiracoxib*. Clin Pharmacokin 2004, 43(5): 341.

Scott, G., Rordorf, C., Reynolds, C. et al. *Pharmacokinetics of lumiracoxib in plasma and synovial fluid*. Clin Pharmacokin 2004, 43(7): 467.

Tannenbaum, H., Berenbaum, F., Reginster, J.Y. et al. *Lumiracoxib is effective in the treatment of osteoarthritis of the knee: A 13-week, randomized, double-blind study versus placebo and celecoxib*. Ann Rheum Dis 2004, 63(11): 1419.

M-40419



M-40419 is a small-molecule superoxide dismutase (SOD) mimetic in early clinical development by MetaPhore for the oral and i.v. treatment of rheumatoid arthritis. The company is also evaluating M-40419 in preclinical studies as a therapy for neuropathic pain. By mimicking the function of SOD, M-40419 removes superoxide, a toxic free radical implicated in several conditions associated with tissue injury, pain and inflammation.

MEDI-522

MedImmune has decided to terminate phase II testing of MEDI-522 (Vitaxin®) in patients with rheumatoid arthritis and psoriasis based on preliminary data suggesting lack of clinical benefit in these diseases. There were no safety concerns identified in the preliminary analyses. The oncology program for MEDI-522 continues with studies in melanoma and prostate cancer. MEDI-522 is a monoclonal antibody that targets the $\alpha_v\beta_3$ integrin, which has been implicated in a number of disease processes, including the growth and metastasis of tumors, bone destruction in rheumatoid arthritis and the inflammatory process in psoriasis (1, 2).

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

2. *MedImmune terminates rheumatoid arthritis and psoriasis trials for Vitaxin*. DailyDrugNews.com (Daily Essentials) Sept 2, 2004.

Metelimumab

Metelimumab (CAT-192) is a human anti-TGFβ_2 monoclonal antibody developed under a collaboration between Cambridge Antibody Technology and Genzyme. The product is in phase I/II clinical evaluation for systemic sclerosis and was granted orphan drug status by the FDA and the European authorities in 2002 for the treatment of scleroderma.

Forty-five patients with diffuse systemic sclerosis participated in a multicenter, double-blind phase I/II clinical trial at centers in the U.S. and Europe and were randomized to receive placebo or metelimumab (0.5, 5 or 10 mg/kg i.v.) once every 6 weeks for 4 doses. The primary objective of the trial was to assess the safety, tolerability and pharmacokinetics of the antibody. The primary objective was met and the treatment was safe and well tolerated at all doses. Only 13 of the 275 adverse events reported by the patients were serious; the 4 deaths recorded during the study were due to the patients' underlying disease. The antibody had an elimination half-life of about 3 weeks. Compared with placebo, greater improvements were found in the modified Rodnan skin score (mRSS) of patients receiving 5 or 10 mg/kg of the antibody. Other efficacy parameters (*i.e.*, skin hardness, Health Assessment Questionnaire, organ-based disease or biomarkers) showed no significant differences between groups at the end of the treatment period (1-4) (see Table X).

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

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

3. *Cambridge Antibody Technology and Genzyme announce preliminary results from phase I/II trial of CAT-192 for scleroderma*. Cambridge Antibody Technology Press Release 2004, Feb 9.

4. Denton, C.P., Merkel, P.A., Furst, D.E. et al. *Anti-TGFbeta1 therapy for diffuse cutaneous systemic sclerosis: A multicenter, randomized, placebo-controlled phase I/II trial of CAT-192*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1851.

Original monograph – Drugs Fut 2004, 29(11): 1081.

MLN-1202

Millennium's MLN-1202, a humanized monoclonal antibody designed to block the chemokine CCR_2 receptor, completed a phase II trial last year in rheumatoid arthritis and is expected to advance to phase IIb trials in this indication; phase II trials are also anticipated to begin in multiple sclerosis, scleroderma and/or secondary atherosclerosis during 2005 (1).

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

MLN-3897 (AVE-9897)

MLN-3897 (AVE-9897), an orally administered small molecule designed to block the chemokine CCR_1 receptor believed to play a role in inflammatory conditions such as rheumatoid arthritis, multiple sclerosis and psoriasis, is the first compound to enter clinical trials from Millennium and Aventis's June 2000 collaboration to develop new therapies for inflammatory diseases. Phase I clinical evaluation is under way and it may advance to phase II trials for rheumatoid arthritis, multiple sclerosis and/or psoriasis this year (1-3).

1. *MLN-3897 enters phase I*. DailyDrugNews.com (Daily Essentials) Dec 29, 2003.

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

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

MM-093

Enrollment has been completed for a phase IIa pilot study of Merrimack's immunomodulatory drug candidate MM-093 (ABI-001) in patients with rheumatoid arthritis. MM-093 is a recombinant version of human α-fetoprotein (AFP). Results are expected to be available during the first quarter of 2005. The randomized, double-blind, placebo-controlled phase IIa study is ongoing at Kings College Hospital, London, and is examining the safety and tolerability of MM-093 in rheumatoid arthritis patients. Each patient receives a once-weekly injection for 12 weeks and is then followed for an additional 4 weeks. Patients are evaluated for changes in their disease state using the ACR scale. The development of MM-093 will be focused on diseases such as rheumatoid arthritis, psoriasis and multiple sclerosis. Merrimack has the exclusive worldwide license to a strong intellectual property estate around MM-093. The company is manufacturing MM-093 under a strategic alliance with GTC Biotherapeutics. MM-093 was purified from the milk of transgenic goats carrying the MM-093 gene (1, 2).

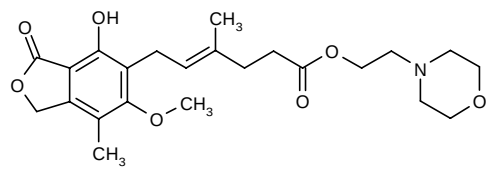
1. *GTC restructures*. DailyDrugNews.com (Daily Essentials) Feb 11, 2004.

2. *Enrollment completed in phase IIa study of MM-093*. DailyDrugNews.com (Daily Essentials) Aug 30, 2004.

MX-1094

MX-1094 (Medinox) is a novel NSAID prodrug based on naproxen in early clinical development for the treatment of arthritis. A phase I trial was completed in December 2002 and the compound was well tolerated and showed the desired pharmacokinetic profile. MX-1094 combines a known NSAID, naproxen, with a proprietary protective group, resulting in a new chemical entity that remains intact and does not damage the gastrointestinal system. When absorbed into the circulation, the conjugate is cleaved, freeing the NSAID so that it can exert its antiinflammatory activities. Preclinical results indicate that Medinox's novel NSAIDs offer equivalent therapeutic benefits to those of the parent NSAID, yet substantially fewer gastrointestinal adverse effects.

Mycophenolate Mofetil



Aspreva has completed a USD 57 million private equity financing, which will be used to initiate and fund clinical trials in several autoimmune diseases with mycophenolate mofetil (CellCept®), its first licensed therapeutic. Aspreva acquired worldwide rights (excluding Japan) to develop and commercialize Roche's transplant medica-

tion mycophenolate mofetil for all autoimmune indications in October 2003. Clinical research has demonstrated the potential value of mycophenolate mofetil over the current standard of care in the treatment of lupus nephritis. The company subsequently initiated a global phase III study of the drug in myasthenia gravis. Mycophenolate mofetil, an inosine-5'-monophosphate (IMP) dehydrogenase inhibitor, is indicated in the U.S. for the prevention of rejection in kidney, liver and cardiac transplant patients, as part of combination therapy (1, 2).

In an open study, mycophenolate mofetil (1.5 g/day for 1 month, then 2-3 g/day) was assessed in 20 SLE patients with refractory proteinuria. A partial response, with significant reductions in proteinuria and prednisone doses and a significant increase in albumin, was seen in all patients after 8.2 ± 3.3 months. A complete response was seen in over half of the patients after 12.2 ± 3 months and 3 patients did not respond (3).

A retrospective study in 53 patients with SLE in whom other immunosuppressive agents were ineffective found that mycophenolate mofetil was associated with significant reductions in daily oral prednisolone doses and in European Consensus Lupus Activity Measure scores in the overall group and in patients with renal involvement. Adverse events were seen in 43% of patients, consisting mostly of gastrointestinal intolerance (29%) and infections (23%) (4).

