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Annual Update 2004/2005 - Treatment of Dermatological Disorders

As in previous issues, the goal of this section 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. Two tables of oncolytic drugs, one for skin cancers and the other for head and neck cancer, have been included at the end of this review.

J.R. Prous
Editor

Treatment of Dermatological Disorders by Condition

Condition	Phase	Drug	Source
Acne	R-2005	Dapsone[1], gel	QLT
	Prereg.	Clindamycin phosphate, foam	Connetics
	Prereg.	Clindamycin phosphate/tretinoin, gel	Connetics
	II	Aminolevulinic acid hydrochloride[1]	Dusa
	II	MDI-101	Molecular Design International
	II	MX-594AN	Migenix
	II	PCL-016	Novactyl
	II	PSK-3841	ProStrakan
	II	Rambazole™	Barrier Therapeutics
	II - On hold	XMP-629	Xoma
	II	Zileuton	Critical Therapeutics
	I/II	Aminolevulinic acid methyl ester[1]	PhotoCure/Galderma
	I	VIC-acne	Vicuron Pharmaceuticals
Actinic keratosis	L-2004	Imiquimod[1]	3M Pharmaceuticals
	II	PEP-005	Peplin
	II	PN-106	Wellstat Therapeutics
	II	Polyphenon® E, ointment	MediGene
Allergy, skin	II	Hivenyl™	Barrier Therapeutics/Janssen (Johnson & Johnson)
Alopecia	II	PSK-3841	ProStrakan
Alopecia areata	II	Bexarotene[1], gel	Ligand
Burns	II	Mecasermin rinfabate	Insmed
	I	Vibriolysin	BioMarin
Dermatitis, atopic	III	Desonide, foam	Connetics
	II	AA-10006	Arachnova
	II	NPI-32101	Nucryst
	II	Recombinant α_1-antitrypsin, gel	ProMetic Life Sciences
	II	Sorafin™-AD	Psiron
	I/II	NF-κB decoy	Corgentech
	I	AWD-12-281 (842470)	elbion/GlaxoSmithKline
	I	TS-022	Taisho
Dermatitis, hand	III	Alitretinoin[1], capsules	Basilea
	III	Pimecrolimus[1], cream	Novartis
	II	Bexarotene[1], gel	Ligand

Continuation

Treatment of Dermatological Disorders by Condition

Condition	Phase	Drug	Source
Dermatitis, seborrheic	III	Ketoconazole[1], foam	Connetics
	III	Ketoconazole[1], gel	Barrier Therapeutics
	II	Azoline	Barrier Therapeutics
	II	Pimecrolimus[1], cream	Novartis
Dermatological disorders	II	Recombinant α_1-antitrypsin, gel	ProMetic Life Sciences
Eczema	II	F-991	Fornix BioSciences
Epidermolysis bullosa	I/II	Thymosin beta 4	RegeneRx Biopharmaceuticals/Sigma-Tau
Ichthyosis, congenital	III	Liarozole fumarate	Barrier Therapeutics
Inflammation, skin	II	IDEA-070	Idea
	II	Pimecrolimus[1], oral/cream	Novartis
Keloid scarring	II	4-Hydroxytamoxifen, gel	Ascend Therapeutics
Keloids	I/II	ChelASE™	Immusol
Lesion, skin	I	PN-105	Wellstat Therapeutics
Pemphigus vulgaris	I	PI-0824	Peptimmune
Photodamage	II	Aminolevulinic acid hydrochloride[1]	Dusa
	II	EPT-1647	EpiTan
	II	NV-07α	Novogen
Pruritus	I/II	LI-412	Enhance Biotech
Pruritus, uremic	III (JP)	Nalfurafine hydrochloride	Toray/Japan Tobacco/Torii Pharmaceutical
	II (EU)	Nalfurafine hydrochloride	Toray/Acologix
Psoriasis	L-2004	Etanercept[1]	Amgen/Wyeth
	Prereg.	Infliximab[1]	Schering-Plough/Centocor (Johnson & Johnson)
	Prereg.	Tazarotene[1], oral	Allergan
	III	Adalimumab[1]	Abbott/Eisai
	III	BG-12	Biogen Idec/Fumapharm
	III	ISA-247	Isotechnika
	III	Rosiglitazone maleate[1]	GlaxoSmithKline
	III	Tacrolimus[1], gel/cream	Astellas Pharma
	II	Becocalcidiol	QuatRx
	II	Bexarotene[1], gel	Ligand
	II	Bimosiamose	Revotar Biopharmaceuticals (Encysive Pharmaceuticals)
	II	BSP-103	BSP Pharma
	II	CC-10004	Celgene
	II	CNTO-1275	Medarex/Centocor (Johnson & Johnson)
	II	CRx-140	CombinatoRx
	II	Kahalalide F	PharmaMar
	II	MV-9411	Miravant
	II	Paclitaxel[1], micellar	Angiotech
	II	Psoraxine™	Astralis/SkyePharma
	II	Rambazole™	Barrier Therapeutics
	II	STA-5326	Synta
	II	VX-765	Vertex
	II	XP-828L	Advitech
	I/II	ATL-1101	Antisense Therapeutics/Isis Pharmaceuticals
	I/II	AVT-02	Avontec
	I/II	CYT-007-TNFQb	Cytos Biotechnology
	I/II	PH-10	Provectus
	I/II	PMX-53	Promics
	I/II	PTH (1-34), nanovesicular topical	Manhattan Pharmaceuticals/IGI
	I	BCX-4208	BioCryst
	I	BT-061	Biotest
	I	Calcithiazol	Intendis
	I	CTA-018	Cytochroma
	I	LL-4218	Lupin

Continuation

Treatment of Dermatological Disorders by Condition

Condition	Phase	Drug	Source
Psoriasis	I	LLL-3348	Lupin
	I	TRX4	TolerRx
Rosacea	Prereg.	Doxycycline hyclate[1], modified-release	CollaGenex
	II	COL-3	CollaGenex
	I/II	Dapsone[1], gel	QLT
Scar, hypertrophic	I/II	ChelASE™	Immusol
	Discontinued	Fibrostat®	Procyon Biopharma
Ulcer, diabetic	II	E-Matrix™	Encelle/Smith & Nephew
	II	OrCel™[1]	Ortec
	II	Talactoferrin alfa, gel	Agennix
	I/II	TP-508	OrthoLogic
	I	GAM-501	Selective Genetics
	I	Iroxanadine	CytRx
	I	MRE-0094	Aderis/King Pharmaceuticals
Ulcer, pressure	I/II	Thymosin beta 4	RegeneRx Biopharmaceuticals/Sigma-Tau
Ulcer, skin	II	Allox™	Healthpoint
Ulcer, venous leg	Prereg.	OrCel™[1]	Ortec
	I/II	Thymosin beta 4	RegeneRx Biopharmaceuticals/Sigma-Tau
Ulcer, venous stasis	II	Glucoprime™	Novogen
Urticaria	II	BF-Derm1	Biofrontera
Xeroderma pigmentosum	III	T4N5 liposome lotion	AGI Dermatics

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

Treatment of Dermatological Disorders by Source

Source	Condition	Drug	Phase
3M Pharmaceuticals	Actinic keratosis	Imiquimod[1]	L-2004
Abbott	Psoriasis	Adalimumab[1]	III
Acologix	Pruritus, uremic	Nalfurafine hydrochloride	II (EU)
Aderis	Ulcer, diabetic	MRE-0094	I
Advitech	Psoriasis	XP-828L	II
Agennix	Ulcer, diabetic	Talactoferrin alfa, gel	II
AGI Dermatics	Xeroderma pigmentosum	T4N5 liposome lotion	III
Allergan	Psoriasis	Tazarotene[1], oral	Prereg.
Amgen	Psoriasis	Etanercept[1]	L-2004
Angiotech	Psoriasis	Paclitaxel[1], micellar	II
Antisense Therapeutics	Psoriasis	ATL-1101	I/II
Arachnova	Dermatitis, atopic	AA-10006	II
Ascend Therapeutics	Keloid scarring	4-Hydroxytamoxifen, gel	II
Astellas Pharma	Psoriasis	Tacrolimus[1], gel/cream	III
Astralis	Psoriasis	Psoraxine™	II
Avontec	Psoriasis	AVT-02	I/II
Barrier Therapeutics	Acne	Rambazole™	II
	Allergy, skin	Hivenyl™	II
	Dermatitis, seborrheic	Azoline	II
		Ketoconazole[1], gel	III
	Ichthyosis, congenital	Liarozole fumarate	III
	Psoriasis	Rambazole™	II
Basilea	Dermatitis, hand	Alitretinoin[1], capsules	III
BioCryst	Psoriasis	BCX-4208	I
Biofrontera	Urticaria	BF-Derm1	II
Biogen Idec	Psoriasis	BG-12	III
BioMarin	Burns	Vibriolysin	I
Biotest	Psoriasis	BT-061	I
BSP Pharma	Psoriasis	BSP-103	II
Celgene	Psoriasis	CC-10004	II
Centocor (Johnson & Johnson)	Psoriasis	CNTO-1275	II
		Infliximab[1]	Prereg.
CollaGenex	Rosacea	COL-3	II
		Doxycycline hyclate[1], modified-release	Prereg.
CombinatoRx	Psoriasis	CRx-140	II
Connetics	Acne	Clindamycin phosphate, foam	Prereg.
		Clindamycin phosphate/tretinoin, gel	Prereg.
	Dermatitis, atopic	Desonide, foam	III
	Dermatitis, seborrheic	Ketoconazole[1], foam	III
Corgentech	Dermatitis, atopic	NF-κB decoy	I/II
Critical Therapeutics	Acne	Zileuton	II
Cytochroma	Psoriasis	CTA-018	I
Cytos Biotechnology	Psoriasis	CYT-007-TNFQb	I/II
CytRx	Ulcer, diabetic	Iroxanadine	I
Dusa	Acne	Aminolevulinic acid hydrochloride[1]	II
	Photodamage	Aminolevulinic acid hydrochloride[1]	II
Eisai	Psoriasis	Adalimumab[1]	III
elbion	Dermatitis, atopic	AWD-12-281 (842470)	I
Encelle	Ulcer, diabetic	E-Matrix™	II
Enhance Biotech	Pruritus	LI-412	I/II
EpiTan	Photodamage	EPT-1647	II
Fornix BioSciences	Eczema	F-991	II
Fumapharm	Psoriasis	BG-12	III
Galderma	Acne	Aminolevulinic acid methyl ester[1]	I/II
GlaxoSmithKline	Dermatitis, atopic	AWD-12-281 (842470)	I
	Psoriasis	Rosiglitazone maleate[1]	III
Healthpoint	Ulcer, skin	Allox™	II
Idea	Inflammation, skin	IDEA-070	II
IGI	Psoriasis	PTH (1-34), nanovesicular topical	I/II
Immusol	Keloids	ChelASE™	I/II
	Scar, hypertrophic	ChelASE™	I/II
Insmed	Burns	Mecasermin rinfabate	II
Intendis	Psoriasis	Calcithiazol	I
Isis Pharmaceuticals	Psoriasis	ATL-1101	I/II
Isotechnika	Psoriasis	ISA-247	III

Continuation

Treatment of Dermatological Disorders by Source

Source	Condition	Drug	Phase
Janssen (Johnson & Johnson)	Allergy, skin	Hivenyl™	II
Japan Tobacco	Pruritus, uremic	Nalfurafine hydrochloride	III (JP)
King Pharmaceuticals	Ulcer, diabetic	MRE-0094	I
Ligand	Alopecia areata	Bexarotene[1], gel	II
	Dermatitis, hand	Bexarotene[1], gel	II
	Psoriasis	Bexarotene[1], gel	II
Lupin	Psoriasis	LL-4218	I
		LLL-3348	I
Manhattan Pharmaceuticals	Psoriasis	PTH (1-34), nanovesicular topical	I/II
Medarex	Psoriasis	CNTO-1275	II
MediGene	Actinic keratosis	Polyphenon® E, ointment	II
Migenix	Acne	MX-594AN	II
Miravant	Psoriasis	MV-9411	II
Molecular Design International	Acne	MDI-101	II
Novactyl	Acne	PCL-016	II
Novartis	Dermatitis, hand	Pimecrolimus[1], cream	III
	Dermatitis, seborrheic	Pimecrolimus[1], cream	II
	Inflammation, skin	Pimecrolimus[1], oral/cream	II
Novogen	Photodamage	NV-07α	II
	Ulcer, venous stasis	Glucoprime™	II
Nucryst	Dermatitis, atopic	NPI-32101	II
Ortec	Ulcer, diabetic	OrCel™[1]	II
Ortec	Ulcer, venous leg	OrCel™[1]	Prereg.
OrthoLogic	Ulcer, diabetic	TP-508	I/II
Peplin	Actinic keratosis	PEP-005	II
Peptimmune	Pemphigus vulgaris	PI-0824	I
PharmaMar	Psoriasis	Kahalalide F	II
PhotoCure	Acne	Aminolevulinic acid methyl ester[1]	I/II
Procyon Biopharma	Scar, hypertrophic	Fibrostat®	Discontinued
ProMetic Life Sciences	Dermatitis, atopic	Recombinant α_1-antitrypsin, gel	II
	Dermatological disorders	Recombinant α_1-antitrypsin, gel	II
Promics	Psoriasis	PMX-53	I/II
ProStrakan	Acne	PSK-3841	II
	Alopecia	PSK-3841	II
Provectus	Psoriasis	PH-10	I/II
Psiron	Dermatitis, atopic	Sorafin™-AD	II
QLT	Acne	Dapsone[1], gel	R-2005
	Rosacea	Dapsone[1], gel	I/II
QuatRx	Psoriasis	Becocalcidiol	II
RegeneRx Biopharmaceuticals	Epidermolysis bullosa	Thymosin beta 4	I/II
	Ulcer, pressure	Thymosin beta 4	I/II
	Ulcer, venous leg	Thymosin beta 4	I/II
Revotar Biopharmaceuticals (Encysive Pharmaceuticals)	Psoriasis	Bimosiamose	II
Schering-Plough	Psoriasis	Infliximab[1]	Prereg.
Selective Genetics	Ulcer, diabetic	GAM-501	I
Sigma-Tau	Epidermolysis bullosa	Thymosin beta 4	I/II
	Ulcer, pressure	Thymosin beta 4	I/II
	Ulcer, venous leg	Thymosin beta 4	I/II
SkyePharma	Psoriasis	Psoraxine™	II
Smith & Nephew	Ulcer, diabetic	E-Matrix™	II
Synta	Psoriasis	STA-5326	II
Taisho	Dermatitis, atopic	TS-022	I
TolerRx	Psoriasis	TRX4	I
Toray	Pruritus, uremic	Nalfurafine hydrochloride	II (EU)
		Nalfurafine hydrochloride	III (JP)
Torii Pharmaceutical	Pruritus, uremic	Nalfurafine hydrochloride	III (JP)
Vertex	Psoriasis	VX-765	II
Vicuron Pharmaceuticals	Acne	VIC-acne	I
Wellstat Therapeutics	Actinic keratosis	PN-106	II
	Lesion, skin	PN-105	I
Wyeth	Psoriasis	Etanercept[1]	L-2004
Xoma	Acne	XMP-629	II - On hold

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

Treatment of Dermatological Disorders

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AA-10006

AA-10006 (Araderm™) is a novel topical preparation of a known oral anxiolytic agent in phase II trials at Arachnova for the treatment of atopic dermatitis. As a nonsteroidal agent, it possesses advantages over the current treatments for dermatitis by avoiding thinning of the skin, as well as the burning at the application site that has been reported with the newer immunosuppressant products.

Adalimumab

To date, adalimumab (D2E7, Humira®) has been approved in 41 countries and launched in 26 for the treatment of moderately to severely active rheumatoid arthritis in adults not adequately responding to one or more disease-modifying antirheumatic drugs (DMARDs). A fully human monoclonal antibody targeting TNF-α developed through a collaboration between Abbott and Cambridge Antibody Technology (CAT), it was first approved in the U.S. in late 2002. Abbott has submitted supplemental BLAs in the U.S. and an MAA in Europe seeking approval for its use in psoriatic arthritis and early rheumatoid arthritis. Late-stage clinical trials are also under way in juvenile rheumatoid arthritis, psoriasis, ankylosing spondylitis and Crohn's disease. Eisai and Abbott recently signed a supplemental agreement for the joint development and marketing of adalimumab for the new indication of psoriasis in Japan. The agreement supplements previous agreements for the joint development and marketing of adalimumab for rheumatoid arthritis and Crohn's disease in Japan (1-6).

New phase II data were presented in 2004 for adalimumab demonstrating that patients with moderate to severe psoriasis receiving 40 mg adalimumab every other week achieved statistically significant results after 12 weeks. More than 50% of patients achieved at least 75% improvement. The data also demonstrated that adalimumab was well tolerated (7).

A recent study investigated the mechanism of anti-TNF-α therapy with adaliumuab for psoriasis. Immunohistochemical examination of biopsies taken from lesioned skin revealed that upon treatment with adalimumab, expression of the immunomodulatory enzyme

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

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis, Arthritis, psoriatic	Randomized Double-blind	Adalimumab, 80 mg at wk 0 → 40 mg 1x/2 wks at wk 1-24 Adalimumab, 80 mg at wk 0 & 1 → 40 mg 1x/wk at wk 2-24 Placebo x 12 wks → Adalimumab, 80 mg at wk 12 → 40 mg 1x/2 wks at wk 13-24	148	Adalimumab was effective and well tolerated in patients with moderate to severe chronic plaque psoriasis with or without psoriatic arthritis	9-14
Psoriasis, Arthritis, psoriatic	Randomized Double-blind Multicenter	Open	10	Adalimumab showed considerable effect in patients with psoriasis and psoriatic arthritis	15
Psoriasis	Double-blind Multicenter	Adalimumab, 80 mg at wk 0 → 40 mg at wk 1 1x/2 wks up to 60 wks (n=43) Adalimumab, 80 mg at wk 0 & 1 → 40 mg 1x/wk at wk 2-60 (n=47) Placebo x 12 wks → Adalimumab, 80 mg at wk 0 → 40 mg 1x/2 wks x 48 wks (n=47)	137	Adalimumab improved quality of life which was sustained for up to 60 weeks in patients with moderate to severe chronic plaque psoriasis	16-18

indoleamine 2,3-dioxygenase (IDO) increased dramatically. This enzyme is a potent T-cell-inhibitory enzyme in dermal mononuclear cells, which therefore could explain the therapeutic effects of this antibody (8).

