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Annual Update 2003/2004 - Treatment of Dermatological Disorders

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

J.R. Prous
Editor

Treatment of Dermatological Disorders by Condition

Condition	Phase	Drug	Source
Acne	Prereg.	Clindamycin phosphate (foam)	Connetics
	III	Clindamycin phosphate/tretinoin	Connetics
	III	Dapsone	Atrix/Fujisawa
	II/III	MDI-403	Molecular Design International
	II/III	Tazarotene[2,3] (oral)	Allergan/Procter & Gamble/Pierre Fabre
	II/III	TU-2100	Tamarkin
	II	Doxycycline hyclate[1]	CollaGenex
	II	MBI-594AN	Micrologix Biotech
	II	MDI-101	Molecular Design International
	II	PCL-016	Novactyl
	II	PSK-3841	ProSkelia
	II	XMP-629	Xoma
	I/II	Aminolevulinic acid hydrochloride[1,3]	Dusa
	I/II	HB-64	Helix BioMedix
	I	BI-ACNE	Vicuron Pharmaceuticals
	I	VAG-624	Novartis
Actinic keratosis	R-2004	Imiquimod[1,3]	3M Pharmaceuticals
	II	PN-106	Wellstat Therapeutics
	IND Filed	PEP-005	Peplin Biotech/Allergan
Alopecia	II	PSK-3841	ProSkelia
	I/II	PTH(7-34)	IGI
Atrophy, cutaneous	II	KB-002611	Karo Bio
Burns	II	Prasterone sulfate	Pharmadigm
	II	rhIGF-I/rhIGFBP-3	Insmed
	I	Vibriolysin	BioMarin
Dermatitis	Prereg.	Ketoconazole[2,3] (foam)	Connetics
	III	Ketoconazole[2,3] (gel)	Barrier Therapeutics
	II/III	Alitretinoin[1,2] (BAL-4079)	Basilea Pharmaceutica
	II	AA-10006[1]	Arachnova
	II	AVAC™	SR Pharma/Genesis Research and Development
	II	Bexarotene[1] (gel)	Ligand
	II	Bimosiamose	Revotar Biopharmaceuticals
	II	Loteprednol etabonate[1,3]	Ivax
	II	NCX-1022	NicOx
	II	NPI-32101	Nucryst
	II	Recombinant α_1-antitrypsin	Arriva-ProMetic
	II	Sorafin™	Psiron
	II	SRP-299	SR Pharma
	II	TU-2100	Tamarkin
	I/II	MX-8899	Maxim
	I	TS-022	Taisho
Ichthyosis, congenital	III	Liarozole fumarate[3]	Barrier Therapeutics
Pemphigus	I	PI-0824	Peptimmune
Photodamage	II	Melanotan®	EpiTan
	II	NV-07a	Novogen
	I/II	Aminolevulinic acid hydrochloride[1,3]	Dusa
Pruritus	Prereg.	Nalfurafine hydrochloride[3]	Fujisawa/Toray/Daiichi Pharmaceutical
Psoriasis	L-2003	Alefacept[3]	Biogen Idec
	L-2003	Efalizumab[3]	Genentech/Xoma/Serono
	R-2003	Tazarotene[2,3] (oral)	Allergan/Procter & Gamble/Pierre Fabre
	Prereg.	Etanercept[1,3]	Amgen/Wyeth Pharmaceuticals
	III	Infliximab[1]	Schering-Plough/Centocor (Johnson & Johnson)
	III	Rosiglitazone maleate[1,3]	GlaxoSmithKline

Continuation

Treatment of Dermatological Disorders by Condition

Condition	Phase	Drug	Source
	II/III	Onercept	Serono
	II/III	PV-10	Provectus
	II/III	Tacrolimus[1,3]	Fujisawa
	II	Adalimumab[1,3]	Abbott/Cambridge Antibody Technology
	II	AVT-02	Avontec
	II	Bexarotene[1] (oral + gel)	Ligand
	II	Bimosiamose	Revotar Biopharmaceuticals
	II	CGC-1072	CellGate
	II	CNTO-1275	Centocor (Johnson & Johnson)/ Medarex
	II	Doramapimod	Boehringer Ingelheim
	II	ISA-247	Isotechnika/Roche
	II	ISIS-104838	Isis Pharmaceuticals
	II	MEDI-522	MedImmune
	II	MV-9411	Miravant
	II	QRX-101	QUATRx
	II-On hold	Siplizumab[3]	MedImmune
	II	T-487	Tularik
	II	Tadekinig-α	Serono
	II	Tisocalcitate	Schering AG
	II	TU-2100	Tamarkin
	II-Suspended	VX-148	Vertex
	I/II	Aminolevulinic acid hydrochloride[1,3]	Dusa
	I/II	Pralnacasan	Aventis Pharma/Vertex
	I/II	SWT-01.100[1]	Switch Biotech
	I	Micellar paclitaxel	Angiotech
	I	MLN-3897 (AVE-9897)	Millennium/Aventis Pharma
	I	Psoraxine™	SkyePharma/Astralis
	I	Sorafin™	Psiron
	I	STA-5326	Synta Pharmaceuticals
	I	Vapaliximab	BioTie Therapies/Seikagaku
	Discontinued-2003	IC-747	Biogen/Icos
Rosacea	L-2003	Azelaic acid[1,3]	Schering AG/Berlex/Allergan
	III	Doxycycline hyclate[1]	CollaGenex
	II	COL-3	CollaGenex
	I/II	Dapsone	Atrix/Fujisawa
Scar (hypertrophic)	II	Fibrostat®	Biovail/Procyon
	I	VIT-100	Immusol
Ulcer, diabetic	II/III	OrCel®[1]	Ortec
	II	Chrysalin®	Chrysalis BioTechnology
	II	E-Matrix™	Encelle/Smith & Nephew
	II	rh-Lactoferrin	Agennix
	I	MRE-0094	King Pharmaceuticals/Aderis
Ulcer, skin	II	Allox™	IsoTis/Healthpoint
	I	PN-105	Wellstat Therapeutics
	I	Thymosin β4	RegeneRx Biopharmaceuticals
Ulcer, venous leg	Prereg.	OrCel®[1]	Ortec
	II	Glucoprime™	Glycotex (Novogen)
Xeroderma pigmentosum	III	T4N5 liposome lotion	AGI Dermatics

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

Treatment of Dermatological Disorders by Source

Source	Condition	Drug	Phase
3M Pharmaceuticals	Actinic keratosis	Imiquimod[1,3]	R-2004
Abbott	Psoriasis	Adalimumab[1,3]	II
Aderis	Ulcer, diabetic	MRE-0094	I
Agennix	Ulcer, diabetic	rh-Lactoferrin	II
AGI Dermatics	Xeroderma pigmentosum	T4N5 liposome lotion	III
Allergan	Acne	Tazarotene[2,3] (oral)	II/III
	Actinic keratosis	PEP-005	IND Filed
	Psoriasis	Tazarotene[2,3] (oral)	R-2003
	Rosacea	Azelaic acid[1,3]	L-2003
Amgen	Psoriasis	Etanercept[1,3]	Prereg.
Angiotech	Psoriasis	Micellar paclitaxel	I
Arachnova	Dermatitis (atopic)	AA-10006[1]	II
Arriva-ProMetic	Dermatitis (atopic)	Recombinant α_1-antitrypsin	II
Astralis	Psoriasis	Psoraxine™	I
Atrix	Acne	Dapsone	III
	Rosacea	Dapsone	I/II
Aventis Pharma	Psoriasis	MLN-3897 (AVE-9897)	I
		Pralnacasan	I/II
Avontec	Psoriasis	AVT-02	II
Barrier Therapeutics	Dermatitis (seborrheic)	Ketoconazole[2,3] (gel)	III
	Ichthyosis, congenital	Liarozole fumarate[3]	III
Basilea Pharmaceutica	Dermatitis (hand)	Alitretinoin[1,2] (BAL-4079)	II/III
Berlex	Rosacea	Azelaic acid[1,3]	L-2003
Biogen Idec	Psoriasis	Alefacept[3]	L-2003
Biogen	Psoriasis	IC-747	Discontinued 2003
BioMarin	Burns	Vibriolysin	I
BioTie Therapies	Psoriasis	Vapaliximab	I
Biovail	Scar (hypertrophic)	Fibrostat®	II
Boehringer Ingelheim	Psoriasis	Doramapimod	II
Cambridge Antibody Technology	Psoriasis	Adalimumab[1,3]	II
CellGate	Psoriasis	CGC-1072	II
Centocor (Johnson & Johnson)	Psoriasis	CNTO-1275	II
		Infliximab[1]	III
Chrysalis BioTechnology	Ulcer, diabetic	Chrysalin®	II
CollaGenex	Acne	Doxycycline hyclate[1]	II
	Rosacea	COL-3	II
		Doxycycline hyclate[1]	III
Connetics	Acne	Clindamycin phosphate (foam)	Prereg.
		Clindamycin phosphate/tretinoin	III
	Dermatitis (seborrheic)	Ketoconazole[2,3] (foam)	Prereg.
Daiichi Pharmaceutical	Pruritus	Nalfurafine hydrochloride[3]	Prereg.
Dusa	Acne	Aminolevulinic acid hydrochloride[1,3]	I/II
	Photodamage	Aminolevulinic acid hydrochloride[1,3]	I/II
	Psoriasis	Aminolevulinic acid hydrochloride[1,3]	I/II
Encelle	Ulcer, diabetic	E-Matrix™	II
EpiTan	Photodamage	Melanotan®	II
Fujisawa	Acne	Dapsone	III
	Pruritus	Nalfurafine hydrochloride[3]	Prereg.
	Psoriasis	Tacrolimus[1,3]	II/III
	Rosacea	Dapsone	I/II
Genentech	Psoriasis	Efalizumab[3]	L-2003
Genesis Research and Development	Dermatitis (atopic)	AVAC™	II
GlaxoSmithKline	Psoriasis	Rosiglitazone maleate[1,3]	III
Glycotex (Novogen)	Ulcer, venous leg	Glucoprime™	II
Healthpoint	Ulcer, skin	Allox™	II
Helix BioMedix	Acne	HB-64	I/II
Icos	Psoriasis	IC-747	Discontinued-2003
IGI	Alopecia	PTH (7-34)	I/II
Immusol	Scar (hypertrophic)	VIT-100	I
Insmed	Burns	rhIGF-I/rhIGFBP-3	II

Continuation

Treatment of Dermatological Disorders by Source

Source	Condition	Drug	Phase
Isis Pharmaceuticals	Psoriasis	ISIS-104838	II
Isotechnika	Psoriasis	ISAtx-247	II
IsoTis	Ulcer, skin	Allox™	II
Ivax	Dermatitis	Loteprednol etabonate[1,3]	II
Karo Bio	Atrophy, cutaneous	KB-002611	II
King Pharmaceuticals	Ulcer, diabetic	MRE-0094	I
Ligand	Dermatitis (hand)	Bexarotene[1] (gel)	II
	Psoriasis	Bexarotene[1] (oral + gel)	II
Maxim	Dermatitis (radiation)	MX-8899	I/II
Medarex	Psoriasis	CNTO-1275	II
MedImmune	Psoriasis	MEDI-522	II
		Siplizumab[3]	II-On hold
Micrologix Biotech	Acne	MBI-594AN	II
Millennium	Psoriasis	MLN-3897 (AVE-9897)	I
Miravant	Psoriasis	MV-9411	II
Molecular Design International	Acne	MDI-101	II
		MDI-403	II/III
NicOx	Dermatitis (atopic)	NCX-1022	II
Novactyl	Acne	PCL-016	II
Novartis	Acne	VAG-624	I
Novogen	Photodamage	NV-07a	II
Nucryst	Dermatitis (atopic)	NPI-32101	II
Ortec	Ulcer, diabetic	OrCel®[1]	II/III
	Ulcer, venous leg	OrCel®[1]	Prereg.
Peplin Biotech	Actinic keratosis	PEP-005	IND Filed
Peptimmune	Pemphigus	PI-0824	I
Pharmadigm	Burns	Prasterone sulfate	II
Pierre Fabre	Acne	Tazarotene[2,3] (oral)	II/III
	Psoriasis	Tazarotene[2,3] (oral)	R-2003
Procter & Gamble	Acne	Tazarotene[2,3] (oral)	II/III
	Psoriasis	Tazarotene[2,3] (oral)	R-2003
Procyon	Scar (hypertrophic)	Fibrostat®	II
ProSkelia	Acne	PSK-3841	II
	Alopecia	PSK-3841	II
Provectus	Psoriasis	PV-10	II/III
Psiron	Dermatitis (atopic)	Sorafin™	II
	Psoriasis	Sorafin™	I
QUATRx	Psoriasis	QRX-101	II
RegeneRx Biopharmaceuticals	Ulcer, skin	Thymosin β4	I
Revotar Biopharmaceuticals	Dermatitis (atopic)	Bimosiamose	II
	Psoriasis	Bimosiamose	II
Roche	Psoriasis	ISAtx-247	II
Schering AG	Psoriasis	Tisocalcitate	II
	Rosacea	Azelaic acid[1,3]	L-2003
Schering-Plough	Psoriasis	Infliximab[1]	III
Seikagaku	Psoriasis	Vapaliximab	I
Serono	Psoriasis	Efalizumab[3]	L-2003
		Onercept	II/III
		Tadekinig-α	II
SkyePharma	Psoriasis	Psoraxine™	I
Smith & Nephew	Ulcer, diabetic	E-Matrix™	II
SR Pharma	Dermatitis (atopic)	AVAC™	II
		SRP-299	II
Switch Biotech	Psoriasis	SWT-01.100[1]	I/II
Synta Pharmaceuticals	Psoriasis	STA-5326	I
Taisho	Dermatitis (atopic)	TS-022	I
Tamarkin	Acne	TU-2100	II/III
	Dermatitis (seborrheic)	TU-2100	II
	Psoriasis	TU-2100	II
Toray	Pruritus	Nalfurafine hydrochloride[3]	Prereg.
Tularik	Psoriasis	T-487	II

Continuation

Treatment of Dermatological Disorders by Source

Source	Condition	Drug	Phase
Vertex	Psoriasis	Pralnacasan	I/II
		VX-148	II Suspended
Vicuron Pharmaceuticals	Acne	BI-ACNE	I
Wellstat Therapeutics	Actinic keratosis	PN-106	II
	Ulcer, skin	PN-105	I
Wyeth Pharmaceuticals	Psoriasis	Etanercept[1,3]	Prereg.
Xoma	Acne	XMP-629	II
	Psoriasis	Efalizumab[3]	L-2003

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

Treatment of Dermatological Disorders

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AA-10006

Arachnova's AA-10006 (Araderm™), a widely used and currently marketed nonsteroidal CNS drug with an excellent safety profile, is presently in phase II clinical development as a topical formulation for the treatment of dermatitis. The compound demonstrated efficacy in a pharmacological model of dermatitis and the topical formulation has successfully completed phase I studies, as well as a phase II proof-of-concept study in patients with mild to moderate atopic dermatitis.

Adalimumab

Adalimumab (D2E7, Humira®, Trudexa™) was discovered through a broad scientific collaboration between Abbott and Cambridge Antibody Technology (CAT). The molecule acts by specifically blocking TNF-α and was the first human monoclonal antibody approved by the FDA (2002) and the European Commission (2003) for rheumatoid arthritis, alone or in combination with methotrexate or other disease-modifying antirheumatic drugs (DMARDs). In addition to the initial indication of moderate to severe active rheumatoid arthritis in adult patients whose response to DMARDs has been inadequate, adalimumab is also being evaluated for juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, early rheumatoid arthritis, ankylosing spondylitis and Crohn's disease (1-6).

Preliminary results of the M02-528 study, a multicenter, randomized, double-blind, placebo-controlled phase II clinical trial that determined the efficacy and safety of adalimumab (40 mg s.c.) given once weekly or once every 2 weeks for 12 weeks to 148 adult patients with moderate to severe chronic plaque psoriasis for at least 1 year and at least 5% of body surface area affected, were recently presented at the American Academy of Dermatology annual meeting. At the end of the 12-week treatment period, the percentage of patients who achieved at least a 75% reduction in their Psoriasis Area and Severity Index (PASI) score was significantly greater with adalimumab (80% weekly and 53% every 2 weeks) compared with placebo (4%). The improvement in the mean PASI scores of the patients was significantly greater with adalimumab after only 1 week of treatment. All study treatments were well tolerated and no differences were found in safety profiles (7).

1. *EMEA hands down positive opinion on Humira*. DailyDrugNews.com (Daily Essentials) May 26, 2003.

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

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

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

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

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

7. Chen, D.M. et al. *Adalimumab efficacy and safety in patients with moderate to severe chronic plaque psoriasis: Preliminary findings from a 12-week dose-ranging trial.* J Am Acad Dermatol 2004, 50(3, Suppl): Abst P2.

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

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 last year in the U.S. under the brand name Amevive® for the treatment of adults with moderate to severe psoriasis.

Biopsies of lesions from 22 patients with psoriasis were analyzed at 2, 6 and 13 weeks after 12 weeks of treatment with alefacept 7.5 mg i.v. Large reductions in CD3+, CD8+ and CD103+ T-cells were seen in responders, while such reductions in nonresponders were small (1).

More than 1,000 patients with chronic plaque psoriasis received alefacept (7.5 mg i.v. and 10 or 15 mg i.m. once weekly for 12 weeks) or placebo in 2 randomized, placebo-controlled phase III trials. Alefacept was more effective than placebo and had a longer duration of response (2). Results from this study and most of the others summarized below are depicted in Table I.

In 2 phase III trials, patients with psoriasis received alefacept (7.5 mg i.v. or 15 mg i.m.) or placebo in combination with an immunosuppressant (methotrexate, ciclosporin, prednisone, etanercept, leflunomide, infliximab or mycophenolate mofetil). Headache, injury, pharyngitis, infection and pruritus were the observed adverse events. Concomitant or prior use of immunosuppressants did not change the frequency or spectrum of adverse events or serious infection (3).

The effects of alefacept on circulating T-cell subsets were investigated in 2 multicenter, randomized, double-blind phase III studies. A total of 1,060 patients with chronic plaque psoriasis received either i.v. or i.m. alefacept or placebo once weekly for 12 weeks. T-cell counts were determined weekly. Baseline T-cell counts were highly variable. Circulating levels of CD4+ and CD8+ subsets were reduced in both alefacept and placebo groups, but to a greater extent in the alefacept treatment group. In the i.m. study, the percentage of patients who had at least one CD4+ T-cell count below 400 cells/μl following the first dose was 8% in placebo-treated patients compared with 28% in the alefacept group. In most patients, there was a recovery of T-cell counts in the 12-week follow-up period after completion of treatment (4).

Subanalyses of pooled data from 2 placebo-controlled studies have shown that alefacept was beneficial and well tolerated in patients who were refractory to, or who had contraindications for, 3 or more other systemic psoriasis treatments or phototherapies. In these phase III studies, alefacept was administered at doses of 7.5 mg i.v., 10 mg i.m. or 15 mg i.m. once weekly for 12 weeks. Overall, patients treated with alefacept experienced a significant improvement in their clinical symptoms and quality of life. In the subanalyses, efficacy was defined as a 50% or greater reduction from baseline in the PASI score. Significantly more patients treated with alefacept compared to placebo (approximately 50% *vs*. 25%) achieved this change in PASI within each of the subsets of patients who were refractory to, or who had contraindications for, 1 or more, 2 or more, or 3 or more other psoriasis treatments. There were also statistically significant improvements in quality-of-life scores in alefacept-treated patients in each of the subsets (5).

The clinical relevance of a 50% or greater improvement in the PASI score was demonstrated in the assessment of this and other indices or scales used to measure the effectiveness of psoriasis treatments in clinical trials of alefacept. In 2 phase III studies of alefacept 7.5 mg i.v. and 15 mg i.m., decreases of at least 50% in the PASI were achieved in 71% and 57% of patients, respectively. Corresponding rates for decreases of 75% or more in the PASI were 40% and 33%. Most of the corresponding significant improvement in quality-of-life assessment was achieved with the 50% reduction in PASI score. Analyses of phase II data showed that, for patients requiring retreatment, the mean and median decrease from baseline in PASI at the time of retreatment was 20% and 29%, respectively. These data suggest that an improvement of 50% or more represents a substantial improvement for patients with psoriasis (6).

Psoriasis patients involved in clinical trials of alefacept were assessed for disease improvement and retreatment and remission times. In placebo-controlled trials, 5 of 7 patients who received alefacept 10 or 15 mg i.m. once weekly for 12 weeks showed significant improvement in psoriasis symptoms and quality of life. In 6 patients who met the criteria for retreatment, this was initiated between 4.5 and 6.5 months after the last alefacept dose. Retreatment induced longer periods of remission. Alefacept was well tolerated. Favorable disease clearance, remission rates and patient satisfaction were also reported by a patient with a 20-year history of extensive plaque psoriasis (7).

Preliminary results of a study of alefacept plus narrow-band ultraviolet B (UVB) light indicated that this treatment may clear chronic plaque psoriasis and be an effective alternative to other psoriasis regimens. All patients received alefacept 15 mg i.m. once weekly for 12 weeks and were randomized to receive either no UVB light or UVB light 3 times per week until plaque clearance for up to 6 or 12 weeks. Thirty patients completed the 4-week assessment. A 75% or greater reduction in PASI was achieved by 78% of patients who received no UVB light and by 100% of patients who received alefacept plus UVB light. The treatments were well tolerated (8).

After participating in a phase III trial of alefacept therapy (7.5 mg i.v.), 214 patients with psoriasis entered an open-label retreatment study. The additional alefacept treatment was well tolerated and 46-56% of patients achieved a reduction in PASI score of over 50% from baseline (2 weeks after the last dose in the phase III trial) (9).

In a phase II study, 229 patients with chronic plaque psoriasis were randomized to treatment with alefacept (0.025, 0.075 or 0.150 mg/kg) or placebo once weekly for 12 weeks. Responses were sustained for a median of 10 months and no patient reported disease rebound when drug treatment was discontinued (10).