Mycophenolate mofetil in doses up to 2 g/day demonstrated efficacy in 22 patients with nonrenal lupus included in a 6-month open study. Of 17 patients completing the trial, a significant response (> 20% improvement in laboratory abnormalities, > 20% reduction in prednisone dose and > 20% improvement in SLAM score/patient/physician assessment) was observed in 11. A partial response was also obtained in 4 patients (5).

Mycophenolate mofetil demonstrated efficacy in treating 5 patients with diffuse proliferative lupus nephritis and chronic hepatitis C virus infection. After failing other immunosuppressants, patients were treated with mycophenolate mofetil 500 mg b.i.d. (titrated up to 1500-2000 mg/day). Serum CRP fell and C3 levels were normalized in all patients, and an improvement in proteinuria of over 50% was seen in 4 patients. Responses lasted for a mean of 8 months. Mycophenolate mofetil was well tolerated and prednisone doses were reduced in all patients (6).

Induction therapy with mycophenolate mofetil (up to 2 g/day) was compared to i.v. cyclophosphamide (given monthly) in a 1-year open study in 20 patients with severe lupus nephritis. Complete remission was achieved by 3 mycophenolate mofetil-treated and 1 cyclophosphamide-treated patients, and partial remissions were also obtained in 3 and 1 mycophenolate mofetil- and cyclophosphamide-treated patients, respectively. The probability of achieving partial remission at 9 months was higher with mycophenolate mofetil (80% *versus* 25%) and the odds of failure at 11 months were higher with cyclophosphamide (73% *versus* 20%) according to Kaplan-Meier analyses (7).

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

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

3. Borba, E.F., Guedes, L.K.N., Figuereido, C.P., Christmann, R.B., Gonçalves, C.R., Bonfá, E. *Prospective study of mycophenolate mofetil in lupus membranous nephritis*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1129.

4. Pisoni, C.N., Sanchez, F.J., Karim, Y., Cuadrado, M.J., D'Cruz, D., Abbs, I., Khamashta, M.A., Hughes, G.R.V. *Mycophenolate mofetil treatment in systemic lupus erythematosus*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1032.

5. Moder, K.G., Mazlumzadeh, M., Amin, S., Ytterberg, S.R. *Use of mycophenolate mofetil in non-renal lupus*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1031.

6. Medina, F., Fuentes, J., Carranza, I., Portela, M., Barile, L., Fraga, A. *Mycophenolate mofetil: A potential treatment for diffuse prolipherative lupus nephritis (DPLN) and chronic hepatitis C virus infection*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1030.

7. Flores-Suárez, L.F., Villa, A.R. *Preliminary results of an open label randomised clinical trial comparing mycophenolate mofetil (MMF) vs. intravenous cyclophosphamide (IV-CYC) as induction therapy for severe lupus nephritis (LN)*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1029.

Original monograph – Drugs Fut 1995, 20(4): 356.

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Flores-Suarez, L.F., Villa, A.R. *Preliminary results of an open randomised clinical trial comparing mycophenolate mofetil (MMF) vs. intravenous cyclophosphamide (IV-CYC) as induction therapy for severe lupus nephritis (LN)*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst THU0413.

Galindo, M. et al. *Mycophenolate mofetil induced myopathy in a patient with lupus nephritis*. J Rheumatol 2005, 32(1): 188.

Kim, H., Kim, S., Kim, S., Park, K., Yoon, C., Kim, W., Lee, S., Park, S., Cho, C., Kim, H. *Efficacy and tolerability of mycophenolate mofetil in patients with lupus nephritis*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst THU0360.

Sanadgol, H. et al. *The efficacy of mycophenolate mofetil on treatment of lupus nephritis*. Nephrol Dial Transplant 2004, 19(5, Suppl.): Abst SP093.

Natalizumab

Natalizumab (Antegren®, Tysabri®) is a humanized monoclonal antibody with a novel mechanism of action which is being jointly developed by Elan and Biogen Idec. It is the first α_4 integrin antagonist in the new selective adhesion molecule (SAM) inhibitor class and is designed to selectively prevent immune cells from leaving the bloodstream and migrating into tissue where they may cause or maintain inflammation. The companies submitted the antibody for approval in the E.U., the U.S. and

Canada last year for use in the treatment of multiple sclerosis and the FDA subsequently approved it for use in relapsing forms of the disease to reduce the frequency of clinical relapses. In September, the companies filed for E.U. marketing approval in Crohn's disease. Natalizumab is also in phase II for rheumatoid arthritis (1-14).

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

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

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

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

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

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

7. *Biogen Idec reports Q1 R&D highlights*. Biogen Idec Press Release 2004, April 30.

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

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

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

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

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

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

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

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

NGD-2000-1

Last year, Neurogen reported that the phase IIa clinical trial of NGD-2000-1, its orally administered drug that blocks the activity of the C5a receptor, for the treatment of rheumatoid arthritis did not achieve statistical significance in the primary endpoint (change in CRP), although a *post hoc* analysis showed a statistically significant effect in terms of ACR20 response at the highest dose tested. Based on the previously reported inhibition of the CYP3A4 enzyme, indicating potential for drug interactions, and the dose levels expected to be necessary for efficacy, the company has decided to postpone further development of NGD-2000-1, but will continue evaluating other candidates in its inflammation program. NGD-2000-1 was also under evaluation for asthma, but displayed no efficacy in a phase II trial (1-4).

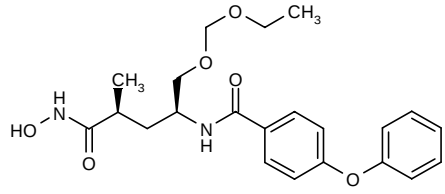
1. *New phase II results described for NGD-2000-1 in asthma*. DailyDrugNews.com (Daily Essentials) Jan 20, 2004.

2. *Disappointing preliminary phase IIa results for NGD-2000-1 in RA*. DailyDrugNews.com (Daily Essentials) June 18, 2004.

3. *Neurogen Corp. reports Q1 R&D highlights*. Neurogen Corp. Press Release 2004, May 5.

4. *Neurogen Corp. reports Q2 R&D highlights*. Neurogen Corp. Press Release 2004, Aug 4.

Ono-4817



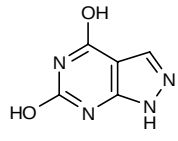
Ono-4817, a matrix metalloproteinase (MMP) inhibitor, is currently in phase I development at Ono Pharmaceutical for the treatment of osteoarthritis and inflammatory bowel disease (1).

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

Org-37663

Organon has discontinued the development of its anti-inflammatory steroid Org-37663, which had reached phase II for the treatment of rheumatoid arthritis.

Oxypurinol



Cardiome Pharma discontinued development of oxypurinol (Oxyprim™) for the treatment of allopurinol-intolerant hyperuricemia, or gout, last year following the receipt of an approvable letter from the FDA requesting additional clinical and manufacturing data prior to full approval. The product is undergoing phase II studies in congestive heart failure (1-8).

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

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

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

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

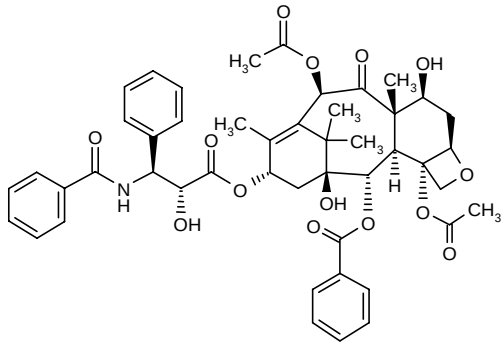
5. *Cardiome Pharma reports Q1 R&D highlights*. Cardiome Pharma Press Release 2004, May 17.

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

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

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

Paclitaxel, New Indication



Angiotech has developed an injectable formulation of paclitaxel, known as Paxceed™, for the i.v. treatment of rheumatoid arthritis and psoriasis. The product is in phase II for rheumatoid arthritis and phase I for psoriasis. The company expects to further its development for rheumatoid arthritis through a strategic alliance with a biopharmaceutical company.

Original monograph – Drugs Fut 1986, 11(1): 45.