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

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

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

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

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

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

7. *Abbott Laboratories reports Q1 R&D highlights.* Abbott Laboratories Press Release 2004, April 8.

8. Gordon, K.B. et al. *Indoleamine 2,3 dioxygenase expression by dermal CD68+ mononuclear cells is increased in psoriatic plaques after treatment with anti-TNF mAb, adalimumab.* J Invest Dermatol 2005, 124(4, Suppl.): Abst 253.

9. Blum, R., Lebwohl, M., Gottlieb, A., Chen, D. *Durability of treatment response in patients with moderate to severe psoriasis following withdrawal from or a dose reduction in adalimumab therapy.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2737 (Table I).

10. Gordon, K., Langley, R., Leonardi, C., Toth, D., Menter, A., Chen, D. *Treatment of moderate to severe plaque psoriasis with 24 weeks of adalimumab.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P06.40 (Table I).

11. Langley, R. et al. *Long-term safety and efficacy of adalimumab in the treatment of moderate to severe chronic plaque psoriasis.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P8 (Table I)

12. Menter, M.A., Gordon, K., Leonardi, C., Chen, D. *Adalimumab efficacy and safety results in patients with moderate to severe chronic plaque psoriasis with and without psoriatic arthritis.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2713 (Table I).

13. Menter, M.A., Gordon, K.B., Leonardi, C., Heffernan, M.P., Chen, D.M. *Adalimumab efficacy and safety results in patients with moderate to severe chronic plaque psoriasis: Subanalysis of patients with and without PsA.* Rheumatology (Oxford) 2005, 44(Suppl. 1): Abst 269 (Table I).

14. Patel, T., Leonardi, C., Kang, S., Gordon, K. *Treatment with adalimumab induces rapid normalization of epidermal keratinocytes in psoriasis patients.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2816 (Table I).

15. Leonardi, C. *Management of difficult psoriasis and psoriatic arthritis patients by transition to adalimumab.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2775 (Table I).

16. Wallace, K., Bissonnette, R., Leonardi, C., Chen, D. *Effects of adalimumab on health status as measured by EQ-5D in patients with moderate to severe plaque psoriasis.* 63 Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2741 (Table I).

17. Wallace, K., Gordon, K., Langley, R., Chen, D. *Dermatologic quality of life in patients with moderate to severe plaque psoriasis receiving 48 weeks of adalimumab therapy.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2734 (Table I).

18. Wallace, K., Leonardi, C., Kempers, S., Chen, D. *General physical and mental health status in patients with moderate to severe plaque psoriasis receiving 48 weeks of adalimumab therapy.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2757 (Table I).

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

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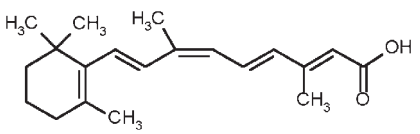
Cather, J., Menter, A., Abramovits, W. *Adalimumab for psoriasis.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2714.

Menter, M.A. et al. *Adalimumab efficacy and safety results in patients with moderate to severe chronic plaque psoriasis with and without PsA.* 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1622.

Wallace, K. et al. *Quality of life in moderate to severe plaque psoriasis patients receiving 24 weeks of adalimumab therapy.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P06.121.

Alitretinoin, Capsules



Enrollment is open in Basilea's phase III program investigating the efficacy and safety of alitretinoin (BAL-4079) in severe chronic hand dermatitis refractory to topical treatment. The company's BACH (Basilea Alitretinoin in Chronic Hand dermatitis) program comprises two double-blind, randomized studies investigating the efficacy and safety of 10- and 30-mg alitretinoin capsules *versus* placebo following 12-24 weeks of once-daily treatment. The primary efficacy endpoint for both studies is response rate as measured by the number of patients having clear or almost clear hands according to a physicians' global assessment. Safety assessments include regular monitoring of clinical and laboratory parameters. The international phase III program, starting in Europe, is designed to enroll over 2,000 patients from around 200 centers. Alitretinoin is a naturally occurring vitamin A derivative with a chemical structure that resembles both natural and synthetic retinoids. The investigational drug has shown activity during phase II studies involving over 200 patients with refractory chronic hand dermatitis. Since alitretinoin is teratogenic, Basilea's phase III studies incorporate a pregnancy risk management program (1). Ligand markets

a gel formulation of alitretinoin (Panretin®) for the treatment AIDS-related Kaposi's sarcoma lesions.

1. *BAL-4079 enters phase III for severe chronic hand dermatitis.* DailyDrugNews.com (Daily Essentials) Nov 2, 2004.

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Ruzicka, T. et al. *Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy. Results of a randomized, double-blind, placebo-controlled, multicenter trial.* Arch Dermatol 2004, 140(12): 1453.

Allox™

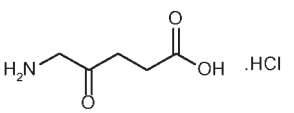
Allox™, an allogeneic product derived from human cells, is currently in phase II development at the DFB Pharmaceuticals' subsidiary Healthpoint for the treatment of chronic skin ulcers. Positive results were reported last year from a dose-escalating phase II trial. Delivered as a spray, it is a combination of keratinocytes, fibroblasts and fibrin. The product was being developed by Healthpoint under a license agreement with IsoTis OrthoBiologics' wound management unit EpiSource, which was sold to DFB Pharmaceuticals late last year (1-3).

1. *Positive phase II results for Allox. DailyDrugNews.com (Daily Essentials) July 13, 2004.*

2. *DFB acquires EpiSource from IsoTis OrthoBiologics. DFB Pharmaceuticals Press Release 2005, Jan 7.*

3. *IsoTis sells wound managment unit to DFB Pharmaceuticals, Inc. IsoTis OrthoBiologics Press Release 2004, Dec 20.*

Aminolevulinic Acid Hydrochloride



Dusa has initiated a multicenter phase II study of its Levulan® Kerastick® (aminolevulinic acid hydrochloride, ALA) photodynamic therapy (PDT) for the treatment of facial photodamage. The study will utilize broad-area, short-contact drug application combined with three different light sources: Lumenis's Intense Pulsed Light (IPL™), Cynosure's Long Pulsed Dye Laser (LPDL) and Dusa's own BLU-U® brand blue light. The study at four U.S. sites consists of two phases. The first phase, with up to 64 patients, will evaluate LPDL and IPL™ to establish the best light doses for PDT using these devices. The second phase, with up to 60 patients, will include up to three treatments per patient for photodamaged skin, given at 3-week intervals, using fixed light doses with one of the light sources. In both phases of the study, prior to treatment with any light source, the left and right sides of each subject's face will be randomized to receive topical Levulan® using Dusa's Kerastick® on one side and vehicle on the other. In addition to safety and tolerability, efficacy will be assessed on each side of the face using standard markers of photodamage. Dusa has also initiated a multicenter phase II study using its Levulan® Kerastick® and BLU-U® PDT for the treatment of moderate to severe acne vulgaris of the face. The study will examine the safety and efficacy of short-contact Levulan® Kerastick® combined with the BLU-U® for the treatment of patients with moderate to severe facial acne vulgaris. The study, with up to 80 patients, including a control group, will be carried out at three U.S. sites. It will examine the effect of varying drug incubation times, followed by a standardized light dose using the BLU-U®. Up to four Levulan® PDT treatments will be given at 2-week intervals. The primary efficacy parameters will be acne lesion count and acne severity score, assessed 8 weeks following the final Levulan® PDT treatment. Safety and tolerability will also be assessed throughout the study. The study is based on information from anecdotal and independent investigator studies. Independent investigator studies reported that a single topical ALA PDT treatment helped to improve moderate and refractory acne vulgaris, with several treatments resulting in significant improvement by both reducing the bacteria at the site of lesions and by acting to reduce activity of sebaceous glands. However, some of the early studies used ALA applied under occlusion for several hours, which was associated with significant side effects such as pain during treatment, a strong inflammatory reaction and hyperpigmentation. More recently, an independent investigator study used the Levulan® Kerastick® applied for 15 min over the face without occlusion, followed by light treatment with Dusa's BLU-U® for 6 min. Using this short drug incubation time, the investigator reported improvement in acne without pain, inflammation or hyperpigmentation. Levulan® PDT was initially approved by the FDA with the BLU-U® for the treatment of actinic keratoses and is marketed worldwide by Schering AG and its U.S. subsidiary Berlex; Draxis holds exclusive marketing rights for Canada. The product is also in phase II development for high-grade dysplasia in patients with Barrett's esophagus (1, 2).

1. *Phase II trials of Levulan PDT in high-grade dysplasia in Barrett's esophagus and facial photodamage.* DailyDrugNews.com (Daily Essentials) June 15, 2004.

2. *Phase II study for Levulan Kerastick in acne.* DailyDrugNews.com (Daily Essentials) Oct 27, 2004.

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

Additional References

Dover, J., Arndt, K., Bhatia, A., Stewart, B. *Adjunctive use of topical aminolevulinic acid with intense pulsed light in the treat-*

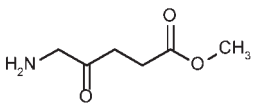
ment of photoaging. 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P3201.

Dover, J.S., Bhatia, A., Stewart, B., Arndt, K. *A bilateral comparison of the efficacy and safety of photodynamic therapy with 20% aminolevulinic acid (ALA) topical solution and intense pulsed light versus intense pulsed light alone in the treatment of mild to moderate photoaging.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P625.

Gold, M.H. *A single center, open label split face investigator study of photodynamic therapy in the treatment of photoaging with topical 20% 5-aminolevulinic acid and intense pulsed light.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P641.

Pollock, B. et al. *Topical aminolaevulinic acid-photodynamic therapy for the treatment of acne vulgaris: A study of clinical efficacy and mechanism of action.* Br J Dermatol 2004, 151(3): 616.

Aminolevulinic Acid Methyl Ester



Metvix® (aminolevulinic acid methyl ester) PDT is currently available in a number of markets from PhotoCure and partner Galderma for the treatment of actinic keratosis and basal cell carcinoma. In June, PhotoCure announced results form the first clinical study of Metvix® PDT in the treatment of acne. The study included 30 patients with moderate to severe acne and compared the efficacy of Metvix® PDT to placebo. Results showed that Metvix® PDT produced a significantly greater reduction in the number of inflammatory acne lesions compared to placebo at 12 weeks after treatment. The company plans to discuss further development strategies for this indication with Galderma (1).

1. *PhotoCure – First study in acne shows promising results.* PhotoCure Press Release 2005, June 10.

ATL-1101

The proof-of-concept study of Antisense Therapeutics' and Isis Pharmaceuticals' ATL-1101 in patients with mild to moderate psoriasis is now fully enrolled and dosing has commenced in all patients. ATL-1101 is a second-generation antisense drug designed to block the synthesis of the IGF-I (insulin-like growth factor-I) receptor, being developed as a topical cream. The microplaque assay will be used to examine the effects of this topical cream applied once every 2 days over a 1-month period. The double-blind, randomized, placebo-controlled trial will test the efficacy of two different drug concentrations of ATL-1101. The study is expected to be completed mid-year, with analysis of results to be reported in the third quarter of 2005. The study is supported by a Commonwealth Government R&D Start grant (1-5).

1. *Approval sought for proof-of-concept study for ATL-1101 in psoriasis.* DailyDrugNews.com (Daily Essentials) Oct 4, 2004.

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

3. *Antisense Therapeutics reports Q4 R&D highlights.* Antisense Therapeutics Press Release 2004, Aug 26.

4. *Antisense Therapeutics reviews progress.* DailyDrugNews.com (Daily Essentials) Feb 7, 2005.

5. *Antisense Therapeutics updates development status.* DailyDrugNews.com (Daily Essentials) June 3, 2005.

AVT-02

AVT-02 is a decoy oligonucleotide-based drug in phase I/II trials at Avontec for the treatment of psoriasis.

AWD-12-281 (842470)

The phosphodiesterase type 4 (PDE4) inhibitor AWD-12-281 (GW-842470, 842470) is in phase IIa development by elbion and partner GlaxoSmithKline for the treatment of chronic obstructive pulmonary disease (COPD), as well as phase I trials for atopic dermatitis (1).

1. *elbion AG increases series A financing to 35 million EUR.* elbion AG Press Release 2005, May 24.

Original monograph – Drugs Fut 2002, 27(2): 11.

Azoline

Barrier Therapeutics reports that oral azoline (R-126638) has produced encouraging results in a phase IIa trial in the treatment of superficial fungal infections. Data from 67 patients with various fungal infections of the skin treated with 200 mg once daily for 1, 3 or 5 days demonstrated response rates at day 28 of 60% for 1 day of treatment and between 78% and 100% for 3-5 days of treatment, depending on the type of skin condition. The drug was studied in tinea pedis, tinea corporis/cruris, tinea versicolor and seborrheic dermatitis. There were no serious treatment-related adverse effects reported. Azoline is a broad-spectrum antifungal agent that Barrier is developing as a short-course oral treatment for skin and mucosal

fungal infections. Studies have shown that azoline has a half-life in the body nearly 3 times longer than that of itraconazole, which may enable a more convenient dosing regimen. Barrier has completed four European phase IIa trials and anticipates initiating phase IIb trials in the U.S. in the second half of 2005 (1).

1. *Phase IIa data show utility of oral azoline in superficial fungal infections.* DailyDrugNews.com (Daily Essentials) Jan 14, 2005.

Additional References

Ausma, J. et al. *Placebo-controlled randomized double-blind multiple dose dose-rising trial in healthy volunteers to assess tolerability, safety and pharmacokinetics of the novel antifungal, R126638.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P08.40.

Ausma, J., Henry, F., Borgers, M., Pierard, G. *Effect of a single dose of R126638 in seborrheic dermatitis.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P1814.

BCX-4208

BioCryst's BCX-4208 has successfully completed a placebo-controlled, single-ascending-dose phase I pharmacokinetic and safety trial in 84 healthy volunteers. The study, which evaluated the pharmacokinetic profile of the oral formulation, measured BCX-4208 inhibition of the target enzyme purine nucleoside phosphorylase (PNP) and included detailed safety evaluations of renal and liver function, hematological parameters, immunological markers and cardiac function as measured through continuous ECG monitoring, including detailed Q-T_c evaluations. Results indicate that single doses of BCX-4208 ranging from 0.5 to 3 mg/kg were well tolerated. BCX-4208 achieved a dose-related inhibition of PNP, which effectively increases the serum level of deoxyguanosine that is necessary for selective suppression of T-cell activation. Based on these results, BioCryst intends to initiate a randomized, double-blind, multiple-escalating-dose phase I trial with BCX-4208 to further evaluate its safety profile and pharmacokinetics in approximately 60 healthy volunteers beginning in the second quarter of 2005. That trial will be immediately followed by an open-label phase II trial in psoriasis patients. BCX-4208 is BioCryst's second-generation, more potent transition-state analogue inhibitor of PNP. The complex of BCX-4208 and PNP has a long half-life (approximately 8 days) and suitable oral bioavailability, supporting its potential for chronic dosing in autoimmune diseases such as psoriasis. BioCryst also intends to investigate BCX-4208 for the treatment of other conditions that may involve T-cell activation, including rheumatoid arthritis, Crohn's disease and transplant rejection (1-5).

1. *BioCryst Pharmaceuticals reports Q1 R&D highlights.* BioCryst Pharmaceuticals Press Release 2004, April 21.

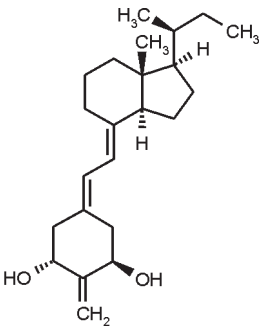
2. *BCX-4208 enters clinical development for psoriasis.* DailyDrugNews.com (Daily Essentials) Nov 10, 2004.

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

4. *Oral BCX-4208 successfully completes phase I trial.* DailyDrugNews.com (Daily Essentials) March 21, 2005.

5. *BioCryst Pharmaceuticals reports Q1 R&D highlights.* BioCryst Pharmaceuticals Press Release 2005, April 21.

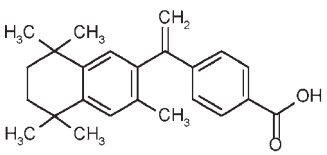
Becocalcidiol



A multicenter, randomized phase IIb clinical trial has evaluated the efficacy and safety of QuatRx's topical vitamin D analogue becocalcidiol (QRX-101) in the treatment of mild to moderate psoriasis. A total of 185 patients were given placebo, low-dose becocalcidiol or high-dose becocalcidiol topically for 8 weeks. High-dose becocalcidiol resulted in a significantly greater number of patients reporting clear or almost clear psoriatic lesions at the end of the study, and was also associated with significant reductions in both psoriasis symptom severity and affected body surface area. Both becocalcidiol doses were well tolerated. Phase III clinical trials are currently being prepared for becocalcidiol in the treatment of skin disorders (1).

1. *Becocalcidiol improves symptoms of mild to moderate psoriasis.* DailyDrugNews.com (Daily Essentials) June 17, 2005.