Intramuscular alefacept was evaluated as a once-weekly treatment for chronic plaque prosiasis in a 12-week, multicenter, randomized, double-blind, placebo-controlled trial. Patients (n=507) received placebo or alefacept 10 or 15 mg. Two weeks after the end of treatment, a reduction of at least 75% in the PASI score was

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

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Randomized	Alefacept, 7.5 mg i.v. 1x/wk. x 12 wks Alefacept, 10 or 15 mg i.m. 1x/wk x 12 wks Placebo		Alefacept was more effective than placebo, with a longer duration of response, in patients with chronic plaque psoriasis	2
Psoriasis	Randomized, double-blind, multicenter, pooled/meta-analysis	Alefacept i.m. 1x/wk x 12 wks Alefacept i.v. 1x/wk x 12 wks Placebo	1060	Alefacept was more effective than placebo in reducing the circulating levels of memory T-cells in patients with chronic plaque psoriasis. The levels of these cells recovered after terminating administration of alefacept	4
Psoriasis	Randomized, double-blind, pooled/meta-analysis	Alefacept, 7.5 mg i.v. 1x/wk x 12 wks Alefacept, 10 mg i.m. 1x/wk x 12 wks Alefacept, 15 mg i.m. 1x/wk x 12 wks Placebo		A 12-week course of alefacept was effective in reducing the PASI score and improving the quality of life of psoriatic patients unresponsive to or with contraindications for other systemic treatments	5
Psoriasis	Pooled/meta-analysis	Alefacept, 7.5 mg i.v. x 12 wks Alefacept, 15 mg i.m. x 12 wks		Alefacept was effective in reducing the scores of patients with psoriasis. Patients who had responded to alefacept were found to be willing to allow their psoriasis to return to levels below 50% of improvement in their PASI scores compared to baseline before asking for retreatment	6
Psoriasis	Multicenter	Alefacept, 10 mg i.m. 1x/wk x 12 wks Alefacept, 15 mg i.m. 1x/wk x 12 wks x 2 Placebo	12	Alefacept was well tolerated and effective in the treatment of recurrent psoriasis. The drug was also associated with a high level of patient satisfaction	7
Psoriasis	Open	Alefacept, 15 mg i.m. 1x/wk x 12 wks Alefacept, 15 mg i.m. 1x/wk x 12 wks + narrow-band UVB light 3x/wk x 6 [max.] wks Alefacept, 15 mg i.m. 1x/wk x 12 wks + narrow-band UVB light 3x/wk x 12 [max.] wks	30	The combination of alefacept and narrow-band UVB light was more effective than alefacept alone in achieving a 75% or greater reduction in the baseline PASI scores of patients with chronic plaque psoriasis. No significant differences were found among the safety profiles of the 3 study groups	8
Psoriasis	Open	Alefacept, 7.5 mg i.v. 1x/wk x 12 wks	214	Alefacept retreatment of patients with psoriasis was well tolerated and effective	9
Psoriasis	Randomized, double-blind, multicenter	Alefacept, 0.025 mg/kg i.v. 1x/wk x 12 wks Alefacept, 0.075 mg/kg i.v. 1x/wk x 12 wks Alefacept, 0.150 mg/kg i.v. 1x/wk x 12 wks Placebo	229	Alefacept treatment produced long-term responses and improved quality of life in patients with chronic plaque psoriasis	10
Psoriasis	Randomized, double-blind	Alefacept, 10 mg i.m. 1x/wk x 12 wks Alefacept, 15 mg i.m. 1x/wk x 12 wks Placebo	507	Alefacept was safe, well tolerated and effective in patients with chronic plaque psoriasis. The greatest reductions in disease activity occurred in patients with the largest decreases in memory T-cells. Alefacept was found to produce dose-related and selective reductions in the circulating memory T-cell subset, which were related to all measures of disease activity evaluated in patients with chronic plaque psoriasis	11-13

achieved by 5%, 12% and 21% of patients given placebo, alefacept 10 mg and alefacept 15 mg, respectively, and the difference between placebo and alefacept 15 mg was statistically significant. At 6 weeks after the end of treatment, the baseline PASI score of the patients had decreased by 25% on placebo and by 41% and 46%, respectively, on 10 and 15 mg alefacept. More patients in the alefacept groups reported at least 50% or 75%

improvement in their PASI scores than in the placebo group. The effects induced by alefacept were durable and were not affected by the baseline severity of the disease. No significant differences were found between the safety profiles of placebo and alefacept, and no drug-related serious adverse events were reported (11, 12) Alefacept therapy produced dose-dependent reductions in CD4+ and CD8+ memory T-cells, with the largest reductions in disease activity occurring in patients with the greatest reductions in memory T-cells (13).

1. Chamian, F., Novitskaya, I., Khatcherian, I., Gilleaudeau, P., Sullivan-Whalen, M., Lee, E., Krueger, J. *Therapeutic improvement induced by alefacept is linked to selective reduction of CD3+, CD8+ and CD103+ T cells from skin lesions of chronic plaque psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 1): Abst SP3-2.

2. Haney, J., McAllister, A. *Clinical efficacy of alefacept in patients with chronic plaque psoriasis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P603.

3. Vaishnaw, A., Lee, S. *Concomitant use of alefacept and immunosuppressants in patients with psoriasis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P620.

4. Lebwohl, M. *The effect of psoriasis and its treatments on circulating T-cell subsets: Results of alefacept studies*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst P27-59.

5. Christophers, E., Vaishnaw, A.K. *A broad spectrum of patients with psoriasis benefit from alefacept therapy*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst FC11-10.

6. Langley, R. *An improvement of 50% or more in Psoriasis Area Severity Index (PASI) represents substantial improvement for patients treated with alefacept*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst FC11-12.

7. Prinz, J.C., Ortonne, J.-P. *Clinical experience with alefacept shows durable improvements in psoriasis symptoms and quality of life*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst FC11-11.

8. Ortonne, J.-P., Khemis, A. *Combination therapy with alefacept plus narrowband ultraviolet B light for the treatment of psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst FC11-9.

9. Rizova, E., O'Gorman, J. *The efficacy and safety of repeated courses of alefacept*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 1): Abst PP1-32.

10. Krueger, G.G., Ellis, C.N. *Alefacept therapy produces remission for patients with chronic plaque psoriasis*. Br J Dermatol 2003, 148(4): 784.

11. Ortonne, J.-P. *Clinical response to alefacept: Results of a phase 3 study of intramuscular administration of alefacept in patients with chronic plaque psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 2): 12.

12. Lebwohl, M., Christophers, E., Langley, R., Ortonne, J.P., Roberts, J., Griffiths, C.E.M. *An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis*. Arch Dermatol 2003, 139(6): 719.

13. Ortonne, J.P., Lebwohl, M., Griffiths, C.E. *Alefacept-induced decreases in circulating blood lymphocyte counts correlate with clinical response in patients with chronic plaque psoriasis*. Eur J Dermatol 2003, 13(2): 117.

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

Additional References

Finlay, A.Y., Salek, M.S., Haney, J. *Intramuscular alefacept improves health-related quality of life in patients with chronic plaque psoriasis*. Dermatology 2003, 206(4): 307.

Frampton, J.E., Wagstaff, A.J. *Alefacept*. Am J Clin Dermatol 2003, 4(4): 277.

Gordon, K.B. et al. *Treatment of psoriasis with alefacept: Correlation of clinical improvement with reductions of memory T-cell counts*. Arch Dermatol 2003, 139(12): 1563.

Gordon, K.B. *Reductions in circulating memory T cells correlate with clinical improvement and prolonged responses to alefacept in psoriasis*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0337.

Gottlieb, A.B. et al. *CD4+ T-cell-directed antibody responses are maintained in patients with psoriasis receiving alefacept: Results of a randomized study*. J Am Acad Dermatol 2003, 49(5): 816.

Griffiths, C.E.M., Lebwohl, M., Lee, S., Rizova, E. *Concomitant use of alefacept and immunosuppressants in patients with psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 1): Abst PP1-11.

Koo, J.Y.M. *Combination therapy with alefacept plus broadband ultraviolet B light for treatment of psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst FC11-7.

Krueger, G.G., Callis, K.P. *Development and use of alefacept to treat psoriasis*. J Am Acad Dermatol 2003, 49(2, Part 2): S87.

Krueger, G.G. et al. *Repeated courses of IM alefacept in psoriasis: Rationale and design of an international study that mimics the clinical practice setting*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0339.

Lowe, N.J., González, J., Bagel, J., Caro, I., Ellis, C.N., Menter, A. *Repeat courses of intravenous alefacept in patients with chronic plaque psoriasis provide consistent safety and efficacy*. Int J Dermatol 2003, 42(3): 224.

Ortonne, J.-P. et al. *Alefacept plus ultraviolet B light as combination therapy for psoriasis*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0338.

Ortonne, J.-P., Khemis, A., Koo, J.Y.M. *Combination therapy with alefacept and ultraviolet B light for treatment of psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 1): Abst PP1-24.

Rizova, E., Freedman, D., Lee, S. *An international study of repeated courses of intramuscular alefacept in patients with psoriasis: Rationale and design of a study that mimics the clinical practice setting*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P616.

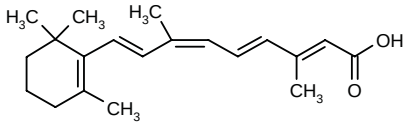
Rizova, E., O'Gorman, J. *Alefacept is efficacious for treatment of psoriasis regardless of response to prior therapy or disease severity: Pooled analyses of phase 3 trials*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0343.

van de Kerkhof, P., Vaishnaw, A., Kragballe, K., Ortonne, J.-P. *Alefacept is efficacious in a broad spectrum of patients with psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 1): Abst PP1-42.

Vigliani, G., Haney, J. *Alefacept is efficacious in a broad spectrum of patients with psoriasis, including those with severe disease*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P14.

Weinberg, J.M. *An overview of infliximab, etanercept, efalizumab, and alefacept as biologic therapy for psoriasis*. Clin Ther 2003, 25(10): 2487.

Alitretinoin



Alitretinoin (BAL-4079), a retinoid currently used topically in the treatment of Kaposi's sarcoma that binds to both intracellular retinoic acid receptors (RAR) and retinoid X receptors (RXR), modulates cell growth and differentiation. Once-daily oral alitretinoin is currently entering phase III clinical development at Basilea Pharmaceutica for the treatment of chronic hand dermatitis refractory to topical steroids.

Additional References

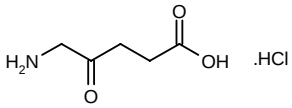
Larsen, F. et al. *BAL4079 (alitretinoin, 9-cis retinoic acid) is effective and well tolerated in the treatment of refractory chronic hand dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst FC17-5.

Allox™

IsoTis has signed an exclusive worldwide licensing agreement for Allox™, its lead cell-based product for the treatment of chronic skin wounds, with Healthpoint. Under the terms of the agreement, IsoTis will complete the ongoing European phase II clinical trial for Allox™ and file an IND application with the U.S. FDA. Healthpoint will be responsible for the clinical validation, market approval and commercialization of Allox™ in the U.S. and the rest of the world. In exhange, IsoTis will receive certain milestone payments and share a percentage of product income (1). Following its merger with GenSci OrthoBiologics to form IsoTis OrthoBiologics, the company established EpiSource as a potential spin-off company for the wound management portfolio, including Allox™.

1. *IsoTis signs licensing agreement for Allox*. DailyDrugNews.com (Daily Essentials) Sept 23, 2003.

Aminolevulinic Acid Hydrochloride



Photodynamic therapy (PDT) with Dusa's aminolevulinic acid hydrochloride (Levulan®) has been available for several years for the treatment of nonhyperkeratotic actinic keratoses of the face or scalp. Phase I/II studies have been completed at Dusa for the treatment of acne and investigator studies are under way for this indication. Independent investigator studies have also been conducted in other dermatological indications, including photodamaged skin, psoriasis, warts, onychomycosis, basal cell carcinoma and cutaneous T-cell lymphoma.

Patients with multiple actinic keratoses and photodamaged skin (n=64) were treated with either PDT with 20% topical aminolevulinic acid and visible blue light or vehicle. Cosmetic improvements were noted with aminolevulinic acid PDT. There were no significant adverse events with either treatment and aminolevulinic acid and blue light at 5 J and 10 J was equally effective (Table II) (1).

Female patients (n=2) with nevoid basal cell carcinoma syndrome and multiple superficial and small nodular basal cell carcinoma syndromes were treated with a 20% topical solution of aminolevulinic acid in a 1.5-ml applicator and a 417 nm blue light source. Aminolevulinic acid and blue light photodynamic therapy was well tolerated, treated all lesions with good cosmetic outcome and decreased the prominence of facial scarring in the more severely affected patients (Table II) (2).

1. Weinstein, G., Glazer, S., Taylor, R., Marcus, S. *A phase II light dose ranging study of photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA) and visible blue light in the treatment of multiple actinic keratoses (AKs) and photodamaged skin*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P533.

2. Itkin, A.M., Gilchrest, B.A. *Delta-aminolevulinic acid and blue light photodynamic therapy in treatment of multiple basal cell carcinomas in two patients with nevoid basal cell carcinoma syndrome*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P556.

Original monograph – Drugs Fut 1997, 22(1): 11.

AVAC™

AVAC™, a derivative of *Mycobacterium vaccae*, is the subject of a new randomized, placebo-controlled phase II trial for pediatric atopic dermatitis in New Zealand. The trial will enroll 120 children aged 5-16 years, who will be randomized to receive 3 injections of either AVAC™ or placebo at intervals of 2 weeks. The efficacy and safety of AVAC™ will be assessed and quality-of-life data will also be collected. Results are expected to be available at

Table II: Clinical studies of aminolevulinic acid hydrochloride (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Actinic keratosis	Randomized, single-blind, multicenter	Aminolevulinic acid hydrochloride 20% top. [14-18 h prior to light treatment at 5 J and 10 J] Vehicle	64	Photodynamic therapy using aminolevulinic acid hydrochloride and blue light 5 and 10 J were equally effective in the treatment of patients with actinic keratosis within a 25 cm^2 field of photodamaged skin	1
Carcinoma, basal cell	Open	Aminolevulinic acid hydrochloride, 20% solution top. in a 1.5-ml applicator and blue light 417 nm	2	Aminolevulinic acid hydrochloride and blue light photodynamic therapy was well tolerated, treated all lesions with good cosmetic outcome and decreased the prominence of facial scarring in the more severely affected patients with nevoid basal cell carcinoma and multiple superficial and small nodular basal cell carcinoma syndromes	2

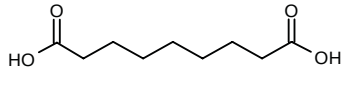
the end of 2004. SR Pharma and Genesis Research and Development are jointly developing AVAC™ for the treatment of atopic dermatitis. In a recent phase I safety trial in children, clinical improvement in atopic dermatitis was observed in the majority of the children, as measured by a standard scoring system for eczema (1).

1. *New Zealand phase II trial for AVAC in pediatric atopic dermatitis*. DailyDrugNews.com (Daily Essentials) Nov 19, 2003.

AVT-02

A decoy oligonucleotide-based drug from Avontec, AVT-02 has reached phase IIa clinical evaluation for the treatment of psoriasis. Decoy oligonucleotides are short double-stranded DNA molecules that imitate the DNA binding region of their transcription factors and neutralize them. This therapeutic approach is expected to be able to block disease-inducing genes, as well as unblock potentially protective genes.

Azelaic Acid



Schering AG's azelaic acid gel (Finacea™) received European approval at the end of last year for the topical treatment of papulopustular rosacea. Three multicenter, randomized, double-blind studies in 915 patients with moderate rosacea evaluated azelaic acid gel. Twice-daily application of the gel was significantly more effective than both its vehicle and the current gold standard metronidazole in reducing inflammatory lesion counts and erythema severity. Azelaic acid gel was initially approved in 2002 in the 15 E.U. countries for the relief of mild to moderate papulopustular acne of the facial area. It is marketed as Skinoren® in Germany, Poland, Switzerland, Finland and South Africa. In the U.S., Schering's Berlex subsidiary launched the drug in the first quarter of 2003 for the topical treatment of the inflammatory papules and pustules of mild to moderate rosacea. Berlex has a copromotion agreement with Allergan for the product in the U.S. (1, 2).

A total of 664 patients with moderate papulopustular rosacea were included in 2 identical phase III clinical trials and randomized to topically apply either azelaic acid 15% gel or vehicle on their lesions twice daily for 12 weeks. The drug was associated with a higher rate of therapeutic success (61-62% *vs*. 40-48%) as compared to vehicle, but had no effect on the telangiectasia symptoms. The static score for the Investigator's Global Assessment, which measures the combined severity of the primary symptoms of rosacea, significantly improved with the azelaic acid gel formulation compared to vehicle alone. At the end of the treatment period, azelaic acid gel was significantly better than placebo in reducing both the mean inflammatory lesion count and the severity of erythema. Azelaic acid gel was well tolerated, no serious adverse events being reported and most treatment-related adverse events consisting of mild or moderate sensory cutaneous symptoms (3-5). These results and those from the following studies are summarized in Table III.

A double-blind, randomized, parallel-group study in 26 patients with papulopustular rosacea assessed treatment with azelaic acid gel 15% administered twice daily for 12 weeks. The cosmetic acceptability of azelaic acid gel was high, being rated as good or very good in about 70% of the subjects (6).

A recent double-blind, randomized clinical trial compared the efficacy and safety of a 0.75% metronidazole gel and the 15% azelaic acid gel formulation in papulopustular (stage 2) rosacea. A total of 251 patients with 10-50 inflamed facial papules and/or pustules, persistent erythema and telangiectasia were randomized to apply the azelaic acid gel or the metronidazole gel topically to the entire face twice daily for 15 weeks. At the end of the

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

Indication	Design	Treatments	n	Conclusions	Ref.
Rosacea	Randomized, double-blind, multicenter	Azelaic acid 15% gel top. b.i.d. x 12 wks Placebo	664	Azelaic acid 15% gel was well tolerated and effective in improving the symptoms and reducing the severity of erythema in patients with moderate papulopustular rosacea	3-5
Rosacea	Randomized, double-blind	Azelaic acid 15% gel top. b.i.d. x 12 wks Placebo	26	Azelaic acid 15% gel was well tolerated and significantly better than placebo in improving the symptoms of moderate papulopustular rosacea	6
Rosacea	Randomized, double-blind, multicenter	Azelaic acid 15% gel top. b.i.d. x 15 wks Metronidazole 0.75% gel top. b.i.d. x 15 wks	251	The azelaic acid gel was more effective than the metronidazole gel in reducing the mean number of inflammatory lesions and the severity of erythema in patients with stage 2 rosacea. Both treatments were well tolerated and were not associated with systemic or serious adverse events	7

treatment, the mean number of inflammatory lesions decreased from 18.1 to 4.5 with the azelaic acid gel and from 19.4 to 7.6 with the metronidazole gel; the percent reduction was significantly greater with azelaic acid (72.7% *vs.* 55.8%). Significantly more patients had improvement in the severity of erythema with azelaic acid gel (56% *vs.* 42%), but neither gel had any effect on telangiectasia. The rates of success and overall improvement were, respectively, 69% and 48% with azelaic acid and 55% and 35% with metronidazole; these results were in accordance with the patient's subjective impression of overall improvement. No evidence of systemic or serious adverse events was found during the study. Both treatments were well tolerated and most adverse events were facial or involved cutaneous signs and symptoms (7).

1. *Finacea approved in E.U. as topical treatment of papulopustular rosacea*. DailyDrugNews.com (Daily Essentials) Dec 17, 2003.

2. *Launch date set for Finacea*. DailyDrugNews.com (Daily Essentials) March 24, 2003.

3. Thiboutot, D., Graupe, K., Thieroff-Ekerdt, R. *Twice-daily azelaic acid 15% gel is effective and well tolerated in treatment of moderate, papulopustular rosacea: Results of two phase 3 randomized, double-blind trials*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P80.

4. Thiboutot, D., Thieroff-Ekerdt, R. *A new static score to assess papulopustular (stage 2) rosacea: Experience from 2 large, vehicle-controlled phase 3 studies comparing a new azelaic acid 15% gel formulation to its vehicle*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P81.

5. Hebert, A.A. *Azelaic acid 15% gel reduces the intensity of erythema in patients with moderate, papulopustular facial rosacea: Data from two phase 3 trials*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P55.

6. Kaminester, L. *Two randomized, vehicle-controlled, double-blind trials of azelaic acid 15% gel in treatment of moderate, papulopustular rosacea: Individual experience from a participating center*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P59.

7. Elewski, B.E., Fleischer, A.B., Pariser, D.M. *A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: Results of a randomized trial*. Arch Dermatol 2003, 139(11): 1444.

Original monograph – Drugs Fut 1983, 8(1): 9.

Additional References

Draelos, Z.D. *Development of a new aqueous gel formulation of azelaic acid 15% as topical therapy for moderate, papulopustular rosacea*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0397.

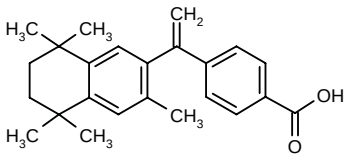
Elewski, B. *A comparison of topical azelaic acid 15% gel and metronidazole 0.75% gel in the treatment of papulopustular facial rosacea: Results of a 15-week, randomized, double-blind, multicenter study*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P50.

Elewski, B.E. *Azelaic acid 15% gel versus metronidazole 0,75% gel as topical therapy for papulopustular facial rosacea: Results of a 15-week randomized trial*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0388.

Hebert, A.A. *Efficacy and tolerability or azelaic acid 15% gel as topical therapy for moderate, papulopustular rosacea established in two phase 3 ransomized trials*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0394.

Thiboutot, D. et al. *Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: Results from two vehicle-controlled, randomized phase III studies*. J Am Acad Dermatol 2003, 48(6, Part 1): 836.

Bexarotene



Ligand's bexarotene (Targretin®) is a selective retinoid X receptor (RXR) agonist which is currently used for the treatment of cutaneous T-cell lymphoma (CTCL) as oral and topical formulations. Phase III trials are under way for oral drug in the treatment of non-small cell lung cancer, as well as phase II trials with the oral formulation for psoriasis and advanced breast cancer and with the gel formulation for psoriasis and hand dermatitis.

The potential use of bexarotene in the treatment of hand eczema was determined in an open-label phase I/II clinical trial. A total of 55 patients with chronic severe hand eczema were randomized to receive bexarotene gel alone (once to 3 times daily) or combined with either a medium-potency steroid (mometasone furoate b.i.d.) or a low-potency steroid (hydrocortisone b.i.d.). An interim analysis of the results obtained after topical administration for 10 weeks to the first 24 patients enrolled in the trial revealed that all treatments were effective in reducing the symptom scores of hand eczema. No significant differences were found between the efficacy scores of the treatments, suggesting that the steroids did not increase the effects induced by bexarotene in the treatment of hand eczema. The only adverse events reported were irritation and rash at the application site (Table IV) (1).

The combination of bexarotene and phototherapy has been suggested to be effective, safe and well tolerated in moderate to severe plaque psoriasis. Three patients received UVB twice weekly plus a daily bexarotene dose of 75 mg (later increased to 150 mg). The treatment significantly reduced the body surface area affected by the disease and improved the symptoms of psoriasis after 4 months, thereby allowing the administration of a lower phototherapy dose. Further clinical trials are needed to better determine the therapeutic benefits of this combination therapy in plaque psoriasis (2).

A phase II clinical trial assessed the benefits of topical bexarotene therapy in the management of parapsoriasis, a precursor stage of CTCL. A total of 6 patients were included in the trial and first received topical 1% bexarotene gel once daily for 2 weeks, followed by twice-daily application for 14 weeks. Five subjects completed the 16-week regimen, and all of them responded to the therapy, with 1 complete response and 4 partial responses. All patients also showed evidence of cutaneous toxicity, which consisted of erythema, scaling and pruritus, and dose reduction was required in 2 patients (Table IV) (3).

1. Stevens, V.J., Hanifin, J., Breneman, D., Sheth, P. *Topical bexarotene gel, an RXR-selective ligand, improves chronic severe hand eczema*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P23.

2. Moore, A.Y., Low, C. *Oral bexarotene and UVB phototherapy in the treatment of moderate-to-severe plaque psoriasis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P613.

3. Lessin, S.R., Steckel, S.D., Wu, H. *A phase II trial to evaluate the efficacy of topical 1% bexarotene (Targretin®) gel in patients with parapsoriasis (T(0) cutaneous T cell lymphoma)*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 1199.

Additional References

Sheth, P., Breneman, D., Stevens, V., Hanifin, J. *Severe hand dermatitis is responsive to topical bexarotene 1% gel*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0356.

Talpur, R., Duvic, M. *Bexarotene gel as adjuvant therapy for mycosis fungoides and lymphomatoid papulosis lesions refractory to oral bexarotene and/or denileukin diftitox*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P438.