PEG-Rasburicase

Savient Pharmaceuticals has completed patient dosing in a phase II clinical study of PEG-rasburicase (Puricase®), a polyethylene glycol (PEG) conjugate of recombinant uricase (urate oxidase), in the treatment of severe, refractory gout. The multicenter study in 41 patients is assessing the effect of repeated i.v. administration of a range of doses and regimens of PEG-rasburicase on uric acid levels, as well as safety and tolerability, in patients with hyperuricemia and symptomatic severe refractory gout. The subjects included in the study are not adequately treated by or are intolerant of allopurinol, the conventional therapy; there is no other approved therapy that treats these refractory symptomatic patients. Preliminary data suggest that i.v. administration of PEG-rasburicase every 2 or 4 weeks rapidly achieves and maintains a level of plasma uric acid within the normal range in the majority of patients. The safety profile appears acceptable. Analysis of the phase II data is expected to be completed in the first quarter of 2005. The company then hopes to hold an end-of-phase II meeting with the FDA to obtain concurrence on the design of the phase III program. In a previous single-dose phase I study in refractory gout patients, PEG-rasburicase was well tolerated and appeared to be safe. Elevated plasma uric acid levels were reduced to well within the normal range and considerably below levels achieved with currently available therapies. Savient has FDA orphan drug designation for PEG-rasburicase in the treatment of gout patients for whom conventional therapy is contraindicated or has been ineffective. Savient licensed worldwide rights to the technologies related to PEG-rasburicase from Duke University and Mountain View Pharmaceuticals. Duke developed the recombinant porcine uricase enzyme and Mountain View developed the PEGylation technology (1-7).

The development of antibodies to PEG upon administration of PEG-rasburicase was investigated in 13 patients with gout and hyperuricemia. Patients were treated with s.c. injections of 4, 8, 12 or 24 mg. Early injection-site reactions were seen in most patients. Eight patients had measurable plasma uricase activity 21 days after dosing and uricase activity was undetectable after 10 days in the other 5 patients. IgM and IgG antibodies to pegylated uricase were seen in the latter group, and delayed injection-site reactions were seen in 3 of these 5 patients. Antibody-positive pegylated uricase plasma reacted with free 10-kD PEG but not with unmodified uricase (8).

1. *Phase II study of Puricase for severe gout begins*. DailyDrugNews.com (Daily Essentials) April 13, 2004.

2. *Savient Pharmaceuticals reports 2003 year-end R&D highlights*. Savient Pharmaceuticals Press Release 2004, Feb 20.

3. *Savient Pharmaceuticals reports Q1 R&D highlights*. Savient Pharmaceuticals Press Release 2004, May 4.

4. *Savient Pharmaceuticals reports Q2 R&D highlights*. Savient Pharmaceuticals Press Release 2004, Aug 9.

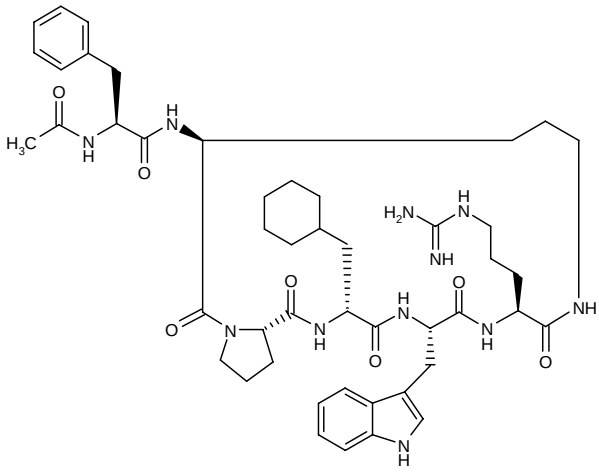
5. *Further restructuring at Savient*. DailyDrugNews.com (Daily Essentials) Nov 2, 2004.

6. *Dosing completed in phase II study of Puricase for severe gout*. DailyDrugNews.com (Daily Essentials) Jan 12, 2005.

7. Sundy, J.S., Ganson, N., Kelly, S.J., Scarlett, E.L., Hershfield, M.S. *A phase I study of pegylated-uricase (Puricase®) in subjects with gout*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 807.

8. Ganson, N.J., Kelly, S.J., Scarlett, E., Sundy, J.S., Hershfield, M.S. *Antibodies to polyethylene glycol (PEG) during phase I investigation of PEG-urate oxidase (PEG-uricase; Puricase®) for refractory gout*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 808.

PMX-53

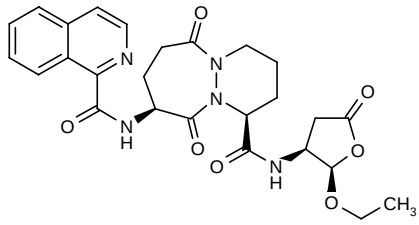


Promics has completed a phase Ib/IIa trial using its novel, innovative antiinflammatory drug PMX-53 administered orally in patients with chronic rheumatoid arthritis. The trial, conducted at the Academic Medical Centre (AMC) in Amsterdam, The Netherlands, included 21 patients aged between 18 and 75 years, diagnosed with rheumatoid arthritis and taking stable doses of methotrexate. There were 7 placebo and 14 active treatment patients enrolled in the trial. The study successfully achieved the primary trial protocol endpoints of safety and tolerability following daily oral administration of PMX-53 for 28 days. Secondary objectives of the study encompassed pharmacokinetic analysis and preliminary assessment of the effect of therapy on disease parameters, including clinical responses to the drug, changes in the cell profile within the joint and pain. Blood levels of PMX-53 were monitored during the study and patients exhibiting higher blood levels showed positive trends in the majority of disease measures, including number of tender joints, number of swollen joints, biochemical markers, patient assessment and physician assessments when compared to patients with lower blood levels of PMX-53. PMX-53 is Promics' lead antiinflammatory agent and acts by blocking the C5a receptor at an earlier stage in the immune and inflammatory process than currently available antiinflammatory drugs. Previously, topically applied PMX-53 was also found to be safe with evidence of efficacy in psoriasis. PMX-53 has applications in a variety of human inflammatory diseases beyond rheumatoid arthritis and psoriasis, including inflammatory bowel disease and ischemia/reperfusion injuries (1, 2).

1. *Topical PMX-53 improves psoriasis lesion scores in pilot study*. DailyDrugNews.com (Daily Essentials) March 15, 2004.

2. *Promics completes study of oral PMX-53 in rheumatoid arthritis*. DailyDrugNews.com (Daily Essentials) Dec 28, 2004.

Pralnacasan

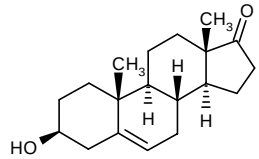


Pralnacasan (HMR-3480, VX-740) is an oral interleukin-converting enzyme (ICE, caspase 1) inhibitor discovered at Vertex and licensed to the former Aventis Pharma (now Sanofi-Aventis) for worldwide development and marketing. Sanofi-Aventis recently notified Vertex that it was terminating their license agreement and worldwide rights will then revert to Vertex. With potential in a broad range of acute and chronic inflammatory conditions, pralnacasan was being developed by Aventis for rheumatoid arthritis and osteoarthritis. It had reached phase II before trials were suspended in 2003 while the companies evaluated findings from a toxicological study. Clinical development could resume this year.

A phase IIa trial of pralnacasan in rheumatoid arthritis patients resulted in a reduction in serum inflammatory biomarkers, increased ACR20 response and corticosteroid sparing. Dose-dependent effects on serum/urinary markers of cartilage and bone collagen turnover were observed in a phase II trial in patients with osteoarthritis of the knee (1).

1. Randle, J.C.R. *Orally-active ICE inhibitors for the treatment of inflammatory and autoimmune diseases*. 228th ACS Natl Meet (Aug 22-26, Philadelphia) 2004, Abst MEDI 200.