Bexarotene, Gel



Bexarotene is a retinoid X receptor (RXR) agonist first launched by Ligand in 2000 in the U.S. as Targretin® capsules and gel for the treatment of cutaneous T-cell

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

Indication	Design	Treatments	n	Conclusions	Ref.
Alopecia areata	Open	Bexarotene 1% gel top. o.d. x 2 wks → b.i.d. x 24 [max.] wks	21	Topical bexarotene was well tolerated and effective in inducing hair regrowth in 38% of patients with alopecia areata	1
Dermatitis	Randomized Open	Bexarotene 1% gel top. 1x/2 d x 2 wks → o.d. x 2 wks → b.i.d. x 2 wks → t.i.d. x 16 wks (n=28) Bexarotene 1% gel top. 1x/2 d x 2 wks → o.d. x 2 wks → b.i.d. x 2 wks → t.i.d. x 16 + Mometasone furoate 0.1% ointment (n=13) Bexarotene 1% gel top. 1x/2 d x 2 wks → o.d. x 2 wks → b.i.d. x 2 wks → t.i.d. x 16 + Hydrocortisone 1% ointment (n=14)	55	Bexarotene gel was safe and well tolerated, and showed useful activity in patients with severe chronic hand dermatitis, with no added benefit upon the addition of corticosteroids	2
Psoriasis	Randomized Double-blind	Bexarotene 1% gel top. 1x/2d x 1 wk → o.d. x 1 wk → b.i.d. [based on tolerability] x 8 wks + Ultraviolet B (narrow-band) 3x/wk at wk 3-10 Placebo + Ultraviolet B (narrow-band) 3x/wk at wk 3-10	9	Bexarotene 1% gel combined with narrow-band ultraviolet B phototherapy was well tolerated and substantially effective in patients with moderate to severe psoriasis vulgaris	3

lymphoma (CTCL) and now also available in many major European countries. Phase II trials are also being conducted by the company with bexarotene gel for the treatment of hand dermatitis, psoriasis and alopecia areata, as are phase II and III trials with the oral formulation in non-small cell lung cancer (NSCLC). Ligand retains marketing rights to the drug in the U.S., Canada and certain European markets, and has marketing agreements with Elan, Ferrer and Alfa Wassermann for other markets.

Researchers conducted a phase II clinical trial to determine the effects and safety of the bexarotene in the management of alopecia areata, an autoimmune disease mediated by T-cells that may cause loss of all scalp hair or body hair. Twenty-one patients were randomized to receive topical 1% bexarotene gel on one-half of the scalp once daily for 2 weeks, followed by twice-daily application for up to 24 weeks. At the end of the treatment period, 4 patients showed more than 50% partial hair regrowth, 4 had minor hair regrowth and 9 showed stabilization. Topical bexarotene was well tolerated, although application frequency was reduced in 5 patients due to erythema, scaling and/or itching caused by local irritation at the application site (1) (see Table II).

1. Talpur, R., Duvic, M., Kunishige, J., Stevens, V. *Results of stage I in a phase II randomized bilateral comparison of bexarotene 1% topical gel in alopecia areata.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P1510.

2. Hanifin, J.M. et al. *Novel treatment of chronic severe hand dermatitis with bexarotene gel.* Br J Dermatol 2004, 150(3): 545 (Table II).

3. Magliocco, M., Dombrovskiy, V., Pandya, K., Gottlieb, A. *A double-blind, vehicle-controlled, bilateral comparison trial of bexarotene gel 1% vs. vehicle gel in combination with narrow-band UVB phototherapy for moderate to severe psoriasis vulgaris.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2702 (Table II).

Additional References

Breneman, D.L., Sheth, P., Stevens, V. *Pilot trial of topical bexarotene gel in mild to moderate plaque psoriasis.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P593.

Kontos, A.P., Kerr, H.A., Fivenson, D.P. *Open-label pilot study of topical bexarotene 1% gel in the treatment of plaque-type body psoriasis in adults.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P06.78.

Smit, J.V. et al. *A phase II multicenter clinical trial of systemic bexarotene in psoriasis.* J Am Acad Dermatol 2004, 51(2, Part 1): 249.

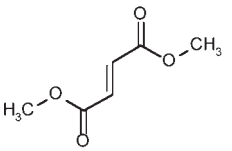
Smit, J.V. et al. *Systemic treatment of psoriatic patients with bexarotene decreases epidermal proliferation and parameters for inflammation, and improves differentiation in lesional skin.* J Am Acad Dermatol 2004, 51(2, Part 1): 257.

BF-Derm1

Biofrontera has reported positive interim data from its adaptive phase II trial for the treatment of severe chronic urticaria. In the multicenter, placebo-controlled study, Biofrontera's lead product, BF-Derm1, a histidine decarboxylase inhibitor, reduced urticaria symptoms in the patients by 30-40% on average, with no relevant side effects. An independent commission that evaluated the interim results strongly recommended the continuation of the study. The study was accompanied by an extensive safety program, particularly relating to laboratory data, cardiovascular analyses and CNS effects, in which the drug did not display any toxicity (1).

1. *Interim results for BF-Derm1 shows reduction of urticaria symptoms.* DailyDrugNews.com (Daily Essentials) April 5, 2004.

BG-12



BG-12, an NF-κB (NF-κB) activation inhibitor, is currently undergoing phase III clinical trials at Biogen Idec and Fumapharm for the oral treatment of mild to moderate psoriasis. Biogen Idec is also studying the drug candidate in phase II clinical trials for the treatment of multiple sclerosis (MS). The product is a second-generation fumarate derivative with an immunomodulatory mechanism of action.

Promising results were reported from a phase II study of BG-12 in the treatment of severe psoriasis at the European Academy of Dermatology and Venereology (EADV) meeting in Budapest in April 2004. Patients who received BG-12 in the trial showed greater improvement in their psoriasis than patients receiving placebo. In the multicenter, double-blind trial, 144 patients were randomized to receive BG-12 120, 360 or 720 mg/day or placebo for 12 weeks. Median Psoriasis Area and Severity Index (PASI) scores were reduced by 31%, 52%, 71% and 6% in these groups, respectively. PASI50 response rates were 29%, 50%, 64% and 14%, respectively. Flushing, minor ALT elevations and common colds or respiratory infections were the most frequent adverse events (1-3) (Table III).

A total of 175 patients with moderate to severe psoriasis participated in a multicenter, double-blind, randomized, placebo-controlled phase III clinical trial conducted by Fumapharm that evaluated the effects and safety of BG-12 (720 mg/day). After 16 weeks, patients given BG-12 showed a significantly lower median PASI score (5.8 *vs*. 14.2) and a greater median reduction from baseline PASI scores (68% *vs*. 10%) than placebo-treated patients. The most common adverse events were flushing and diarrhea. These data will be used to support a filing for market authorization in Germany this year. Biogen Idec is also assessing the efficacy and safety of BG-12 in the treatment of multiple sclerosis. The company recently announced that it has started a multicenter, dose-finding, placebo-controlled phase II clinical trial that will administer different doses of BG-12 to approximately 250 patients with relapsing-remitting multiple sclerosis (4-6) (Table III).

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

2. Langner, A., Roszkiewicz, J., Baran, E., Placek, W. *Fumaric acid ester for the treatment of severe forms of psoriasis.* Result of a phase II clinical study. J Eur Acad Dermatol Venereol 2004, 18(Suppl. 1): Abst PS296.

3. Langner, A., Spellman, M.C. *Results of a phase 2 dose-ranging and safety extension study of a novel oral fumarate, BG-12, in patients with severe psoriasis.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2787.

4. *BG-12 reduces symptom scores in moderate-severe psoriasis.* DailyDrugNews.com (Daily Essentials) April 12, 2005.

5. Biogen reports Q1 R&D highlights. Biogen Idec Press Release 2005, April 27.

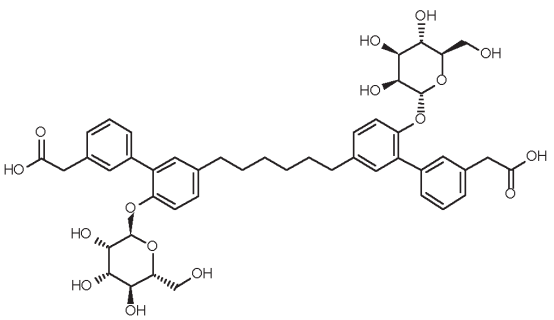
6. Mrowietz, U., Spellman, M.C. *Efficacy and safety of a novel formulation of an oral fumarate, BG-12, in patients with moderate to severe plaque psoriasis: Results of a phase III study.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2743.

Additional References

Langner, A. et al. *Effects of a novel oral fumarate, BG-12, in patients with severe psoriasis: Results of a phase 2 extension study.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P06.111.

Langner, A. et al. *Results of a phase II study of a novel oral fumarate, BG-12, in the treatment of severe psoriasis.* Eur Congr Psoriasis (Oct 21-24, Paris) 2004, Abst P075.

Bimosiamose



Bimosiamose (TBC-1269) is a glycomimetic panselectin antagonist in phase II evaluation by Revotar Biopharmaceuticals as an inhaled formulation for the

Table III: Clinical studies of BG-12 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Double-blind Multicenter	BG-12, 120 mg p.o. o.d. x 12 wks BG-12, 360 mg p.o. o.d. x 12 wks BG-12, 720 mg p.o. o.d. x 12 wks Placebo	144	Oral BG-12 was well tolerated and dose-dependently improved the PASI scores in patients with severe psoriasis	3
Psoriasis	Randomized Double-blind Multicenter	BG-12, 240 mg p.o. t.i.d. x 16 wks Placebo	175	Good efficacy and safety results were achieved with oral BG-12 in patients with moderate to severe plaque psoriasis	6

Table IV: Clinical studies of bimosiamose (from Prous cience ntegity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Randomized Double-blind Multicenter	Bimosiamose top. x 12 d Placebo	12	Topical bimosiamose significantly reduced infiltrate thickness in the plaques of patients with psoriasis vulgaris	2

treatment of asthma and as subcutaneous and topical formulations for the treatment of psoriasis, as well as phase I trials for COPD. Bimosiamose blocks the initial slowing of leukocyte traffic, prevents leukocytes from migrating into the tissue and may alter cell activation and cell-cell signaling pathways. It was originally discovered by Encysive Pharmaceuticals and was licensed in 2000 to Revotar, a majority-owned German affiliate of Encysive, which retained North American territorial rights to topical uses of the compound. However, the companies recently signed a new licensing and related agreements regarding bimosiamose and certain follow-on compounds, whereby Encysive will license all worldwide rights to bimosiamose to Revotar in return for substantial royalties on future revenues from the commercialization or licensing of this compound and certain follow-on compounds (1).

A multicenter, double-blind, randomized, placebo-controlled phase IIa clinical trial assessed the antipsoriatic effects of bimosiamose in 12 patients with stable psoriasis. Compared with vehicle, topical application of bimosiamose for 12 days had no significant effect on mean redness but significantly reduced infiltrate thickness of the psoriatic plaques as measured by 20-MHz sonography (2) (Table IV).

1. *Encysive restructures agreement with Revotar.* DailyDrugNews.com (Daily Essentials) April 29, 2005.

2. Friedrich, M., Vollhardt, K., Zahlten, R., Sterry, W., Wolff, G. *Demonstration of antipsoriatic efficacy of a new topical formulation of the small molecule selectin antagonist bimosiamose.* Eur Congr Psoriasis (Oct 21-24, Paris) 2004, Abst P016.

BSP-103

Studies have demonstrated the antiinflammatory properties BSP-103, a purified concentrate derived from sheanuts from the African tree *Butyrospermum parkii* that has been shown in normal human monocytes to act as a nonsteroidal antiinflammatory agent in that it inhibits the production of inflammatory cytokines (*e.g.*, TNF-α, IL-6) and significantly inhibits NF-κB activity, without interfering with the glucocorticoid receptor. The agent is formulated in capsules for oral use and is registered as a dietary supplement by BSP Pharma. When administered at a dose of 2.25 g/day (3 capsules) to 20 patients with psoriasis, patient and clinician assessment revealed significant improvements in skin symptoms, with significant reductions in plaque size, inflammation, induration and scaling in 12 patients after 3-6 weeks of treatment. One patient experienced complete remission. Slight gastrointestinal discomfort was reported in 1 patient after a few days of treatment, which resulted in discontinuation. A phase II clinical trial has been initiated to examine the efficacy of the agent as a treatment for psoriasis (1).

1. Gronhoj Larsen, C. BSP-103, *an anti-inflammatory triterpene product derived from Butyrospermum parkii, is a possible new therapeutic agent for the treatment of psoriasis.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2725.

BT-061

Biotest's BT-061 is a monoclonal antibody targeting T-cells which has shown promising results in early clinical trials in patients with psoriasis and rheumatoid arthritis. The company is currently producing material to continue its clinical development in these autoimmune diseases. Biotest and Boehringer Ingelheim also recently signed an agreement for a joint research effort to investigate the efficacy of the antibody in animal models of asthma (1).

1. *Biotest AG and Boehringer Ingelheim enter into collaboration agreement.* Biotest AG Press Release 2005, June 28.

Calcithiazol

Calcithiazol is a vitamin D analogue in early clinical development at Intendis for the oral treatment of psoriasis.

CC-10004

Celgene's lead oral PDE4 and TNF-α inhibitor CC-10004 has advanced to phase II development for the treatment of psoriasis and asthma.

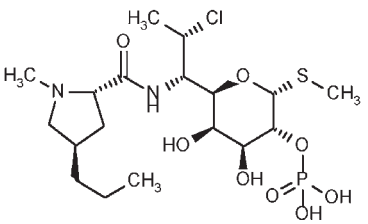
Table V: Clinical studies of clindamycin phosphate/tretinoin (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Acne	Randomized Double-blind Multicenter	Clindamycin 1% hydrogel o.d. x 12 wks (n=635) Tretinoin 0.025% hydrogel o.d. x 12 wks (n=635) Clindamycin 1% hydrogel + Tretinoin 0.025% hydrogel o.d. x 12 wks (n=634) Placebo (n=315)	2219	The combination of clindamycin and tretinoin was well tolerated, with a similar rate of application-site reactions when compared to tretinoin alone in patients with mild to moderate acne vulgaris	5,6
Acne	Randomized Double-blind Multicenter	Clindamycin 1% hydrogel top. x 12 wks Tretinoin 0.025% hydrogel top. x 12 wks Clindamycin 1% hydrogel top. + Tretinoin 0.025% hydrogel top.x 12 wks Placebo		The combination of clindamycin and tretinoin was more effective when compared to either clindamycin or tretinoin alone in patients with acne vulgaris	7

ChelASE™

Immunsol's lead compound ChelASE™ (formerly VIT-100) is a first-in-class treatment that has been tested in a phase I trial for keloids and hypertrophic scars and is expected to enter phase II trials soon.

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 currently under review by the FDA, and a first-in-class combination gel formulation containing clindamycin phosphate 1% and tretinoin 0.025% (Velac®).

In 2004, Connetics reported the positive outcome of its phase III trials evaluating Velac® in the topical treatment of acne vulgaris. The two identical phase III trials included more than 2,200 patients with mild to moderate acne at 37 centers, in which patients were treated for 12 weeks in double-blind, placebo- and active-controlled studies. Each study compared the effect of Velac® to the single active ingredients, clindamycin gel and tretinoin gel, and with placebo gel on two primary efficacy endpoints: lesion count and Investigator's Static Global Assessment (ISGA). Each trial demonstrated a consistently robust and statistically superior treatment effect for Velac® compared with clindamycin, tretinoin and placebo gel on both of the primary endpoints. In a combined analysis of data from the two trials, the proportion of patients achieving treatment success on the ISGA was 37% for Velac®, 27% for clindamycin gel, 25% for tretinoin gel and 14% for vehicle gel. The mean percent reduction in total lesion counts was 49% for Velac®, 38% for clindamycin gel, 40% for tretinoin gel and 23% for vehicle gel. Velac® combines the antiinflammatory and antimicrobial effects of clindamycin with the beneficial comedolytic effects of tretinoin in normalizing the plugging of pores. Connetics licensed rights from the former Yamanouchi (now Astellas Pharma) to develop and commercialize Velac® exclusively in the U.S. and Canada, and nonexclusively in Mexico, in May 2002. Although Velac® is approved in Europe, the FDA recently issued a nonapprovable letter for the product. The FDA raised the issue of a positive carcinogenicity signal that was detected in a TgAC mouse dermal carcinogenicity study. Connetics remains committed to bringing Velac® to market and will work with the FDA to determine the next steps towards gaining approval (1-4).

1. *Positive phase III results for Velac.* DailyDrugNews.com (Daily Essentials) March 26, 2004.

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

3. *Velac NDA accepted for filing.* DailyDrugNews.com (Daily Essentials) Oct 27, 2004.

4. *Non-approvable letter for Velac.* DailyDrugNews.com (Daily Essentials) June 15, 2005.

5. Leyden, J., Yaroshinsky, A., Krochmal, L. *Tolerability assessment of combination clindamycin/tretinoin hydrogel for the treatment of acne vulgaris in 2219 subjects.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P158 (Table V).

6. Leyden, J., Yaroshinsky, A., Krochmal, L. *Two randomized, controlled trials of a combination clindamycin/tretinoin hydrogel compared with each agent alone for the treatment of acne vulgaris in 2219 subjects.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P160 (Table V).

7. Krochmal, L., Yaroshinsky, A. *The novel combination clindamycin/tretinoin hydrogel: A randomized, double-blind, active- and vehicle-controlled study.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P153 (Table V).

Additional References

Yaroshinsky, A., Krochmal, L. *Acne treatment outcomes with a once-daily combination of clindamycin and tretinoin in hydrogel compared with single agents.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P163.

CNTO-1275

CNTO-1275 is a fully human anti-IL-12/IL-23 monoclonal antibody which is being developed by Centocor under license from Medarex for inflammatory disorders such as Crohn's disease, multiple sclerosis and psoriasis. Phase II trials have been completed in psoriasis and phase II trials are ongoing in Crohn's disease.

The short-term safety, pharmacokinetics and efficacy of a single s.c. dose (0.3, 0.75, 1.5 or 3 mg/kg) of CNTO-1275 were examined in a 24-week, multicenter, randomized, double-blind, placebo-controlled phase I trial involving 21 subjects with moderate to severe psoriasis vulgaris. The pharmacokinetics obtained were dose-proportional. Slow systemic absorption was observed with the C_{max} occurring at 12 days postdosing; the mean terminal half-life was 20 days. PASI scores positively correlated with dose and improvements in scores were first seen at 2 weeks postdosing. Between weeks 4 and 24, 77% of the antibody-treated patients had a 75% improvement in PASI scores as compared to no subjects on placebo. All 4 patients who received the 3 mg/kg dose exhibited sustained clinically significant responses throughout the 24-week evaluation period. CNTO-1275 therefore appears to be a promising antipsoriatic agent (1).