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

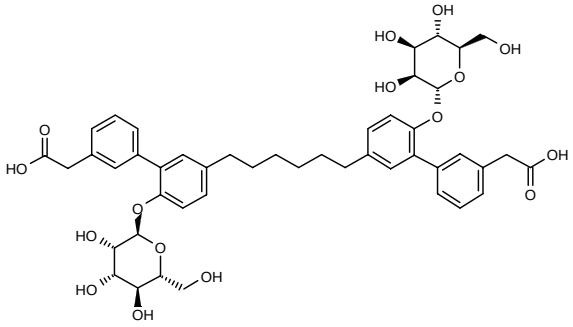
Indication	Design	Treatments	n	Conclusions	Ref.
Eczema	Open	Bexarotene top. o.d. [increased to t.i.d.] x 10 wks Bexarotene top. o.d. [increased to t.i.d.] + Mometasone furoate top. b.i.d. x 10 wks Bexarotene top. o.d. [increased to t.i.d.] + Hydrocortisone top. b.i.d. x 10 wks	24	Topical bexarotene was well tolerated and effective in improving the symptoms of chronic severe hand eczema	1
Parapsoriasis	Open	Bexarotene 1% gel top. o.d. x 2 wks → b.i.d. x 14 wks	6	Topical administration of bexarotene 1% gel for 16 weeks was well tolerated and induced complete or partial response in all patients with parapsoriasis, although 2 patients required dose reduction due to cutaneous toxicity	3

BI-ACNE

Vicuron Pharmaceuticals has completed a phase I trial of its topical antibiotic BI-ACNE (VIC-ACNE, formerly BI-K0376) for the treatment of acne. The semisynthetic compound has a novel mechanism of action and shows high selectivity against *Propionibacterium acnes*. The double-blind, randomized trial compared the safety of BI-ACNE 1.5% or 3% and gel alone applied twice daily to the face for 4 weeks in 75 subjects. No safety concerns were raised. In *in vitro* assays, BI-ACNE has shown excellent activity against a large number of *P. acnes* strains, including some that are resistant to currently used broad-spectrum antibiotics, such as clindamycin and erythromycin. Vicuron plans to license the compound out, as drugs for this indication are not central to the company's core focus (1).

1. *VIC-acne completes phase I safety study*. DailyDrugNews.com (Daily Essentials) June 25, 2003.

Bimosiamose



The small-molecule pan-selectin antagonist bimosiamose (TBC-1269) is being tested at Revotar Biopharmaceuticals, a majority-owned German affiliate of Encysive Pharmaceuticals, as a potential new treatment for psoriasis, atopic dermatitis and asthma in phase II trials. Two double-blind, placebo- and standard drug-controlled phase IIa trials of a new topical formulation of bimosiamose were recently commenced in psoriasis and atopic dermatitis (1-3).

Based on preclinical studies demonstrating that bimosiamose reduced the severity of psoriasis and prevented the appearance of psoriasis in symptomless skin in SCID mice, an initial open-label phase II clinical trial was conducted in which a daily dose of 600 mg was administered to 5 psoriatic patients. After 14 days of treatment, the patients showed significant improvement in their PASI scores; these effects were associated with reductions in epidermal thickness, CD3+ and CD4+ cell counts, P-selectin expression and the number of peripheral CD45RO+ T-cells. Bimosiamose was well tolerated (4).

1. *Texas Biotechnology renamed*. DailyDrugNews.com (Daily Essentials) May 21, 2003.

2. *Bimosiamose decreases LAR in asthmatics following allergen challenge*. DailyDrugNews.com (Daily Essentials) Aug 7, 2003.

3. *Topical bimosiamose studied in psoriasis and atopic dermatitis*. DailyDrugNews.com (Daily Essentials) Oct 14, 2003.

4. Friedrich, M., Wolff, G., Philipp, S. et al. *Bimosiamose, a pan-selectin antagonist improves disease manifestation both in human psoriatic skin SCID mice and psoriatic patients - Selectin antagonists as a new treatment strategy for inflammatory diseases*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0367.

CGC-1072

CGC-1072, or PsorBan®, is CellGate's topical ciclosporin conjugate ointment for the treatment of psoriasis. CellGate has chemically transformed ciclosporin to increase absorption into tissues and cells using its proprietary molecular transporter technologies. Although orally administered ciclosporin is known to be effective as a treatment for psoriasis, organ toxicity limits its systemic use, and the drug has shown poor absorption when applied topically. CellGate's PsorBan® product has been designed to leverage the drug's efficacy while reducing toxicities when applied locally at the site of disease, thereby creating a highly safe topical ointment suitable for direct application to the chronic plaques that characterize psoriasis. In phase I clinical studies in healthy volunteers, PsorBan® was shown to penetrate skin and retain biological activity. A multicenter phase IIb registration trial is currently under way.

A double-blind, placebo-controlled phase IIa clinical trial was conducted to determine the safety and efficacy of the ciclosporin prodrug CGC-1072 in mild to moderate plaque psoriasis. A total of 24 subjects were randomized to receive either placebo or topical CGC-1072 (0.4% or 4.0% ointment), self-applied to contralateral psoriatic plaques for 42 days. At the end of the treatment, the patients who received CGC-1072 showed improvement in psoriasis symptoms, erythema and induration. No ciclosporin was detected in blood and no serious adverse events were reported during the study. Six patients showed drug-related adverse events, but these were not the systemic adverse events usually associated with ciclosporin (1).

1. Levin, C., Fiorentino, D.F., Vosganian, G., Chon, S., Kimball, A.B. *The safety of topical cyclosporin A conjugate (CGC1072) in the treatment of mild to moderate psoriasis*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 1201.

Additional References

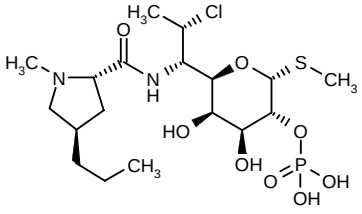
Fiorentino, D.F. et al. *A double-blind placebo-controlled randomized parallel dose comparison of topically applied cyclosporin A conjugate (CGC1072) versus vehicle control in psoriasis patients*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P590.

Chrysalin®

L-Alanyl-glycyl-L-tyrosyl-L-lysyl-L-prolyl-L-aspartyl-L-glutamyl-glycyl-L-lysyl-L-arginyl-glycyl-L-aspartyl-L-alanyl-L-cysteinyl-L-glutamyl-glycyl-L-aspartyl-L-seryl-glycyl-glycyl-L-prolyl-L-phenylalanyl-L-valine

Chrysalis BioTechnology's lead product Chrysalis® (TP-508) is currently in phase II trials for the treatment of chronic diabetic ulcers, as well as phase III trials for bone fracture healing and phase II evaluation for spinal fusion. Chrysalis obtained an exclusive license to this technology from the University of Texas Medical Branch and is collaborating with OrthoLogic on its development for use in bone fractures. The peptide stimulates healing of open dermal wounds and surgical incisions by stimulating the healing cascade through the thrombin receptor mechanism, activating the release of natural growth factors and accelerating wound repair. In addition to the clinical program in diabetic ulcers, the company has plans for clinical research in venous ulcers, infected wounds, burns and pressure sores, as well as acute wounds.

Clindamycin Phosphate



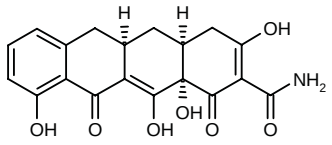
Connetics has two clindamycin-based products for acne in late-stage development: clindamycin phosphate foam 1% (Actiza™), a new drug formulation based on the company's VersaFoam™ delivery vehicle which was submitted to the FDA in December 2003, and a first-in-class combination gel formulation containing clindamycin phosphate 1% and tretinoin 0.025% (Velac®). In January, the company announced that it had completed enrollment in its 2 phase III clinical trials of Velac® Gel, with 2,218 acne patients enrolled at 37 centers. Connetics expects to submit the product for review by the FDA later this year (1).

1. *End of patient enrollment announced for two clinical trials with Velac® Gel*. DailyDrugNews.com (Daily Essentials) Jan 13, 2004.

CNTO-1275

CNTO-1275 is a fully human anti-IL-12 antibody designed by Medarex and being developed by Centocor (Johnson & Johnson). Phase II clinical trials are under way to evaluate its potential in the treatment of psoriasis and multiple sclerosis.

COL-3



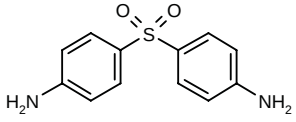
A nonantimicrobial tetracycline derivative based on CollaGenex's proprietary IMPACS™ (Inhibition of Multiple Proteases And CytokineS) technology, COL-3 is being developed as a potential new treatment for rosacea. COL-3 is a potent inhibitor of cytokines and proteases which may prove more effective than antibiotics in treating rosacea, while being devoid of the side effects of the latter and the risk of resistance development. The product is being tested in a double-blind, placebo-controlled phase II study in 30 patients with rosacea. COL-3 at higher doses (known as Metastat®) has also demonstrated potential for the treatment of HIV-related Kaposi's sarcoma and is being evaluated in phase II studies sponsored by the National Cancer Institute (NCI) (1-3). A phase I/II study in astrocytoma and gliobastoma, also sponsored by the NCI, is currently under way.

1. *New phase II study evaluates COL-3 in rosacea*. DailyDrugNews.com (Daily Essentials) July 29, 2003.

2. *CollaGenex reports Q3 R&D highlights*. CollaGenex Pharmaceuticals Press Release 2003, Oct 28.

3. *Recruitment completed in phase II trial of Metastat in Kaposi's sarcoma*. DailyDrugNews.com (Daily Essentials) April 2, 2003.

Dapsone



Atrix Laboratories' proprietary acne drug Atrisone™ (5% dapsone topical gel) has successfully completed 2 pivotal, double-blind, randomized, vehicle-controlled phase III efficacy studies. Over 3,000 patients were enrolled at more than 100 U.S. and Canadian sites. An NDA submission is anticipated for the topical gel in July 2004. Atrisone™ contains dapsone, an antibiotic with independent antiinflammatory activity, formulated in Atrix's SMP technology to allow for topical administration. Under a codevelopment agreement, Fujisawa has licensed the marketing rights to Atrisone™ (1-3).

Atrisone™ is in earlier stage clinical evaluation for the treatment of rosacea.

A treatment method for acne, including inflammatory (*e.g.*, lesions) and primary noninflammatory (*e.g.*, closed comedones) acne has been claimed, comprising the topical administration of a dermatological medicament containing dapsone in both a dissolved and microparticulate form, such as in a semisolid aqueous gel (4).

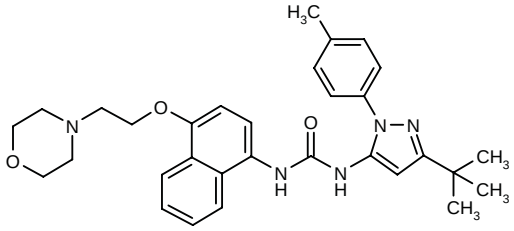
1. *Enrollment completed in Atrisone phase III studies*. DailyDrugNews.com (Daily Essentials) June 5, 2003.

2. *Atrisone completes pivotal phase III acne studies*. DailyDrugNews.com (Daily Essentials) Jan 8, 2004.

3. *Atrix Laboratories reports Q3 R&D highlights*. Atrix Laboratories Press Release 2003, Oct 30.

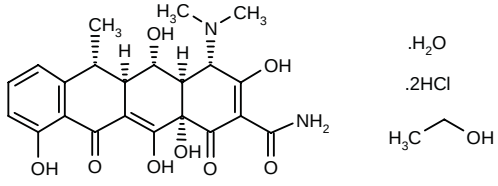
4. Osborne, D.W. (Atrix Laboratories, Inc.) *Topical dapsone for the treatment of acne*. WO 0372071, US 2003157036.

Doramapimod



Doramapimod (BIBR-796) is a potential new antipsoriatic agent discovered at Boehringer Ingelheim that inhibits an enzyme involved in the production of TNF-α and certain interleukins: p38 MAP (mitogen-activated protein) kinase. The compound has shown promise in phase II trials in patients with psoriasis.

Doxycycline Hyclate



CollaGenex is conducting phase III clinical trials with Periostat® (doxycycline hyclate, capsules 20 mg) for rosacea, as well as phase II trials for acne. Periostat® is already available for use as an adjunct to scaling and root planing for the treatment of adult periodontitis.

In mid-2003, the company reported the results of a double-blind, placebo-controlled phase II study of Periostat® combined with MetroLotion® (metronidazole 0.75% topical lotion) for the treatment of rosacea. The study, conducted at the University of Puerto Rico, randomized 40 patients to receive either MetroLotion® and Periostat® or MetroLotion® and placebo for 12 weeks. After week 12, the use of MetroLotion® was discontinued and patients were maintained on either Periostat® or placebo for an additional 4 weeks. Lesion counts, an assessment of erythema and overall clinical disease severity were obtained at baseline, 4, 8, 12 and 16 weeks. At all time points, patients receiving Periostat® had significantly fewer inflammatory lesions than those on placebo. At week 12, there was a 59% reduction in lesion count in the group receiving MetroLotion® and Periostat®, compared with a 34% reduction in the group receiving MetroLotion® and placebo, a highly clinically significant difference. In the Periostat® group, the global clinical severity score was also significantly improved, and there was a trend towards improvement in the erythema scores. Improvement was maintained in the patients who remained on Periostat® for a further 4 weeks, while the condition began to deteriorate in those on placebo (1).

Just recently, the company reported positive results from a phase III trial of Periostat® monotherapy in the treatment of rosacea. The largest clinical trial every conducted to evaluate a systemic therapy for rosacea (134 patients), the study involved administration of placebo or doxycycline hyclate tablets 20 mg b.i.d. for 16 weeks. Preliminary data analysis indicated that patients treated with Periostat® showed continuous improvement over the course of the study compared to those on placebo, with significantly greater reductions in the number of inflammatory lesions (papules and pustules). Overall clinical disease severity also declined significantly in patients on Periostat®, a greater number of patients on Periostat® showing complete clearing at 16 weeks, and a trend for greater improvement in erythema was also seen in the Periostat® group (2).

The potential use of subantimicrobial doses of doxycycline in moderate facial acne was recently investigated in a multicenter, double-blind, randomized phase II clinical trial that compared the effects of placebo and doxycycline (20 mg p.o. twice daily) on the number of skin lesions and the skin flora of 51 adult patients. After 6 months of treatment, patients receiving doxycycline showed greater reductions in the number of inflammatory lesions (50.1% *vs.* 30.2%) and comedones (53.6% *vs.* 10.6%) than those randomized to receive placebo. The evolution of clinician's global assessment and patient self-assessment scores during the trial also provided evidence of greater improvement in acne symptoms with doxycycline. The antibiotic was well tolerated and, when administered at a dose of 20 mg twice daily, it induced no changes in the composition or the resistance profile of the normal skin flora of the patients. Most adverse events reported were mild or moderate, and only 2 patients withdrew from the trial due to adverse events (gastric ulcer and vaginitis) (3).

1. *Positive outcome for phase II study of Periostat as adjunctive treatment for rosacea*. DailyDrugNews.com (Daily Essentials) July 3, 2003.

2. *CollaGenex Pharmaceuticals reports positive outcome of phase 3 study evaluating Periostat as a treatment for rosacea.* CollaGenex Pharmaceuticals Press Release 2004, Feb 17.

3. Skidmore, R., Kovach, R., Walker, C., Thomas, J., Bradshaw, M., Leyden, J., Powala, C., Ashley, R. *Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne*. Arch Dermatol 2003, 139(4): 459.

Efalizumab

Last October, the FDA approved efalizumab (Raptiva™) for the treatment of chronic, moderate to severe plaque psoriasis in adults aged 18 or older who are candidates for systemic therapy or phototherapy. Efalizumab is the first biologic therapy designed to provide continuous control of chronic, moderate to severe plaque psoriasis and can be self-administered by patients as a single once-weekly s.c. injection. The humanized therapeutic antibody is designed to selectively and reversibly block the activation, reactivation and trafficking of T-cells that lead to the development of psoriasis symptoms. The approval was based on a BLA submission including data on more than 2,700 patients treated with efalizumab in 13 controlled and uncontrolled clinical trials, including results from 4 randomized, placebo-controlled phase III studies in chronic, moderate to severe plaque psoriasis. The primary efficacy endpoint was a 75% improvement in the PASI score. Secondary endpoints included physician assessment and patient-reported outcomes. Efalizumab demonstrated efficacy and maintained response in most patients after 12 weeks of treatment. Sustained responses were observed in uncontrolled open-label extension treatment trials when patients received efalizumab without interruption for 24 weeks or up to 2 years. The pooled results showed that efalizumab was well tolerated; acute flu-like symptoms only appeared after the first or second dose, while the safety profile after the third dose was similar to that of placebo. Long-term administration was not associated with a higher risk of end-organ damage, infection or malignancies. Genentech and Xoma are collaborating on the development of efalizumab in the U.S. Serono, Genentech's marketing partner outside the U.S. and Japan, has submitted the product for approval for psoriasis in the E.U., Canada, Switzerland, Australia and New Zealand (1-7).

The correlation of the pharmacokinetic and pharmacodynamic profiles of efalizumab with the clinical efficacy of the drug has been reported. The more rapid clearance of efalizumab at concentrations below 10 μg/ml indicates a receptor-mediated mechanism which is saturable at higher concentrations. During efalizumab treatment, a 2-fold increase in circulating lymphocyte counts has been observed, although generally maintained within normal limits. This increase is probably related to altered trafficking patterns. A relationship was demonstrated among efalizumab plasma levels, receptor saturation and down-modulation, and histological changes, such as the decrease in the number of epidermal and dermal T-cells in psoriatic plaques observed with efalizumab treatment. The histological changes were also associated with a significant decrease in PASI and Physician Global Assessment of change assessments (8).

The open-label ACD2243g study assessed the efficacy and safety of efalizumab in 339 patients with moderate to severe psoriasis. After 12 weeks of treatment with a weekly dose of 2 mg/kg, the percentage of patients showing at least 75% and at least 50% improvement in the PASI score was 41.0% and 81.1%, respectively. Over 90% of the subjects entered the maintenance phase of treatment, where they received weekly injections of 1 mg/kg efalizumab, which could be increased to 2 mg/kg if relapse occurred. At the end of the study, 55.9% of the patients who received efalizumab continuously for 21 months improved their baseline PASI by at least 75%. The percentage of patients with PASI improvements of 90% or more increased from 13% after 3 months to 30% at the end of the maintenance phase. Efalizumab was well tolerated, with no evidence of increased end-organ toxicity or malignancy upon long-term treatment, in contrast to available systemic therapies for psoriasis. The most common adverse events associated with efalizumab were headache, nonspecific infections, chills, pain, nausea, asthenia and fever (9-11). The results from this and the following studies are summarized in Table V.

A total of 1,651 patients with moderate to severe plaque psoriasis were enrolled in 3 double-blind, randomized phase III clinical trials and received placebo or efalizumab (1 or 2 mg/kg s.c. once weekly) for 12 weeks. The percentage of patients who achieved at least a 75% improvement in the PASI score was 28% with efalizumab and 4% with placebo. The rapid onset of clinical benefit with efalizumab was demonstrated in these trials, with significant improvement in PASI score in patients treated with efalizumab compared to placebo by 2 weeks. Significant improvements compared to placebo were also observed in the Dermatology Life Quality Index, the Itching Scale score and the Psoriasis Symptom Assessment (PSA) Frequency and Severity scores of the patients, indicating improvement in the quality of life, functional status and well-being of patients treated with efalizumab. Most drug-related adverse events were mild or moderate, and the most common were headache, nonspecific infection, nausea, chills, pain, asthenia, myalgia, pharyngitis, diarrhea, accidental injury and rhinitis (12-16).

The safety and efficacy of efalizumab were evaluated in a randomized, double-blind phase III clinical trial in 597 patients with moderate to severe plaque psoriasis. Patients received efalizumab (1 or 2 mg/kg/week s.c.) or placebo for 12 weeks. Subjects who had received active treatment were rerandomized at 12 weeks according to their response and received a further 12 weeks' treatment

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

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Open	Efalizumab, 2 mg/kg s.c. 1x/wk x 12 wks → 1 mg/kg [increased to 2 mg/kg if relapse] s.c. 1x/wk x 18 mos	339	The long-term administration of efalizumab was effective in maintaining symptom improvements in patients with moderate to severe plaque psoriasis, without increasing the incidence of serious adverse events, adverse events leading to withdrawal, infection-related events or malignancies	9-11
Psoriasis	Randomized, double-blind, multicenter, pooled/meta-analysis	Efalizumab, 1 mg/kg s.c. 1x/wk x 12 wks Efalizumab, 2 mg/kg s.c. 1x/wk x 12 wks Placebo	1651	Efalizumab was well tolerated and effective in improving the signs and symptoms of moderate to severe plaque psoriasis. Compared with placebo, efalizumab improved quality of life, physical symptoms, functional status, relief from itch and social well-being	12-16
Psoriasis	Randomized, double-blind, multicenter	Efalizumab, 1 mg/kg s.c. 1x/wk x 12 wks → [according to response] 2 mg/kg s.c. 1 x/15 d, 2 mg/kg s.c. 1x/wk or 4 mg/kg s.c. 1x/wk x 12 wks Efalizumab, 2 mg/kg s.c. 1x/wk x 12 wks → [according to response] 2 mg/kg s.c. x 1/15 d, 2 mg/kg s.c. 1x/wk or 4 mg/kg s.c. 1x/wk x 12 wks Placebo	597	After the first 12 weeks of treatment, efalizumab was significantly more effective than placebo in improving the PASI and health-related quality-of-life scores in patients with moderate to severe plaque psoriasis. The second 12-week treatment cycle with efalizumab improved or maintained the beneficial effects on the quality of life. The drug was well tolerated, and most adverse events were mild or moderate	17, 18
Psoriasis	Open	Efalizumab, 1 mg/kg s.c. x 12 wks Efalizumab, 2 mg/kg s.c. x 12 wks	365	Satisfaction with the efficacy and convenience of efalizumab treatment was high among psoriasis patients	19
Psoriasis	Randomized, double-blind, multicenter	Efalizumab, 1 mg/kg s.c. 1x/wk x 12 wks Placebo	556	Efalizumab significantly improved signs and symptoms of moderate to severe plaque psoriasis as well as dermatology-specific patient-reported health-related quality of life	20
Psoriasis	Open	Efalizumab, 1.0 mg/kg s.c. 1x/wk x 12 wks Efalizumab, 2.0 mg/kg s.c. 1x/wk x 12 wks	340	The administration of a second treatment course of efalizumab was well tolerated and improved the symptoms of psoriasis	21

(efalizumab 2 mg/kg every other week, 2 mg/kg every week, 4 mg/kg every week or placebo). All subjects then entered a nontreatment follow-up phase. At week 12, significantly more patients in both efalizumab groups had improvement of 50% or more and 75% or more in their PASI compared to placebo. Significant differences between the treatment groups were evident within 4 weeks of treatment initiation. After 12 weeks, patients treated with efalizumab also had a significantly greater improvement in Dermatology Life Quality Index, Psoriasis Symptom Assessment (PSA) Frequency and Severity scales and the Itching Scale compared to placebo. Patient-reported measures and physician-assessed PASI were positively correlated during both treatment and retreatment periods. Efalizumab therapy for a further 12-week period resulted in continued benefits and improved responses in many subjects. There was a gradual loss of clinical benefit in the nontreatment phase, and the authors concluded that control of psoriasis might be best achieved by continuous administration of efalizumab. The therapy was generally well tolerated (17, 18).

Weekly s.c. treatment with efalizumab 1 or 2 mg/kg, which could be self-injected, was given to 365 patients with moderate to severe plaque psoriasis who had completed earlier trials with the agent. After 12 weeks of therapy, most patients (76%) were satisfied with the efficacy of the treatment, and most (80%) considered it more convenient than other therapies (19).