Prasterone



Genelabs Technologies' lead compound, prasterone (GL-701, Prestara™ in the U.S., Anastar™ in the E.U.), a synthetic form of the human hormone dehydroepiandrosterone (DHEA), is being investigated in partnership with Watson in the U.S., Tanabe Seiyaku in Japan, Teva in Israel and Genovate Biotechnology in Australia, New Zealand and Asia as a potential new treatment for women with SLE, specifically for limiting bone loss in women with SLE taking glucocorticoids. Genelabs received an approvable letter from the FDA for prasterone in August 2002, and filed for approval in Europe in December 2002. The company subsequently withdrew its European marketing authorization application (MAA) after the European

Agency for the Evaluation of Medicines (EMEA) issued a list of questions to be addressed by the company. The EMEA considered that the data submitted were not sufficient for approval. Genelabs intends to resubmit the application in the future and discussions are continuing with regard to forming a European partnership for the product (1, 2). Other companies are also developing proprietary formulations of prasterone. Paladin's Fidelin™ is in phase II for Addison's disease and InflaBloc's IP-1001 is in phase I/II for Crohn's disease. Prasterone has been designated an orphan drug in both the E.U. and the U.S. for adrenal insufficiency (including Addison's disease) and in the U.S. for SLE.

In order to comply with the approvable letter from the FDA requiring confirmation of the positive effects of prasterone on bone mineral density (BMD) observed in the company's previous phase III study, GL95-02, Genelabs conducted a confirmatory multicenter, double-blind, placebo-controlled phase III trial (GL02-01) of prasterone in 155 women with lupus in the U.S. and Mexico. Patients received either 200 mg/day of prasterone or placebo for 6 months and were evaluated for the primary endpoint of BMD at the lumbar spine. According to a preliminary analysis, Study GL02-01 failed to meet its primary endpoint. Genelabs plans to continue its analysis of the study data and will seek to meet with the FDA to determine its next steps (3-5).

Prasterone 200 mg/day was found to improve or stabilize SLE disease activity in a significant proportion of patients enrolled in a multicenter, randomized, double-blind trial. The 381 female patients were given the drug or placebo in addition to their current medications for up to 1 year. The domains of disease activity, organ damage and health-related quality of life were integrated into a single primary outcome measure in which a response was defined as improvement or stabilization in 2 disease activity measures and 2 quality-of-life measures. Of patients with active disease, 58.5% of those given prasterone experienced improvement or stabilization compared to 44.5% of those given placebo. Also, fewer prasterone-treated patients experienced a first flare during treatment and the time to flare was longer, although not significantly so, in the prasterone group. Acne and hirsutism occurred significantly more often with prasterone treatment (33% and 16%, respectively), but were mild in most cases. Myalgias and oral stomatitis occurred more often in the placebo group. Testosterone and estradiol levels increased in the prasterone group, while serum HDL cholesterol, triglycerides and C3 complement significantly decreased in this group (6).

1. *Tanabe gains Japanese rights to prasterone*. DailyDrugNews.com (Daily Essentials) Jan 30, 2004.

2. *Genelabs to withdraw Anastar MAA with resubmission planned*. DailyDrugNews.com (Daily Essentials) June 10, 2004.

3. *Enrollment completed in confirmatory phase III trial of Prestara*. DailyDrugNews.com (Daily Essentials) Feb 11, 2004.

4. *Preliminary analysis of phase III Prestara study shows primary endpoint not met*. DailyDrugNews.com (Daily Essentials) Oct 8, 2004.

5. *Genelabs completes Prestara study*. DailyDrugNews.com (Daily Essentials) Aug 18, 2004.

6. Petri, M.A., Mease, P.J., Merrill, J.T. et al. *Effects of prasterone on disease activity and symptoms in women with active systemic lupus erythematosus. Results of a multicenter randomized, double-blind, placebo-controlled trial*. Arthritis Rheum 2004, 50(9): 2858.

Original monograph – Drugs Fut 1995, 20(6): 575.

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Hartkamp, A. et al. *The effect of dehydroepiandrosterone on lumbar spine bone mineral density in patients with quiescent systemic lupus erythematosus*. Arthritis Rheum 2004, 50(11): 3591.

Nordmark, G., Bengtsson, C., Larsson, A., Karlsson, A.F., Sturfelt, G., Ronnblom, L. *Effects of DHEA on quality of life in glucocorticoid treated women with SLE*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst OP0180.

PRO-70769 (R-1594)

PRO-70769 (R-1594) is a fully humanized anti-CD20 monoclonal antibody under phase II development by Genentech and partners Roche and Biogen Idec for the treatment of rheumatoid arthritis.

R-406

Rigel has selected R-406 as its lead therapeutic compound for the treatment of rheumatoid arthritis and initiated a phase I clinical safety and pharmacokinetic trial. The escalating-single-dose, placebo-controlled safety trial will include 36 volunteers and will be followed by a multiple-dose study including an additional 24 subjects. Results are expected by the second half of 2005. Broader and longer term safety and efficacy trials may follow in patients with rheumatoid arthritis. R-406 is a novel oral Syk kinase inhibitor that blocks the activation of mast cells and B-cells which promote swelling and inflammatory responses. Preclinical studies indicate that R-406 is effective at low doses in a rodent arthritis model, and is without obvious toxicities at doses well above the effective dose. Rigel believes that R-406 may become a first-line DMARD with greater efficacy, safety and improved delivery and patient compliance, and thus may be used early in the course of the disease before significant bone and cartilage damage occurs (1-5).

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

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

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

4. *Rigel initiates phase I study of R-406*. DailyDrugNews.com (Daily Essentials) Dec 23, 2004.

5. *Rigel Pharmaceuticals reports Q2 R&D highlights*. Rigel Pharmaceuticals Press Release 2004, Aug 3.

R-1295/R-1503

Roche has two compounds in early clinical development for the treatment of rheumatoid arthritis: the integrin receptor antagonist R-1295 and the protein kinase inhibitor R-1503. R-1295 is also being evaluated for its potential in other autoimmune diseases such as multiple sclerosis.

Rituximab

Rituximab (Rituxan®), a therapeutic antibody that selectively targets B-cells, received initial FDA approval in November 1997 for the treatment of relapsed or refractory low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL). It was also approved in the E.U. under the trade name MabThera® in June 1998. Genentech and Biogen Idec comarket rituximab in the U.S. and Roche markets it in the rest of the world, except Japan, where it is comarketed by Chugai and Zenyaku Kogyo. Rituximab is also in phase III evaluation for relapsed chronic lymphocytic leukemia (CLL), phase II/III clinical development for the treatment of rheumatoid arthritis, primary progressive multiple sclerosis and vasculitis, and phase II trials for relapsing-remitting multiple sclerosis; phase II/III clinical trials are in preparation for lupus nephritis and systemic lupus erythematosus (1-6).

A phase IIb study of rituximab met its primary endpoint of a greater proportion of rituximab-treated patients achieving an ACR20 response at week 24, compared to placebo, in patients who were also treated with methotrexate. In this study, patients with moderate to severe rheumatoid arthritis who received 2 infusions of rituximab over a 2-week period in combination with a stable dose of methotrexate experienced improved symptoms compared to patients who received placebo and methotrexate. The benefit in the rituximab-treated patients was present regardless of whether additional corticosteroids were administered. DANCER (Dose-ranging Assessment iNternational Clinical Evaluation of Rituximab in RA) is a phase IIb study evaluating the efficacy and safety of varying doses of both rituximab and corticosteroids in combination with a stable dose of methotrexate in patients who have failed 1-5 DMARDs and are inadequately responding to methotrexate. A total of 465 patients from the U.S., Canada, Europe and Australia were randomized in the multicenter, double-blind, placebo-controlled study. Nine groups of patients received a stable dose of methotrexate and a varying dose of rituximab (2 x 500 mg; 2 x 1000 mg) or placebo and corticosteroids (200 mg i.v.; and 200 mg i.v. + 570 mg p.o.) or placebo. Further analyses of the data are ongoing and will be submitted for presentation at an upcoming medical meeting (7).

1. *Roche submits European MAA for MabThera*. DailyDrugNews.com (Daily Essentials) Jan 21, 2004.

2. *Phase III MabThera trial meets primary endpoints two years early*. DailyDrugNews.com (Daily Essentials) April 15, 2004.

3. *Europe's CHMP hands down positive opinion for MabThera in indolent NHL*. DailyDrugNews.com (Daily Essentials) July 2, 2004.

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

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

6. *European approval for MabThera for first-line treatment of indolent NHL*. DailyDrugNews.com (Daily Essentials) Aug 12, 2004.

7. *Phase IIb RA study of Rituxan meets primary endpoint*. DailyDrugNews.com (Daily Essentials) Nov 8, 2004.