1. Gottlieb, A., Frederick, B., Everitt, D., McCormick, T. *A phase 1 study evaluating the safety, pharmacokinetics, and clinical response of a human IL-12 P40 antibody administered subcutaneously in subjects with plaque psoriasis.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2705.

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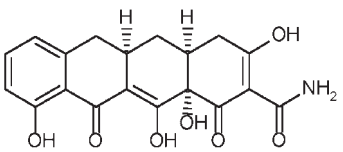
Kauffman, C.L., Aria, N., Toichi, E. et al. *A phase I study evaluating the safety, pharmacokinetics, and clinical response of a human IL-12 p40 antibody in subjects with plaque psoriasis.* J Invest Dermatol 2004, 123(6): 1037.

COL-3



CollaGenex has released the results of a double-blind, placebo-controlled phase II study designed to evaluate the safety and efficacy of COL-3 for the treatment of rosacea. The small proof-of-principle study enrolled 13 patients who received either COL-3 or placebo for 28 days. Patients were evaluated at baseline and at days 14, 28 and 42. Inflammatory lesion counts and assessments of erythema and overall clinical disease severity were obtained at each of these time points. At all time points during the course of the study, patients receiving COL-3 had significantly fewer inflammatory lesions than those on placebo. At day 42, patients treated with COL-3 experienced a 69% reduction in lesion counts compared to an increase of 12% in the placebo group. A treatment benefit was also apparent in the overall clinical severity score and less pronounced in the assessment of erythema, which showed a trend towards improvement. COL-3 is a second-generation IMPACs™ (Inhibitors of Multiple Proteases And CytokineS) compound that has demonstrated a range of potent antiinflammatory activities. CollaGenex plans to begin shortly a proof-of-principle phase II study in patients with acne (1, 2). A higher dose product, known as Metastat®, has completed phase II trials in Kaposi's sarcoma.

1. *Positive findings in proof-of-principle study for COL-3 in rosacea.* DailyDrugNews.com (Daily Essentials) April 19, 2005.

2. *Positive results of CollaGenex Pharmaceuticals' phase 2 clinical study evaluating effects of COL-3 for treating rosacea presented at North Carolina Dermatology Association.* CollaGenex Pharmaceuticals Press Release 2005, Aug 2.

CRx-140

CRx-140 is an enhanced calcineurin inhibitor in phase II trials at CombinatoRx for the treatment of psoriasis. The drug contains a reduced-dose calcineurin inhibitor combined with an antihistamine. Preclinical studies suggest that the antihistamine in CRx-140 selectively boosts the immunomodulatory activity of the reduced-dose calcineurin inhibitor without a comparable increase in adverse side effects.

CTA-018

Seventeen patients with mild to moderate psoriasis participated in a double-blind, randomized phase Ia clinical trial that assessed the efficacy and safety of Cytochroma's novel vitamin D analogue CTA-018 in this indication. Each patient applied placebo, CTA-018 (3, 10 or 20 μg/g) or betamethasone 0.1% cream as an active control topically to the skin once daily for 13 consecutive days. All three CTA-018 doses were more effective than placebo in reducing the severity of psoriasis, and significant residual effects were still detected for 1 week after the end of administration. No treatment-related adverse events were reported. An ongoing phase Ib study is evaluating the systemic safety and pharmacokinetics of CTA-018. Cytochroma anticipates initiating a phase II clinical trial with CTA-018 in the fourth quarter of 2005. CTA-018 is a member of a new class of vitamin D analogues with a dual mechanism of action and known as vitamin D signal amplifiers. It is a potent inhibitor of CYP24 and a potent activator of vitamin D signaling pathways. CTA-018 is the first drug with

this novel dual mechanism of action to enter clinical development. Preclinical studies have shown that CTA-018 inhibits the proliferation of rapidly dividing cells such as human epidermal keratinocytes and is also effective in inhibiting proinflammatory cytokine secretion, which may be involved in the etiology of psoriasis. Cytochroma anticipates that CTA-018 will be more potent than currently marketed vitamin D analogues, such as calcitriol and calcipotriol, and it is also expected to have a wider safety index. CTA-018 is protected under patents and patent applications exclusively licensed to Cytochroma from The Johns Hopkins University. Cytochroma, in collaboration with a research group at The Johns Hopkins University, has discovered a number of proprietary vitamin D signal amplifiers for use in topical and systemic applications. Cytochroma has commenced discussions with companies with an interest in licensing and codeveloping CTA-018 for mild to moderate psoriasis (1-3).

1. C*ytochroma cleared to begin Canadian phase Ia study of CTA-018 for psoriasis.* DailyDrugNews.com (Daily Essentials) Nov 25, 2004.

2. *Cytochroma secures financing.* DailyDrugNews.com (Daily Essentials) May 9, 2005.

3. *Results of phase Ia trial of CTA-018 in psoriasis reported.* DailyDrugNews.com (Daily Essentials) June 6, 2005.

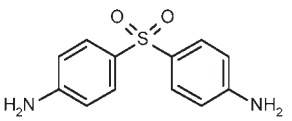
CYT-007-TNFQb

Cytos Biotechnology has initiated a combined phase I/II trial with the Immunodrug™ candidate CYT-007-TNFQb, a therapeutic vaccine for the treatment of psoriasis. The randomized, double-blind, placebo-controlled, single-site study will include 48 patients with moderate to severe plaque psoriasis and is designed to evaluate safety, tolerability and efficacy of the vaccine. Efficacy will be monitored according to the PASI and the Physician Global Assessment (PGA). The study period of 4 months per individual will be followed by long-term monitoring of safety and efficacy over a further 8 months. First results are expected within the first half of 2006. CYT-007-TNFQb, a therapeutic vaccine in development for the treatment of psoriasis and rheumatoid arthritis, is designed to instruct the patient's immune system to produce a specific anti-TNF-α antibody response, thereby helping the body to slow down the inflammatory process and inhibit skin or joint deterioration. Preclinical experiments have shown that antibodies induced by CYT-007-TNFQb bind and neutralize endogenous TNF-α. Experience with other Immunodrug™ candidates in humans shows that such antibody responses decline over time with a half-life of approximately 100 days. This should allow for very convenient dosing schedules and low amounts of vaccine administered to individual patients (1, 2).

1. *New phase I/II study for CYT007-TNFQb for psoriasis.* DailyDrugNews.com (Daily Essentials) Oct 28, 2004.

2. *Cytos Biotechnology reports 2004 achievements.* DailyDrugNews.com (Daily Essentials) March 2, 2005.

Dapsone, Gel



QLT has received final approval from the FDA to market Aczone™ (dapsone) gel 5% for the topical treatment of acne vulgaris. Aczone™ is comprised of dapsone, an antimicrobial agent with antiinflammatory properties, in a Solvent Microparticulate (SMP) gel, which enables dapsone to be applied topically and safely. In two randomized, double-blind, vehicle-controlled studies in 3,000 acne patients, Aczone™ achieved a statistically significant reduction in the number of acne lesions and a better success rate on the Global Acne Assessment Score. Under the FDA approval, patients must be screened to detect if they are predisposed to hemolytic anemia because of glucose 6-phosphate dehydrogenase (G6PD) deficiency. Patients who have this enzyme deficiency will need to be monitored with regular blood counts. In the Aczone™ clinical trial program, 1.4% of about 3,500 patients had this disorder, which is consistent with the incidence in the general North American population. QLT will undertake a postapproval phase IV study in 50 acne patients who have G6PD deficiency and follow them for 6 months, after which QLT expects to submit an application to the FDA to re-evaluate the Aczone™ label. QLT reaquired worldwide marketing rights to Aczone™ after its collaboration, licensing and supply agreement with Astellas Pharma was terminated earlier this year. The product was originally developed by Atrix, which QLT acquired in 2004, in collaboration with the former Fujisawa Healthcare. Aczone™ is also being investigated for its use in rosacea (phase I/II) (1-3).

A stable, aqueous-based emulsion formulation suitable for topical application of dapsone has been claimed for use in treating skin disorders such as psoriasis, dermatitis and itch related to healing or burn wounds, without causing drying or cracking of the skin. The claim further embodies the inclusion of appropriate exogenous oils, emollients and surfactants in order to ensure favorable release of the drug whilst maintaining the moistness and integrity of the skin surface (4).

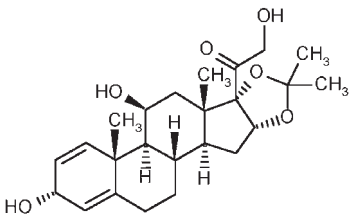
1. *NDA submission for Aczone.* DailyDrugNews.com (Daily Essentials) Sept 3, 2004.

2. *Astellas ends Aczone agreement for North America.* DailyDrugNews.com (Daily Essentials) J uly 8, 2005.

3. *FDA approval for Aczone.* DailyDrugNews.com (Daily Essentials) July 11, 2005.

4. Lathrop, R., Osborne, D.W. (Atrix Laboratories, Inc.) *Emulsive composition containing dapsone.* WO 2005016296.

Desonide, Foam

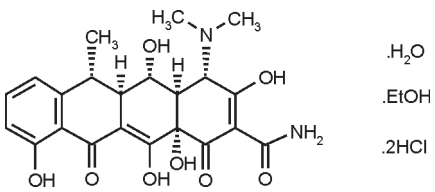


Connetics has reported a positive outcome from its phase III trial evaluating Desilux™, a low-potency topical steroid comprising 0.05% desonide formulated in the company's proprietary VersaFoam-EF™ emollient foam delivery vehicle for the treatment of atopic dermatitis. The phase III trial included 581 patients aged 3 months to 17 years and was designed to demonstrate the superiority of Desilux™ over placebo foam. In the randomized, blinded study, subjects received either Desilux™ or placebo foam twice daily for 4 weeks, followed by 3 weeks of follow-up. The data from the trial demonstrate a consistently robust and highly statistically significant treatment effect for Desilux™ compared to placebo foam on the primary trial composite endpoint evaluating improvement in the ISGA, erythema and induration/papulation. The proportion of patients achieving treatment success on the primary endpoint was 39% for Desilux™ and only 9% for placebo foam. Treatment success for a given subject was defined as clear or almost clear based on ISGA, with a minimum of two-grade improvement in ISGA score from baseline, and absent or minimal erythema and induration/papulation. Connetics plans to submit an NDA by the end of the year (1, 2).

1. *Desilux enters phase III program for atopic dermatitis.* DailyDrugNews.com (Daily Essentials) Sept 30, 2004.

2. *Positive phase III results for Desilux.* DailyDrugNews.com (Daily Essentials) Aug 18, 2005.

Doxycycline Hyclate, Modified-Release



CollaGenex has just filed an NDA with the FDA for Oracea™ (COL-101), its once-daily, modified-release formulation of doxycyline hyclate (40 mg), the first orally administered, systemically delivered drug to treat rosacea. Two double-blind, placebo-controlled phase III clinical trials that included 537 patients with rosacea confirmed that COL-101 given once daily for 16 weeks was more effective than placebo in reducing inflammatory lesions associated with this condition (61% *vs.* 29% in one study, and 49% *vs.* 20% in the second study). Secondary endpoints, such as the Investigator's Global Assessment (IGA) scores and the degree of erythema, also improved significantly more in patients treated with the product. COL-101 also showed a good safety profile. In a previous phase III study using Periostat®, a twice-daily 20-mg formulation of doxycycline with a similar pharmacokinetic profile to COL-101, patients showed clinically and statistically highly significant improvements in their rosacea conditions compared with patients on placebo. There were significantly greater reductions in the number of inflammatory lesions and in overall disease severity based on the Clinician's Global Severity Assessment Scale, with a greater number of patients on Periostat® showing a complete clearing of the disease at 16 weeks compared to placebo patients. Erythema scores in patients in the Periostat® group showed greater improvement compared with the placebo group. COL-101, which has been developed using extended-release drug delivery technology from Shire, could become the first systemic treatment for rosacea. Periostat® has been available for the treatment of adult periodontitis since 1998. Periostat® MR (modified-release) is also in phase III testing for the adjunctive treatment of adult periodontitis (1-9).

1. *Enrollment under way in phase III Periostat MR study for adult periodontitis.* DailyDrugNews.com (Daily Essentials) April 13, 2004.

2. *CollaGenex Pharmaceuticals initiates two phase 3 clinical trials to evaluate Col-101 for the treatment of rosacea.* CollaGenex Pharmaceuticals Press Release 2004, June 15.

3. *CollaGenex Pharmaceuticals reports Q2 R&D highlights.* CollaGenex Pharmaceuticals Press Release 2004, July 22.

4. *Enrollment completed in phase III studies of Oracea.* DailyDrugNews.com (Daily Essentials) Dec 27, 2004.

5. *Phase III data show Oracea is effective and safe in patients with rosacea.* DailyDrugNews.com (Daily Essentials) June 10, 2005.

6. *CollaGenex files for trademark Oracea for rosacea treatment Col-101.* DailyDrugNews.com (Daily Essentials) Sept 15, 2004.

7. *CollaGenex Pharmaceuticals reports Q1 R&D highlights.* CollaGenex Pharmaceuticals Press Release 2004, April 27.

8. *Positive results of CollaGenex Pharmaceuticals' phase III clinical study evaluating Periostat as a treatment for rosacea presented at Phoenix Dermatology Open Seminar.* CollaGenex Pharmaceuticals Press Release 2004, March 22.

9. *Oracea NDA filed.* DailyDrugNews.com (Daily Essentials) Aug 4, 2005.

E-Matrix™

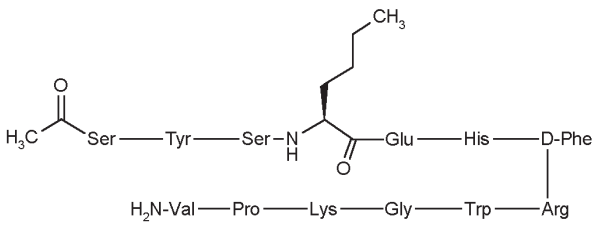
E-Matrix™ is a sterile, injectable biopolymer designed to mimic extracellular matrix found in early development,

currently in phase II trials for diabetic foot ulcers. The drug candidate stimulates tissue-specific repair and regeneration by interacting with host tissues and then altering the expression of key genes which leads to the cell replication and differentiation responsible for the healing response. The product, developed by Encelle, is licensed to Smith & Nephew worldwide for use in the treatment of cutaneous wounds and the company is seeking other partners for other indications, including bone repair, connective tissue repair and soft tissue augmentation.

Encelle has successfully completed a second phase II clinical trial for its E-Matrix™ treatment for diabetic foot ulcers. The novel approach demonstrated the potential to improve healing rates. Data from the controlled, randomized 56-patient feasibility study will allow the design of the next pivotal premarket trial (1).

1. *Second clinical study completed for E-Matrix.* DailyDrugNews.com (Daily Essentials) May 31, 2005.

EPT-1647



EpiTan has obtained approval from the U.K. Medicines and Healthcare products Regulatory Agency (MHRA) to begin a phase I/II trial of a newly developed topical formulation of its melanin-inducing drug EPT-1647 (previously known as Melanotan®), a synthetic analogue of the naturally occurring hormone α-MSH which stimulates melanin production. Up to 30 healthy volunteers will receive increasing doses of EPT-1647 in a transdermal delivery formulation. The topical formulations will be applied as a 1-ml solution sprayed onto the arm daily for 10 days. This formulation is expected to enable the drug to be equally distributed throughout the body systemically. The trial's objectives include investigating both the safety and efficacy of the new EPT-1647 formulation, as well as establishing the optimal dose. The patented TDS® transdermal delivery technology was developed by TransDermal Technologies. TDS® is unique because the composition is specific for each drug. The results of EpiTan's preclinical studies have shown that the TDS® formulation can systemically deliver a large peptide through the skin of animals. EPT-1647 has completed a phase II trial in Australia which demonstrated that it increases melanin content by up to 100% and reduces sunburn injury by up to 50% in fair-skinned volunteers. EpiTan is expanding its clinical studies of EPT-1647 in Europe and the U.S. to assess its potential both as a preventive to reduce the effects of ultraviolet (UV) damage and as a therapy for UV-associated skin disorders such as polymorphous light eruption (PMLE). A number of delivery formulations are in development, with the most advanced being a biodegradable sustained-release implant, administered by a single injection (see below) (1).

EpiTan has also received approvals to conduct two other trials of EPT-1647. Regulatory and ethics approval has been granted for a second PMLE trial of EPT-1647 in Europe. The trial is scheduled to start at the Turku University Central Hospital in Finland. The open, controlled study will evaluate the safety, tolerability and efficacy of a subcutaneous implant of EPT-1647 in patients suffering from recurrent PMLE. The primary endpoint is to determine whether EPT-1647 implants given as a prophylactic can prevent or reduce the occurrence of symptoms like urticae, vesiculae, papulae, eczema, erythema and itching associated with PMLE. The trial will enroll approximately 15-25 male and female patients aged 18-70 and diagnosed with PMLE-like syndrome. The trial is expected to last 5 months. This is the second PMLE trial involving EPT-1647 in Europe. The first began in Germany in January 2005. The trials have been scheduled for the European winter/spring when people's natural melanin levels are at their lowest. The company has also received ethics approval for a phase II study in Australia to evaluate the photoprotective effect of a sustained-release dose of EPT-1647 administered as an implant, and enrollment has commenced. The double-blind, randomized, placebo-controlled trial is designed to validate a specific endpoint for EPT-1647 for fair-skinned Caucasians and to establish a protection rating for EPT-1647 similar to that used in sunscreens. Subject to regulatory acceptance, this endpoint will be used in phase III studies. A total of 48 healthy male and female fair-skinned Caucasians will be enrolled at Royal Prince Alfred Hospital, Sydney, Australia. The endpoint trial is expected to take 6 months to complete. It is anticipated that it will be one of the final trials of EPT-1647 before phase III studies. EPT-1647 stimulates the body to make melanin, inducing a protective tan without the need to expose the skin to UV radiation (2, 3).

pSivida has reported results from a proof-of-concept preclinical study under way in collaboration with EpiTan which demonstrated that a single injection of pSivida's porous BioSilicon™ technology resulted in release of EPT-1647 over a sustained period of time. The injection under development by the companies holds an advantage over conventional daily injections of EPT-1647 in that significantly lower quantities of drug are required for treatment. pSivida and EpiTan will now focus on developing the second-generation injectable formulation of EPT-1647 for commercial sale. Separately, EpiTan recently reported final results from a phase I/II trial with EPT-1647 sustained-release implants, administered by a single subcutaneous injection, demonstrating a statistically signifi-

cant increase in melanin density in all doses. These results confirm interim data from a dose-escalation trial released at the end of 2004. An improved safety and tolerability profile compared with earlier trials was also reported. The trial, results from which are being used to design phase III studies, was extended to include a lower dose implant due to unexpected efficacy in the first two cohorts given EPT-1647 (4).