The multicenter phase III ACD2390g study randomized 556 patients with moderate to severe psoriasis to receive either placebo or s.c. efalizumab (1.0 mg/kg) once weekly for 12 weeks. The drug was significantly better than placebo in reducing the severity of the itch and symptoms associated with psoriasis and therefore improving the quality of life of the patients (20).

An open-label study determined the safety of a second 12-week course of efalizumab (1.0 or 2.0 mg/kg s.c. once weekly) in 340 psoriatic patients who had been randomized to receive the drug in previous phase I-III clinical trials. At the end of the treatment, 56.8% and 25.6% of the patients reported at least 50% and at least 75% improvement in their PASI, respectively. Efalizumab was well tolerated and was associated with a high level of satisfaction and comfort among the patients (21).

1. *Raptiva rheumatoid arthritis trial discontinued*. DailyDrugNews.com (Daily Essentials) May 14, 2003.

2. *FDA advisory committee sets review date for Raptiva*. DailyDrugNews.com (Daily Essentials) Aug 5, 2003.

3. *Raptiva approved for chronic, moderate to severe plaque psoriasis*. DailyDrugNews.com (Daily Essentials) Oct 30, 2003.

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

5. *Raptiva recommended for approval by advisory committee*. DailyDrugNews.com (Daily Essentials) Sept 15, 2003.

6. Leonardi, C., Goffe, B., Sobell, J., Caro, I. *The safety of efalizumab in patients with moderate to severe plaque psoriasis: Summary of clinical trial experience*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P613.

7. Rosoph, L. *Safety of efalizumab, a humanized monoclonal antibody, in patients with moderate to severe plaque psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst P27-60.

8. Gilbert, M., Shear, N.H. *Pharmacokinetics and pharmacodynamics of efalizumab in the treatment of plaque-type psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst P27-57.

9. Gottlieb, A.B., Blacker, K., Duvic, M., Leonardi, C.L. *Efficacy and safety of efalizumab (anti-CD11a) long-term treatment: Preliminary findings from an open-label trial*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P11.

10. Gottlieb, A., Gordon, K., Caro, I., Leonardi, C. *Long-term efalizumab therapy safely maintains Psoriasis Area and Severity Index improvement: Preliminary results from an open-label trial*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P611.

11. Gilbert, M., Lynde, C.W. *The benefits of continuous efalizumab therapy in patients with moderate to severe plaque-type psoriasis: Preliminary results from an open-label trial*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst P27-58.

12. Ouellet, J.P., Toth, D., Gratton, D. *Efalizumab provides rapid onset of clinical benefit in patients with moderate to severe plaque psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst P27-37.

13. Langley, R.G.B. *The efficacy and safety of efalizumab for patients with moderate to severe plaque psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P27-40.

14. Stone, S., Papp, K., Caro, I., Bresnahan, B. *Interpretation of positive patient response to efalizumab for the treatment of moderate to severe plaque psoriasis*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P610.

15. Menter, A., Hamilton, T., Caro, I., Chen-Rundle, A. *Impact of efalizumab on patient-reported outcomes in patients with moderate to severe plaque psoriasis: Pooled results from three randomized phase III trials*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P608.

16. Gordon, K., Pariser, D., Langley, R., Caro, I. *Efficacy and safety of efalizumab in a large cohort of patients with moderate to severe plaque psoriasis: Pooled results from randomized phase III trials*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P4.

17. Lebwohl, M., Tyring, S.K., Hamilton, T.K. et al. *A novel targeted T-cell modulator, efalizumab, for plaque psoriasis*. New Engl J Med 2003, 349(21): 2004.

18. Carey, W., Gulliver, W.P. *Efalizumab therapy improves and sustains health-related quality of life in patients with moderate to severe plaque psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst P27-38.

19. Papp, K., Bissonnette, R. *Patients report high level of satisfaction with efalizumab therapy*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P27-39.

20. Feldman, S.R., Siegfried, E.C., Langley, R., Koo, J.Y. *Effects of efalizumab (anti-CD11a) on patient-reported outcomes in subjects with moderate to severe plaque psoriasis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P588.

21. Papp, K.A., Miller, B., Lynde, C., Leonardi, C.L. *Efalizumab (anti-CD11a) retreatment: Final results from an open-label study in psoriasis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P614.

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

Additional References

Gordon, K.B. et al. *Efalizumab for patients with moderate to severe plaque psoriasis. A randomized controlled trial*. JAMA - J Am Med Assoc 2003, 290(23): 3073.

Gordon, K.B., Trying, S., Hamilton, T., Lebwohl, M. *Examining duration of response and relapse during treatment with efalizumab*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P594.

Gottlieb, A.B. et al. *Efficacy, safety, and pharmacokinetic outcomes observed in subjects with plaque psoriasis during long-term efalizumab therapy: Results from an open-label trial*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 1247.

Gottlieb, A.B., Miller, B., Lowe, N. et al. *Subcutaneously administered efalizumab (anti-CD11a) improves signs and symptoms of moderate to severe plaque psoriasis*. J Cutan Med Surg 2003, 7(3): 198.

Gulliver, W. *Efalizumab - An innovative biological that combines safety and efficacy*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst SAT21-2.

Hamilton, T., Powers, J., Carey, W., Menter, A. *Efficacy and safety of efalizumab (anti-CD11a) in subjects with moderate to severe plaque psoriasis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P602.

Kuebler, P., Joshi, A., Mortensen, D., Krueger, J., Walicke, P., Dummer, W., Gourlay, S. *Chronic treatment with efalizumab does not deplete lymphocytes as seen in PK/PD study ACD2142G*. Clin Pharmacol Ther 2003, 73(2): Abst PII-91.

Leonardi, C. et al. *The efficacy, safety, pharmacokinetics, and pharmacodynamics of efalizumab in patients with plaque psoriasis: Results of phase III trials*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 1246.

Leonardi, C. *Efalizumab - Now a long-term treatment solution*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst SAT21-5.

Leonardi, C.L. *Efalizumab: An overview*. J Am Acad Dermatol 2003, 49(2, Part 2): S98.

Menter, A. et al. *Effects of efalizumab (anti-CD11a) on pruritus in subjects with moderate to severe plaque psoriasis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P612.

Mortensen, D. et al. *The pharmacokinetics and pharmacodynamics of efalizumab following 12 weeks of subcutaneous treatment in subjects with moderate to severe plaque psoriasis in a phase I, open-label, multi-center study*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0379.

Sterry, W. *Psoriasis - Impact on QoL - Efalizumab shows positive outcomes*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst SAT21-4.

Sun, Y., Lu, J., Amita, J., Compton, P., Bruno, R.A. *Population pharmacokinetics of efalizumab (humanized monoclonal anti-CD11a antibody) following weekly dosing in psoriasis patients*. Clin Pharmacol Ther 2003, 73(2): Abst PIII-90.

Vugmeyster, Y. et al. *Efalizumab modulates an array of adhesion-related and activation-controlling surface proteins on T lymphocytes and inhibits anti-CD3-induced T cell activation in adults with moderate to severe psoriasis*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0047.

Weinberg, J.M. *An overview of infliximab, etanercept, efalizumab, and alefacept as biologic therapy for psoriasis*. Clin Ther 2003, 25(10): 2487.

E-Matrix™

E-Matrix™ (Encelle) is an injectable copolymer of a high-molecular-weight protein and a high-molecular-weight carbohydrate designed to mimic early fetal mesenchymal connective tissue. The bioactive film stimulates fetal-like wound healing, resulting in rapid, nearly scarless healing of chronic recalcitrant ulcers. It is hypothesized that E-Matrix™ activates this process by altering gene expression in appropriate host target cells.

The National Institutes of Health (NIH) has granted Encelle a 3-year USD 1.7 million grant to accelerate development of E-Matrix™ for the treatment of diabetic foot wounds. The grant will help Encelle to advance E-Matrix™ into clinical development, commercial-scale production and studies on its molecular mechanism of action. A multicenter, controlled pilot clinical study of E-Matrix™ for the treatment of diabetic foot ulcers is under way at U.S. centers. E-Matrix™ is being compared to standard wound care in 60 patients with chronic ulcers. The study is being conducted in collaboration with Smith & Nephew, which holds worldwide rights to the polymer for cutaneous wounds (1).

1. *NIH grant supports development of E-Matrix for diabetic foot ulcers.* DailyDrugNews.com (Daily Essentials) May 28, 2003.

Etanercept

The first therapy targeting TNF-α, the major inflammatory cytokine in psoriasis, has been submitted to the FDA for review as a treatment for moderate and severe plaque psoriasis. A supplemental BLA was filed last summer by Amgen and Wyeth Pharmaceuticals for etanercept (Enbrel®) based on data from pivotal trials in almost 1,200 patients, results of which were reported in March 2003 at the American Academy of Dermatology meeting and in June 2003 at the International Psoriasis Symposium. Etanercept is a fully human anti-TNF receptor that acts by binding TNF and rendering the bound TNF biologically inactive, resulting in a significant reduction in inflammatory activity. The product is already approved for rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Etanercept is marketed outside the U.S. by other Wyeth affiliates (1-8).

Significant and rapid improvement in symptoms was reported in a phase III study of etanercept in patients with moderate to severe plaque psoriasis. In the global, double-blind, placebo-controlled study, 583 patients were randomized to receive 25 or 50 mg of etanercept twice weekly or placebo. The primary endpoint was the proportion of patients achieving a 75% or greater improvement in the PASI score after 12 weeks of treatment. This was achieved by 49% of the patients treated with 50 mg of etanercept and 34% of patients treated with 25 mg of etanercept, compared with only 3% of patients receiving placebo. Using the Dermatology Life Quality Index, patients treated with etanercept 50 mg reported 71% improvement after 12 weeks, and those receiving a dose of 25 mg reported 66% improvement. Improvement was experienced after just 2 weeks of treatment in both groups (9).

The efficacy and safety of etanercept were evaluated in a double-blind phase III clinical trial in 672 patients with moderate to severe plaque psoriasis. Patients were randomized to receive etanercept at doses of 25 mg s.c. once weekly, 25 mg s.c. twice weekly or 50 mg s.c. twice weekly, or placebo. Treatment was continued for 24 weeks, and patients assigned to placebo were switched to etanercept 25 mg twice weekly from weeks 12 to 24. After 12 weeks, there was an improvement of at least 75% in the PASI score in significantly more patients in all etanercept groups than in the placebo group (14%, 34% and 49%, respectively, of patients in the increasing etanercept dose groups *vs*. 4% of patients in the placebo

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

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Randomized, double-blind, multicenter	Etanercept, 25 mg s.c. 1x/wk x 24 wks Etanercept, 25 mg s.c. 2x/wk x 24 wks Etanercept, 50 mg s.c. 2x/wk x 24 wks Placebo x 12 wks → Etanercept, 25 mg s.c. 2x/wk x 12 wks	672	Subcutaneous etanercept was well tolerated and produced dose-dependent improvements in symptom scores and quality of life in patients with stable plaque psoriasis	10
Arthritis, psoriatic, Psoriasis	Open	Etanercept x 64 wks [max. 97 wks] Placebo x 27 wks → Etanercept	168	Etanercept for up to 97 wks was found to be well tolerated and effective in reducing the clinical signs and symptoms in patients with psoriatic arthritis and psoriasis	11

group). There were further improvements after 24 weeks. In patients who switched from placebo at 12 weeks, 33% achieved an improvement in PASI of at least 75% at week 24. Corresponding improvements were observed in the physician's global assessments and the quality-of-life measures. Etanercept was well tolerated (Table VI) (10).

Patients with psoriatic arthritis and psoriasis (n=168) were treated with etanercept for a maximum of 97 weeks or placebo followed by etanercept after 27 weeks in open-label extension trial. Etanercept for up to 97 weeks was found to be well tolerated and effective in reducing clinical signs and symptoms. Extended exposure to etanercept did not lead to an increase in serious adverse events or infections (Table VI) (11).

1. *Amgen/Wyeth seek approval for fifth indication for anti-TNF therapy*. DailyDrugNews.com (Daily Essentials) July 9, 2003.

2. *Enbrel recommended by FDA panel to treat ankylosing spondylitis*. DailyDrugNews.com (Daily Essentials) June 30, 2003.

3. *Enbrel becomes the first FDA-approved biologic for ankylosing spondylitis*. DailyDrugNews.com (Daily Essentials) July 28, 2003.

4. *Enbrel approved for inhibition of bone and joint damage in psoriatic arthritis patients*. DailyDrugNews.com (Daily Essentials) Aug 28, 2003.

5. *Enbrel receives E.U. approval for treatment of ankylosing spondylitis*. DailyDrugNews.com (Daily Essentials) Jan 22, 2004.

6. *Once-weekly Enbrel approved*. DailyDrugNews.com (Daily Essentials) Oct 23, 2003.

7. *Enbrel approved to improve physical function in RA patients*. DailyDrugNews.com (Daily Essentials) Aug 5, 2003.

8. *Second phase of landmark rheumatoid arthritis study program enrolls 5,000 patients*. DailyDrugNews.com (Daily Essentials) July 10, 2003.

9. *Enbrel improves plaque psoriasis symptoms in phase III study*. DailyDrugNews.com (Daily Essentials) June 27, 2003.

10. Leonardi, C.L., Powers, J.L., Matheson, R.T., Goffe, B.S., Zitnik, R., Wang, A., Gottlieb, A.B. *Etanercept as monotherapy in patients with psoriasis*. New Engl J Med 2003, 349(21): 2014.

11. Mease, P.J., Ruderman, E.M., Kivitz, A.J., Burch, F.X., Siegel, E.L., Cohen, S.B., Ritchlin, C., Tsuji, W., Burge, D.J. *Etanercept (Enbrel) in patients with psoriatic arthritis and psoriasis: Continued observations*. Annu Eur Congr Rheumatol (EULAR) (June 18-21, Lisbon) 2003, Abst FRI0180.

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

Additional References

Caro, I. et al. *Effects of etanercept therapy on the health-related quality of life of subjects with moderate to severe psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst FC12-1.

Caro, I. et al. *Efficacy and safety of Enbrel® (etanercept) in patients with psoriasis: Results of a 24-week US phase III study*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst FC12-2.

Gottlieb, A.B. et al. *A randomized trial of etanercept as monotherapy for psoriasis*. Arch Dermatol 2003, 139(12): 1627.

Gottlieb, A.B., Feng, A., Zitnik, R. *Prolonged response durability following Enbrel® (etanercept) monotherapy*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0406.

Leonardi, C., Gottlieb, A., Zitnik, R. *Efficacy and safety of Enbrel® (etanercept) in patients with psoriasis: Results of a phase III study*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0409.

Mease, P.J., Ruderman, E.M., Kivitz, A.J., Burch, F.X., Siegel, E.L., Cohen, S.B., Ritchlin, C.T., Tsuji, W.H., Burge, D.J. *Continued efficacy and safety of etanercept (Enbrel®) in patients with psoriatic arthritis and psoriasis*. 67th Annu Meet Am Coll Rheumatol (Oct 23-28, Orlando) 2003, Abst 343.

Nayak, A.S., Zitnik, R. *Enbrel (etanercept) monotherapy in patients with psoriasis: Clinical and pathologic improvements*. J Allergy Clin Immunol 2003, 111(2, Part 2): Abst 819.

Wanke, L.A. et al. *Cost efficacy comparison of biologics in the treatment of psoriasis*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P699.

Fibrostat®

Fibrostat® is a late-stage product in development at Procyon for the management and prevention of excessive scar formation (hypertrophic scarring) following dermal insult (surgery, grafting, trauma, burns, *etc.*). Fibrostat® appears to regulate collagen production by inhibiting tissue transglutaminase.

The product (0.8% cream) is being tested for safety and efficacy in a phase IIb trial for the treatment of hypertrophic scars. The placebo-controlled, double-blind, randomized study will enroll 200 patients at 7 centers in Canada and the U.S. A 4-week run-in period aims to minimize the placebo effect often seen in vehicle cream-controlled trials due to occlusion and hydration. Treatment will last for 8 weeks. Results are expected by July 2004. Marketing rights to Fibrostat® are licensed to Biovail in North America (1).

1. *Fibrostat phase IIb trial cleared to commence*. DailyDrugNews.com (Daily Essentials) June 16, 2003.

Glucoprime™

A phase II trial of the novel skin ulcer repair compound Glucoprime™ is being conducted at 3 Australian centers in Sydney and will enroll 60 patients. Glucoprime™ is a carbohydrate-based drug derived from Novogen's glucan technology and designed to stimulate wound healing in skin ulcers in which the normal healing process is delayed. Novogen's glucan technology is licensed to the company's subsidiary Glycotex, which is conducting the clinical development. Novogen holds patents covering the use of Glucoprime™ for the treatment of vascular ulcers in the U.S., the U.K. and Australia, and has patent applications pending in other major territories. In two phase I studies, Glucoprime™ showed the ability to potently and safely promote healing in patients with venous stasis ulcers (1). Glucoprime™ acts by stimulating macrophages, cells which are vital to the healing process, attracting them to the wound and activating them to promote events leading to wound closure.

1. *Phase II testing commences for Glucoprime*. DailyDrugNews.com (Daily Essentials) May 14, 2003.

HB-64

HB-64 is one of Helix BioMedix's proprietary peptides and is under early clinical evaluation for use in acne patients. The company plans to license out its peptides for marketing and is actively engaged in licensing discussions.

In a preliminary study in 20 subjects with mild to moderate acne, HB-64 was applied as a gel solution (0.1%) to affected areas of the face twice daily for 12 weeks. As assessed by physicians, 75% of the participants showed clinical improvement; 85% of the subjects reported an improvement in their complexion and 90% indicated that the peptide gel was at least as effective as other acne products. No irritation or sensitization was seen and none of the subjects withdrew from the study due to treatment-related effects (1). In a follow-up study in 27 subjects who used the peptide gel twice daily for 12 weeks at one-tenth the dose used in the earlier trial, 78% of the participants indicated that the treatment improved their complexion and 96% indicated that it was at least as effective as other previously used acne products (2).

1. *Helix BioMedix peptide studied in acne patients.* Helix BioMedix Press Release 2003, Sept 8.

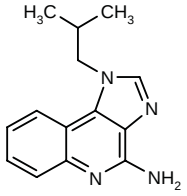
2. *Helix BioMedix skin care products advance*. Helix BioMedix Press Release 2003, Nov 10.

IC-747

The former Biogen, now Biogen Idec, concluded its collaboration with Icos for the development of leukocyte function-associated antigen-1 (LFA-1) antagonists last summer. As part of the collaboration, the companies were studying IC-747, an orally active LFA-1 antagonist designed to interfere with T-cell activation and leukocyte trafficking by inhibiting the binding of LFA-1 to its ligand. IC-747 was being studied for the treatment of inflammatory conditions and had completed a phase IIa study in psoriasis. However, results from the 28-day exploratory study showed that the treatment was safe but not sufficiently effective to warrant further development (1).

1. *Biogen/Icos LFA-1 collaboration is concluded.* DailyDrugNews.com (Daily Essentials) 2003, June 11.

Imiquimod



3M Pharmaceuticals announced in early March 2004 that the FDA had approved imiquimod (Aldara™, 5% cream) as the first immune response modifier (IRM) for the treatment of actinic keratosis. The sNDA submitted by the company was based on results from 2 double-blind, randomized, placebo-controlled trials involving 435 patients with multiple actinic keratoses. Patients were treated with imiquimod or placebo cream twice a week for 16 weeks. At 8 weeks posttreatment, half of the imiquimod-treated patients had at least an 83% reduction in the number of actinic keratosis lesions counted at baseline, compared to 0% in the placebo group. 3M originally launched imiquimod in 1997 for the treatment of external genital and perianal warts, and it is also under review at the FDA for the treatment of superficial basal cell carcinoma (1-3).

1. *3M submits Aldara sNDA for actinic keratosis*. DailyDrugNews.com (Daily Essentials) May 14, 2003.

2. *3M Pharmaceuticals obtains FDA approval for first immune response modifier to treat actinic keratosis.* 3M Pharmaceuticals Press Release 2004, March 3.

3. *3M submits sNDA for Aldara in superficial basal cell carcinoma*. DailyDrugNews.com (Daily Essentials) June 13, 2003.

Original monograph – Drugs Fut 1989, 14(9): 870.

Additional References

Berman, B., Jacob, S., Vincek, V., Nassiri, M. *Topical application of imiquimod 5% cream to keloids alters gene expression of markers of apoptosis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P294.

Berman, B., Villa, A. *Imiquimod 5% cream for keloid management*. Dermatol Surg 2003, 29(10): 1050.

Bianchi, L. et al. *Actinic keratosis treated with an immune response modifier: A case report of six patients*. Clin Exp Dermatol 2003, 28(Suppl. 1): 39.

Del Rosso, J.Q., Berman, B. *The use of topical imiquimod 5% cream for actinic keratoses: Results from private practice experience with focus on optimal application regimens*. 9th World Congr Cancer Skin (May 7-10, Seville) 2003, Abst P036.

Del Rosso, J.Q. *The use of topical 5% imiquimod 5% cream for actinic keratosis: Results from private practice experience with focus on optimal application regimens*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P305.

Mandekou-Lefaki, I. et al. *Successful treatment of seborrheic keratosis with imiquimod cream 5%*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst P5-25.

Peres, K. et al. *Successful treatment of keratoacanthoma and actinic keratoses with imiquimod 5% cream*. Eur J Dermatol 2003, 13(4): 413.

Popova, I. *Imiquimod - Treatment of atypical actinic keratoses localized on the lower lip*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P25-32.

Salasche, S., Shumack, S. *A review of imiquimod 5% cream for the treatment of various dermatological conditions*. Clin Exp Dermatol 2003, 28(Suppl. 1): 1.

Sierra, X. *Efficacy of imiquimod 5% cream for the treatment of actinic keratosis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P25-52.

Sotiriadis, D. et al. *The effect of imiquimod 5% cream in the treatment of actinic keratosis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 3): Abst P5-24.

Stockfleth, E., Sterry, W., Benninghoff, B., Christophers, E. *Successfully treatment of multiple actinic keratosis with imiquimod 5% cream, a placebo controlled study, 18 months follow-up*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P531.

Infliximab

A monoclonal antibody that specifically and irreversibly binds to TNF-α, the overproduction of which is believed to play a significant role in a range of immunomediated inflammatory disorders, infliximab (Remicade®) has been approved for use in rheumatoid arthritis and Crohn's disease and is under review for the treatment of ankylosing spondylitis. Discovered by the Johnson & Johnson subsidiary Centocor, which holds exclusive marketing rights to the product in the U.S., it is marketed by Schering-Plough in all countries outside the U.S., except in Japan and parts of the Far East where it is licensed to Tanabe Seiyaku. Studies are under way in a wide range of immune-mediated inflammatory disorders, including early rheumatoid arthritis, psoriatic arthritis and psoriasis. Phase III trials are in progress for psoriasis (1-9).

The phase II SPIRIT study assessed the efficacy and safety of infliximab in 248 patients with moderate to severe plaque psoriasis who were randomized to receive i.v. infusions of placebo or 3 or 5 mg/kg of infliximab at the beginning of the study and at weeks 2 and 6. The preliminary results obtained at 10 weeks from the beginning of the study revealed that the percentage of patients with an at least 75% improvement in their PASI score was 72% and 88%, respectively, at infliximab doses of 3 and 5 mg/kg *versus* only 6% with placebo. Compared to placebo, the most common adverse effects associated with infliximab were headache, pruritus and upper respiratory tract infections. A subgroup analysis of results from the SPIRIT trial showed that PASI 75% responses were much more common in infliximab-treated patients than placebo-treated patients regardless of patient age, weight, baseline PASI score, percent of body surface area involved and history of antipsoriasis therapy. Analysis of the percent change from baseline in the Dermatology Life Quality Index showed that, compared to placebo, both infliximab doses were associated with significant improvements in quality of life at week 10 (10-14). Results from this study and those that follow are summarized in Table VII.