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Anolik, J.H. et al. *Rituximab improves peripheral B cell abnormalities in human systemic lupus erythematosus*. Arthritis Rheum 2004, 50(11): 3580.

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Looney, R.J. et al. *B cell depletion as a novel treatment for systemic lupus erythematosus. A phase I/II dose-escalation trial of rituximab*. Arthritis Rheum 2004, 50(8): 2580.

Looney, R.J. et al. *B lymphocytes in systemic lupus erythematosus: Lessons from therapy targeting B cells*. Lupus 2004, 13(5): 381.

Moore, J. et al. *A phase II study of rituximab in rheumatoid arthritis patients with recurrent disease following haematopoietic stem cell transplantation*. Bone Marrow Transplant 2004, 34(3): 241.

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Roll, P., Feuchtenberger, M., Kneitz, C., Tony, H.-P. *B-cell depletion with rituximab in patients with RA causes a sustained suppression of CD27+ B-cells and is followed by a period of increased levels of naive B-cells in the peripheral blood*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1486.

Ryan, J.P., Singer, N.G., Scalzi, L.V. *Treatment of resistant SLE with rituximab administered without cyclophosphamide*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1026.

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Wallerskog, T., Gunnarsson, I., Van Vollenhoven, R., Malmstroem, V., Trollmo, C. *Anti B cell treatment with rituximab affects cells of the immune system in patients with systemic lupus erythomatosus*. Clin Invest Med 2004, 27(4, Suppl.): Abst W51.201.

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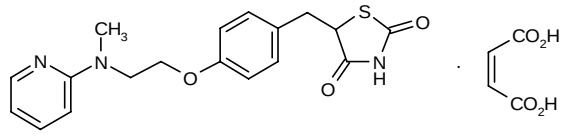
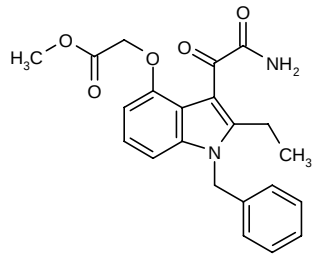
Rosiglitazone Maleate



Rosiglitazone maleate is a selective PPARγ agonist from the thiazolidinedione class, currently marketed by GlaxoSmithKline as Avandia® in the U.S. and the E.U. for the treatment of type 2 diabetes. The drug is also under development for a variety of other indications, including phase III trials for the treatment of psoriasis and phase II trials for the treatment of Alzheimer's-type dementia and rheumatoid arthritis.

Original monograph – Drugs Fut 1998, 23(9): 977.

S-3013/S-3536



S-3013

S-3013, a human secretory phospholipase A_2 ($sPLA_2$) inhibitor, had reached phase II development by Shionogi and codevelopment partner Lilly for the oral treatment of inflammatory disorders including arthritis, but was recently discontinued. Shionogi also discontinued development of S-3536, a selective MMP inhibitor for the treatment of osteoarthritis last year.

SC-12267

4SC has granted Serono exclusive worldwide rights to develop and commercialize 4SC's program of dihydroorotate dehydrogenase (DHODH) inhibitors. The program comprises a series of small molecules with potential as orally active treatments in autoimmune disorders, such as rheumatoid arthritis and multiple sclerosis. The agreement covers the lead compound SC-12267, currently completing phase I evaluation, as well as further back-up compounds and related intellectual property. 4SC will be responsible for completion of the current multiple-dose phase I study of SC-12267, while Serono will be solely responsible for further development, regulatory approvals and commercialization, both of SC-12267 and of any

Table XI: Clinical studies of SCIO-469 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Open	SCIO-469, 0.03-5 mg/kg p.o. [before food, in young males] SCIO-469, 3 mg/kg p.o. [after food, in young males & females & elderly males]		SCIO-469 was safe and well tolerated and produced a dose-dependent inhibition of endotoxin-stimulated TNF-α production, with similar maximal inhibition at 3 and 5 mg/kg in young male and female and elderly male subjects	1

other products from the collaboration. SC-12267 interferes with cell proliferation by blocking the synthetic pathway of pyrimidines. Its mode of action is of therapeutic relevance for the treatment of autoimmune disorders such as rheumatoid arthritis and multiple sclerosis. SC-12267 has shown activity in *in vitro* and *in vivo* models. Phase I studies indicate favorable pharmacokinetic properties, suggesting a likely once-daily dosing regimen (1, 2).

1. *4SC and Serono enter DHODH inhibitor agreement*. DailyDrugNews.com (Daily Essentials) May 6, 2004.

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

SCIO-469

Scios has developed a novel oral p38 MAP kinase inhibitor –SCIO-469– which is undergoing phase II clinical trials as a potential new treatment for rheumatoid arthritis.

A phase I study examined the safety and pharmacokinetics of single ascending doses of SCIO-469 (0.03-5 mg/kg p.o.) in young and elderly male and female subjects in the fasted and fed states. Results showed that the agent was well tolerated, with dose-dependent inhibition of lipopolysaccharide-stimulated TNF-α production observed in whole blood *ex vivo*. Two major metabolites were observed in blood at levels that were about 25% and 7%, respectively, those of the parent compound. Systemic exposure to the agent and its 2 metabolites increased dose-proportionately. Elimination half-life values for SCIO-469 and the major metabolites were 6, 11 and 20 h, respectively. Food intake slowed absorption and reduced C_{max} values, although systemic exposure was not altered. However, C_{max} and systemic exposure following dosing with 3 mg/kg were lower in female and elderly male subjects as compared to young males (1) (Table XI).

1. Amakye, D., Tong, S., Ward, C., Beazley, W. *Pharmacokinetics (PK) and pharmacodynamics (PD) of SCIO-469, a p38 γ MAP kinase inhibitor*. Clin Pharmacol Ther 2004, 75(2): Abst PII-7.

SD-6010

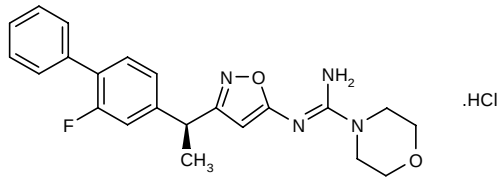
SD-6010 is an inositol-1 (or 4)-monophosphatase inhibitor in phase II development by Pfizer for the treatment of osteoarthritis.

SIM-916

Wyeth has terminated the development program for SIM-916, the result of a collaboration with ArQule dating from 1997. Instead, the company has progressed a new compound in the rheumatoid arthritis program to phase I evaluation (1).

1. *ArQule announces additional milestone payments from Wyeth*. ArQule Press Release 2005, Jan 10.

SMP-114



Sumitomo is conducting phase II clinical studies with SMP-114, a DMARD, in the U.S. and Europe for the treatment of rheumatoid arthritis.

STA-5326

Synta's first-in-class, small-molecule oral inhibitor of the cytokine IL-12, STA-5326, is in a phase II trials for Crohn's disease and psorasis following the successful completion of phase I trials. Trials for additional indications, including rheumatoid arthritis and multiple sclerosis, are planned (1, 2).