1. *U.K. approves phase I/II trial of topical Melanotan.* DailyDrugNews.com (Daily Essentials) Jan 27, 2005.

2. *New Melanotan trials cleared to begin in Australia and Finland.* DailyDrugNews.com (Daily Essentials) March 10, 2005.

3. *Melanotan studied in new Australian phase IIb study.* DailyDrugNews.com (Daily Essentials) June 28, 2005.

4. *Sustained-release Melanotan shows promise in preclinical and clinical studies.* DailyDrugNews.com (Daily Essentials) May 24, 2005.

Additional References

Humphrey, S.M. et al. *Clinical potential of Melanotan® (NDP-α-MSH) in skin protection - Current status and future perpective.* 1st Int Meet Neurobiol Skin (Feb 13-15, Münster) 2004, Abst.

Etanercept

In 2004, etanercept (Enbrel®) was approved first in the U.S. and subsequently in Europe for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, have a contraindication for or are intolerant of other systemic therapies. Approval was based on data from three randomized, double-blind, placebo-controlled studies in more than 1,300 adults with plaque psoriasis, of whom more than 1,200 received etanercept. In all three studies, patients who received etanercept demonstrated a rapid and significant response to treatment and improvement in quality-of-life scores compared with placebo. In one of the three clinical studies, which included a discontinuation period, patients were able to recapture response upon retreatment. Rebound was not associated with discontinuation of treatment. In addition, etanercept significantly and rapidly improved quality of life in patients with moderate to severe psoriasis in as early as 2 weeks, as measured by Dermatology Life Quality Index (DLQI) scores. This response continued to improve through 24 weeks. Etanercept is now available for the following indications: moderately to severely active rheumatoid arthritis, chronic moderate to severe plaque psoriasis, active psoriatic arthritis, active ankylosing spondylitis and moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs. It is also being investigated for other TNF-mediated diseases such as idiopathic pulmonary fibrosis and asthma, with proof-of-concept studies ongoing. As an anti-TNF therapy, etanercept binds to overproduced TNF and renders it biologically inactive, which can result in a significant reduction in inflammation. Amgen and Wyeth market etanercept in North America, while Wyeth alone handles markets outside North America. Immunex, a wholly owned subsidiary of Amgen, manufactures etanercept (1-6).

The effect of etanercept on the number of patients achieving a clinically significant enhancement in health-related quality of life was examined in a multicenter, double-blind, randomized, placebo-controlled study in 652 patients with stable moderate to severe psoriasis.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Randomized Double-blind Multicenter	Etanercept, 25 mg 1x/wk x 24 wks Etanercept, 25 mg 2x/wk x 24 wks Etanercept, 50 mg 2x/wk x 24 wks Placebo	652	A significantly greater proportion of etanercept-treated patients with moderate to severe psoriasis reported clinically meaningful improvements in health-related quality of life compared with placebo	7
Psoriasis	Pooled/meta-analysis	Etanercept, 25 mg 2x/wk x 12 wks (n=415) Etanercept, 50 mg 2x/wk x 12 wks (n=358) Placebo (n=773)	1187	Etanercept was highly effective in patients with chronic plaque psoriasis and considerably improved the quality of life	12, 14, 33, 34, 42
Psoriasis	Pooled/meta-analysis	Etanercept, 25 mg 1x/wk x 12 wks (n=160) Etanercept, 25 mg 2x/wk x 12 wks (n=358) Etanercept, 50 mg 2x/wk x 12 wks (n=358) Placebo (n=359)	1235	Continued etanercept therapy increased the response rate in patients with psoriasis	18
Psoriasis	Randomized Double-blind Multicenter	Etanercept, 25 mg 2x/wk x 12 wks Etanercept, 50 mg 2x/wk x 12 wks Placebo	611	Etanercept improved quality of life reported by psoriasis patients	19
Psoriasis	Randomized Double-blind Multicenter	Etanercept, 25 mg s.c. 2x/wk x 12 wks (n=196) Etanercept, 50 mg s.c. 2x/wk x 12 wks (n=194) Placebo (n=193)	583	Etanercept therapy was safe and effectively improved PASI scores in patients with psoriasis, with an incidence of adverse events and infections similar to in the placebo group	20, 25, 35, 36

Psoriasis	Pooled/meta-analysis	Etanercept, 25 mg 2x/wk x 24 wks Placebo	415	The response to etanercept was similar in patients with psoriasis with or without a previous history of systemic therapy or phototherapy	24
Psoriasis	Randomized Double-blind- Multicenter Pooled/meta-analysis	Etanercept, 25 mg 2x/wk x 12 or 24 wks (n=585) Etanercept, 50 mg 2x/wk x 12 or 24 wks (n=388) Placebo x 12 wks → Etanercept, 25 mg 2x/wk x 12 wks (n=359)	1332	Etanercept resulted in a dose-dependent, rapid and prolonged reduction in pruritus compared with placebo in patients with moderate to severe psoriasis	26
Psoriasis	Pooled/meta-analysis	Etanercept, 25 mg 1x/wk x 12 wks (n=160) Etanercept, 25 mg 2x/wk x 12 wks (n=415) Etanercept, 50 mg 2x/wk x 12 wks (n=358) Placebo (n=414)	1347	Etanercept was safe and well tolerated in patients with chronic plaque psoriasis	27
Psoriasis, Arthritis, psoriatic	Case report	Alefacept, 15 mg i.m. 1x/wk x 12 wks + Etanercept, 25 mg s.c. 1x/2 wks x 7 wks (n=1) Alefacept, 15 mg i.m. 1x/wk x 12 wks + Etanercept, 25 mg s.c. 2x/wk + Ultraviolet B light (n=1)	2	The observed efficacy in these patients suggested that alefacept plus etanercept was effective as a treatment for psoriasis and psoriatic arthritis	28
Psoriasis	Open	Etanercept, 0.4 mg/kg [50 kg] 2x/wk	10	Etanercept was well tolerated, improved symptoms and allowed tapering or discontinuation of other drugs in patients with moderate to severe psoriasis	29
Psoriasis	Randomized	Etanercept, 50 mg/wk s.c. x 6 mo [continued or withdrawn after 24 wk based on PASI50 response] (n=162) Etanercept, 50 mg s.c. 2x/wk x 6 mo [continued or withdrawn after 24 wk based on PASI50 response] → Etanercept, 50 mg/wk s.c. (n=164) Placebo x 6 mo [continued or withdrawn after 24 wk based on PASI50 response] → Etanercept, 50 mg/wk s.c. (n=166)	492	Etanercept retreatment effectively improved quality of life and reduced symptoms in patients with psoriasis	31
Psoriasis	Randomized Double-blind Pooled/meta-analysis	Etanercept, 25 mg 2x/wk x 12 wks (n=415) Etanercept, 50 mg 2x/wk x 12 wks (n=358) Placebo (n=773)	1546	Etanercept 25 or 50 mg produced robust improvement in the quality of life and was well tolerated in patients with chronic plaque psoriasis	32, 43
Psoriasis	Randomized Double-blind Multicenter	Etanercept, 50 mg 2x/wk x 12 wks Placebo		Etanercept showed significant improvement in patients with nail psoriasis	37
Psoriasis	Randomized Double-blind Pooled/meta-analysis	Etanercept, 25 mg 1x/wk (n=159) Etanercept, 25 mg 2x/wk (n=412) Etanercept, 50 mg 2x/wk (n=357) Placebo (n=414)	1342	Etanercept produced clinically meaningful improvements in the quality of life in patients with chronic plaque psoriasis compared with placebo	38
Psoriasis	Randomized Double-blind Pooled/meta-analysis	Etanercept, 50 mg 2x/wk x 12 wks (n=669) Placebo (n=666)	1335	Etanercept was well tolerated and effective in adult patients with moderate to severe psoriasis	39
Psoriasis	Randomized Double-blind	Etanercept, 25 mg 1x/wk x 24 wks → [if no complete response] 25 mg 2x/wk x 12 wks Etanercept, 25 mg 2x/wk x 24 wks [36 wks if no complete response @ 24 wks] Etanercept, 50 mg 2x/wk x 24 wks → [if no complete response] 25 mg 2x/wk x 12 wks Placebo x 12 wks → Etanercept, 25 mg 2x/wk x 12 wks → [if no complete response] 25 mg 2x/wk x 12 wks	159	Etanercept therapy continued after early incomplete response was well tolerated with substantial clinical improvement in patients with psoriasis	41
Psoriasis	Open	Etanercept, 25 mg s.c. 2x/wk x 12 wks + Methoxsalen, 10 mg p.o. → [1.5 h later] + Ultraviolet A [dose based on body weight] 3x/wk	12	Preliminary results suggested that combination of methoxsalen plus ultraviolet A with etanercept was well tolerated and an effective alternative, showing rapid efficacy in patients with severe psoriasis	44

Etanercept (25 mg every week, 25 or 50 mg biweekly) produced a significantly greater clinical response and favorable outcome in terms of quality of life compared to placebo (7). The results from this and many of the following studies are depicted in Table VI.

A study showed that the improvements in the DLQI scores of patients with chronic plaque psoriasis after receiving twice-weekly etanercept for 12 weeks were 4-5 times more likely to be clinically meaningful compared to placebo (8).

A multicenter, blinded, randomized clinical trial administered placebo or etanercept (25 mg s.c.) twice weekly to 112 patients with stable chronic psoriasis. The percentages of patients who showed a 75% improvement in their PASI scores were greater with etanercept compared to placebo (30% *vs*. 2% at 12 weeks, and 54% *vs*. 5% at 24 weeks). Skin biopsy samples taken after 12 weeks of treatment revealed that etanercept was more effective than placebo in reducing epidermal thickness, the number of Ki67-positive and CD3-positive cells, and the expression of keratinocyte ICAM-1 and keratin 16. Etanercept was also well tolerated, and all injection-site reactions were low-grade (9).

Pooled data from one phase II and two phase III clinical trials were used to evaluate the efficacy of etanercept in chronic plaque psoriasis. A total of 1,187 patients were randomized to receive placebo or etanercept (25 or 50 mg) twice weekly. At 12 weeks, the percentage of patients who achieved an improvement of at least 75% in their PASI scores was significantly greater with 25 and 50 mg of etanercept (33% and 49%, respectively) compared to placebo. Etanercept also significantly improved the DLQI scores of the patients and was associated with a greater degree of clearing (21% *vs*. 1% with placebo). The incidence of serious adverse events was 1.2% in the placebo group and 1.7% among etanercept-treated patients. Few serious infections were seen, and opportunistic infections and tuberculosis did not occur. Low-grade injection-site reactions occurred more frequently with etanercept, however (14% *vs*. 6%) (10-14).

Etanercept treatment was investigated in patients with psoriatic arthritis and psoriasis in a 24-week, randomized, double-blind, placebo-controlled study which was followed by a 1-year extension study. Among the 168 patients continuing in the extension study, those originally given etanercept maintained their previous improvements in both psoriatic arthritis and psoriasis. Those switching from placebo improved. After 36 weeks of etanercept treatment, ACR20 improvement criteria were met by 60% of patients, and a PASI50 response was seen in 64%. Neither adverse events nor infections increased with extended etanercept therapy (15, 16).

Thirteen outpatients with moderate to severe stable psoriasis were given etanercept 25 mg twice weekly for up to 120 days. An interim analysis revealed that 1 of 4 patients achieved PASI75 and another achieved PASI90 after 60 days of treatment. All adverse events were mild, and no patients withdrew from the study due to safety issues (17).

An analysis of two phase II trials indicated that psoriasis patients may respond to etanercept therapy with extended treatment, even if they do not respond within 4 weeks. In the studies reviewed, 1,235 patients received etanercept doses of 25 mg once or twice weekly or 50 mg twice weekly. Among those not achieving a PASI50 response at 4 weeks, the rates of response at 8 weeks were 7%, 18%, 33% and 53%, respectively, for placebo, etanercept 25 mg once weekly, etanercept 25 mg twice weekly and etanercept 50 mg twice weekly. At week 12, the rates of response were 8%, 34%, 51% and 67% in these groups, respectively (18).

Outcomes reported by psoriasis patients on the SF-36 physical and mental domains and the DLQI were improved with etanercept treatment in a multicenter, randomized, double-blind, placebo-controlled trial. Etanercept 25 or 50 mg twice weekly or placebo was administered to 611 patients for 12 weeks. The 6 scales of the DLQI were significantly improved with etanercept at week 12 as compared to placebo; the DLQI total score was significantly different at week 2. SF-36 physical and mental scores were also significantly superior with etanercept at week 12. The mean improvements in DLQI at week 12 were 65-70% for the etanercept doses and 6% with placebo (19).

In an international phase III trial, 583 psoriasis patients were randomized to s.c. etanercept 25 or 50 mg twice weekly or placebo for 12 weeks. The primary endpoint, a PASI75 response at 12 weeks, was achieved by 34%, 49% and 3% of patients in these groups, respectively. Significantly more patients were clear or almost clear according to physician's Static Global Assessment at 12 weeks, and patient-reported outcomes were significantly improved. The safety profile of etanercept was comparable to that of placebo (20).

The PASI scores of 44 patients with moderate to severe plaque psoriasis previously treated with systemic therapies improved by a median of 52.3% and 72.3% after receiving etanercept (25 mg s.c.) twice weekly for 12 and 24 weeks, respectively. The percentage of patients who improved their PASI scores by at least 75% (PASI75) was 43.1% at week 12 and 65% at week 24 (21).

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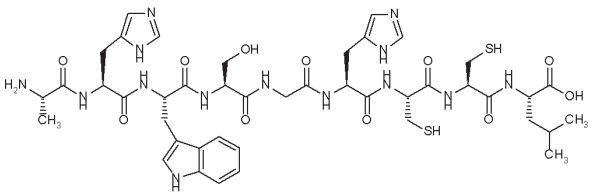
F-991



Fornix BioSciences' F-991 peptide shows good promise in the treatment of a range of disorders, including asthma, multiple sclerosis, contact eczema and Crohn's disease. F-991 prevents the binding of immunoglobulin free light chains to their receptors. The F-991 development project is at phase IIa. The first of these studies investigated the efficacy of F-991 in patients presenting with symptoms of contact sensitivity to nickel. This study, which was completed at the end of 2003, found that topical application of F-991 produced a reduction in allergic skin reactions such as redness, itching and swelling. Expanding into other indications, a further phase IIa study has been launched to investigate the efficacy of F-991 in patients with clinical symptoms (asthma, rhinitis and eczema) resulting from exposure to dust mite and food allergens. Completion of the study was originally scheduled for the end of 2004, but this has now been extended until the second quarter of 2005 at the latest. Fornix is seeking to form joint ventures with partners for the further development of F-991 (1).

1. *Fornix reviews R&D progress.* DailyDrugNews.com (Daily Essentials) Jan 3, 2005.

Fibrostat®

Procyon Biopharma has discontinued further development of Fibrostat® following the analysis of results from its phase IIb clinical trial for the treatment of hypertrophic scars. The North American double-blind, randomized, placebo-controlled study was conducted at 12 centers in 136 patients who were treated with either placebo or Fibrostat® 0.8% cream daily for 8 weeks. The primary objectives of the trial were to evaluate the safety and efficacy of Fibrostat® for the treatment of excessive scar formation. Although the results indicated that Fibrostat® was safe and well tolerated, the primary efficacy endpoint was not reached, with no overall significant improvement on Fibrostat® compared to placebo (1, 2).

1. *Procyon reports Fibrostat® phase IIb results for the treatment of hypertrophic scars. Procyon Biopharma Press Release 2005, Jan 18.*

2. *Procyon Biopharma reports progress and new acquisition at Annual Meeting. Procyon Biopharma Press Release 2005, June 30.*

GAM-501

Selective Genetics is currently developing a gene-activated matrix (GAM™) product, GAM-501, containing the gene encoding PDGF-β (platelet-derived growth factor-β) formulated with a collagen matrix. GAM-501 is in early clinical development for the treatment of diabetic ulcers.

Glucoprime™

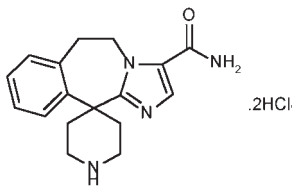
The results of a phase II clinical trial of the macrophage-activating wound-healing compound Glucoprime™ in venous stasis ulcers, conducted in Australia by the Novogen subsidiary Glycotex, which holds the rights to the Novogen glucan technology, were recently reported. The trial involved 60 patients with chronic deep venous stasis ulcers of the legs. In the double-blind trial, patients were randomized to either a placebo arm or to a low- or high-dose Glucoprime™ arm. Glucoprime™ was formulated as a gel and applied to the wound surface 3 times weekly over 12 weeks and the ulcers were monitored for size every 2 weeks. Glucoprime™ was assessed for its effect on both the rate of wound closure and the degree of healing. Glucoprime™ promoted the rate at which wounds healed, with Glucoprime™-treated ulcers healing at a significantly faster rate (mm^2/day) compared to placebo-treated ulcers. The overall mean level of healing over the 12 weeks was 10% for placebo, 59% for 0.1% Glucoprime™ and 55% for 1.0% Glucoprime™, although this outcome was confounded by the large discrepancy in the size of the ulcers, with the two Glucoprime™ treatment groups having substantially larger average ulcer sizes than the

placebo group, despite patients being randomized. Based on these results, the company intends to conduct a regulatory study with a view to obtaining marketing approval for venous stasis ulcers. Glycotex is also planning on pursuing other applications of this product and the technology in general across a range of wound-healing applications (1, 2).