The experience of a single center in administering infliximab to patients with severe active psoriasis was presented. Infliximab 3-5 mg/kg was administered at weeks 0, 2, 6 and every 8 weeks thereafter to 11 patients, 64% of whom achieved a PASI 50 response by week 2 and 73% of whom achieved a PASI 50 response by week 6 (15).

In an open study in 9 patients with severe atopic dermatitis, patients were treated with infliximab 5 mg/kg i.v. at weeks 0, 2, 6, 14, 22, 30 and 38. The treatment was moderately effective, and a good clinical response was seen in 2 patients over the course of the 58-week study. The only side effect noted was a single infusion reaction (16).

Treatment with infliximab was associated with improvements in patients (n=11) with moderate to severe pyoderma gangrenosum. Study subjects had previously proven refractory to prednisone and/or ciclosporin. Doses of infliximab 5 mg/kg given at 7- to 8-week intervals, however, quickly led to pain relief as well as healing of ulcers

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

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Randomized, double-blind, multicenter	Infliximab, 3 mg/kg i.v. on wk 0, 2 & 6 Infliximab, 5 mg/kg i.v. on wk 0, 2 & 6 Placebo	78	Infliximab improved PASI scores and quality of life in patients with severe psoriasis regardless of baseline characteristics	11-14
Psoriasis	Retrospective	Infliximab, 3-5 mg/kg i.v. on wk 0, 2 & 6 → 1x/8 wks	11	Infliximab was safe and beneficial in patients with severe, refractory psoriasis	15
Dermatitis, atopic	Open	Infliximab, 5 mg/kg i.v. on wk 0, 2, 6, 14, 22, 30 & 38	9	Infliximab was safe and demonstrated moderate clinical efficacy in patients with atopic dermatitis	16
Pyoderma gangrenosum	Open	Infliximab, 5 mg/kg i.v. 1x/7-8 wks x 5 [mean]	11	Infliximab was beneficial in patients with refractory pyoderma gangrenosum	17

in 6 patients. Retreatment of relapsed ulcers produced new responses. Adverse events, the most common of which were infections and fever, were reported by 7 patients (17).

1. *First anti-TNF agent approved for ankylosing spondylitis in E.U.* DailyDrugNews.com (Daily Essentials) May 22, 2003.

2. *Remicade approved in E.U. for maintenance therapy in Crohn's disease*. DailyDrugNews.com (Daily Essentials) May 22, 2003.

3. Joven, B.E., Almodovar, R., Mateo, I. *Treatment with infliximab in spondyloarthropathy*. Annu Eur Congr Rheumatol (EULAR) (June 18-21, Lisbon) 2003, Abst AB0380.

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

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

6. *CPMP recommends approval of Remicade for maintenance dosing in fistulizing CD*. DailyDrugNews.com (Daily Essentials) July 30, 2003.

7. *Johnson & Johnson reports Q3 R&D highlights*. Johnson & Johnson Press Release 2003, Oct 14.

8. Gupta, A.K. *A literature review of the use of infliximab in dermatological diseases.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P619.

9. *Remicade approved for long-term use in fistulizing Crohn's disease.* DailyDrugNews.com (Daily Essentials) April 7, 2003.

10. Gottlieb, A.B., Li, S., Evans, R., Menter, M.A. *Infliximab in the treatment of psoriasis: Results from the first 10 weeks of the phase II trial*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P596.

11. Gottlieb, A.B., Evans, R., Li, S., Leonardi, C. *The efficacy of infliximab across a variety of subgroups with plaque psoriasis*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P615.

12. Gottlieb, A.B., Evans, R., Matheson, R., Miller, B. *The efficacy of infliximab in specific areas of the body*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P614.

13. 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.

14. Feldman, S.R., Bala, M., Menter, A., Gordon, K.B. *The quality of life of patients with severe psoriasis treated with infliximab*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P7.

15. Mahiques-Santos, L., Martínez-Menchon, T., Sanchez-Carazo, J.L., Oliver-Martínez, V. *Infliximab in the management of severe and refractory psoriasis*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P549.

16. Jacobi, A., Schuler, G., Hertl, M. *Long-term efficacy and safety of TNF-α-inhibitor infliximab in severe atopic dermatitis*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P10.

17. Andersen, T.H., Moerk, N.-J. *Infliximab therapy in patients with severe active refractory pyoderma gangrenosum*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P39.

Additional References

Andersen, T.H., Mork, N.J. *Infliximab therapy in patients with severe active refractory pyoderma gangrenosum*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P25-40.

Birbara, A.C., Coughlin, M. *Infliximab therapy in the treatment of psoriasis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P582.

Fairley, J.A. *Infliximab in the management of pyoderma gangrenosum*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P144.

Finkelstein, W. *Treatment of peristomal pyoderma gangrenosum associated with Crohn's disease with infliximab*. 68th Annu Sci Meet Am Coll Gastroenterol (Oct 13-15, Baltimore) 2003, Abst 45.

Geren, S.M. et al. *Infliximab: A treatment option for ulcerative pyoderma gangrenosum*. Wounds 2003, 15(2): 49.

Gottlieb, A.B. et al. *Infliximab monotherapy provides rapid and sustained benefit for plaque-type psoriasis*. J Am Acad Dermatol 2003, 48(6, Part 1): 829.

Gottlieb, A.B. *Infliximab for psoriasis*. J Am Acad Dermatol 2003, 49(2, Part 2): S112.

Gulliver, W.P., Brown-Maher, T., Tabrizi, M. *Low dose infliximab improves psoriasis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P598.

Jensen, S.L., Leonardi, C. *Novel uses of infliximab in dermatology*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P139.

Mahe, E. et al. *CD30+T-cell lymphoma in a patient with psoriasis treated with ciclosporin and infliximab*. Br J Dermatol 2003, 149(1): 170.

Malara, G., Sciarrore, C., Guerra, A.P. *Infliximab: First results in severe psoriasis treatment*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst SSS12-8.

Menter, A., Evans, R., Dooley, L.T., Patel, K., Guzzo, C., Matheson, R. *Infliximab improves signs of plaque psoriasis in patients with psoriatic arthritis*. 67th Annu Meet Am Coll Rheumatol (Oct 23-28, Orlando) 2003, Abst 337.

Mimouni, D. et al. *Infliximab for peristomal pyoderma gangrenosum*. Br J Dermatol 2003, 148(4): 813.

Mork, N.J., Andersen, T.H. *Efficacy of infliximab monotherapy in patients with severe active refractory psoriasis and psoriatic arthritis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P27-76.

Pardo, J. et al. *Infliximab in the management of severe pemphigus vulgaris*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P361.

Revenga, F., Juan, A., Ros, I., Nadal, C., Taberner, R. *Infliximab: A promising therapy for severe plaque type psoriasis and psoriatic arthropathy*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P27-90.

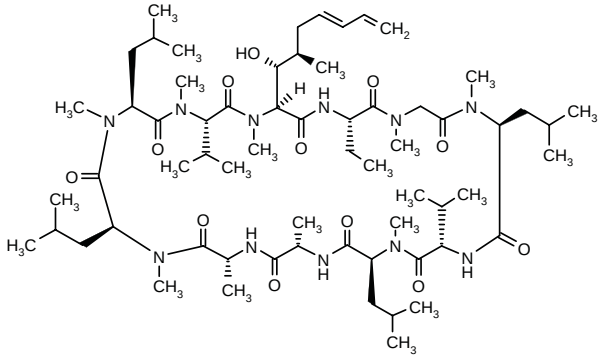
Santos, L.M., Martinez-Menchon, T., Sanchez, J.P., Martinez, V.O., Carazo, J.S., Baixauli, J.F. *Infliximab: A new therapeutic agent in plaque type psoriasis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P27-11.

Stotsky, S., Calamia, K., Walsh, J. *Observational study of the treatment of psoriasis with infliximab*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P618.

Weinberg, J.M. *An overview of infliximab, etanercept, efalizumab, and alefacept as biologic therapy for psoriasis*. Clin Ther 2003, 25(10): 2487.

Zhu, Y. et al. *Pharmacokinetics of infliximab in patients with severe plaque psoriasis*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P617.

ISA-247



Final data from Isotechnika's phase II study of its novel immunosuppressive therapy ISA-247 (ISAtx-247) in 201 Canadian patients with moderate to severe psoriasis demonstrated that ISA-247 is well tolerated and effective. ISA-247 met or exceeded all of the primary and secondary efficacy and safety endpoints. The primary efficacy endpoint for the study was the achievement of a 2-point reduction in patient Static Global Assessment scores from baseline to the end of the treatment period. In the high-dose arm of the study (0.75 mg/kg twice a day), 54% of the patients achieved this endpoint compared to 17% in the low-dose group (0.25 mg/kg twice a day) and 0% in the placebo group. One of the secondary efficacy endpoints for the trial was the achievement of a 75% reduction in the PASI patient scores from baseline. In the high-dose arm of the study, 74% of the patients achieved this endpoint compared to 18% for the low-dose group and 0% in the placebo group. A reduction of 50% in PASI scores was observed in 88% of the patients in the high-dose group and 40% of the patients in the low-dose group. There were no significant adverse effects on blood pressure and lipid levels. Mean serum creatinine levels remained within the acceptable reference range. ISA-247 is a novel calcineurin inhibitor in phase II development as immunosuppressive therapy in organ transplantation and for the treatment of autoimmune diseases. It is being developed under a global collaboration with Roche (1).

1. *Phase II results announced for ISA-247 in psoriasis*. DailyDrugNews.com (Daily Essentials) March 12, 2003.

ISIS-104838

20-Mer antisense chimeric phosphorothioate oligonucleotide whose sequence is:
5'-GCTGATTAGAGAGAGGTCCC-3',
in which the central ten nucleotides are 2'-deoxynucleotides, the last five nucleotides flanking the 5'- and 3'-ends are 2'-*O*-methoxyethyl nucleotides and the cytidines in positions 2, 18, 19 and 20 are 2'-*O*-methoxyethyl-5'-methylcytidines

ISIS-104838, a TNF-α-targeting antisense drug, is the first drug based on Isis Pharmaceuticals' second-generation 2'-*O*-methoxyethyl technology to enter clinical trials. Phase II trials have been conducted with s.c. drug in rheumatoid arthritis and with topical drug in psoriasis, and oral formulations are being tested (1).

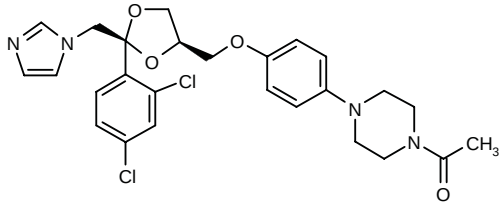
1. *R&D highlights from the Rodman & Renshaw Techvest Healthcare Conference: Isis Pharmaceuticals*. DailyDrugNews.com (Daily Essentials) Nov 24, 2003.

KB-002611

Two clinical studies have been performed by Karo Bio with the thyroid hormone analogue KB-002611 to assess its activity in skin atrophy. Results from studies in animal models demonstrated that thyroid hormone analogues, including KB-002611, can restore collagen production after exposure to potent steroids. In the first study in healthy volunteers, initial treatment with a potent glucocorticosteroid was followed by treatment with high- or

low-dose cream formulations of KB-002611 or placebo. Active treatment was associated with increased production of procollagen in the skin and the low-dose preparation appeared to be more effective than the high-dose cream. In another study to determine if KB-002611 could reverse established skin atrophy following long-term steroid exposure, no significant change in skin thickness was seen, but histological examination is ongoing. The company is seeking a partner for further development.

Ketoconazole



Several new formulations of the antifungal agent ketoconazole are in development for the treatment of seborrheic dermatitis: Connetics' Extina™ and Barrier Therapeutics' Sebazole™.

In July, Connetics submitted an NDA for Extina™, an investigational new drug formulation of 2% ketoconazole foam formulated using the company's proprietary platform delivery vehicles, for the treatment of seborrheic dermatitis (1).

Phase III findings were reported by Connetics in April for Extina™ in the treatment of seborrheic dermatitis. The 4-week, double-blind, active- and placebo-controlled trial enrolled 619 patients across 25 centers and was designed to demonstrate that Extina™ is not inferior to Nizoral® (ketoconazole 2% cream), as measured by the primary endpoint of Investigator's Static Global Assessment (ISGA). The treatment success based on ISGA showed a 50% response for Extina™, a 44% response for Nizoral®, a 40% response for placebo foam and a 26% response for placebo cream. The trial also compared Extina™ to placebo foam. Extina™ produced a favorable ISGA result which did not, however, achieve statistical significance. This was due to an unusually high placebo foam response at 1 of the 25 sites, and an analysis excluding this site showed statistical significance. Based on the other efficacy endpoint of improvement in signs of seborrheic dermatitis, the data showed that Extina™ was statistically superior to placebo foam, with a median improvement of 80% for Extina™, 67% for Nizoral®, 57% for placebo foam and 54% for placebo cream (2).

Barrier Therapeutics recently announced results from 2 blinded, placebo-controlled phase III trials indicating that the company's proprietary 2% gel formulation of ketoconazole (Sebazole™) is effective in the treatment of facial seborrheic dermatitis upon once-daily dosing for only 2 weeks. The trials compared 4 different treatments: Sebazole™, Barrier's proprietary gel formulation of the steroid desonide, the company's proprietary combination gel containing 2% ketoconazole and 0.05% desonide (Seboride™) and placebo gel. Although the studies were initially designed primarily for Seboride™, which was expected to emerge as the most effective therapy, Sebazole™ proved to be statistically significantly superior to placebo in the primary efficacy endpoint –the proportion of patients effectively treated at day 28– and comparable to the combination of ketoconazole and desonide, indicating that the addition of a steroid to the topical regimen does not provide additional benefit in this patient population. Furthermore, another study in volunteers demonstrated that Sebazole™ was about 5 times less irritating than a 2% ketoconazole cream (3, 4).

1. *Connetics submits NDA for Extina in seborrheic dermatitis*. DailyDrugNews.com (Daily Essentials) July 7, 2003.

2. *Phase III findings for Extina in seborrheic dermatitis to support NDA filing*. DailyDrugNews.com (Daily Essentials) April 28, 2003.

3. *Phase III program under way for Seboride*. DailyDrugNews.com (Daily Essentials) April 4, 2003.

4. *Barrier Therapeutics reports results from phase III seborrheic dermatitis studies – Non-steroidal Sebazole with once-a-day dosing emerges as best treatment option.* Barrier Therapeutics Press Release 2004, Jan 12.

Original monograph – Drugs Fut 1979, 4(7): 496.

Additional References

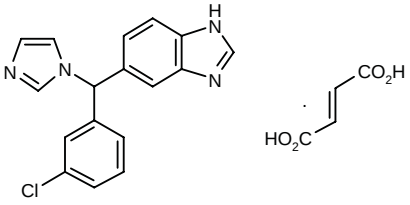
Chosidow, O. et al. *Randomized, open-labeled, non-inferiority study between ciclopiroxolamine 1% cream and ketoconazole 2% foaming gel in mild to moderate facial seborrheic dermatitis*. Dermatology 2003, 206(3): 233.

Chosidow, O.M., Maurette, C., Dupuy, P. *Randomized, open-labeled, non-inferiority study between ciclopiroxolamine 1% cream and ketoconazole 2% foaming gel in mild-to-moderate facial seborrheic dermatitis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P587.

Koller, T., Rocco-Wood, S., Yaroshinsky, A., Spellman, M. *A randomized, open-label study to evaluate the comparative bioavailability of ketoconazole foam, 2%, versus ketoconazole 2% cream in the treatment of moderate to severe seborrheic dermatitis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P446.

Spellman, M., Myers, J., Yaroshinsky, A., Elewski, B. *A randomized, double-blind, double-dummy, placebo-controlled study of the safety and efficacy of ketoconazole foam, 2%, versus ketoconazole 2% cream in the treatment of seborrheic dermatitis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P452.

Liarozole Fumarate

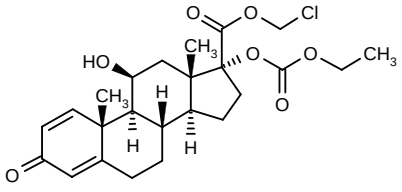


Barrier Therapeutics has received orphan drug designation from the European Commission for liarozole for the treatment of congenital ichthyosis. Liarozole is the first molecule in the RAMBA (retinoic acid metabolism-blocking agents) class with potential for the congenital ichthyosis disease cluster. It blocks the intracellular metabolism of endogenously produced retinoic acid, thereby increasing endogenous retinoic acid levels to therapeutic quantities. This provides the same benefits as synthetic retinoid therapy, but with less of the risk for chronic toxicity or long-term teratogenic effects that may occur with synthetic retinoids (1). The company has also applied for orphan drug desigation in the U.S. and plans to commence phase III trials this year. Liarozole was licensed from originator Janssen, which discontinued its development as an anticancer agent due to insufficient efficacy.

1. *Liarozole granted E.U. orphan drug designation for congenital ichthyosis*. DailyDrugNews.com (Daily Essentials) July 4, 2003.

Original monograph – Drugs Fut 1994, 19(6): 552.

Loteprednol Etabonate



Loteprednol etabonate is one of a class of "soft" corticosteroids being developed by Ivax for a number of inflammatory disorders, including allergic rhinitis, asthma, Crohn's disease, ulcerative colitis and dermatitis. The product was discovered at Pharmos and Bausch & Lomb acquired all rights in 2001. Bausch & Lomb currently markets it as an ophthalmic suspension for reducing inflammation of the eye, including that resulting from cataract surgery and other types of eye surgery (Lotemax®) and for the relief of itchy, red, teary and irritated eyes associated with seasonal allergies (Alrex™). Ivax is conducting phase II clinical evaluation of the drug for the treatment of dermatitis.

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

MBI-594AN

Micrologix Biotech's MBI-594AN, a topical drug candidate under development as a first-in-class prescription treatment for acne, achieved statistically and clinically significant efficacy results in a phase IIb study. The double-blind, randomized, vehicle-controlled, dose-ranging efficacy study evaluated acne lesion count reductions at various time points (3, 6, 9 and 12 weeks) following twice-daily treatment over 12 weeks with MBI-594AN (1.25% or 2.5%) or alcohol vehicle. The study enrolled 255 acne patients at 9 U.S. centers. Preliminary results showed that MBI-594AN 2.5% achieved statistically significant superiority at 6 weeks in reducing all 3 lesion parameters measured: inflammatory lesions, noninflammatory lesions and total lesions. A Physician's Global Severity Assessment, the fourth parameter measured, also resulted in clear superiority of the product as compared to the vehicle. The 40% reduction in inflammatory lesions at 6 weeks was maintained throughout the remainder of the study. Between 6 and 12 weeks, the control group receiving the vehicle alone displayed a gradual decrease in lesion counts, a placebo effect seen frequently in acne studies, making the analyses beyond 6 weeks not statistically significant. A clear dose-response relationship was seen between the active treatment groups, with the 1.25% group showing a trend toward efficacy. The data confirmed results achieved in the previous phase IIa study. Further clinical and nonclinical studies required for NDA submission will now be drawn up. Final decisions about the design of these studies will be made in conjunction with a licensing partner and/or upon meeting with the FDA. These activities are expected to be completed by mid-2004, with phase III trials commencing in the second half of 2004. MBI-594AN is an antimicrobial cationic peptide demonstrating rapid *in vitro* and *ex vivo* antibacterial effect against *Propionibacterium acnes*. Benefits over currently available topical acne products include rapid action, reduction of both inflammatory and noninflammatory acne lesions, bactericidal activity with no demonstrated induction of resistance, rapid efficacy against multiresistant *P. acnes,* no evidence of toxicity and ease of use (1, 2).

A double-blind clinical trial determined the efficacy and safety of MBI-594AN in 75 patients with mild to moderate acne vulgaris who were randomized to receive either MBI-594AN 2.5% solution, MBI-594AN 5% solution or vehicle for up to 6 weeks. Both drug solutions were significantly better than vehicle in reducing the number of inflammatory and noninflammatory acne lesions, with respective decreases in total acne lesion counts on day 43 of 30.9%, 24.8% and 13.6% on 2.5% MBI-594AN, 5% MBI-594AN and vehicle. The study treatments were well tolerated, and although the incidence of transient, mild to moderate skin dryness was somewhat higher in patients treated with the drug solutions (28 and 21 events for the 2.5% and 5% solutions, respectively, compared to 8 events with placebo), no serious drug-related adverse events were reported (3).

1. *Treatment completed in phase IIb trial of MBI-594AN for acne*. DailyDrugNews.com (Daily Essentials) Oct 6, 2003.

2. *MBI-594AN shows efficacy in phase IIb acne study*. DailyDrugNews.com (Daily Essentials) Nov 19, 2003.

3. Friedland, D., Sharp, D., Robinson, J. *Double-blind, randomized, vehicle-controlled study to assess the safety and efficacy of MBI 594AN in the treatment of acne vulgaris*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P51.

MDI-403/MDI-101

The patented synthetic retinoid derivative MDI-403 is available for licensing from Molecular Design International. The compound, which is slowly converted to isotretinoin and then tretinoin, has reached phase II/III clinical evaluation as a topical treatment for acne following phase I and II studies demonstrating its safety. The retinoid may also find use in the repair of photodamage. MDI-101 is another patented retinoid derivative developed by the company that is also available for licensing. It is reportedly ready for phase II trials in the topical treatment of acne. Both MDI-403 and MDI-101 appear to have similar eficacy to tretinoin (Retin A), without the toxicity.

MEDI-522

MedImmune's MEDI-522 (Vitaxin®) is an investigational monoclonal antibody targeting $\alpha_v\beta_3$ integrin, which is expressed on the surface of newly forming blood vessels and certain tumor types, as well as other cell types including macrophages and osteoclasts, with potential in cancer and immunological diseases such as psoriasis and rheumatoid arthritis. Phase II trials for MEDI-522 are in progress in psoriasis, as well as in patients with stage IV metastatic melanoma, rheumatoid arthritis and prostate cancer that has metastasized to the bone. The psoriasis trial is a 2-part, randomized, double-blind, placebo-controlled study in approximately 180 patients with plaque psoriasis involving at least 10% of body surface area and with a minimum PASI score of 12. The study will be conducted at about 30 sites and is designed to evaluate the safety and activity of MEDI-522, administered subcutaneously for 12 weeks, compared to placebo. Preliminary phase II safety and efficacy data are expected in the second half of 2004 (1-3).

1. *Vitaxin enters phase II trials in melanoma and rheumatoid arthritis*. DailyDrugNews.com (Daily Essentials) Sept 16, 2003.

2. *Phase II trials evaluate Vitaxin for prostate cancer and psoriasis*. DailyDrugNews.com (Daily Essentials) Dec 19, 2003.

3. *MedImmune reports Q3 R&D highlights*. MedImmune Press Release 2003, Oct 23.

Melanotan®

Ac-L-Ser-L-Tyr-L-Ser-L-Nle-L-Glu-L-His-D-Phe-L-Arg-L-Trp-Gly-L-Lys-L-Pro-L-Val-NH_2

EpiTan expects to file an IND application for its new photoprotective agent Melanotan®, a synthetic analogue of α-melanocyte-stimulating hormone (α-MSH), in mid-2004 and begin clinical trials shortly thereafter. Based on discussions with the FDA, the indication for Melanotan® is expected to be for the prevention or reduction of UV-induced skin damage in subjects at high risk using a sustained-release implant formulation. Melanotan® stimulates the production of melanin in the skin, increasing the body's melanin levels before exposure to harmful UV radiation. EpiTan recently completed a phase IIb sunburn injury trial in Sydney and Adelaide, Australia, demonstrating that Melanotan® significantly increased skin melanin density and reduced sunburn injury. EpiTan is also investigating Melanotan® as a therapeutic agent for UV-induced skin allergies such as polymorphous light eruption and solar urticaria. Trials are expected to begin in Europe in early 2004 to examine the ability of Melanotan® to alleviate or cure polymorphous light eruption (1).