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

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

TACI-Ig

TACI-Ig has entered a new phase Ib dose-escalation study in patients with systemic lupus erythematosus. The double-blind, placebo-controlled study will first assess the systemic and local tolerability of TACI-Ig as single escalating doses and will then move into a multiple-dose study in the same population. The trial will also characterize the pharmacokinetics and pharmacodynamics of TACI-Ig and monitor the effects on biological markers of disease activity. It will be conducted by Serono in the U.S. in a total of 32 patients, 24 receiving TACI-Ig and 8 receiving placebo. Data analysis is ongoing from a previous phase I study in 24 healthy volunteers, in which a single dose of TACI-Ig was administered. Preliminary findings indicate that TACI-Ig was well tolerated and not associated with serious adverse events. TACI-Ig is a soluble fusion protein that links the extracellular portion of the TACI receptor to the Fc portion of human immunoglobulin (Ig). TACI has been shown to bind to BLyS and APRIL, TNF family cytokines that promote B-cell survival and the production of harmful autoantibodies which cause certain autoimmune diseases such as SLE. Recently, investigators have shown that BLyS plays a role in the survival of antibody-producing B-cells and it has therefore been postulated that TACI-Ig will produce a different effect than other drugs being used for the treatment of these diseases. TACI has been shown to affect several stages of B-cell development and may inhibit the survival of the cells responsible for making antibodies. ZymoGenetics demonstrated that in TACI transgenic mice there are very few mature B-cells and reduced levels of circulating antibody. Similar results were observed in normal mice treated with soluble TACI-Ig receptor. ZymoGenetics has reported data showing the effectiveness of TACI-Ig in inhibiting the progression of autoimmune disease in mouse models of lupus and rheumatoid arthritis. TACI-Ig is also being tested in a phase Ib study in patients with rheumatoid arthritis. The double-blind, placebo-controlled study will evaluate the systemic and local tolerability of TACI-Ig given as single and repeated escalating doses. The secondary objective is to characterize the pharmacokinetics and pharmacodynamics of TACI-Ig and to monitor the effects on biological markers of disease activity. The study will be conducted by Serono in a total of 60 patients in Europe and Australia. Furthermore, ZymoGenetics has received FDA clearance to initiate studies with TACI-Ig in patients with advanced B-cell malignancies. Phase Ib studies evaluating the safety and pharmacokinetics of multiple doses of TACI-Ig are planned in patients with multiple myeloma, CLL and NHL. The Centre Hospitalier Universitaire de Montpellier (L'Hopital Lapeyronie) will evaluate TACI-Ig in patients with advanced multiple myeloma, and the Mayo Clinic will conduct a trial in patients with other advanced B-cell malignancies. ZymoGenetics and Serono entered into an exclusive codevelopment and commercialization agreement in 2001 focused on the development of TACI-Ig. The companies share research and development expenses worldwide, except for Japan, where Serono covers all expenses. ZymoGenetics retains the option to copromote products with Serono in North America. If ZymoGenetics exercises that option, the two companies will share commercialization expenses and profits equally. Serono has exclusive rights to market TACI-Ig in the remainder of the world, for which ZymoGenetics is entitled to receive royalty payments. Serono is responsible for manufacturing the product for both clinical trials and commercial sale (1-4).

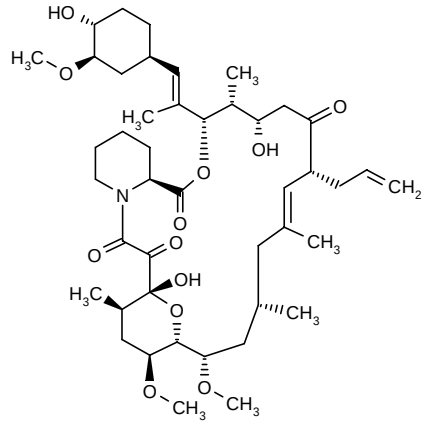
1. *Phase Ib study of TACI-Ig in SLE*. DailyDrugNews.com (Daily Essentials) July 29, 2004.

2. *ZymoGenetics announces start of TACI-Ig clinical study in rheumatoid arthritis; Second phase 1b study initiated in patients with autoimmune disease*. ZymoGenetics Press Release 2004, Aug 30.

3. *TACI-Ig cleared to enter phase Ib studies in advanced B-cell malignancies*. DailyDrugNews.com (Daily Essentials) Oct 6, 2004.

4. *ZymoGenetics updates pipeline progress*. DailyDrugNews.com (Daily Essentials) Dec 15, 2004.

Tacrolimus



Fujisawa continues to study expanded indications for its first-in-class topical immunomodulator tacrolimus, available worldwide for organ transplant rejection as Prograf® and for atopic dermatitis in adults and children as Protopic®. In Japan, an oral formulation has been submitted for review for the treatment of rheumatoid arthritis and ulcerative colitis; phase III trials are ongoing in the U.S. and phase II studies in the E.U. for rheumatoid arthritis. It is also in phase II-III clinical development

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

Indication	Design	Treatments	n	Conclusions	Ref.
Arthritis, rheumatoid	Randomized Double-blind Multicenter	Tacrolimus, 1.5 mg p.o. o.d. x 16 wks (n=68) Tacrolimus, 3 mg p.o. o.d. x 16 wks (n=70) Placebo (n=74)	212	Tacrolimus was more effective than placebo in inducing therapeutic responses in patients with rheumatoid arthritis refractory to DMARDs. No significant differences were found between the incidence of adverse events in each study group	1
Arthritis, rheumatoid	Randomized Double-blind	Tacrolimus [C_{min} 5-9 ng/ml] x 3 mo (n=10) Tacrolimus [C_{min} 10-14 ng/ml] x 3 mo (n=11)	21	Tacrolimus was generally well tolerated and showed efficacy in the treatment of patients with severe refractory rheumatoid arthritis. The optimal trough level of tacrolimus was 9.8 ng/ml, but this was associated with a greater incidence of nausea	2

around the world for the treatment of psoriasis, lupus nephritis, asthma, vernal conjunctivitis, etc. Clinical studies reported during the past year with tacrolimus in rheumatoid arthritis are summarized here.

A multicenter, double-blind, randomized clinical trial compared the administration of placebo or tacrolimus (1.5 or 3 mg p.o.) once daily for 16 weeks in 212 patients with rheumatoid arthritis resistant to at least 1 DMARD. The ACR20 response rate was significantly higher on the high-dose tacrolimus regimen (48.3%) than with low-dose tacrolimus (24.6%) or placebo (14.1%); in contrast, no significant differences were found in the ACR50 response rates of the treatment groups. The incidence of adverse events was 44.4% with high-dose tacrolimus, 61.3% with low-dose tacrolimus and 46.3% with placebo. The differences among groups were not statistically significant, and the most common adverse events were gastrointestinal symptoms and renal function abnormalities. The authors concluded that 3 mg/day was the optimal dose for tacrolimus in patients with rheumatoid arthritis unresponsive to DMARDs (1) (Table XII).

A double-blind clinical trial compared the efficacy and safety of 2 regimens of the immunosuppressant tacrolimus at doses based on plasma trough concentration in the treatment of refractory rheumatoid arthritis. Twenty-one patients with severe rheumatoid arthritis unresponsive to conventional drugs and biological agents were randomized to receive low-dose (trough concentration of 5-9 ng/ml) or high-dose (trough concentration of 10-14 ng/ml) tacrolimus monotherapy, maintained at the desired concentration for 3 months. The average trough levels achieved with these regimens were 6.5 ng/ml with low-dose monotherapy and 9.8 ng/ml with high-dose monotherapy. Both treatments significantly improved the Health Assessment Questionnaire (HAQ) score and the Disease Activity Score (DAS) of the patients compared to baseline. The ACR20, ACR50 and ACR70 response rates achieved in each group were, respectively, 50%, 40% and 20% for low-dose tacrolimus and 45%, 18% and 9% for high-dose tacrolimus. High-dose monotherapy was significantly more effective than low-dose monotherapy in improving tender joint count, swollen joint count and patient-assessed pain, but the former was also associated with a greater incidence of nausea, diarrhea, dizziness and tremor (2) (Table XII).

1. Kondo, H., Abe, T., Hashimoto, H., Uchida, S., Irimajiri, S., Hara, M., Sugawara, S. *Efficacy and safety of tacrolimus (FK506) in treatment of rheumatoid arthritis: A randomized, double blind, placebo controlled dose-finding study*. J Rheumatol 2004, 31(2): 243.

2. Mpofu, S., Grundy, G., Dodd, S., Moots, R.J. *A double blind pilot study dosing tacrolimus in refractory rheumatoid arthritis based on plasma trough concentration*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 366.

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

Tadekinig Alfa

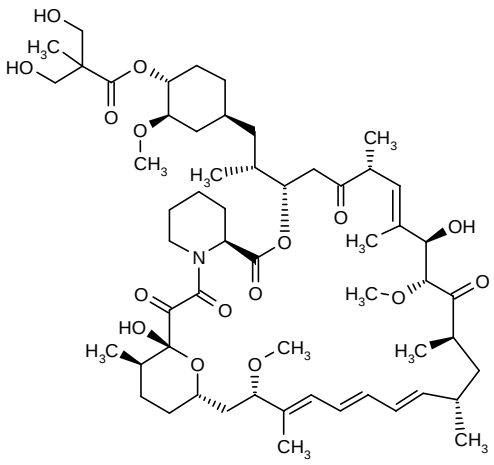
Serono began phase IIa studies with tadekinig alfa (rhIL-18bp, recombinant human IL-18-binding protein) for the treatment of rheumatoid arthritis and psoriasis in 2003 (1). However, the present status of the protein is unclear as the company now indicates that it is in phase I for autoimmune diseases in general.