1. *Novogen US subsidiary, Glycotex Inc., settles a private capital raising. Novogen Press Release 2005, April 14.*

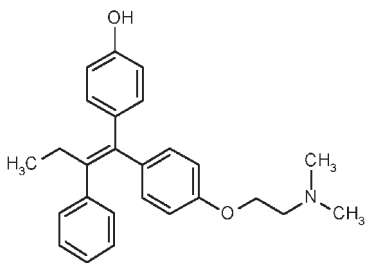
2. *Australian product promotes healing in venous stasis ulcers. Novogen Press Release July 11, 2005.*

Hivenyl™



Hivenyl™, a norpiperidine imidazoazepine histamine H_1 receptor antagonist, is currently undergoing phase II clinical trials for the oral treatment of allergic reactions of the skin, including types of reactions associated with hives and poison ivy. Hivenyl™ may not cause the sedation associated with traditional antihistamines. The compound is being developed by Barrier Therapeutics under license from Janssen (Johnson & Johnson).

4-Hydroxytamoxifen, Gel



A topical gel formulation of 4-hydroxytamoxifen (TamoGel™), a selective estrogen receptor modulator (SERM), is in phase II clinical trials at Ascend Therapeutics for the treatment for keloid scarring, severe breast pain, breast fibrosis, breast cancer and gynecomastia in patients receiving hormonal treatment for prostate cancer. The topical formulation was developed using the company's Enhanced Hydroalcoholic Gel (EHG™) technology.

IDEA-070

Idea's IDEA-070 is a novel carrier-based transdermal formulation employing the Transfersome® technology. The active drug is ketoprofen, an analgesic and antiinflammatory that inhibits both cyclooxygenase and lipoxygenase activity. IDEA-070 has demonstrated excellent drug targeting into peripheral tissues in preclinical studies using pigs. IDEA-070 is being tested for safety and efficacy in the treatment of various inflammatory skin diseases in a phase II study. The double-blind, placebo-controlled study is designed to identify dermatological diseases that might benefit from topical treatment with IDEA-070. Subsequently, IDEA-070 will be further tested in a phase III program focusing on such selected dermal maladies. The study will test the safety and efficacy of IDEA-070 for the treatment of diseases displaying inflammatory reactions as part of their etiopathogenetic background, such as atopic eczema, dishydrotic hand eczema, plaque-type psoriasis, seborrheic eczema and acne vulgaris. Patients with these diseases will receive topical application of IDEA-070 or placebo over a 3-week period. In total, 225 patients will be enrolled at 6 centers in Germany (1).

Idea announced positive results from a phase I clinical study testing the efficacy and safety of IDEA-070 for the treatment of inflammatory skin reactions induced by different means, such as sunburn. The randomized, double-blind, placebo- and active-controlled clinical study took place in Germany. The primary objective was to compare the effects of IDEA-070 and placebo on UVB-induced skin inflammation in 37 healthy volunteers. Further objectives included a comparison with an equal volume of a commercial product containing hydrocortisone 21-acetate (HC), the testing of two lower doses of IDEA-070, and an evaluation of different application regimes (immediately following UVB irradiation or with a delay of 6 h). In addition, the effects of different treatments on the irradiated-site erythema were assessed by clinical scoring. IDEA-070 showed clear statistical significance on the primary objective. The suppression of heat-induced skin pain was significantly greater for IDEA-070 compared with placebo, untreated control and HC when the test formulation was applied immediately after UVB irradiation. With delayed treatment, IDEA-070 was also significantly superior to placebo, untreated control and HC. In contrast to placebo, untreated control and HC, IDEA-070 suppressed UVB irradiation-induced skin erythema with high statistical significance at all tested doses and irrespective of whether the product was applied immediately after irradiation or with a delay. Furthermore, IDEA-070 demonstrated a good safety profile, with no evidence of dermal intolerance (2-5).

1. *IDEA-070 studied in phase II trial for inflammatory skin diseases.* DailyDrugNews.com (Daily Essentials) Feb 21, 2005.

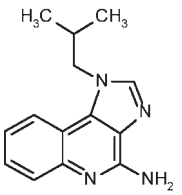
2. *Phase I study evaluates IDEA-070 for skin inflammation and pain.* DailyDrugNews.com (Daily Essentials) March 5, 2004.

3. *IDEA-070 shows excellent efficacy in treatment of UVB-induced skin inflammation.* DailyDrugNews.com (Daily Essentials) May 21, 2004.

4. Lehmann, J., Mazgareanu, S., Vierl, U., Grossmann, M., Schmelz, M., Rother, M. *Analgesic and anti-inflammatory efficacy of IDEA-070 in UVB-induced sunburn.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst FC09.1.

5. Lehmann, J., Burger, M., Schmelz, M., Rother, M. *Analgesic and anti-inflammatory efficacy of IDEA-070 compared with hydrocortisone acetate in UVB-induced sunburn.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P1004.

Imiquimod



Imiquimod (Aldara™), a topical immune response modifier, was initially launched in 1997 by 3M Pharmaceuticals for the topical treatment of genital and perianal warts. In 2004, the product was introduced in the U.S. for the topical treatment of actinic keratosis and superficial basal cell carcinoma.

The approval for nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in adults with normal immune systems was based on two double-blind, randomized, placebo-controlled trials involving 436 patients with multiple lesions. Patients were treated with imiquimod cream or placebo twice a week for 16 weeks. Nearly half of the patients treated with imiquimod cream achieved complete clearance of all lesions compared to only 3% in the placebo group. A majority of patients experienced lesion clearance of 75% or more. Among patients treated with imiquimod cream, a number of previously undetectable lesions appeared and cleared during treatment (1).

The efficacy and safety of a short course of imiquimod 5% cream in the management of solar keratosis was evaluated in a multicenter, randomized, double-blind, placebo-controlled clinical trial. Forty-four patients with 5-15 solar keratoses within one treatment area (scalp, forehead and temples, or both cheeks) applied placebo or imiquimod 5% cream topically to one treatment area 3 times weekly for 3 weeks. At 4 weeks after the first course, 16 of the 33 imiquimod-treated patients and 9 of 11 placebo-treated patients showed clearance of less than 75% of their keratosis lesions and thus received a second 3-week course of their originally allocated treatment. At 4 weeks after the second course, the rate of patients with clearance of at least 75% of baseline keratosis lesions was 72% with imiquimod and 50% with placebo. Patients treated with imiquimod showed a greater incidence of local skin reactions (erythema, erosions, scabbing/crusting, edema and flaking/scaling), most of which were mild or moderate, but no patients withdrew from the study because of them (2).

FDA approval for use in the treatment of biopsy-confirmed primary superficial basal cell carcinoma (sBCC) in adults with normal immune systems was based on results from two double-blind, placebo-controlled trials in 364 patients with primary sBCCs. Patients with one biopsy-confirmed sBCC tumor were enrolled and randomized to receive imiquimod cream or placebo cream once daily, 5 times a week for 6 weeks. Results showed that 75% of patients treated with imiquimod achieved composite clearance compared with 2% in the placebo group. The histological clearance rate was 82% for patients treated with imiquimod compared to 3% percent in the placebo group. Histological and composite clearance rates were assessed at 12 weeks posttreatment (3, 4).

The efficacy of imiquimod 5% cream in treating BCC was examined in an open-label study in 4 renal transplant patients and 1 cardiac transplant patient who were diagnosed with 10 BCCs. Half of the BCCs were treated with imiquimod for 4 nights a week for 6 weeks, and the other half were treated for 5 nights a week for 5 weeks. Treatment was well tolerated in all patients. Biopsies were taken 6 weeks after treatment and no tumor was observed in 4 of 4 superficial BCCs, 2 of 3 nodular BCCs and 1 of 3 infiltrative BCCs. After 8 months of follow-up, there was no evidence of BCC relapse in the 7 BCCs with clinical and histological clearance. Imiquimod 5% cream therefore shows promise as a new therapy for BCC in transplant patients, particularly in those with small tumors of nonaggressive pattern that are located outside high-risk areas (5).

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4. *Aldara receives approval for superficial basal cell carcinoma.* DailyDrugNews.com (Daily Essentials) July 20, 2004.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Hyperkeratosis	Case report	Imiquimod 5% cream top. 4x/wk	1	Imiquimod improved lesions in a patient with porokeratosis of Mibelli	6
Bowen's disease Cancer, skin (basal cell carcinoma)	Open Multicenter	Imiquimod, 250 mg top. o.d. 5x/wk x 8 wks	20	Imiquimod demonstrated good tolerability and efficacy in most patients with basal ell carcinoma or Bowen's disease	7
Cancer, skin (basal cell carcinoma)	Open	Imiquimod 5% cream top. 3-5x/wk x 14 [min.] wks	26	Imiquimod 5% cream demonstrated favorable efficacy in elderly patients with basal cell carcinoma	8
Keratosis, actinic	Open	Imiquimod 5% cream top. 3x/wk x 4 wks 1x/8 wks x up to 3 cycles (n=10) Imiquimod 5% cream top. 3x/wk x 12 [max.] wks (n=10)	20	Although both treatment schedules were effective, imiquimod administered in cycles demonstrated better safety in patients with actinic keratosis	9
Keratosis, actinic	Randomized Double-blind Multicenter	Imiquimod 5% cream top. o.d. 3x/wk x 16 wks (n=147) Placebo (n=139)	286	Imiquimod was effective and well tolerated in patients with actinic keratosis on the face or scalp	10
Cancer, skin (basal cell carcinoma)	Randomized Double-blind Multicenter Pooled/meta-analysis	Imiquimod 5% cream top. o.d. x 5 d 1x/wk x 6 wks (n=185) Imiquimod 5% cream top. o.d. x 6 wks (n=179) Placebo (n=360)	724	Imiquimod was potent and safe and associated with complete clearance rates, with no significant difference when applied 5 or 7 days per week. Imiquimod for 5 days a week was the recommended regimen in patients with superficial basal cell carcinoma	11
Cancer, skin (basal cell carcinoma)	Case report	Imiquimod 5% cream top. 5x/wk	2	Imiquimod 5% cream was effective as a treatment for multiple radiation-induced and genetically mediated basal cell carcinomas	12
Cancer, skin (basal cell carcinoma)	Open	Imiquimod 5% top.	60	Imiquimod cream was safe and effective in the treatment of basal cell carcinoma	13
Keratosis, actinic	Open	Imiquimod 5% cream, 12.5 [face], 25 [scalp] and/or 75 [hands/arms] mg top. 3x/wk [bedtime] x 16 wks (n=23)	58	Minimal systemic absorption and good safety margins for topical imiquimod were seen in subjects with actinic keratosis at doses as high as 75 mg 3 times per week for 16 wks	14
Cancer, skin (basal cell carcinoma)	Open	Imiquimod 5% cream top. 3x/wk x 12 wks	15	Imiquimod 5% cream may be a treatment option for nodular basal cell carcinoma, with a 100% cure rate	15
Keratosis, actinic	Randomized Double-blind	Imiquimod 5% cream 3x/wk x 4 wks [repeated if lesions persisted] Placebo	246	Imiquimod 5% cream was safe and effective in patients with actinic keratosis of the head	16
Keratosis, actinic	Randomized Double-blind Pooled/meta-analysis	Imiquimod 5% cream top. 2x/wk x 16 wks (n=215) Placebo (n=221)	436	Imiquimod 5% cream was well tolerated and effective compared with placebo in patients with actinic keratosis lesions on the face or balding scalp	17
Keratosis, actinic	Randomized	Imiquimod 5% cream top. 2x/wk x 16 wks (n=77) Imiquimod 5% cream top. 3x/wk x 16 wks (n=54)	146	Imiquimod 5% cream was safe and offered long-term benefits with low recurrence rates in most patients with actinic keratosis	18
Keratosis, actinic		Imiquimod 5% cream top. o.d. x 16 wks Imiquimod 5% cream top. 2x/wk x 16 wks Imiquimod 5% cream top. 3x/wk x 16 wks Placebo		Imiquimod demonstrated long-term beneficial clinical effects in most patients, with complete clearance of actinic keratosis lesions	19
Cancer, skin (basal cell carcinoma)	Randomized Open Multicenter	Imiquimod 5% cream top. 5x/wk x 6 wks (n=36) Imiquimod 5% cream top. 7x/wk x 6wks (n=31)	67	Imiquimod applied 5 or 7 times a week was safe and effective in patients with basal cell carcinoma	20

Keratosis, actinic	Open	Imiquimod 5% cream top. 3x/wk x 4 wks	22	Imiquimod 5% cream was well tolerated and complete resolution of lesions was seen in all patients with actinic keratosis	21
Cancer, skin (basal cell carcinoma)	Open	Imiquimod 5% top. 5x/wk x 6 wks	18	Imiquimod 5% was effective and well tolerated in patients with superficial basal cell carcinoma	22
Cancer, skin (basal cell carcinoma)	Case report	Imiquimod 5% cream top. o.d. x 5 mo	1	The results suggested that imiquimod 5% cream was effective as a treatment for basal cell carcinoma	23
Cancer, skin (basal cell carcinoma)	Open	Curettage → [1 wk later] Imiquimod 5% cream top. o.d. 5x/wk x 6 wks	8	Curettage with imiquimod was well tolerated and increased cosmetic outcomes and cure rates in patients with nodular basal cell carcinoma	24
Cancer, skin (basal cell carcinoma)	Randomized Double-blind Multicenter	Imiquimod 5% cream top. o.d. x 6 wks Placebo	166	Once-daily imiquimod 5% cream was safe and effective in patients with superficial basal cell carcinoma	25
Cancer, skin (basal cell carcinoma)	Randomized Multicenter Pooled/meta-analysis	Imiquimod 5% cream top. o.d. x 6 wks Imiquimod 5% cream top. 5x/wk x 6 wks Placebo	890	Similar efficacy was seen with imiquimod 5% cream applied 5 or 7 times a week, although the former regimen was associated with fewer adverse events in patients with superficial basal cell carcinoma	26
Cancer, skin (basal cell carcinoma)	Randomized Double-blind	Imiquimod 5% top. o.d. x 1 mo (n=10) Placebo (n=10)	20	Imiquimod significantly reduced the incidence of residual tumor following curettage and electrodessication, but delayed the time to complete healing, although with better cosmetic results, in patients with primary nodular basal cell carcinoma	27
Keratosis, actinic	Open	Imiquimod 5% top. 5x/wk x 4 wks 1x/8 wks x 2 cycles	3	Imiquimod was a safe, effective and nondestructive treatment with good cosmetic results in patients with multiple actinic keratoses	28
Cancer, skin (basal cell carcinoma)	Open	Imiquimod 5% cream top. [at night] x 3 d 1x/wk x 8 wks (n=35) Imiquimod 5% cream top. [at night] x 5 d 1x/wk x 5 wks (n=20)	55	Imiquimod increased apoptotic index and peritumoral inflammatory infiltrate of basal cell carcinoma, decreased Bcl-2 expression and was well tolerated in patients with basal cell carcinoma	29

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Infliximab

Infliximab (Remicade®), a monoclonal antibody that specifically targets and irreversibly binds to TNF-α on the cell membrane and in the blood, is the only agent approved for the treatment of both rheumatoid arthritis and Crohn's disease in North America, the E.U. and Japan, and has also been approved in the U.S. and the E.U. for ankylosing spondylitis and psoriatic arthritis. The antibody is also undergoing FDA review for use in ulcerative colitis and was recommended for approval in the treatment of moderate to severe plaque psoriasis by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Evaluation Agency (EMEA) earlier this month. The positive opinion for psoriasis was based primarily on data from the SPIRIT (Study of Psoriasis with Infliximab Induction Therapy) and EXPRESS (European Infliximab for Psoriasis Efficacy and Safety Study) trials, multicenter, randomized, double-blind studies that assessed the efficacy of infliximab in patients with plaque psoriasis. Centocor (Johnson & Johnson) discovered infliximab and has exclusive marketing rights to the product in the U.S. Schering-Plough has rights to market the product in all countries outside the U.S., except in Japan and parts of the Far East where Tanabe Seiyaku markets the product. Tanabe Seiyaku has also filed for approval in Japan for the treatment of Behçet's disease (1-17).

Infliximab was successfully used to treat a case of severe pustular psoriasis of von Zumbusch type in a 61-year-old man. The psoriasis had been unresponsive to conventional therapies. Messenger RNA *in situ* hybridization of lesional skin demonstrated an immediate downregulation of the chemokines IL-8, growth-related oncogene-a (GRO-α) and monocyte chemoattractant protein-1 (MCP-1) (18) (see Table VIII).

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

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

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

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

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

8. *Priority review for Remicade for ulcerative colitis.* DailyDrugNews.com (Daily Essentials) June 1, 2005.

9. *Johnson & Johnson reports Q1 R&D highlights.* Johnson & Johnson Press Release 2005, April 19.

10. *Remicade approved for psoriatic arthritis.* DailyDrugNews.com (Daily Essentials) May 18, 2005.

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

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

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

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

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

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

17. *Expanded indication for Remicade recommended for approval in Europe.* DailyDrugNews.com (Daily Essentials) Aug 1, 2005.

18. Benoit, S., Toksoy, A., Bröcker, E.-B., Gillitzer, R., Goebeler, M. *Treatment of recalcitrant pustular psoriasis with infliximab: Effective reduction of chemokine expression.* Br J Dermatol 2004, 150(5): 1009.

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20. Bianchi, L., Bergamin, A., De Felice, C., Capriotti, E., Chimenti, S. *Remission and time of resolution of nail psoriasis during infliximab therapy.* J Am Acad Dermatol 2005, 52(4): 736 (Table VIII).

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23. 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 (Table VIII).

24. Gottlieb, A.B. et al. *Infliximab induction therapy for patients with severe plaque-type psoriasis: A randomized, double-blind, placebo-controlled trial.* J Am Acad Dermatol 2004, 51(4): 534 (Table VIII).