Final results from EpiTan's definitive sunburn clinical trial of Melanotan® showed that the drug achieved the trial's key objective of reducing sunburn injury by increasing melanin density. Data revealed a highly significant increase in skin melanin in Melanotan®-treated volunteers compared to placebo at all body sites measured. In fairer skinned volunteers in particular, melanin density increases as high as 100% percent were observed and sunburn injury, as induced with solar-simulated UV radiation, was reduced by more than 50%. The double-blind, randomized, placebo-controlled comparative study, conducted at Sydney's Royal Prince Alfred Hospital and the Royal Adelaide Hospital, involved 81 Caucasian volunteers. Prior to receiving Melanotan®, volunteers were subjected to controlled levels of UVA and UVB radiation onto a small area of skin, resulting in a level of burning similar to spending 30-120 min in strong sun without sunscreen. A skin biopsy was taken. After the volunteers had received the regimen of Melanotan®, they were re-exposed to the same amount of UV radiation and a second skin biopsy was taken. Melanin density levels at various skin sites were monitored throughout the 3-month study period. Several genotypes in the volunteer population were identified as having a higher risk of developing skin cancer, and these subjects performed better than the normal population after taking Melanotan® (2).

EpiTan has reported better than expected efficacy in its biodegradable slow-release implant dose-escalation

trial of the melanin-producing drug Melanotan®, which commenced in November 2003. The first 6 volunteers, who received the 2 lowest levels of Melanotan®, quickly demonstrated a substantial increase in melanin levels. After 60 days, the volunteers still had a profound natural tan. The trial, which is being conducted at Q-Pharm, aims to identify an optimal dose for a long-acting implant, as well as to evaluate safety, compliance and efficacy. EpiTan expects the implant trials to conclude in the third quarter of 2004 (3).

1. *EpiTan plans IND filing for Melanotan*. DailyDrugNews.com (Daily Essentials) Nov 13, 2003.

2. *Melanotan reduces sunburn injury by increasing melanin density in clinical trial*. DailyDrugNews.com (Daily Essentials) Dec 3, 2003.

3. *Melanotan implant study produces encouraging results*. DailyDrugNews.com (Daily Essentials) Feb 16, 2004.

Micellar Paclitaxel

Paxceed™ is Angiotech's proprietary micellar formulation of paclitaxel for injection that avoids the negative side effects often associated with other formulations of the drug. Positive results were reported from a pilot phase I trial completed by the National Cancer Institute (NCI) using Paxceed™ in severe psoriasis. Eligible patients had a PASI score of at least 20 and had been treated with at least 2 other systemic agents. Patients received either 75 mg/m^2 of Paxceed™ every 4 weeks for 6 treatments, or 37.5 mg/m^2 every 2 weeks for 3 treatments followed by 6 doses of 50 mg/m^2 every 2 weeks. Nine patients completed the study. All patients demonstrated a positive response to Paxceed™. In the optimal dose regimen group of 75 mg/m^2 monthly, the average PASI score improvement was 64%. Once patients came off therapy, there was no rapid rebound effect or exaggerated recurrence of disease. Angiotech is currently enrolling patients in a phase II rheumatoid arthritis study, results from which will be available in 2004. The company plans to seek a strategic partnership for its systemic Paxceed® program subject to the completion of the rheumatoid arthritis trial (1, 2).

1. *Enrollment completed in phase II study of Paxceed*. DailyDrugNews.com (Daily Essentials) Dec 1, 2003.

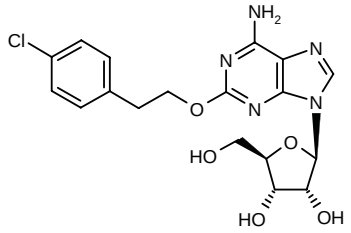
2. *Paxceed produces positive response in psoriasis patients*. DailyDrugNews.com (Daily Essentials) March 21, 2003.

MLN-3897 (AVE-9897)

Late last year, partners Millennium and Aventis initiated a phase I trial of MLN-3897 (AVE-9897), an orally administered small molecule designed to block CCR1, a chemokine receptor believed to play a role in inflammatory conditions such as rheumatoid arthritis, multiple sclerosis and psoriasis. The double-blind, placebo-controlled, single-dose study will evaluate the safety, tolerability and pharmacokinetics of escalating doses of the drug, and aims to collect preliminary information on receptor binding properties of the compound. MLN-3897 is the first compound to enter clinical trials from Millennium and Aventis's June 2000 collaboration to develop new therapies for inflammatory diseases (1).

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

MRE-0094



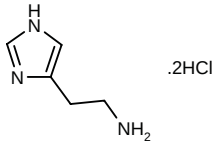
King Pharmaceuticals has completed dosing of the initial concentration of the adenosine A_{2A} receptor agonist MRE-0094 in its ongoing phase I safety program. MRE-0094 is an investigational drug for the topical treatment of chronic diabetic neuropathic foot ulcers that is being developed under license from Aderis Pharmaceuticals. In mice and diabetic rats, adenosine A_{2A} receptor agonists have been shown to promote wound closure by regulating the response of inflammatory cells and mediators, promoting tissue formation through endothelial cell proliferation and migration, and promoting tissue remodeling. A phase II program for MRE-0094 is expected to begin in the first half of 2005 (1).

1. *Initial dosing completed in phase I trial of MRE-0094*. DailyDrugNews.com (Daily Essentials) Jan 16, 2004.

MV-9411

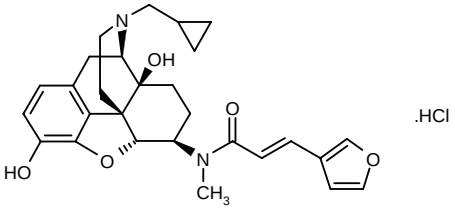
Development efforts in dermatology at Miravant have resulted in a topical gel formulation for the delivery of MV-9411, a PhotoPoint™ (photoreactive) drug, directly to the skin for the local photodynamic therapy (PDT) of skin diseases such as psoriasis. Following the successful completion of a phase I clinical safety study, the company initiated a phase II trial in 2002 in patients with plaque psoriasis, which is expected to be completed this year.

MX-8899



Histamine dihydrochloride, the active ingredient in Maxim's MX-8899 gel, has been shown in preclinical studies to reduce inflammation by preventing the production and release of oxygen free radicals and proinflammatory cytokines such as TNF-α and IL-1β, and it is thought to be able to improve blood circulation and thereby improve wound healing. MX-8899 topical gel is currently being tested in phase I/II clinical trials for alleviating two debilitating side effects of certain cancer therapies: radiation dermatitis and oral mucositis.

Nalfurafine Hydrochloride



The kappa opioid receptor agonist nalfurafine hydrochloride (TRK-820) is in development in Japan by Toray and Daiichi Pharmaceutical as a potential oral antipruritic agent. Toray and Fujisawa signed an agreement for the codevelopment in Europe of an injectable formulation of the compound last year. Toray has been developing the injectable formulation of TRK-820 in Europe for the treatment of uremic pruritus in patients receiving dialysis as a first indication. A marketing application was filed in Sweden at the end of 2002. Toray and Fujisawa will work to gain approval in other European countries. The drug is expected to be launched in Europe in 2004.

Original monograph – Drugs Fut 2003, 28(3): 237.

NCX-1022

A topical formulation of NCX-1022, a nitric oxide (NO)-donating derivative of hydrocortisone, is in clinical development at NicOx for the treatment of dermatitis. Promising results and excellent tolerability were seen in a phase I trial and results from the first phase II study in patients with seborrheic dermatitis are expected soon.

NPI-32101

Late last year, Nucryst Pharmaceuticals commenced its first phase II clinical trial of a topical cream formulation of nanocrystalline silver, known as NPI-32101, for the treatment of atopic dermatitis. Preclinical studies have demonstrated that the company's patented nanocrystalline silver possesses both antiinflammatory and broad-spectrum antimicrobial properties (1, 2).

1. *Nucryst Pharmaceuticals announces third quarter results.* Nucryst Pharmaceuticals Press Release 2003, Nov 4.

2. Nucryst Pharmaceuticals begins first phase 2 clinical trial of novel dermatology drug. Nucryst Pharmaceuticals Press Release 2003, Dec 4.

NV-07a

Novogen's NV-07a has completed phase II trials as a treatment for photodamaged skin. The compound is a potential new topical therapy for use after sun exposure to reverse the effects of aging and damage caused by long-term sun exposure. In addition to reversing damage to skin caused by exposure to ultraviolet light, including wrinkling and thickening, NV-07a also enhanced the immune response in preclinical studies, which is expected to translate into reduced development of skin cancer. The company is currently in license negotiations.

Onercept

Serono's onercept (r-hTBP-1, recombinant human TNF-binding protein-1) is a recombinant, unmodified, fully human soluble type I TNF receptor (p55) that acts as an anti-TNF agent. Positive phase II results for onercept in both psoriasis and psoriatic arthritis were presented at the 9th International Psoriasis Symposium in New York. In a multicenter, double-blind, placebo-controlled study in psoriasis, patients treated with onercept at a dose of 150 mg s.c. 3 times a week for a period of 12 weeks showed a significant improvement in their PASI score. After 12 weeks of therapy, 54% of patients receiving onercept 150 mg demonstrated 75% or greater PASI score improvement *versus* 12% of patients on placebo. Furthermore, 74% achieved at least 50% PASI score improvement *versus* 26% in the placebo group. Patients treated with onercept showed significant improvement in PASI scores after 2 weeks of treatment compared with placebo. Patients treated with onercept 150 mg also experienced a significant improvement in quality of life. The trial enrolled 130 patients with moderate to severe psoriasis to receive either placebo, onercept 150 mg 3 times a week or onercept 100 mg 7 times a week. In an earlier multicenter, double-blind, placebo-controlled study of onercept in 126

patients with psoriatic arthritis, doses of 50 and 100 mg were given s.c. 3 times a week for a period of 12 weeks. The improvement in the psoriatic arthritis response criteria (PsARC) was more favorable at the 100-mg dose. After 12 weeks of treatment at 100 mg, 86% of patients on onercept met the PsARC primary endpoint compared with 45% on placebo. The secondary endpoint of ACR20 was achieved by 67% of onercept patients compared to 31% on placebo. Based on the positive results, Serono plans to initiate phase III trials with onercept in psoriasis (1).

1. *Phase II findings for onercept in psoriasis and psoriatic arthritis*. DailyDrugNews.com (Daily Essentials) June 30, 2003.

OrCel®

Ortec has developed a tissue-engineered wound-healing product –OrCel®– which is a bilayered cellular matrix produced from allogeneic living cells. OrCel® is composed of cultured donor neonatal human keratinocytes and fibroblasts in separate compartments of a bilayered collagen sponge. These cells secrete growth factors and cytokines normally found in acute human wounds and are believed to have a beneficial role in promoting tissue repair. The first FDA approvals were obtained in 2001 for the treatment of acute surgical excisions, such as contracture release sites and donor sites in epidermolysis bullosa patients undergoing hand reconstruction surgery, and donor sites in burn victims undergoing excision and autografting. OrCel® was introduced in the U.S. in 2002 for these indications. In addition, a pivotal clinical trial has been completed for venous ulcers and PMA filing is under way, and the FDA has granted Ortec approval to initiate a pivotal trial in diabetic foot ulcers. The company recently granted a license to the Teva subsidiary Teva Medical to promote and sell OrCel® in Israel for the treatment of chronic wounds and other dermatological applications. Under the 10-year agreement, Teva will provide marketing and sales services for OrCel® and will seek regulatory approval and reimbursement in Israel (1-3).

An analysis of data from Ortec's pivotal trial of the cryopreserved version of OrCel® in the treatment of chronic, hard-to-heal venous leg ulcers (VLU) showed statistically significant differences between OrCel® and control for both the primary and secondary clinical endpoints of the trial: time to 100% healing and the percentage of patients achieving 100% healing. OrCel® was associated with 64% improvement over standard of care at the end of the 12-week treatment phase of the study. At 12 weeks, 59% of the patients treated with OrCel® achieved 100% wound closure and had a median healing time of 57 days. In comparison, 36% of the patients in the control group achieved 100% wound closure and had a median healing time of > 90 days. For the control group, the primary endpoint of median days to 100% healing was not achieved, as less than 50% of these patients healed during the 12-week evaluation period. In a pilot diabetic foot ulcer study, 47% of patients completely healed with OrCel® compared to 23% with standard of care (2-4).

1. *Teva to commercialize OrCel in Israel*. DailyDrugNews.com (Daily Essentials) Oct 28, 2003.

2. *PMA filing commences for OrCel for venous leg ulcers*. DailyDrugNews.com (Daily Essentials) Dec 30, 2003.

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

4. *OrCel achieves primary and secondary endpoints in venous leg ulcer study*. DailyDrugNews.com (Daily Essentials) Dec 15, 2003.

PCL-016

Novactyl is seeking a licensing partner for its acne vulgaris compound PCL-016, which has shown activity against *Propionibacterium acnes*, as well as broad antiviral and immunomodulatory activity, by targeting zinc finger proteins. Novactyl has an active IND application with the FDA for the evaluation of PCL-016 in the treatment of mild to moderate acne, and phase II testing in acne patients commenced in 2002 (1). PCL-016 is a small, naturally occurring compound, a metabolite of the essential amino acid tryptophan. Novactyl has an active IND with the FDA for the clinical evaluation of PCL-016 in the treatment of herpes labialis and a phase I topical safety study was successfully completed. Upsher-Smith has been granted rights for the topical use of PCL-016 for herpes labialis and genitalis, with phase II trials expected to begin soon.

1. *Novactyl seeks licensing partner for PCL-016*. DailyDrugNews.com (Daily Essentials) Dec 11, 2003.

PEP-005

Just recently, Allergan announced the filing of 3 separate IND applications with the FDA for a topical formulation of Peplin Biotech's lead compound PEP-005, covering the treatment of actinic keratosis, basal cell carcinoma and squamous cell carcinoma. PEP-005 is single molecular entity isolated and purified from a common nonindigenous plant. Peplin's proprietary rights to PEP-005 and other related compounds for the treatment of skin cancer are through patents granted in Australia, Singapore and the U.S. Peplin previously conducted a proof-of-concept pilot study using topical application of PEP-001, the raw sap from which PEP-005 is purified, in patients with non-melanoma skin cancer and actinic

keratosis in Australia in May 1999. Allergan and Peplin entered into their collaborative development and license agreement in November 2002, under which Allergan obtained rights to develop and market PEP-005 in a topical and intralesional format to treat non-melanoma skin cancer and actinic keratosis in North and South America. Peplin retains all rights to PEP-005 for the topical or intralesional treatment of skin cancer in markets outside North and South America, and all rights for PEP-005 in other formulations for the treatment of other forms of cancer (1, 2).

1. *Peplin Biotech reaches final stages of pre-IND activities for PEP-005.* DailyDrugNews.com (Daily Essentials) 2004, Feb 27.

2. I*NDs filed for topical PEP-005.* DailyDrugNews.com (Daily Esentials) 2004, March 26.

PI-0824

Peptimmune has commenced dosing in a multicenter phase I trial to test the safety of PI-0824 in patients with pemphigus vulgaris, an autoimmune disease of the skin and mucous membranes. The trial is under way at four sites: New York University College of Dentistry, Johns Hopkins School of Medicine, Case Western Reserve School of Medicine and the University of California at San Francisco (UCSF) School of Medicine. PI-0824, a synthetic peptide being developed as an immunotherapy for the treatment of pemphigus vulgaris, is the only investigational therapy in development for the treatment of the disease. PI-0824 targets the disease-causing immune cells without affecting the beneficial components of the immune system. The therapy aims to selectively suppress the production of autoantibodies against desmoglein 3, a self-adhesion molecule that holds skin cells together. PI-0824 would provide alternative treatment to steroids currently used for relief, which often produce side effects. Pending a successful outcome, Peptimmune anticipates conducting a randomized, placebo-controlled, multiple-dose study to examine the ability to wean patients from their chronic immunosuppressive therapies while maintaining clinical efficacy (1).

1. *PI-0824 evaluated in new phase I trial in patients with pemphigus vulgaris*. DailyDrugNews.com (Daily Essentials) Oct 10, 2003.

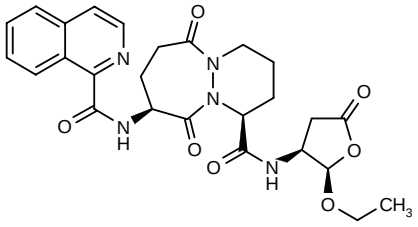
PN-105

Wellstat Therapeutics' PN-105 is a wound-healing agent which is being developed as a hydrogel formulation for topical application. Phase I clinical testing has been completed.

PN-106

Following successful phase I trials, PN-106, a topically applied (gel) agent developed for the treatment of certain forms of sunlight-induced DNA damage and cancers, is now being tested at Wellstat Therapeutics in phase II studies as a potential new treatment for actinic keratosis. PN-106 is reported to be able to prevent the development of tumors and reduce the frequency of mutations when applied after exposure to ultraviolet radiation.

Pralnacasan

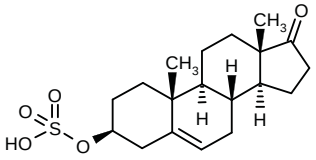


The oral anticytokine therapy pralnacasan (HMR-3480, VX-740) is an ICE (IL-1β-converting enzyme) inhibitor from Aventis and Vertex in clinical development for psoriasis, osteoarthritis and rheumatoid arthritis. Phase IIb trials for the initial indication of rheumatoid arthritis were recently discontinued after liver abnormalities were observed in an animal toxicology study following 9 months' exposure to pralnacasan at high doses. There have been no significant adverse events associated with liver toxicity in subjects participating in clinical trials. Following a discussion with the FDA, it was determined that two ongoing shorter term phase I trials will continue as planned, given that the toxicity findings were based on longer term regimens. The findings observed in the 9-month toxicology study were not observed in prior toxicology studies conducted with pralnacasan, including 6-month studies in 2 different species. Decisions on further clinical trials of pralnacasan will be made after the final analysis of the 9-month toxicology study and data from an ongoing 12-month toxicology study are available (1, 2).

1. *Pralnacasan phase IIb clinical trial begins enrollment*. DailyDrugNews.com (Daily Essentials) July 11, 2003.

2. *Phase IIb trials of pralnacasan in rheumatoid arthritis discontinued*. DailyDrugNews.com (Daily Essentials) Nov 12, 2003.

Prasterone Sulfate



Pharmadigm is developing an injectable formulation of dehydroepiandrosterone sulfate (DHEAS, prasterone sulfate, Inflarest™) for accelerating wound closure in patients undergoing autologous skin grafting for severe burns. Phase II trials were completed several years ago. The product is also in phase II trials for acute exacerbations of asthma.

PSK-3841

The topical antiandrogen PSK-3841 is available for licensing from ProSkelia. In preclinical studies, PSK-3841 displayed promising activity in animal models of acne, hirsutism and alopecia, with good systemic and dermal tolerance. No systemic antiandrogenic activity was detected in humans and it was also well tolerated. Phase I trials have been completed and PSK-3841 is now in phase II clinical testing for alopecia and acne.

Psoraxine™

Astralis has completed enrollment in a U.S. double-blind, placebo-controlled phase I trial of its lead product, Psoraxine™, a new biological treatment for psoriasis. Two sites enrolled a total of 20 patients. No clinically significant adverse effects related to Psoraxine™ have been reported so far. The study was designed to evaluate the safety of a single dose of Psoraxine™ administered by intramuscular injection in patients with stable, moderate psoriasis covering 3-15% of the body surface. Secondary endpoints will include efficacy measured by PASI and improvement in quality of life. Three dose levels (50, 150 and 300 μg) are being evaluated in addition to a placebo control arm. A phase II trial is planned for 2004. Psoraxine™ is a protein-based therapy that is believed to stimulate cells from the patient's immune system to reverse the inflammatory process responsible for psoriasis symptoms. Last year, the company completed clinical trials in Venezuela using a first-generation version of Psoraxine™ to treat 2,770 patients with psoriasis, the majority of whom responded positively. Of treated patients, 28% achieved complete remission, and a further 46% of patients experienced a reduction in disease of 70-99%, as measured by the PASI (1-3). SkyePharma has an option on worldwide rights to Psoraxine™ exercisable upon completion of phase II trials.

1. *Astralis cleared to begin phase I testing of Psoraxine in U.S.* DailyDrugNews.com (Daily Essentials) Aug 6, 2003.

2. *Phase I trial evaluates Psoraxine for psoriasis*. DailyDrugNews.com (Daily Essentials) Sept 12, 2003.

3. *Enrollment completed in phase I Psoraxine trial*. DailyDrugNews.com (Daily Essentials) Jan 26, 2004.

PTH(7-34)

IGI has received FDA approval to begin phase I/II trials for the topical use of PTH(7-34) encapsulated in a Novasome® cream for use in preventing chemotherapy-induced alopecia in breast cancer patients. Scientists at Boston University Medical Center previously reported that PTH(7-34) stimulated epidermal proliferation and hair growth in mice (1).

1. *Phase I/II trials cleared for topical PTH (7-34) in chemotherapy-induced alopecia*. DailyDrugNews.com (Daily Essentials) Aug 26, 2003.

PV-10

Provectus has an active IND application with the FDA for its Xantryl™ (PV-10) drug therapy for psoriasis. Xantryl™ is now set to enter phase II/III clinical studies in the U.S. and Europe and is positioned for expedited approval in major Asian markets. Xantryl™ is a topical preparation containing rose bengal, the active substance also used in the company's Provecta™ injectable agent for oncology, although at much lower concentrations. It is activated by green light and specifically targets only diseased tissue, the effects of light activation being confined to areas of the skin affected by psoriasis. The agent is so sensitive to light that only ambient room or sunlight may be required for treatment. A green laser or a simple tanning bed can also activate the drug (1). Eczema and diabetic and decubital ulcers are other potential indications under consideration by the company.

1. *Xantryl advances for psoriasis*. DailyDrugNews.com (Daily Essentials) Nov 25, 2003.

QRX-101

QUATRx has exclusive worldwide rights to the topical use of a series of novel vitamin D analogues synthesized at the University of Wisconsin and Deltanoid. The lead analogue, QRX-101, is being studied in phase II trials in patients with mild to moderate psoriasis.