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

TAK-715

A p38 MAP kinase inhibitor synthesized at Takeda, TAK-715 is in phase II studies for the treatment of rheumatoid arthritis.

Temsirolimus



Phase III trials are under way for temsirolimus (CCI-779), an mTOR inhibitor developed at Wyeth, in several cancers including renal cell carcinoma, advanced metastatic breast cancer and mantle cell lymphoma. The product has fast track status for the first-line treatment of poor-prognosis patients with advanced renal cell carcinoma and for the treatment of renal cell carcinoma after failure of initial therapy. Phase II trials are also investigating whether it may have therapeutic utility in other diseases such as rheumatoid arthritis and multiple sclerosis (1, 2).

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

2. *Fast track status for temsirolimus for first-line treatment of advanced RCC*. DailyDrugNews.com (Daily Essentials) Aug 19, 2004.

Original monograph – Drugs Fut 2002, 27(1): 7.

tgAAC-94

Targeted Genetics has initiated a phase I trial of its product candidate tgAAC-94 in patients with rheumatoid arthritis. The multicenter, double-blind, randomized, placebo-controlled, dose-escalation study is designed to assess the safety of intraarticular delivery of tgAAC-94. Secondary parameters include the ability of intraarticular administration of tgAAC-94 to reduce pain and swelling in the injected joint and overall disease activity. The amount of local and circulating TNFR:Fc protein also will be measured. Up to 32 patients in the U.S. and Canada will receive a single injection of tgAAC-94 or placebo directly into an affected joint and will be followed for 24 weeks after injection. tgAAC-94 utilizes Targeted Genetics' recombinant adeno-associated vector (rAAV) technology platform to deliver the DNA sequence encoding TNFR:Fc, a potent inhibitor of TNF-α, to cells within arthritic joints. The TNF-α inhibitor is synthesized by the patients' own joint cells to reduce inflammation associated with disease. tgAAC-94 is designed to treat rheumatoid arthritis patients who either continue to suffer from symptoms of disease in 1 or more affected joints despite successful systemic therapy, or who suffer from only a few problematic joints and are not considered candidates for receiving systemic anti-TNF therapy. In preclinical studies, a single injection of rAAV-TNFR:Fc vector into the ankles of arthritic rats resulted in a significant reduction in ankle and hind paw swelling as measured by arthritis index scores. Animals treated in a single joint experienced a reduction in swelling in both the treated joint and the untreated joint, without significantly elevated levels of circulating TNFR:Fc protein (1).

1. *tgAAC94 enters phase I rheumatoid arthritis study*. DailyDrugNews.com (Daily Essentials) March 19, 2004.

Tocilizumab

The humanized anti-human IL-6 receptor antibody tocilizumab (atlizumab, MRA, R-1569) was developed at Chugai and licensed to Roche for global joint development in 2003. Chugai is awaiting approval in Japan for the treatment of Castleman's disease, and plans to market it there as Actemra®. Phase III trials are in progress in rheumatoid arthritis and systemic-onset juvenile rheumatoid arthritis, phase II studies in multiple myeloma and Crohn's disease, and phase I studies in systemic lupus erythematosus (1-3).

A multicenter, randomized, placebo-controlled phase II clinical trial enrolled 359 patients with active rheumatoid arthritis unresponsive to methotrexate therapy (average dose of 15 mg/week for at least 6 months) who were treated once every 4 weeks with tocilizumab alone, methotrexate alone or tocilizumab combined with methotrexate. Doses of 4 and 8 mg/kg of tocilizumab significantly improved the signs and symptoms of the disease compared to baseline. The effects of tocilizumab increased when coadministered with methotrexate (4) (Table XIII).

The effect of tocilizumab on serum levels of IL-6 and soluble IL-6 receptor were assessed as part of a phase I/II trial in patients with rheumatoid arthritis. Serum IL-6 increased significantly after administration of a dose of 8 mg/kg, but decreased upon repeated antibody administration. Serum soluble IL-6 receptor also increased, but soluble IL-6 receptor signal transduction was blocked when tocilizumab was detectable in serum. C-reactive proteins levels were reduced from 5.4 ± 1.9 mg/dl at baseline to 0.2 ± 0.2 mg/dl at day 14 (5).

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

Indication	Design	Treatments	n	Conclusions	Ref.
Arthritis, rheumatoid	Randomized Double-blind Multicenter	Tocilizumab 1x/4 wks x 4 Tocilizumab 1x/4 wks + Methotrexate 1x/4 wks x 4 Placebo + Methotrexate 1x/4 wks x 4	359	Tocilizumab 4 and 8 mg/kg significantly improved the signs and symptoms of active rheumatoid arthritis. The effects of tocilizumab increased when coadministered with methotrexate	4

Data from a double-blind, placebo-controlled trial in rheumatoid arthritis patients showed that serum IL-6 levels were significantly reduced in patients achieving an ACR70 response while receiving tocilizumab treatment. In 5 patients who achieved an ACR50 response, serum IL-6 levels gradually decreased with tocilizumab treatment, and the responses lasted for 3-22 months after withdrawal of the antibody (6).

The INVITED study was a dose-finding phase II clinical trial that determined the effects and safety of tocilizumab in systemic-onset juvenile idiopathic arthritis. Eleven patients aged 2-19 years with active disease unresponsive to high-dose, long-term corticosteroids received a single i.v. dose of 2 mg/kg of tocilizumab, followed by 3 i.v. doses of 2 mg/kg every 2 weeks. The dose given to each child was increased to 4 mg/kg, and then to 8 mg/kg, if they experienced disease flares during the study. Tocilizumab therapy significantly reduced high-grade or quotidian fever, improved the symptoms of severe arthritis and normalized the CRP levels of the children. An analysis conducted at 2 weeks after 3 equal doses of tocilizumab had been administered to each child showed ACR30, ACR50 and ACR70 responses in 90.9%, 90.9% and 63.6% of all patients, respectively. The most common adverse events were upper respiratory tract infections, pustules on extremities and eczema. All laboratory abnormalities were mild, and no children died or discontinued the treatment during the study (7).

A study in patients with severe systemic-onset juvenile idiopathic arthritis found that tocilizumab treatment can induce catch-up growth. The 4 patients evaluated had received treatment every 2 weeks for 2-3.5 years. As serum IL-6 levels declined, growth velocity increased. All experienced catch-up growth, with body height z scores increasing 0.2-1.6. Bone mineral density z scores were 0.3-9.78 after disease remission (8).

1. Mihara, M. *Research for anti-IL-6 receptor antibody, a novel anti-rheumatic agent.* J Pharmacol Sci 2004, 94(Suppl. 1): Abst S19-3.

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

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

4. Maini, R.N. *Anti-IL6 receptor therapy: Rationale and early results in rheumatoid arthritis*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst SP0074.

5. Nishimoto, N., Terao, K., Kakehi, T., Kishimoto, T. *Increase in serum levels of IL-6 and soluble IL-6 receptor after anti-IL-6 receptor antibody therapy in patients with rheumatoid arthritis*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 131.

6. Nishimoto, N., Nakahara, H., Terao, K., Kakehi, T., Kishimoto, T. *Repeated treatments with anti-IL-6 receptor antibody (MRA) lead to an extended clinical response in rheumatoid arthritis even after cessation of MRA*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 339.

7. Yokota, S., Imagawa, T., Mori, M., Miyamae, T., Nishimoto, N., Nishimoto, T. *Phase II trial of anti-IL-6 receptor antibody (MRA) for systemic-onset juvenile idiopathic arthritis*. 4th Int Congr Autoimmun (Nov 3-7, Budapest) 2004, Abst.

8. Imagawa, T., Miyamae, T., Umebayashi, H. et al. *Catch-up growth in severe systemic-onset juvenile idiopathic arthritis: Long-term treatment with humanized anti-IL6 receptor monoclonal antibody*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 76.

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

Additional References

Nishimoto, N. et al. *Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: A multicenter, double-blind, placebo-controlled trial*. Arthritis Rheum 2004, 50(6): 1761.