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

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Case report	Infliximab	1	Infliximab downregulated IL-8, GRO-α and MCP-1 levels and was effective in the treatment of pustular psoriasis	18
Psoriasis, Arthritis, psoriatic	Open	Infliximab, 5 mg/kg i.v. infusion x 5	25	Infliximab produced complete resolution of nail psoriasis in patients with psoriasis	19
Psoriasis	Open	Infliximab, 5 mg/kg i.v. on wk 0, 2, 6, 14 & 22	25	Infliximab induced complete remission in all patients with nail psoriasis unresponsive or with contraindications to standard therapies	20
Psoriasis	Open	Infliximab, 5 mg/kg i.v. infusion on wk 0, 2 & 6	12	Preliminary results suggested that infliximab was safe and induced complete clinical remission in patients with severe psoriasis	21
Psoriasis	Open	Infliximab i.v. over 2.5-3 h on wk 0, 2, 6 & 8 wks 1x/8 wks		Infliximab was useful with an acceptable toxicity profile in patients with moderate to severe psoriasis	22
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	249	Infliximab improved the quality of life in patients with severe psoriasis	23
Psoriasis	Randomized Double-blind Multicenter	Infliximab, 3 mg/kg i.v. infusion on wk 0, 2 & 6 (n=99) Infliximab, 5 mg/kg i.v. infusion on wk 0, 2 & 6 (n=99)	249	Infliximab was well tolerated, with rapid and significant improvement in psoriasis and quality of life in patients with severe plaque psoriasis	24
Psoriasis, Arthritis, psoriatic	Open	Infliximab, 3-5 mg/kg i.v. infusion o.d. → [after 2 wks] another dose o.d.	14	Infliximab produced rapid regression of psoriatic rash with improvement in psoriatic arthropathy and was well tolerated in patients with psoriatic lesions of the skin and joints	25
Psoriasis	Case report	Infliximab, 75 mg on wk 0, 2 & 6 1x/7wks	1	Infliximab was well tolerated and effective in the treatment of pustular psoriasis	26

Gottlieb, A.B., Evans, R., Li, S., Leonard, C. *The efficacy of infliximab across a variety of subgroups with plaque psoriasis.* Eur Congr Psoriasis (Oct 21-24, Paris) 2004, Abst P093.

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Gupta, A. *Infliximab: An update on psoriasis.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2770.

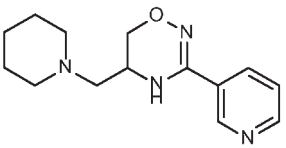
Gupta, A.K. *Biologic therapeutics in the treatment of moderate to severe psoriasis.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P06.43.

Reich, K. *Optimizing outcomes with infliximab in active psoriasis.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst SAT18.3.

Strober, B.E., Perelman, R.O. *Successful treatment of psoriasis and psoriatic arthritis with etanercept and methotrexate in a patient newly unresponsive to infliximab.* Arch Dermatol 2004, 140(3): 366.

Vincek, V. et al. *Infliximab monotherapy in psoriasis: A case of rapid clinical and histological response.* Int J Dermatol 2004, 43(4): 303.

Iroxanadine



The acquisition of Biorex's assets last year provided CytRx with a pipeline of several clinical drug candidates and a library of 500 small-molecule drug candidates. For example, iroxanadine, with potential for diabetes and cardiovascular disease, has been tested in two phase I trials and one phase II trial, where it was well tolerated and showed signs of efficacy, significantly improving the function of endothelial cells in blood vessels of patients at risk of cardiovascular disease. CytRx intends to initially develop the drug to improve endothelial dysfunction in indications such as diabetic wound healing. The company hopes to potentially outlicense iroxanadine for cardiovascular indications. Iroxanadine is believed to work through the activation of certain molecular chaperone proteins that repair normal damage to each cell. Data also suggest

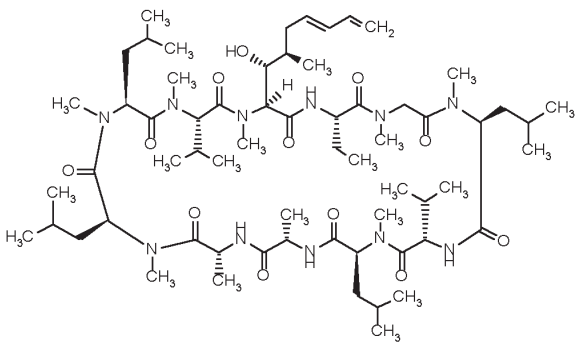
that iroxanadine may be useful in the treatment of diseases of poor blood circulation, such as diabetic foot ulcers. In experiments in rats, iroxanadine was tested for its ability to protect the function of endothelial cells in the capillaries of the legs of animals with spontaneously high blood pressure. Capillaries in the hind limbs of rats with high blood pressure were further damaged by blocking the large artery that normally provides the blood supply. After 60 min of blockage, blood flow was restored and the average flow of blood through the leg tissues was measured by laser doppler flowmetry. The results demonstrated that iroxanadine significantly improved the flow of blood to the tissues of the leg of the rats by protecting endothelial cells from damage. CytRx believes that restoring proper circulation to the extremities of diabetic patients, who often have damaged capillaries, may accelerate the abnormally slow healing of wounds characteristic of diabetes (1-3).

1. *CytRx acquires assets of Biorex Research & Development.* DailyDrugNews.com (Daily Essentials) Oct 8, 2004.

2. *Iroxanadine shows promise for cardiovascular disease in mouse study.* DailyDrugNews.com (Daily Essentials) Dec 3, 2004.

3. *Data supports development of iroxanadine for cardiovascular diseases.* DailyDrugNews.com (Daily Essentials) Jan 19, 2005.

ISA-247



Isotechnika is conducting a multicenter phase III psoriasis trial (SPIRIT) of its lead immunosuppressive compound *trans*-ISA-247 in Canada. A total of 457 patients with stable moderate to severe psoriasis were randomized to receive placebo or *trans*-ISA-247 (0.2, 0.3 or 0.4 mg/kg p.o.) twice daily for up to 24 weeks (although at 12 weeks placebo-treated patients switched to 0.3 mg/kg of *trans*-ISA-247 twice daily until the end of the study). An interim analysis of the first 369 patients who were given treatment for at least 12 weeks has shown that *trans*-ISA-247 is significantly more effective than placebo in improving the PASI scores of the patients. Response to *trans*-ISA-247 was first detected as early as 4 weeks after the beginning of administration. Previous studies have shown that calcineurin inhibitors may induce negative effects on kidney function; however, to date no patients enrolled in the SPIRIT study have experienced changes in their serum creatinine levels or glomerular filtration rates. This study follows the successful completion of single- and multiple-dose-finding studies in healthy volunteers, as well as food effect, bioequivalence and Q-T_c studies. The immunosuppressant is also undergoing phase IIb trials for kidney transplantation. Isotechnika began studying ISA-247 as a mixture of the *cis*- and *trans*-isomers, but the *trans*-isomer was found to be a more potent immunosuppressant, to have better predictability between dosing and resultant blood concentrations, and to allow dosing at therapeutic blood concentrations of drug without significant side effects. Roche has the right to opt in to the development of *trans*-ISA-247 for renal transplantation up to the end of phase II trials, while Isotechnika holds worldwide rights to all nontransplant indications (1-13).

1. *FDA agrees to dose range finding study for ISA-247.* DailyDrugNews.com (Daily Essentials) March 1, 2004.

2. *Roche and Isotechnika restructure ISA-247 collaboration agreement.* DailyDrugNews.com (Daily Essentials) April 22, 2004.

3. *Health Canada clears multiple dose range finding study for trans-ISA-247.* DailyDrugNews.com (Daily Essentials) April 26, 2004.

4. *Isotechnika reports Q1 R&D highlights.* Isotechnika Press Release 2004, March 13.

5. *All endpoints met in multiple ascending dose study of ISA-247.* DailyDrugNews.com (Daily Essentials) Nov 5, 2004.

6. *Enrollment completed in phase III psoriasis trial for ISA-247.* DailyDrugNews.com (Daily Essentials) Jan 31, 2005.

7. *Isotechnika gets go-ahead for phase IIb kidney transplant study of ISA-247.* DailyDrugNews.com (Daily Essentials) May 4, 2005.

8. *FDA approval for phase IIb kidney transplant study of ISA-247.* DailyDrugNews.com (Daily Essentials) May 17, 2005.

9. *Update on the efficacy of ISA-247 in psoriasis.* DailyDrugNews.com (Daily Essentials) April 28, 2005.

10. *ISA-247 investigated for psoriasis in Canadian phase III study.* DailyDrugNews.com (Daily Essentials) Dec 9, 2004.

Table IX: Clinical studies of ISA-247 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Randomized Double-blind Multicenter	ISA-247, 0.5 mg/kg/d x 12 wks (n=77) ISA-247, 1.5 mg/kg/d x 12 wks (n=83) Placebo (n=41)	201	ISA-247 was well tolerated and reduced symptom scores in patients with chronic plaque psoriasis	14

11. I*nterim results of QTc study of ISA-247.* DailyDrugNews.com (Daily Essentials) Sept 13, 2004.

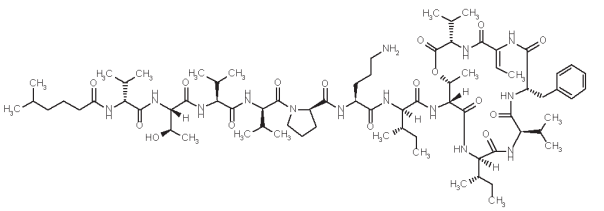
12. *trans-ISA-247 completes single ascending dose study.* DailyDrugNews.com (Daily Essentials) July 9, 2004.

13. *Promising phase III data shows ISA-247 is safe and effective in plaque psoriasis.* DailyDrugNews.com (Daily Essentials Aug 8, 2005.

14. Bissonnette, R. et al. *A randomized, multicenter, double-blind, placebo-controlled phase 2 trial of ISA247 in patients with chronic plaque psoriasis.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst FC06.9 (Table IX).

Original monograph – Drugs Fut 2004, 29(7): 680.

Kahalalide F



PharmaMar's marine-origin compound kahalalide F, a depsipeptide derived from the sea slug *Elysia rufescens*, has entered phase II trials for the treatment of patients with severe psoriasis. Kahalalide F is also undergoing phase II trials in various tumors: melanoma, non-small cell lung cancer and hepatocarcinoma. In phase I trials in oncological patients treated with kahalalide F, it was found that the compound had clinical potential to treat severe psoriasis. These signs of activity, together with the product's excellent safety profile, led to the initiation of the clinical development of kahalalide F for psoriasis (1, 2).

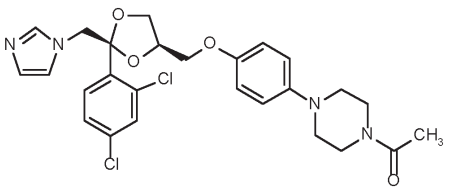
Pharmaceutical compositions comprising kahalalide compounds, notably the cytotoxic and antiviral peptide kahalalide F, have been claimed for the treatment of skin diseases characterized by hyperproliferation of cells of the dermis, in particular refractory psoriasis (3).

1. *Kahalalide F enters phase II trials in NSCLC and melanoma.* DailyDrugNews.com (Daily Essentials) July 23, 2004.

2. *Kahalalide F enters phase II trials for severe psoriasis.* DailyDrugNews.com (Daily Essentials) Nov 4, 2004.

3. Izquierdo Delso, M.A. (PharmaMar, SA) *Use of kahalalide compounds for the manufacture of a medicament for the treatment of psoriasis.* WO 2004075910.

Ketoconazole, New Formulations



Connetics plans to resume development of Extina®, an investigational new drug formulation of 2% ketoconazole delivered via the company's VersaFoam™ delivery system, for the treatment of seborrheic dermatitis. The company received a nonapprovable letter from the FDA for Extina® in November 2004 due to insufficient clinical data. Following meetings with the FDA, Connetics will recommence development by initiating a final phase III trial intended to demonstrate that Extina® is superior to placebo foam. The phase III trial is expected to commence in the third quarter of 2005, which should lead to an NDA resubmission by the end of 2006 and potential launch in 2007. Based on the company's original NDA submission in November 2004, the FDA concluded that Extina® did not show superiority to placebo foam. Previous phase III results with Extina® demonstrated non-inferiority to Nizoral® (ketoconazole) 2% cream as measured by the endpoint of the Investigator's Static Global Assessment (1-5).

Barrier Therapeutics has announced positive results from its confirmatory phase III trial of Sebazole™, a topical gel formulation of ketoconazole for once-daily application, for the treatment of seborrheic dermatitis. Compared to currently approved ketoconazole cream products, Sebazole™ requires only one-half of the applications and for half of the treatment length. It also has a lower propensity for skin irritation as compared to current ketoconazole cream products. In this pivotal double-blind, placebo-controlled study, which enrolled 459 subjects at 24 U.S. centers, 25.8% (59/229) of subjects treated with Sebazole™ reached the primary endpoint as compared to 13.9% (32/230) of the vehicle-treated patients. The study compared once-a-day Sebazole™ treatment to the vehicle gel. The primary efficacy endpoint was the proportion of subjects who were effectively treated at day 28, *i.e.*, 14 days following the end of a 2-week treatment period. Effectively treated was defined as a subject who at day 28 had a reduction in the signs and symptom scores for redness

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

Indication	Design	Treatments	n	Conclusions	Ref.
Dermatitis, seborrheic	Randomized Double-blind Multicenter	Ketoconazole 2% gel top. o.d. x 14 d (n=229) Placebo (n=230)	459	Ketoconazole gel was well tolerated, reduced the severity of scaling and improved the total sign and symptom score in patients with seborrheic dermatitis	9

and scaling to none or mild, as well as an Investigator's Global Assessment of completely cleared or almost cleared. This primary efficacy endpoint was identical to that used in Barrier's prior supportive phase III trials for seborrheic dermatitis. Of the secondary efficacy endpoints, the mean change from baseline for scaling was statistically significantly better as compared to vehicle alone. Of the secondary efficacy endpoints for redness and itching, the results were better as compared to the vehicle alone, but were not statistically significant. There were no treatment-related serious adverse events in the trial. Nonserious treatment-related adverse events were evenly distributed between the groups at a rate of approximately 7%. These results confirm the findings from two previous supportive phase III studies. In these trials, Sebazole™ achieved statistical significance in the primary efficacy endpoint against the vehicle gel. Both studies had four treatment arms (Sebazole™, vehicle, desonide and the combination of desonide with Sebazole™). Barrier plans to file an NDA for Sebazole™ by mid-2005 based on the positive results from all three of these studies. The company has an exclusive distribution and license agreement with Ferrer for several countries throughout Europe, Latin America and Africa (6-8).

1. *Extina NDA accepted for filing.* DailyDrugNews.com (Daily Essentials) April 14, 2004.

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

3. *Non-approvable letter for Extina.* DailyDrugNews.com (Daily Essentials) Nov 29, 2004.

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

5. *Connetics to resume Extina development.* DailyDrugNews.com (Daily Essentials) June 10, 2005.

6. *Enrollment underway in confirmatory phase III trial of Sebazole.* DailyDrugNews.com (Daily Essentials) June 1, 2004.

7. *Ferrer to distribute Barrier's products.* DailyDrugNews.com (Daily Essentials) Nov 9, 2004.

8. *Barrier Therapeutics announces positive phase 3 results for pivotal study with Sebazole™.* Barrier Therapeutics Press Release 2004, Dec 16.

9. Beger, B., Highton, A., Barranco, C., Legendre, R. *A double-blind, randomized, vehicle-controlled, parallel group, multicenter study to assess the efficacy and safety of a topical gel product containing ketoconazole USP 2% in the treatment of seborrheic dermatitis.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P1803 (Table X).

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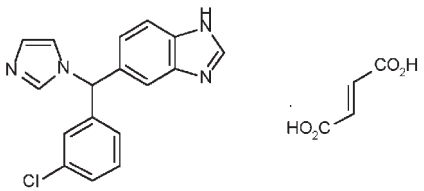
Koller, T., Spellman, M., Yaroshinsky, A., Elewski, B. *A randomized, double-blind, double-dummy, placebo-controlled study of the safety and efficacy of ketoconazole foam, 2% versus ketoconazole 2% cream in the treatment of seborrheic dermatitis.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P397.

LI-412

LI-412 is a reformulation in phase I/II trials at Enhance Biotech for the oral and topical treatment of itch associated with allergy or eczema. The compound acts by blocking 5-HT and histamine receptors.

Liarozole Fumarate



Barrier Therapeutics' liarozole has received orphan drug designation in the U.S. for the treatment of congenital ichthyosis. In phase II and phase III trials, oral liarozole, a new concept in treating this condition, was well tolerated, with a majority of patients showing marked improvement in their condition. The drug also has orphan drug status in the E.U. Liarozole belongs to the novel retinoic acid metabolism-blocking agents (RAMBAs) class. RAMBAs slow the metabolism or degradation of the body's own retinoic acid, causing the body to maintain higher, potentially therapeutic levels of the natural vitamin in cells of the skin. The increased vitamin levels return to normal soon after stopping treatment with liarozole. RAMBAs such as liarozole may provide the same therapeutic benefits as synthetic retinoid therapy but with less risk of retinoid build-up in tissues and associated side effects. The company has an exclusive distribution and license agreement with Ferrer for several countries throughout Europe, Latin America and Africa (1, 2).

An open-label clinical trial and a comparative controlled clinical trial evaluated the efficacy and safety of liarozole (75 or 150 mg p.o. b.i.d.) *versus* twice-daily acitretin (10 mg in the morning, followed by 25 mg in the evening) given for 12 weeks to 44 patients with severe ichthyosis. Both liarozole and acitretin significantly improved scaling and the severity of skin lesions of the patients. All study regimens were well tolerated, and the most common adverse events were dry mouth, itching, dry lips, skin exfoliation, eczema and epistaxis (3) (Table XI).

Pooled data from two open-label trials, four placebo-controlled trials and two acitretin-controlled trials were used to determine the safety profile of liarozole in patients with ichthyosis and psoriasis. Liarozole was associated with dose-dependent increases in the incidence of dry mouth, skin disorder, dry skin and rash, and also in the number of patients withdrawing from the study due to adverse events. No evidence of a dose-effect relationship was found on the incidence of abnormalities in laboratory tests, vital signs or electrocardiograms (4) (Table XI).