Recombinant α_1-Antitrypsin

α_1-Antitrypsin is a natural protease inhibitor involved in regulating inflammatory responses and chronic tissue degradation in conditions such as hereditary emphysema, asthma, cystic fibrosis and dermatological diseases. A glycoprotein primarily produced by hepatocytes and immune system cells, α_1-antitrypsin belongs to a family of structurally related proteins classified as serine protease inhibitors (serpins), which inhibit several proteases including trypsin, cathepsin G, thrombin, tissue kallikrein, as well as neutrophil elastase. The molecular basis for AAT's activity is thought to be mainly the regulation of neutrophil elastase. Recombinant AAT is being evaluated by Arriva Pharmaceuticals and Baxter in phase I trials for hereditary emphysema. Arriva-ProMetic, the joint venture company between ProMetic Life Sciences and Arriva, also began a phase II proof-of-concept trial last year for a topical gel formulation for the treatment of atopic dermatitis. The randomized, double-blind, vehicle-controlled study will evaluate the safety and efficacy of AP-102 gel containing rAAT in subjects with atopic dermatitis. Up to 40 patients will be randomized to receive either placebo or AP-102 gel at 4 sites in Canada. The study aims to characterize the effect of AP-102 gel on the resolution of atopic dermatitis lesions. It is also designed to demonstrate the efficacy of the recombinant version compared to the positive clinical effect observed several years ago with plasma-derived AAT in recalcitrant atopic dermatitis. At that time, all patients showed significant clinical improvement within 6-21 days of initiation of treatment. α_1-Antitrypsin stopped the pain and pruritus and promoted tissue healing without scarring. Recombinant AAT is being developed as the current supply of natural plasma-derived AAT is only available in limited quantities (1, 2).

1. *Interim results for rAAT in otitis media*. DailyDrugNews.com (Daily Essentials) June 17, 2003.

2. *Recombinant α_1-antitrypsin enters proof-of-concept study for atopic dermatitis*. DailyDrugNews.com (Daily Essentials) Oct 13, 2003.

rhIGF-I/rhIGFBP-3

Insmed's rhIGF-I/rhIGFBP-3 (SomatoKine®) is the recombinant protein complex of insulin-like growth factor-I (IGF-I) and its most abundant binding protein, insulin-like growth factor-binding protein-3 (IGFBP-3). It is a novel delivery composition of IGF-I for once-daily s.c. injection that, by restoring IGF-I levels to a more normal range, regulates essential metabolic and anabolic (growth-promoting) processes, including glucose uptake and tissue regeneration. A deficiency of IGF-I results in significantly impaired growth, and is associated with other metabolic abnormalities, including insulin resistance, increased adiposity and delayed wound healing. In the human body, IGF-I naturally circulates complexed with IGFBP-3. rhIGF-I/rhIGFBP-3 is currently in phase III clinical development at Insmed for growth hormone insensitivity syndrome (GHIS), phase II trials in both type 1 and type 2 diabetes, and phase II studies for severe burn injury. Following severe burn injury in adults and children, administration of SomatoKine® demonstrated a significant improvement in muscle protein synthesis and a significant reduction in the inflammatory response associated with trauma (1-5).

1. *Insmed begins named-patient program for SomatoKine*. DailyDrugNews.com (Daily Essentials) April 11, 2003.

2. *Insmed's rhIGF-I/rhIGFBP-3 granted orphan drug designation in Europe*. DailyDrugNews.com (Daily Essentials) June 26, 2003.

3. *rhIGF-I/rhIGFBP-3 enters phase III trial for GHIS*. DailyDrugNews.com (Daily Essentials) July 7, 2003.

4. *University of Rochester to study rhIGF-I/rhIGFBP-3 for myotonic dystrophy*. DailyDrugNews.com (Daily Essentials) Jan 12, 2004.

5. *SomatoKine granted orphan drug designation for extreme insulin resistance*. DailyDrugNews.com (Daily Essentials) Dec 18, 2003.

rh-Lactoferrin

Lactoferrin, a protein found naturally in milk and other exocrine secretions, is a key multifunctional protein with antiinflammatory and immunomodulating properties. Agennix was the first to produce commercial quantities of the human protein using recombinant technology. Recombinant human lactoferrin (rh-lactoferrin, rh-LF) is currently being tested in phase II trials for the treatment of chronic diabetic ulcers, cancer and asthma.

The company has been awarded a Phase I/II Fast Track Small Business Innovation Research (SBIR) grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) to test the safety and efficacy of rh-LF gel in patients with diabetic neuropathic foot ulcers. The Phase I USD 100,000 award has been released to support the initial clinical safety component of the study. The USD 750,000 Phase II award will later support a randomized, placebo-controlled efficacy trial. The protein accelerates wound healing via a novel mechanism of action. Animal studies have demonstrated rh-LF-induced accelerated healing using uninfected and infected wounds, and in diabetic animals with impaired healing. Recombinant protein consistently increased the rate of wound healing and the incidence of closure relative to mice treated with placebo and relative to those treated with the currently approved drug. To date, rh-LF has been administered to over 300 people both topically and orally. A phase I/II trial in patients with diabetic foot ulcers is currently under way at the Joslin Diabetes

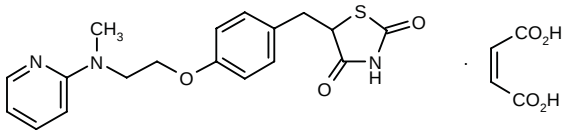
Center/Beth Israel Deaconess Medical Center affiliated with Harvard University, New York University School of Medicine and Scott & White Hospital (1).

1. *SBIR grant awarded for clinical trials of rhLF for diabetic foot ulcers*. DailyDrugNews.com (Daily Essentials) Sept 22, 2003.

Additional References

Engelmayer, J., Varadhachary, A. *Properties and application of recombinant human lactoferrin to enhance healing of diabetic wounds*. Wounds 2003, 15(9): 294.

Rosiglitazone Maleate



GlaxoSmithKline's oral antidiabetic agent rosiglitazone maleate (Avandia) was found to improve psoriasis in diabetic patients being treated with the drug. It has now advanced to phase III clinical evaluation for this new indication.

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

Siplizumab

MedImmune announced last year its plans to postpone the initiation of further clinical studies in psoriasis for siplizumab (MEDI-507), a humanized monoclonal antibody exclusively licensed from BioTransplant that binds to the CD20 receptor on T-cells and natural killer (NK) cells, pending the completion of a phase II trial of Vitaxin™ (MEDI-522; see above), a proprietary investigational monoclonal antibody also being developed for psoriasis. The company's plans to evaluate MEDI-507 for T-cell lymphoma have not changed and a trial for that indication is still planned (1).

1. *MedImmune postpones MEDI-507 trials in psoriasis.* DailyDrugNews.com (Daily Essentials) April 29, 2003.

Original monograph – Drugs Fut 2002, 27(6): 558.

Sorafin™

A combination of auranofin (synthetic gold) and a steroid, Sorafin™ is being developed at Psiron for use in atopic dermatitis and psoriasis. Auranofin acts as a steroid-sparing agent, allowing significant reductions in steroid dose and therefore potential side effects. Phase II clinical trials in atopic dermatitis recently began in Australia.

SRP-299

SRP-299 is an immunomodulator developed at SR Pharma for the treatment of allergic diseases. A phase II trial is in progress in the U.K. and Ireland in children with atopic dermatitis, with results expected to be reported during the second quarter of 2004. Clinical trials are also under way in the U.K. and Poland in patients with moderate asthma. SRP-299's unique mode of action stops the immune system from overreacting to nonthreatening agents such as cat dander or house dust mites and prevents asthma attacks and allergic reactions, rather than treating allergic symptoms or blocking reactions to specific allergens like current agents (1).

1. *Enrollment completed in phase II trial of SRP-299 for asthma*. DailyDrugNews.com (Daily Essentials) July 2, 2003.

STA-5326

The first orally available, selective inhibitor of IL-12, the small-molecule compound STA-5326 (Synta Pharmaceuticals) offers potential for the treatment of Th1-mediated autoimmune disorders including Crohn's disease, psoriasis, multiple sclerosis and rheumatoid arthritis. Two phase I clinical studies have been successfully completed and a phase II trial in Crohn's disease has been initiated, with further phase II efficacy trials in additional indications planned.

SWT-01.100

Data from Switch Biotech's first clinical trial of SWT-01.100 support the drug's novel mode of action –ion channel modulation– for the treatment of psoriasis. Initial *in vitro* tests previously showed that some of the company's compounds succeeded in inhibiting T-cell activation and keratinocyte proliferation. Further trials were conducted with topically applied SWT-01.100, a reprofiled drug already marketed for a different indication, in psoriasis patients in order to verify the biological principle of its ion channel-modulating effect. The double-blind pilot trial compared SWT-01.100 to placebo in terms of clinical and biological parameters in 38 patients. Topical application of SWT-01.100 caused a reduction in thickness of the affected epidermal tissue of about 20%, while skin areas treated with placebo displayed slight thickening of the epidermis. The PASI score was reduced by 50% in patients treated with SWT-01.100 (1).

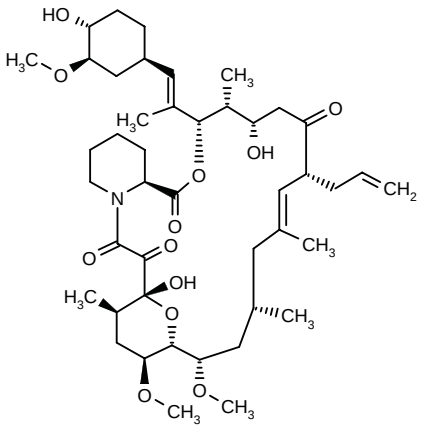
1. *Pilot study of SWT-01.100 supports mode of action for treatment of psoriasis*. DailyDrugNews.com (Daily Essentials) Nov 27, 2003.

T-487

Tularik's small-molecule chemokine antagonist T-487, under development for the treatment of autoimmune and inflammatory diseases, entered a phase II trial in patients with psoriasis in December 2003 and another phase II study of T-487 in patients with rheumatoid arthritis is expected to commence in the first quarter of 2004 (1).

1. *Pipeline progress report from Tularik*. DailyDrugNews.com (Daily Essentials) Jan 16, 2004.

Tacrolimus



Fujisawa continues to study expanded indications for its first-in-class topical immunomodulator tacrolimus, already available worldwide for organ transplant rejection as Prograf® and for atopic dermatitis in adults and children as Protopic®. Phase III trials are currently in progress in the U.S. with a gel formulation of the drug for the treatment of psoriasis, as are phase II studies with a cream formulation; in Europe, both formulations are undergoing phase II evaluation. It is also in various stages of development around the world for the treatment of rheumatoid arthritis, ulcerative colitis, lupus nephritis, asthma, vernal conjunctivitis, etc. Fujisawa launched Protopic® (tacrolimus hydrate 0.03%) in Japan for the treatment of pediatric (children aged 2-15 years) atopic dermatitis last year. Protopic® has been available for individuals with atopic dermatitis aged 16 years and older since November 1999. Both adult and pediatric Protopic® formulations are approved and marketed in more than 20 countries outside Japan, including the U.S., Europe and Asia. Also during 2003, Fujisawa entered a copromotion agreement with GlaxoSmithKline for the U.S. whereby GSK will detail pediatricians and Fujisawa will continue to promote the drug to dermatologists (1, 2). Clinical studies reported during the past year with tacrolimus in psoriasis, atopic dermatitis and several other dermatological conditions are summarized here.

A double-blind, randomized clinical trial evaluated the efficacy of combining tacrolimus and salicylic acid in the treatment of psoriasis. Thirty adult patients with generally symmetric plaque psoriasis were randomized to receive salicylic acid 6% gel combined with placebo or tacrolimus 0.1% ointment topically for 8 weeks following a left-right comparison design. At the end of the study, the combination treatment was more effective than salicylic acid alone in improving the erythema, scale and thickness sum score of the target lesions of the patients. The combination of tacrolimus and salicylic acid was generally well tolerated and the most common adverse event was a minor stinging sensation, experienced by 4 patients (3, 4). The results of this and a selection of the following clinical trials are depicted in Table VIII.

Topical tacrolimus 0.1% ointment was found to improve the symptoms of psoriasis involving the face and intertriginous areas of adults. Based on these findings, a retrospective study was conducted to determine the effects of topical tacrolimus 0.1% ointment in 12 patients with inverse psoriasis aged between 22 months and 16 years. The results revealed that all disease symptoms disappeared after the ointment had been applied for 7 days (5).

A clinical trial evaluated the effects of 0.1% tacrolimus ointment applied twice daily without occlusion on the facial lesions of 21 Japanese patients with psoriasis vulgaris. After 4 weeks, 47.6% and 42.9% of the patients showed complete and partial response, respectively. Topical tacrolimus was associated with significant reductions in the mean erythema score (from 1.76 to 0.42), the mean infiltration score (from 1.33 to 0.43) and the mean desquamation score (from 0.95 to 0.24). The drug had no significant effects on the renal and liver function of the patients, and the most common adverse event was slight transient skin tingling. Ten complete responders showed recurrence of the disease within 1 month after discontinuing the treatment but responded again to topical tacrolimus (6).

In a multicenter, open-label clinical trial, tacrolimus 0.03% ointment was administered as monotherapy twice daily to 582 children and adults suffering from atopic dermatitis until 1 week after clearance. A total of 70% of the patients completed the study, and 1% and 5% of the patients discontinued due to lack of efficacy and adverse events, respectively. The percentage of patients who showed at least 90% improvement in disease symptoms was 24% and 61%, respectively, after 1 and 9 months of treatment. The most common adverse events associated with the drug were skin burning and pruritus; both were usually mild and transient, and their prevalence decreased with time (7).

In 26 children aged 2-12 years with atopic dermatitis involving at least 10% of their body surface area, topical

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

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Randomized, double-blind	Tacrolimus 0.1% ointment top. + Salicylic acid 6% gel top. x 8 wks Salicylic acid 6% gel top. x 8 wks	30	The combination of tacrolimus and salicylic acid was well tolerated and significantly more effective than salicylic acid monotherapy in improving the erythema, scaling and thickness of plaque-type psoriasis lesions	3, 4
Psoriasis	Retrospective	Tacrolimus 0.1% ointment top. x 7 [max.] d	12	Topical tacrolimus was effective in clearing the lesions of children with inverse psoriasis	5
Psoriasis	Open	Tacrolimus 0.1% ointment top. b.i.d. x 4 wks	21	Topical tacrolimus induced complete and partial responses in facial lesions in 47.6% and 42.9% of patients with psoriasis vulgaris, respectively. The drug was well tolerated and had no significant effects on renal or liver function	6
Dermatitis, atopic	Open, multicenter	Tacrolimus 0.03% ointment top. b.i.d. x 114 [mean] d	582	Topical treatment with tacrolimus 0.03% ointment was safe and effective in patients with atopic dermatitis	7
Dermatitis, atopic	Open	Tacrolimus 0.03% ointment top. b.i.d. x 7 wks	26	The topical administration of tacrolimus 0.03% ointment showed evidence of selective immune modulation in skin and was well tolerated in children with atopic dermatitis	8
Dermatitis, atopic	Open, multicenter	Tacrolimus 0.03% ointment top. b.i.d. x 3 wks	125	The mean baseline erythema score of patients with moderate to severe dermatitis decreased by 47.0% after 3 weeks of treatment with tacrolimus 0.03% ointment and by 66.8% after follow-up for 1 week	9
Dermatitis, atopic	Randomized, double-blind, pooled/meta-analysis	Tacrolimus 0.03% ointment top. b.i.d. x 6 wks Placebo	599	Tacrolimus 0.03% ointment was well tolerated and improved the symptom scores of pediatric and adult patients with mild to moderate atopic dermatitis	10
Dermatitis	Open, multicenter	Tacrolimus ointment, 0.1% b.i.d top. x > 3 y	300	Tacrolimus ointment was safe and effective in the long-term therapy of patients with atopic dermatitis	11
Periostomal skin disease	Open	Tacrolimus 0.1% ointment top. o.d. x 3 wks Tacrolimus 0.1% ointment top. o.d. x 8 wks Tacrolimus 0.1% ointment top. o.d. x 3 mo	3	Topical tacrolimus was well tolerated and effective in the treatment of periostomal skin disease. All 3 patients achieved complete resolution of their skin disorders	14

administration of tacrolimus 0.03% ointment twice daily on all affected areas for 3 weeks was well tolerated and not associated with severe adverse events (8).

A multicenter, open-label phase III clinical trial assessed the efficacy and safety of tacrolimus 0.03% ointment administered topically twice daily to 125 Indian patients aged 12-69 years with moderate to severe atopic dermatitis. After 3 weeks of treatment, the mean score of erythema, oozing/crusting, excoriation, edema/induration/papulation of the patients decreased by 47.0% compared to baseline. The symptoms continued to improve during a 1-week follow-up period, at the end of which the mean symptom score of the patients was 66.8% lower compared to baseline (9).

Two double-blind, randomized, placebo-controlled clinical trials evaluated the efficacy and safety of tacrolimus ointment 0.03% in the treatment of mild to moderate atopic dermatitis. A total of 599 patients at least 2 years old were treated with vehicle or tacrolimus ointment twice daily for 6 weeks. Evaluations conducted at different times during the study revealed that tacrolimus was significantly more effective than vehicle in improving the Investigator's Global Atopic Dermatitis Assessment (IGADA) score, the Eczema Area and Severity Index (EASI), the Assessment of Itch score and the Total Percent Body Surface Affected of the patients. The most frequent cutaneous adverse events were skin burning and stinging, increased itching and skin erythema; the

latter two were more common among vehicle-treated patients compared with tacrolimus. No cases of warts, molluscum or herpes zoster were found, and the incidence of herpes simplex and eczema herpeticum was very low in both study groups (10).

A total of 300 patients with atopic dermatitis were treated with tacrolimus ointment (0.1%) applied topically twice daily to affected areas for more than 3 years in an open-label, multicenter extension study. Continual improvement was noted from week 1 of treatment and throughout the 3 years. Tacrolimus ointment was safe and effective in long-term therapy and did not produce tachyphylaxis (11).

The potential use of tacrolimus as a therapeutic adjunct in the treatment of cutaneous lupus erythematosus (CLE) was evaluated in a pilot study. Three women aged 31-51 years with systemic lupus erythematosus (SLE) or subacute CLE and manifestations of the disease in the face were included in the study. Each patient continued receiving her baseline systemic therapy with antimalarials, isotretinoin, methotrexate and/or low-dose prednisolone, and was also treated with tacrolimus 0.03% or 0.1% ointment topically once daily on her facial lesions. All patients showed significant improvements in their facial lesions within 4-8 weeks after the first tacrolimus dose. The ointment was well tolerated and no adverse effects were found on healthy facial skin. The authors concluded that topical tacrolimus may be suitable for long-term treatment of chronic inflammatory facial lesions (12).

The finding that both topical tacrolimus and a 308 nm excimer laser treatment were effective for treating vitiligo led researchers to conduct a randomized clinical trial to determine the potential efficacy of a combination of both therapies. Fourteen patients with vitiligo were enrolled, and 2-4 target lesions per patient were treated with the laser (at an initial fluency of 50 mJ/cm^2 less than the minimal erythemal dose in vitiligo skin, twice weekly for 24 sessions) alone or combined with topical tacrolimus 0.1% ointment twice daily. The rate of repigmentation of the target lesions was 100% with the combination therapy and 85% with the laser monotherapy. The combination therapy was also associated with a greater percentage of lesions achieving a repigmentation rate of at least 75% (69.6% *vs.* 20%) and a shorter onset of repigmentation. No significant differences were found between the safety profiles of the study regimens, and the most common adverse events were moderate to severe erythema, localized bullous eruption and pruritus (13).

A recent study assessed the potential benefits of tacrolimus 0.1% ointment in the treatment of peristomal skin disease. Three patients who had undergone an ostomy surgical procedure and had skin problems (irritant contact allergy, pyoderma gangrenosum or an inflamed, traumatic erosive plaque) at their stoma sites received topical tacrolimus 0.1% ointment daily for 3 weeks to 3 months. All patients achieved complete resolution after tacrolimus therapy and no significant adverse events were found (14).

Results of a recent study in 2 patients indicated that tacrolimus 0.1% ointment may be effective in the treatment of plasma cell balanitis (15).

The use of topical tacrolimus as a treatment for chronic, steroid-dependent, cutaneous graft-versus-host disease was evaluated in 10 patients who underwent hematopoietic stem cell transplantation for non-Hodgkin's lymphoma, acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia or myelodysplastic syndrome. None of the patients had responded to conventional therapy. Patients initially used tacrolimus 0.03% ointment 2-3 times per day before the dose was increased to 0.1%. An objective response was seen in 7 patients, with 6 patients experiencing a good or moderate response and 1 patient experiencing a mild response. In terms of subjective responses, a complete response was noted by 1 patient, a good response by 2 patients, a moderate response by 4 patients and 3 patients noted no response. Responses were seen as early as 1 day after treatment initiation. Mild burning at the application site was observed in 1 patient (16).

1. *Fujisawa launches pediatric Protopic in Japan*. DailyDrugNews.com (Daily Essentials) Dec 16, 2003.

2. *Fujisawa and GSK sign U.S. copromotion agreement for Protopic*. DailyDrugNews.com (Daily Essentials) June 10, 2003.

3. Carroll, C.L., Clarke, J., Balkrishnan, R., Feldman, S. *Topical tacrolimus ointment in combination with 6% salicylic acid gel for treatment of psoriasis: Results of a randomized, double blind, right to left clinical trial*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P579.

4. Carroll, C.L., Feldman, S.R., Balkrishan, R. *Use of topical tacrolimus in combination with 6% salicylic acid for treatment of psoriasis: Results of a double blind right to left trial*. 64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0341.

5. Steele, J.A., Choi, C., Kwong, P. *Topical tacrolimus is safe and effective treatment for inverse psoriasis in children*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P510.

6. Yamamoto, T., Nishioka, K. *Topical tacrolimus: An effective therapy for facial psoriasis*. Eur J Dermatol 2003, 13(5): 471.

7. Abramovits, W., Cornell, R., Chipps, B., Gottlieb, A. *Monotherapy with 0.03% tacrolimus ointment is a safe and effective treatment for atopic dermatitis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P201.

8. Stiehm, E.R., Roberts, R., Kaplan, M., Corren, J. *The effect of tacrolimus ointment on the immune system of children aged 2-12*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P545.

9. Desai, A.A., Dongre, N., Ballary, C., Saple, D. *Evaluation of the efficacy, safety and tolerability of tacrolimus ointment in Indian patients with moderate to severe atopic dermatitis*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P233.

10. Chapman, M.S., Schachner, L., Breneman, D., Boguniewicz, M. *Tacrolimus ointment 0.03% is safe and effective for the treatment of mild to moderate atopic dermatitis in pediatric and adult patients*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P11.

11. Paller, A., Hanifin, J., Eichenfield, L., Clark, R. *Tacrolimus ointment monotherapy is a safe and effective treatment for atopic dermatitis long-term (more than 3 years)*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P24.

12. Bohm, M., Gaubitz, M., Luger, T.A., Metze, D., Bonsmann, G. *Topical tacrolimus as a therapeutic adjunct in patients with cutaneous lupus erythematosus. A report of three cases*. Dermatology 2003, 207(4): 381.

13. Passeron, T., Ostovari, N., Zakaria, W., Ortonne, J.-P. *Connection of tacrolimus and 308NM excimer laser in treating vitiligo*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P537.

14. Chapman, M.S., Brown, J., Manganiello, W. *Tacrolimus 0.1% ointment for peristomal skin disease*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P648.

15. Moreno-Arias, G.A., Camps-Fresneda, A., Palou-Almerich, J., Llaberia, C. *Plasma cell balanitis successfully treated with tacrolimus 0.1% ointment*. J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P162.

16. Elad, S., Or, R., Resnick, I., Shapiro, M.Y. *Topical tacrolimus - A novel treatment alternative for cutaneous chronic graft-versus-host disease*. Transpl Int 2003, 16(9): 665.

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

Additional References

Assmann, T. et al. *Tacrolimus ointment for the treatment of vulvar lichen sclerosus*. J Am Acad Dermatol 2003, 48(6, Part 1): 935.

Bens, G. et al. *Topical treatment of Netherton's syndrome with tacrolimus ointment without significant systemic absorption*. Br J Dermatol 2003, 149(1): 224.