TRU-015

TRU-015, Trubion's most advanced product, is a member of the SMIPs™ (Small Modular ImmunoPharmaceuticals) class. SMIPs™ utilize key structures in naturally occurring proteins that the company optimizes to function together in a single molecule; they have improved biodistribution and can be designed for optimal potency in different diseases, unlike currently available immunopharmaceuticals. TRU-015 is being developed for indications in autoimmune and inflammatory diseases and just recently entered its first phase I trial, a study designed to evaluate the safety of increasing

doses of TRU-015 in patients with rheumatoid arthritis. TRU-015 was specifically designed to target and eliminate CD20-bearing B-cells (1, 2).

1. *Series B financing at Trubion to fund pipeline advancement*. DailyDrugNews.com (Daily Essentials) July 19, 2004.

2. *TRU-015 enters phase I for rheumatoid arthritis*. DailyDrugNews.com (Daily Essentials) Jan 13, 2005.

VX-702

VX-702 is a novel, orally administered p38 MAP kinase inhibitor in phase I and phase II development at Vertex for the treatment of rheumatoid arthritis and acute coronary syndrome, respectively. The company is collaborating with Kissei on the development and commercialization of VX-702, with Kissei holding exclusive rights to p38 MAP kinase inhibitor compounds in Japan and Southeast Asian countries, as well as semiexclusive rights in China, Taiwan and South Korea.

In the summer of 2004, Vertex announced top-line results from the pilot phase IIa study designed to evaluate the safety and tolerability of VX-702 in patients with unstable angina undergoing percutaneous coronary intervention (PCI). Preliminary results indicated that VX-702 met its primary endpoint of safety and tolerability. Treatment with VX-702 also resulted in dose-dependent inhibition of CRP. As part of its development program for VX-702, Vertex is also evaluating the clinical and commercial potential for VX-702 in additional indications, including chronic indications in which a reduction of CRP is associated with clinical activity (1, 2).

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

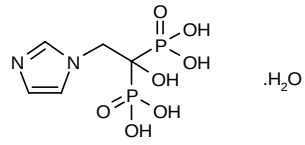
2. *Vertex Pharmaceuticals reports Q2 R&D highlights*. Vertex Pharmaceuticals Press Release 2004, July 26.

YS-IL-6

Y's Therapeutics has submitted applications to the Ethics Committee and Ministry of Health (BfArM) in Germany to begin phase II trials for its most advanced projects: YS-IL-6 for rheumatoid arthritis and YS-TH2 for asthma. The multinational, randomized, double-blind, placebo-controlled, dose-ranging trials will generate safety and efficacy data. YS-IL-6 is a small-molecule drug in development for the treatment of inflammatory diseases, including rheumatoid arthritis and psoriasis. The molecule works by inhibiting TNF-α and IL-6 production in T-cells and macrophages, and by inhibiting T-cell proliferation and migration (1).

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

Zoledronic Acid Monohydrate



Zoledronic acid monohydrate, the first i.v. bisphosphonate, is currently marketed by Novartis as Zometa® for the treatment of hypercalcemia of malignancy and for the treatment and prevention of bone metastases due to various cancers. Approvals are pending in the U.S. and the E.U. for the treatment of Paget's disease of bone and in the E.U. for postmenopausal osteoporosis (Aclasta®). Phase II clinical trials are under way for the treatment of rheumatoid arthritis.

Original monograph – Drugs Fut 2000, 25(3): 259.

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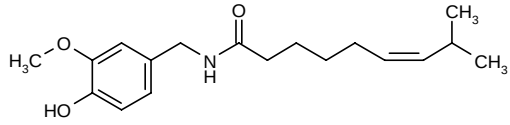
Jarrett, S., O'Connor, P., Conaghan, P., Sloan, V., Papanastasiou, P., Grainger, A., Ortmann, C., Emery, P. *First evidence of structural benefit from a bisphosphonate, zoledronic acid, in rheumatoid arthritis*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst OP0002.

Zucapsaicin



Winston Laboratories is conducting phase III clinical evaluation of zucapsaicin (WI-1002, civamide), a vanilloid VR_1 receptor agonist, for the topical treatment of osteoarthritis. A nasal spray formulation (WL-1001) is in phase III clinical trials for cluster headache, and phase II studies for migraine prophylaxis and postherpetic neuralgia.

Annual Update 2004/2005 - Treatment of Musculoskeletal Cancers

According to the National Cancer Institute (NCI) classification, the group of musculoskeletal cancers covers cancer of the bone, cartilage, fat, muscle, blood vessels or other connective or supportive tissue (1). Musculoskeletal cancer can be divided into two main groups: bone cancer and soft tissue sarcoma. Primary bone cancer and soft tissue sarcoma are uncommon types of cancer, accounting for less than 1% of new cancer cases diagnosed each year in the U.S. (2).

Soft tissue sarcoma refers to cancer that develops in soft tissue, or the tissue that connects, supports or surrounds other structures and organs of the body. Sarcomas are named after the primary tissue they grow in: fibrosarcoma arises in fibrous tissue, chondrosarcoma in cartilage, liposarcoma in fat tissue, leiomyosarcoma in smooth muscle, rhabdomyosarcoma in striated muscle tissue, synovial sarcoma in synovial tissue, lymphangiosarcoma in lymph vessels and neurofibrosarcoma in peripheral nerves.

In a previous Annual Update (3), drugs under active development for the treatment of bone cancer and cancer metastatic to the bone were reviewed. In the table that follows, drugs for the treatment of soft tissue sarcoma are shown (*Source: Prous Science Integrity®*).

References

1. NCI website (www.cancer.gov)

2. Cancer Statistics 2004 (American Cancer Society, Inc.)

3. Drugs Fut 2004, 29(8): 872.

Itziar Escudero

Treatment of Musculoskeletal Cancers

Condition	Phase	Drug	Target	Source
Chondrosarcoma	II	Gemcitabine	Pyrimidine nucleotides	National Cancer Institute
Fibrosarcoma	II	Imatinib mesilate	PDGFRα/β, KIT, ABL	National Cancer Institute
Leiomyosarcoma	II	Trabectedin		Johnson & Johnson
Liposarcoma	II	Trabectedin		Johnson & Johnson
Neurofibrosarcoma	II	Erlotinib hydrochloride	EGFR (erbB1)	National Cancer Institute
	II	Tipifarnib	Farnesyltransferase	National Cancer Institute
Rhabdomyosarcoma	III	Vincristine	Tubulin	National Cancer Institute
	II	Irinotecan hydrochloride	DNA topoisomerase I	National Cancer Institute
	II	Temozolomide	DNA	National Cancer Institute
	I	PEG-filgrastim		National Cancer Institute
Synovial sarcoma	II	Gefitinib	EGFR (erbB1)	EORTC
	I	PEG-filgrastim		National Cancer Institute
Sarcoma	III	Trabectedin		PharmaMar
	II	ABT-510		Abbott
	II	AP-23573	mTOR	Ariad Pharmaceuticals
	II	Exatecan mesilate	DNA topoisomerase I	EORTC
	II	Vincristine sulfate TCS	Tubulin	Inex
	II	Trabectedin		Ortho Biotech/National Cancer Institute
	II	Sabarubicin hydrochloride	DNA topoisomerase II	Menarini
	II	Gemcitabine	Pyrimidine nucleotides	National Cancer Institute
	II	Perifosine	Protein kinase B (PKB/Akt)	National Cancer Institute

Continuation

Treatment of Musculoskeletal Cancers

Condition	Phase	Drug	Target	Source
Sarcoma	II	Temsirolimus	mTOR	National Cancer Institute
	II	Imatinib mesilate	PDGFRα/β, KIT, ABL	National Cancer Institute
	II	Erlotinib hydrochloride	EGFR (erbB1)	National Cancer Institute
	II	Tipifarnib	Farnesyltransferase	National Cancer Institute
	II	Temozolomide	DNA	National Cancer Institute
	II	L-Alanosine	Purine nucleotides	Salmedix
	II	SP-1049C	DNA topoisomerase II	Supratek
	II	STA-4783	HSP70	Synta Pharmaceuticals
	I/II	Rubitecan	DNA topoisomerase I	SuperGen
	I	Paclitaxel	Tubulin	Bristol-Myers Squibb
	I	Ad.Egr.TNF.11D		GenVec