Berth-Jones, J., Reitamo, S. *The short- and long-term efficacy of tacrolimus ointment in adult and paediatric patients: A review of five clinical trials*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 1): Abst PP1-6.

Braza, T.J. et al. *Tacrolimus 0.1% ointment for seborrhoeic dermatitis: An open-label pilot study*. Br J Dermatol 2003, 148(6): 1242.

Chen, E.H., Girardi, M., Linowski, G. *The use of topical tacrolimus 0.1% ointment in the management of acute cutaneous graft-versus-host disease*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P299.

Chu, J. et al. *Topical tacrolimus is a useful adjunctive therapy for bullous pemphigoid*. Arch Dermatol 2003, 139(6): 813.

Clayton, T.H. et al. *Topical tacrolimus for facial psoriasis*. Br J Dermatol 2003, 149(2): 419.

Clayton, T.H., Sala, J., Buddo, V., Harrison, P.V. *Facial psoriasis: Benefit of topical tacrolimus*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P27-1.

Freeman, A.K. et al. *Tacrolimus ointment for the treatment of psoriasis on the face and intertriginous areas*. J Am Acad Dermatol 2003, 48(4): 564.

Freeman, A.K., Singer, G., Lebwohl, M., Linowski, G. *Tacrolimus ointment for the maintenance of atopic dermatitis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P208.

Fujita, W.H. *A phase IV open label, proof of concept study to determine the efficacy of tacrolimus ointment 0.1% in the treatment of the chronic red face*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P145.

Geskin, L.J., McCann, S., Vetter, C., Falo, L.Jr. *Topical tacrolimus is effective in the treatment of pruritus in patients with cutaneous T-cell lymphoma*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P486.

Goldman, D., Gruchalla, D., Shull, T. *Tacrolimus ointment for the treatment of steroid-induced rosacea*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P311.

Graf, J. et al. *The use of topical tacrolimus (FK506/Protopic) in cutaneous manifestations of autoimmune diseases*. J Clin Rheumatol 2003, 9(5): 310.

Guanzon, M.A., Faltay, B.B., Ishida-Yamamoto, A., Silverman, B.A., Schneider, A.T. *Treatment of keratoderma hereditara mutilans with topical tacrolimus: A case study with histopathology pre- and post-treatment*. J Allergy Clin Immunol 2003, 111(2, Part 2): Abst 1014.

Gulliver, W.P. *Tacrolimus 0.1% ointment is useful in treating rosacea patients with seborrheic dermatitis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P90.

Günther, C. et al. *Topical tacrolimus treatment for cicatricial pemphigoid*. J Am Acad Dermatol 2004, 50(2, Part 1): 325.

Hanifin, J.M., Leung, D.Y., Paller, A., Rico, J. *Tacrolimus ointment monotherapy is safe and effective for the long-term treatment (more than 3 years) of atopic dermatitis in pediatric patients*. J Allergy Clin Immunol 2003, 111(2, Part 2): Abst 244.

Hodgson, T.A. et al. *Topical tacrolimus: A novel therapeutic intervention for recalcitrant labial pemphigus vulgaris*. Eur J Dermatol 2003, 13(2): 142.

Kawalek, A.Z. et al. *Combined excimer laser and topical tacrolimus for the treatment of vitiligo: A pilot study*. Dermatol Surg 2004, 30(2): 130.

Kempers, S., Boguniewicz, M., Carter, E., Jarrat, M., Pariser, D., Stewart, D., Stiller, M., Tschen, E., Chon, K., Wisseh, S., Abrams, B. *Comparison of pimecrolimus cream 1% and tacrolimus ointment 0.03% in paediatric patients with atopic eczema*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-41.

Koo, J.Y.M. et al. *Tacrolimus ointment 0.1% is safe and effective in the treatment of atopic dermatitis: Final results of a large (over 7,000 patients) open-label study*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P22.

Lepe, V. et al. *A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo*. Arch Dermatol 2003, 139(5): 581.

Lin, P. et al. *Tacrolimus ointment promotes repigmentation of vitiligo in children*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P573.

Lubbe, J. *Evolution of ointment use in long-term treatment with 0.03% and 0.1% tacrolimus ointment in patients with atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-23.

Lubbe, J., Saurat, J.H. *A monograph on topical tacrolimus (Protopic®)*. Ann Dermatol Venereol 2003, 130(2): 290.

Lubbe, J., Saurat, J.H. *Cutaneous infections with herpes simplex virus and tacrolimus ointment*. J Am Acad Dermatol 2003, 49(5): 965.

Mandelin, J. *A review of the short- and long-term efficacy of tacrolimus ointment versus corticosteroids in atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-24.

Meshkinpour, A., Sun, J., Weinstein, G. *Tacrolimus ointment in the treatment of seborrheic dermatitis*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P165.

Milingou, M., Antille, C., Saurat, J.H., Lubbe, J. *Alcohol intolerance in adult patients with atopic dermatitis treated with 0.1% topical tacrolimus ointment*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst SSS10-8.

Miura, H. et al. *Treatment of facial lesion of cutaneous plasmacytosis with tacrolimus ointment*. J Am Acad Dermatol 2003, 49(6): 1195.

Motter, M.R., Fleming, T., Bedocs, P. *Treatment of granuloma annulare with topical tacrolimus*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P170.

Niwa, Y. *Carcinogenesis of an immunosuppressant, topical tacrolimus used for therapy of atopic dermatitis*. Jpn J Cancer Res 2002, 93(Suppl.): Abst 2650.

Plettenberg, H. et al. *Childhood vitiligo and tacrolimus: Immunomodulating treatment for an autoimmune disease*. Arch Dermatol 2003, 139(5): 651.

Popescu, R., Popescu, C.M., Damian, A., Sbenghe, M.M., Voiculescu, V. *Seborrhoeic dermatitis successfully treated with topical tacrolimus*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P25-46.

Reitamo, S. *Superior efficacy of 0.1% tacrolimus ointment in treating adults with moderate to severe atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst FC16-9.

Reitamo, S. *0.1% Tacrolimus ointment is significanlty more efficacious than a steroid regimen in adults with moderate to severe atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 1): Abst PP1-28.

Reitamo, S. *0.1% Tacrolimus ointment twice daily is an effective treatment for adults with moderate or severe atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P20-31.

Remitz, A. *0.1% Tacrolimus ointment monotherapy effectively prevents flare in adults with moderate to severe atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 1): Abst PP1-29.

Remitz, A., Petan, J. *Flare prevention with long-term use of 0.1% tacrolimus ointment in children and adults with atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-17.

Rico, M.J., Hanifin, J., Leung, D., Paller, A. *Long-term use of tacrolimus ointment monotherapy is safe and efficacious in paediatric patients with atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-28.

Rico, M.J., Koo, J., Fleischer, A., Abramovits, W. *Long-term tacrolimus ointment monotherapy effectively controls atopic dermatitis - Results in 8000 patients*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-29.

Rico, M.J., Naylor, M., Elmets, C.A., Zheng, S., Petan, J. *Treatment with tacrolimus ointment is not associated with an increase in non-melanoma skin cancer*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 1): Abst PP1-30.

Rico, M.J., Paller, A., Hanifin, J., Eichenfeld, L. *Long-term (more than 3 years) tacrolimus ointment monotherapy effectively controls atopic dermatitis in children and adults*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-30.

Rico, M.J., Petan, J., Lawrence, I. *Tacrolimus ointment is safe and effective in the treatment of atopic dermatitis: Results of two large (about 8700 patients), long-term (three years) open-label studies in paediatric and adult patients*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 1): Abst PP1-31.

Rico, M.J., Schneider, L., Berger, W. *Tacrolimus ointment monotherapy is effective in patients with severe atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-26.

Rico, M.J., Spergel, J., Prenner, B. *Patients with mild atopic dermatitis benefit from tacrolimus ointment monotherapy*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-27.

Rico, M.J., Stiehm, E.R., Roberts, R.L., Kaplan, M.S., Corren, J., Parker, J.C. *Tacrolimus ointment does not suppress the immune system of children aged 2-12*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-25.

Rikkers, S.M. et al. *Topical tacrolimus treatment of atopic eyelid disease*. Am J Ophthalmol 2003, 135(3): 297.

Rubins, A., Gutmane, R., Rubins, S., Valdmane, N., Chigarevska, L., Zigure, S. *Long-term treatment of atopic dermatitis with tacrolimus ointment*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-33.

Ruzicka, T. et al. *Potential future dermatological indications for tacrolimus ointment*. Eur J Dermatol 2003, 13(4): 331.

Sand, C., Thomsen, H.K. *Topical tacrolimus ointment is an effective therapy for Hailey-Hailey disease*. Arch Dermatol 2003, 139(11): 1401.

Saripalli, Y.V. et al. *Tacrolimus ointment 0.1% in the treatment of nickel-induced allergic contact dermatitis*. J Am Acad Dermatol 2003, 49(3): 477.

Schneider, L., Berger, W., Rico, M. *Patients with severe atopic dermatitis benefit from tacrolimus ointment monotherapy*. J Allergy Clin Immunol 2003, 111(2, Part 2): Abst 348.

Simon, D., Conus, S., Vassina, E., Braathen, L.R., Simon, H.-U. *Immunopharmacological effects of topical tacrolimus in atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst FC16-10.

Spergel, J.M., Prenner, B.M., Rico, J. *Tacrolimus ointment monotherapy is a safe and effective treatment for mild atopic dermatitis*. J Allergy Clin Immunol 2003, 111(2, Part 2): Abst 349.

Stiehm, E.R., Roberts, R.L., Kaplan, M.S., Corren, J. *Tacrolimus ointment does not alter immune responses of eczematous children*. J Allergy Clin Immunol 2003, 111(2, Part 2): Abst 245.

Sugai, J., Kakurai, M., Otsuki, M., Nakagawa, H. *Combination therapy with 0.1% tacrolimus ointment and cetirizine for facial atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-8.

Tanghetti, E.A. *Tacrolimus ointment 0.1% produces repigmentation in patients with vitiligo: Results of a prospective patient series*. Cutis 2003, 71(2): 158.

Tanojo, H., Lenn, J., Sykes, J., Huang, X. *Effects of co-application on the in vitro skin penetration and drug distribution of betamethasone 17-valerate and tacrolimus*. 61st Annu Meet Am Acad Dermatol (March 21-26, San Francisco) 2003, Abst P342.

Tomson, N., Tan, C.Y. *Recurrent widespread severe infection of the skin in a young patient on topical tacrolimus*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst FC18-3.

Torok, H.M. et al. *Clocortolone pivalate cream 0.1% used concomitantly with tacrolimus ointment 0.1% in atopic dermatitis*. Cutis 2003, 72(2): 161.

Travis, L.B. et al. *Successful treatment of vitiligo with 0.1% tacrolimus ointment*. Arch Dermatol 2003, 139(5): 571.

Undre, N.A., Moloney, F., Ahmadi, S., Stevenson, P., Murphy, G.M. *Skin pharmacokinetics of tacrolimus ointment in adult patients with moderate to severe atopic dermatitis*. J Eur Acad Dermatol Venereol 2003, 17(Suppl. 1): Abst PP1-41.

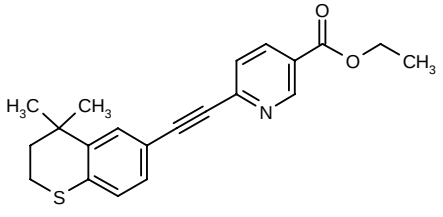
Vecchietti, G. et al. *Topical tacrolimus (FK506) for relapsing erosive stomatitis in paraneoplastic pemphigus*. Br J Dermatol 2003, 148(4): 833.

Yudate, T., Yajima, A., Aragane, Y., Yamazaki, F., Kawada, K. *Clinical effectiveness of tacrolimus ointment on atopic dermatitis other than facial lesions*. J Eur Acad Dermatol Venereol 2003, 17(8): Abst P2-9.

Tadekinig-α

Tadekinig-α is a recombinant unmodified form of the naturally occurring human IL-18-binding protein (rhIL-18bp) prepared at Serono that is capable of neutralizing the biological activity of IL-18, thereby inhibiting the secretion of TNF-α, interferon gamma and IL-1, and preventing inflammation. By reducing the levels of these proinflammatory cytokines to the normal range, it is believed that the immunological balance in psoriasis will be restored. Phase I studies have been completed and a phase II clinical study is under way in psoriasis. It is also in phase evaluation for rheumatoid arthritis.

Tazarotene



Allergan has submitted an NDA for oral tazarotene, a highly selective retinoid, for the treatment of moderate to very severe psoriasis. The submission is based on results from multicenter, double-blind, randomized, placebo-controlled studies of 12-week treatment with oral tazarotene (4.5 mg/day) followed by 12-week posttreatment follow-up. Oral tazarotene demonstrated a statistically significant difference compared with placebo and significant improvements observed at the end of the treatment in all clinical measures were maintained during the post-treatment period. Clinical improvement with oral tazarotene was seen as early as 4 weeks, with significant improvement seen within 8 weeks of treatment. Allergan plans to outlicense the tazarotene molecule for indications in both psoriasis and acne outside North America. In North America, Allergan will seek an acne development partner for the phase III trials (1, 2). Topical formulations (gel and cream) of tazarotene (Tazorac®, Zorac® in Europe) were previously introduced by Allergan for the treatment of psoriasis and acne. A cream formulation has also been available for several years under the brand name Avage™ as an adjunct for mitigating some of the signs associated with overexposure to the sun. The company is collaborating on the development of this product with Procter & Gamble in North America and with Pierre Fabre in Europe.

1. *Allergan submits NDA for oral tazarotene for psoriasis*. DailyDrugNews.com (Daily Essentials) Nov 27, 2003.

2. *Allergan reports Q4 R&D highlights*. Allergan Press Release 2004, Jan 28.

Original monograph – Drugs Fut 1997, 22(3): 249.

Thymosin β4

Ac-Ser-Asp-Lys-Pro-Asp-Met-Ala-Glu-Ile-Glu-Lys-Phe-Asp-Lys-Ser-Lys-Leu-Lys-Lys-Thr-Glu-Thr-Gln-Glu-Lys-Asn-Pro-Leu-Pro-Ser-Lys-Glu-Thr-Ile-Glu-Gln-Glu-Lys-Gln-Ala-Gly-Glu-Ser-OH

RegeneRx Biopharmaceuticals has successfully completed a phase I trial with its lead therapy thymosin β4 (Tβ4, TB4), a novel wound-healing drug. The 6-month study begun in March 2003 evaluated 4 different dose regimens in 15 volunteers. Tβ4 was well tolerated. The next series of clinical trials will evaluate the efficacy of Tβ4 in patients with different types of chronic dermal wounds. Tβ4, a naturally occurring 43-amino-acid peptide vital for the repair and remodeling of injured tissues, is present in virtually all human cells. Its gene is upregulated following tissue injury and during the remodeling and differentiation of cells. Tβ4 promotes endothelial and keratinocyte cell migration, downregulates a number of inflammatory cytokines and chemokines, promotes angiogenesis, and has a very low molecular weight that allows it to diffuse relatively long distances through tissues. A key mechanism of action is its ability to regulate the cell-building protein actin. Tβ4 has been shown to be effective in the repair of dermal and corneal wounds in numerous animal models. RegeneRx is developing Tβ4 for the treatment of acute and chronic wounds and a variety of diseases involving tissue and organ repair under an exclusive worldwide license from the National Institutes of Health (NIH). Phase II trials are expected to begin in the second quarter of 2004. The company also recently licensed certain European rights to Tβ4 to Sigma-Tau's

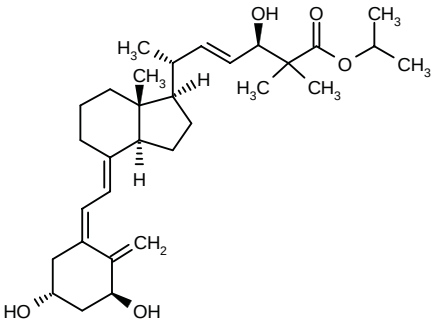
subsidiary Defiante Farmaceutica. According to the license agreement, in order to maintain the license, Defiante must either pay RegeneRx USD 5 million or initiate pivotal phase III clinical trials in Europe when RegeneRx successfully completes U.S. phase II trials (1-3).

1. *Clinical testing of Tβ4 begins at RegeneRx*. DailyDrugNews.com (Daily Essentials) April 10, 2003.

2. *Successful completion of phase I trial of Tβ4*. DailyDrugNews.com (Daily Essentials) Oct 10, 2003.

3. *RegeneRx licenses out European rights to TB4*. DailyDrugNews.com (Daily Essentials) Jan 27, 2004.

Tisocalcitate



The calcitriol analogue tisocalcitate is a topically active substance presently in phase II clinical development at Schering AG for use in the treatment of mild to moderate psoriasis.

T4N5 Liposome Lotion

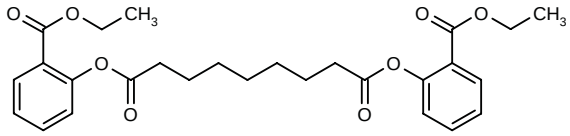
AGI Dermatics is developing T4N5 liposome lotion (Dimericine®) as the first skin enzyme replacement therapy for repairing DNA damage due to sun exposure. T4N5 liposomes encapsulate a purified DNA repair enzyme that is delivered to the skin, and can be used before, during and especially after exposure to the sun. Results from preclinical studies have demonstrated its ability to enhance DNA repair, prevent immunosuppression and reduce skin cancer from UV exposure. Clinical testing of the product in patients with xeroderma pigmentosum, a rare genetic disease in which patients lack DNA repair of sun damage and develop skin cancer at an early age, has demonstrated efficacy in reducing skin cancer and precancerous skin damage. AGI Dermatics regained all rights to T4N5 liposome lotion last year in connection with the termination of its Dimericine Development Corporation joint venture with Elan. Elan concluded its participation in the joint venture due to its restructuring effort. The company sold its portion of the partnership and now remains only as a shareholder of AGI Dermatics (1).

1. *AGI Dermatics regains rights to Dimericine*. DailyDrugNews.com (Daily Essentials) April 23, 2003.

TS-022

TS-022 is reportedly in phase I clinical development at Taisho for the treatment of atopic dermatitis.

TU-2100



Tamarkin Pharmaceutical Innovation's most advanced product, TU-2100, is a dual-action prodrug designed to treat acne, psoriasis, seborrhea and hair growth disorders. In a phase II trial, TU-2100 proved effective in ameliorating the symptoms of acne without causing skin irritation. The company is also currently evaluating its potential in patients with psoriasis and seborrheic dermatitis.

VAG-624

A potential antiacne agent VAG-624 is in phase I clinical trials at Novartis.

Vapaliximab

As part of BioTie Therapies' vascular adhesion protein-1 (VAP-1) monoclonal antibody program, clinical studies with the humanized (chimeric) antibody vapaliximab (HuVAP®, BTT-1002) began in the second half of 2002. Available results from a first phase I study with vapaliximab suggest that, although the antibody was well tolerated, the pharmacokinetic profile was not consistent with the needs for a product for chronic conditions. BioTie in collaboration with its partner Seikagaku therefore decided that vapaliximab will be structurally modified and that BioTie will focus on developing a humanized (nonchimeric) or a fully human VAP-1 monoclonal antibody. A decision will be made during the third quarter of this year, at which time the company will also decide on the schedule of the next clinical studies. The decision will not affect the licensing agreement with Seikagaku

covering Japan, Taiwan, Singapore, New Zealand and Australia. BioTie also plans to stick to its timeline for signing a licensing agreement for North American and European rights on the VAP-1 antibody program. The VAP-1 inflammation receptor is an endothelial cell adhesion molecule with a potential role in inflammatory diseases such as rheumatoid arthritis, psoriasis and ulcerative colitis. Vapaliximib was developed in collaboration with Cambridge University, the University of Turku and Boehringer Ingelheim (1, 2).

1. *BioTie enters VAP-1 licensing agreement with Seikagaku*. DailyDrugNews.com (Daily Essentials) May 13, 2003.

2. *BioTie Therapies updates progress*. DailyDrugNews.com (Daily Essentials) May 28, 2003.

Vibriolysin

BioMarin is developing vibriolysin (Vibrilase™) as a topically applied enzyme therapy for the debridement of serious burns**.** Vibriolysin preferentially digests burned skin, leaving healthy tissue intact. A phase Ib trial of vibriolysin in patients with partial thickness burns is under way (1).

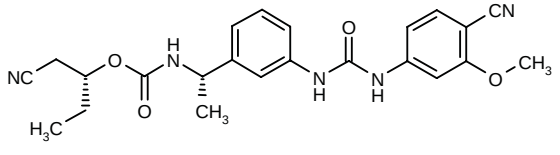
1. *BioMarin reports Q3 R&D highlights*. BioMarin Pharmaceutical Press Release 2003, Nov 4.

VIT-100

The first patient was treated about a year ago in a phase I physician-sponsored trial evaluating the safety and efficacy of Immusol's investigational drug VIT-100 (ChelASE™) to treat keloids and hypertrophic scars. In preclinical studies, VIT-100 inhibited the growth of cells taken from multiple keloid biopsies as compared to the same keloid cells treated with a control (1). VIT-100 is also in more advanced development (phase II) for the treatment of proliferative vitreoretinopathy.

1. *Patient treatment begins in phase I trial of VIT-100*. DailyDrugNews.com (Daily Essentials) April 23, 2003.

VX-148

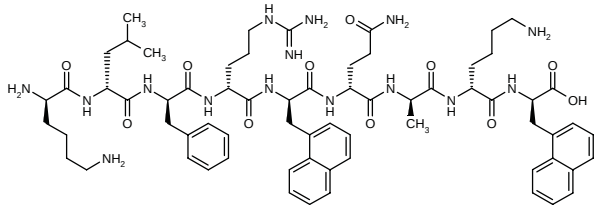


A phase II study of VX-148, a second-generation IMP dehydrogenase (IMPDH) inhibitor, in moderate to severe psoriasis has been completed. Final analysis of the results is continuing, but additional dose range testing will likely be needed prior to initiating a phase IIb clinical study in psoriasis. Vertex does not expect to proceed with additional trials in 2004 and may pursue an alliance to provide resources for development and commercialization of VX-148 in autoimmune indications including multiple sclerosis, psoriasis and systemic lupus erythematosus (SLE) (1, 2).

1. *Vertex reviews internal and partnered progress*. DailyDrugNews.com (Daily Essentials) May 23, 2003.

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

XMP-629



Xoma has initiated a phase II trial with its XMP-629 peptide, which is being developed as a topical treatment for acne. The randomized, double-blind, placebo-controlled, dose-ranging efficacy and safety study will enroll 240 patients with mild to moderate acne. One of 3 concentrations of XMP-629 or placebo will be administered to each patient once daily for 12 weeks. Efficacy will be evaluated based on the decrease in the number of inflammatory lesions, noninflammatory lesions, total lesions and Physician's Global Severity Assessment. Safety and tolerability will also be assessed. Preclinical studies found XMP-629 to be a potent agent against *Propionibacterium acnes* and other related skin microorganisms associated with acne. The drug demonstrated favorable topical properties, safety and rapid bactericidal activity. Phase I studies also showed favorable properties in terms of skin irritation and penetration. Xoma will decide by the end of 2004 whether or not to advance XMP-629 into phase III trials. XMP-629 is a synthetic peptide compound derived from bactericidal/permeability-increasing protein (BPI) (1, 2).

1. *XMP-629 enters phase I trial for topical treatment of acne*. DailyDrugNews.com (Daily Essentials) Oct 2, 2003.

2. *XMP-629 enters phase II for acne*. DailyDrugNews.com (Daily Essentials) Jan 26, 2004.