1. *Liarozole receives U.S. orphan drug status for congenital ichthyosis.* DailyDrugNews.com (Daily Essentials) June 25, 2004.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Ichthyosis	Pooled/meta-analysis	Liarozole, 75 mg p.o. b.i.d. x 12 wks (n=15) Liarozole, 150 mg p.o. b.i.d. x 12 wks (n=12) Acitretin, 10/25 mg p.o. b.i.d. x 12 wks (n=17)	44	Liarozole was as effective and well tolerated as acitretin in the treatment of patients with severe ichthyosis	3
Ichthyosis, Psoriasis	Pooled/meta-analysis	Liarozole	876	Oral liarozole was generally well tolerated in patients with psoriasis or ichthyosis	4

2. *Ferrer to distribute Barrier's products.* DailyDrugNews.com (Daily Essentials) Nov 9, 2004.

3. Verfaille, C., Steylen, P., Blanchet-Bardon, C., Vandeplassche, G., Vanhoutte, F., Cauwenbergh, G. *Phase II and III studies to evaluate the efficacy and safety of oral liarozole and acitretin in the treatment of severe ichthyosis.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst FC03.8.

4. Vandeplassche, G., Verfaille, C., Beger, B., Wouters, L., Snoeck, E., Cauwenbergh, G. *Safety of oral liarozole in patients with ichthyosis or psoriasis.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P09.9.

LL-4218/LLL-3348

Lupin has two products in early clinical evaluation for the treatment of chronic stable plaque-type psoriasis. LL-4218 (Desoside-P) is an orally available pure compound isolated from a plant and LLL-3348 (Desoris) is an aqueous herbal extract with a novel mechanism of action, effectively modulating cellular function to improve psoriatic lesions without toxicity.

MDI-101

MDI-101, an *all-trans*-retinoic acid derivative, is being evaluated in phase II clinical trials for the topical treatment of acne at Molecular Design International. The company is currently seeking a licensing partner for further development of the compound.

Mecasermin Rinfabate

Insmed has received notification from the FDA that the agency expects to complete the priority review of SomatoKine® (mecasermin rinfabate) on or before October 3, 2005, a 3-month extension from the original user fee goal date. The extension is a result of the agency classifying responses to questions about the NDA as a major amendment to the NDA. SomatoKine® has been submitted for the treatment of growth hormone insensitivity syndrome (GHIS). SomatoKine® is a proprietary delivery composition of insulin-like growth factor-I (IGF-I) and its principal binding protein IGFBP-3. The novel compound, which has orphan drug status, is administered as a single daily subcutaneous injection, which can restore IGF levels into the normal range. In diabetic subjects, administration of SomatoKine® demonstrated a significant improvement in blood sugar control and a significant reduction in daily insulin use. Following severe burn injury in both children and adults, SomatoKine® demonstrated a significant improvement in muscle protein synthesis and a significant reduction in the inflammatory response associated with the trauma. Following recovery from hip fracture, SomatoKine® demonstrated a significant improvement in functional recovery and bone mineral density. It is also in phase II trials for the treatment of HIV-associated lipodystrophy (1-7).

1. *Statistically significant increase in growth rate at six months in SomatoKine study.* DailyDrugNews.com (Daily Essentials) July 23, 2004.

2. *SomatoKine designated orphan drug in Europe for extreme insulin resistance.* DailyDrugNews.com (Daily Essentials) Oct 28, 2004.

3. *Insmed completes SomatoKine NDA.* DailyDrugNews.com (Daily Essentials) Jan 4, 2005.

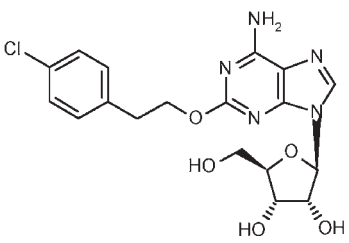
4. *Priority review for SomatoKine.* DailyDrugNews.com (Daily Essentials) April 18, 2005.

5. *FDA extends action date for SomatoKine NDA.* DailyDrugNews.com (Daily Essentials) June 14, 2005.

6. *Insmed studies SomatoKine for HIV-associated lipodystrophy.* DailyDrugNews.com (Daily Essentials) April 22, 2005.

7. *SomatoKine NDA accepted for filing.* DailyDrugNews.com (Daily Essentials) March 15, 2005.

MRE-0094



MRE-0094, an adenosine A_{2A} agonist, is currently undergoing phase I clinical trials for the topical treatment of chronic diabetic foot ulcers. Originally discovered at

Aderis, the compound is being developed in collaboration with King Pharmaceuticals under a worldwide development and commercialization agreement established in 1997.

MV-9411

A photoreactive drug from Miravant, MV-9411 is undergoing phase II clinical trials as a topical gel for the treatment of moderate plaque psoriasis using PhotoPoint™ photodynamic therapy (PDT).

MX-594AN

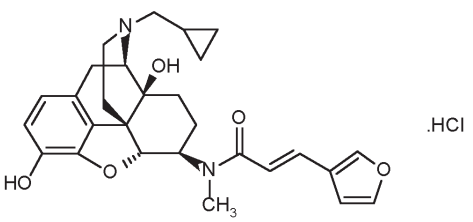
MX-594AN (omiganan 2.5% solution) is a cationic antimicrobial peptide that has completed phase IIa trials at Migenix for the topical treatment of acne. Development has been delayed until the company finds a partner for its further development (1-3).

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

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

3. *Migenix reports fourth quarter and fiscal year 2005 financial results.* Migenix, Inc. Press Release 2005, July 14.

Nalfurafine Hydrochloride



.HCl

Acologix and Toray Industries have entered into a collaboration and license agreement for Toray's nalfurafine hydrochloride (TRK-820, AC-820) in North America and Europe. Under the agreement, Acologix is granted an exclusive license to develop and commercialize nalfurafine in North America, while in Europe, Acologix and Toray will codevelop the compound and Acologix retains a commercialization option. Nalfurafine is a highly selective kappa opioid receptor agonist that has completed multiple phase II studies for the treatment of uremic pruritus. Nalfurafine has a different mechanism from existing antipruritic drugs such as antihistamines and is thought to suppress pruritus via opioid-related mechanisms and, as such, is expected to be effective in treating itching that is resistant to existing treatments such as antihistamine drugs. A pivotal phase III study is planned to begin in Europe later this year. Acologix and Toray plan to submit a marketing authorization application in Europe following the completion of the pivotal study. In North America, Acologix will begin discussions with regulatory agencies to determine the appropriate development plan for product approval. In Japan, Toray is codeveloping nalfurafine with Japan Tobacco and Torii Pharmaceutical for uremic pruritus, and with Maruho for atopic dermatitis. The drug has entered the final phase of clinical trials before submission in Japan (1-3).

1. *Joint agreement for TRK-820 in Japan.* DailyDrugNews.com (Daily Essentials) March 21, 2005.

2. *Maruho and Toray Industries to jointly develop TRK-820 in Japan.* DailyDrugNews.com (Daily Essentials) April 4, 2005.

3. *Acologix and Toray sign agreement for TRK-820.* DailyDrugNews.com (Daily Essentials) June 20, 2005.

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

Additional References

Kumagai, H., Maruyama, S., Ebata, T., Takamori, K. *A kappa-agonist reduced itch in hemodialysis patients.* 35th Annu Int Narc Res Conf (July 18-23, Kyoto) 2004, Abst O V-2.

NF-κB Decoy

Corgentech has begun treating patients in two multicenter phase I/II clinical trials of NF-κB decoy, a highly selective and potent oligonucleotide inhibitor of the transcription factor NF-κB, for the treatment of atopic dermatitis (eczema). The first multicenter, randomized, double-blind, dose-ranging trial will evaluate the safety and feasibility of repeated application of three concentrations of NF-κB decoy to the skin of adult patients with mild to moderate eczema. The study will involve approximately 75 individuals randomized in parallel to one of three active treatment groups or a control group. Patients will apply the study drug twice daily for 21 days to targeted areas of the skin and will be followed for 28 days after the final treatment. The study will assess the safety, tolerability and systemic pharmacokinetic profile of NF-κB decoy. Periodic physician assessments of the targeted area will be made to measure the degree of symptom severity as well as patient evaluations of itchiness. Data from this trial are anticipated in early 2006. The second trial is being conducted in Australia and Switzerland in approximately 120 patients. It will evaluate the safety, tolerability and pharmacokinetic profile of once-a-day *versus* twice-a-day applications of NF-κB decoy to the skin of adult patients with mild to moderate

eczema. Study participants will apply the drug for 28 days to targeted areas of the skin and will then be followed for 14 days after the final treatment. Periodic physician assessments of the targeted area will be made to measure the degree of symptom severity as well as patient evaluations of itchiness. In preclinical animal studies, NF-κB decoy was efficiently delivered to intact skin using several easy-to-manufacture, inexpensive formulations and was effective in reducing the swelling and inflammation associated with eczema, with minimal side effects (1-3).

1. *Corgentech files IND to begin phase I/II trial of NF-κB decoy in eczema.* DailyDrugNews.com (Daily Essentials) Jan 18, 2005.

2. *First patient treated in phase I/II trial of NF-κB decoy.* DailyDrugNews.com (Daily Essentials) May 26, 2005.

3. *Enrollment open in second phase I/II eczema study of NF-κB decoy.* DailyDrugNews.com (Daily Essentials) July 26, 2005.

NPI-32101

Nucryst, a subsidiary of The Westaim Corporation, has reported results from its initial phase IIa efficacy and safety study of NPI-32101 in a cream formulation in adult patients with mild to moderate atopic dermatitis. NPI-32101 is a topical form of Nucryst's proprietary silver Rx nanocrystals. The double-blind, randomized, placebo-controlled study involved 224 adult patients with mild to moderate symptoms of atopic dermatitis enrolled across 23 U.S. sites. Patients were treated twice daily for a 6-week period with one of two concentrations of NPI-32101 (0.5% and 1.0%) in a cream formulation or with the vehicle alone. The study evaluated the safety and effectiveness of topical NPI-32101 in improving the signs and symptoms of atopic dermatitis. Using the intent-to-treat analysis with last observation carried forward, statistical significance was not met in the investigator overall assessment of disease improvement. However, statistical significance was achieved with 1.0% NPI-32101 compared to vehicle using intent-to-treat patients who completed 6 weeks of treatment. In patients who completed the study in accordance with the protocol, statistical significance was achieved with 1.0% NPI-32101. NPI-32101 was well tolerated with no serious adverse events. Additional studies will further explore the safety profile of NPI-32101 and Nucryst plans to conduct additional phase II studies before phase III. Preclinical laboratory studies have demonstrated that NPI-32101 possesses both antiinflammatory and broad-spectrum antimicrobial activities (1, 2).

1. *Nucryst reports phase IIa results for NPI-32101 in atopic dermatitis.* DailyDrugNews.com (Daily Essentials) Sept 10, 2004.

2. *Nucryst Pharmaceuticals announces year-end results.* Nucryst Pharmaceuticals Press Release 2005, Feb 17.

NV-07α

Novogen has completed phase II trials with its antiinflammatory compound NV-07α for the topical treatment of acute photodamage and license negotiations are under way.

OrCel™

OrCel™ is a composite cultured skin composed of a bilayered cellular matrix seeded with epidermal and dermal cells, which secrete growth factors and cytokines normally found in acute human wounds and are believed to have a beneficial role in promoting tissue repair. The tissue-engineered product was initially launched in the U.S. in 2001 by Ortec for the treatment of epidermolysis bullosa. The following year, Ortec launched the product for the facilitation of wound closure of split thickness skin donor site wounds in burn patients. OrCel™ is currently awaiting registration in the U.S. as a treatment for venous leg ulcers and it is also being evaluated by Ortec in phase II clinical trials as a treatment for diabetic foot ulcers; earlier this year the company received FDA clearance to begin a pivotal trial in the latter indication, but expects to wait until approval is obtained for the venous ulcer indication. OrCel™ is marketed and distributed in collaboration with Cambrex, Teva and Ferrer.

Following the submission by Ortec of all the information required by the FDA to complete its review of the premarket approval (PMA) application for OrCel™, the agency has requested that Ortec conduct a confirmatory trial involving only those patients for whom OrCel™ is indicated. Ortec submitted clinical data that demonstrated clinical significance in both the intent-to-treat (ITT) population, as well as those patients with ulcers for which use of OrCel™ is indicated (partial and full thickness ulcers extending into the dermis but not into the fascia). Although the FDA indicated the clinical data showed promise for the effective treatment of venous ulcers, the agency believes additional data are necessary to demonstrate reasonable assurance of safety and efficacy of OrCel™ in patients with venous leg ulcers. The FDA believes the analysis of the patients for which OrCel™ is indicated was not prospectively defined, and accordingly recommended an additional prospective clinical trial to confirm Ortec's findings. Ortec estimates that approximately 40 patients will be required in the study. Ortec intends to work closely with the FDA to design and undertake the confirmatory trial, which is expected to lead to the approval of the PMA for OrCel™. Concurrently, Ortec intends to initiate a resolution process with the FDA (1-5).

1. *FDA accepts OrCel PMA.* DailyDrugNews.com (Daily Essentials) April 5, 2004.

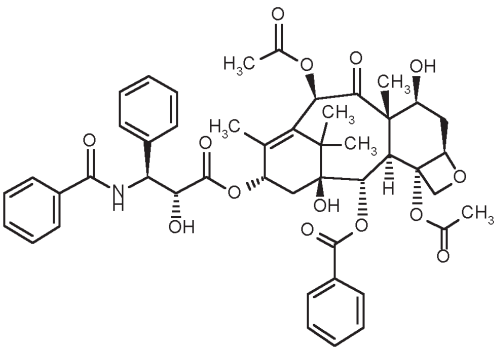
2. *Cambrex to market and distribute Orcel.* DailyDrugNews.com (Daily Essentials) Oct 20, 2004.

3. *FDA ready to review OrCel PMA application.* DailyDrugNews.com (Daily Essentials) April 19, 2005.

4. *Ortec provides update on PMA review status.* Ortec International Press Release 2005, March 23.

5. *FDA requests confirmatory trial for approval of PMA for OrCel in the treatment of venous ulcers.* Ortec International Press Release 2005, April 29.

Paclitaxel, Micellar



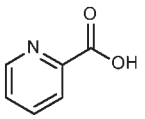
Angiotech has developed an intravenous treatment for severe psoriasis and rheumatoid arthritis. Micellar paclitaxel, or Paxceed®, has been tested in a small phase II trial in patients with severe psoriasis (see below) and has also entered phase II evaluation for rheumatoid arthritis. The company expects to seek a strategic partnership for the further development of the product.

In an open-label, nonrandomized phase II clinical trial, 12 patients with baseline PASI scores of 20 or more were treated with a micellar formulation of paclitaxel, administered either at a constant dose level (6 injections of 75 mg/m^2 i.v. every 4 weeks) or at an initial dose of 3 injections of 37.5 mg/m^2 i.v. every 4 weeks, which if well tolerated was followed by 6 injections of 50 mg/m^2 i.v. every 4 weeks. Only 3 patients receiving the second paclitaxel course withdrew from the study due to infusion reactions or worsening Crohn's disease. Both paclitaxel courses improved the PASI scores of the patients, with best percent improvements found at week 22 (average of 66.5%) for the constant-dose course and at week 18 (average of 56.6%) for the second course. The most common adverse event was mild fatigue, and no evidence of myelosuppression or gonadal dysfunction was observed. Additional studies are needed to determine the optimal dose of micellar paclitaxel for treating patients with severe psoriasis (1) (Table XII).

1. Ehrlich, A., Booher, S., Becerra, Y., Borris, D.L., Figg, D., Turner, M.L., Blauvelt, A. *Micellar paclitaxel improves severe psoriasis in a prospective phase II pilot study.* J Am Acad Dermatol 2004, 50(4): 533.

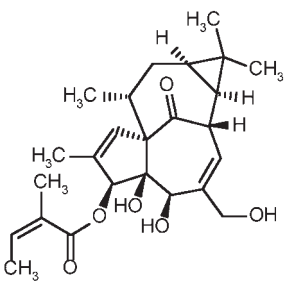
Original monograph – Drugs Fut 1986, 11(1): 45.

PCL-016



Novactyl's lead drug candidate, PCL-016, is a pyridinecarboxylate with broad-spectrum antiviral and immunomodulatory properties. PCL-016 is a small, naturally occurring molecule, a terminal metabolite of tryptophan that is naturally produced in peripheral tissues. It has been shown to bind with the zinc associated with zinc finger proteins and thereby affect their structure and function. Phase II trials for the topical treatment of mild to moderate acne have been performed, as well as phase I trials for the topical treatment of herpes labialis. For the latter indication, the company has a licensing agreement with Upsher-Smith.

PEP-005



Peplin completed ahead of schedule its U.S.-based phase I trial for its nonmelanoma skin cancer treatment PEP-005 Topical and subsequently released positive safety and efficacy results. The study was conducted under an IND filed in June 2004 by the company's former partner Allergan. The multicenter, double-blind, placebo-controlled study evaluated the safety of a single application of PEP-005 Topical gel directly onto actinic keratoses

Table XII: Clinical studies of paclitaxel, micellar (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Open	Paclitaxel (micellar), 37.5 mg/m^2 i.v. 1x/2 wks x 3 → 50 mg/m^2 i.v. 1x/2 wks x 6 (n=5) Paclitaxel (micellar), 75 mg/m^2 i.v. 1x/4 wks x 6 (n=7)	12	Micellar paclitaxel was well tolerated and effective in improving PASI scores in patients with severe psoriasis	1

followed by a posttreatment follow-up period. All enrolled patients completed the trial without any serious adverse event reports. The trial also demonstrated indications of its ability to clear lesions, with 40% of treated lesions either completely cleared or almost cleared. This compares with 15% of lesions treated with placebo. One patient saw all 5 lesions completely cleared by single applications of PEP-005 Topical, while another patient saw 4 of 5 lesions completely cleared, all within 21 days after treatment. PEP-005, an angeloyl-substituted ingenane that acts as an activator of protein kinase C (PKC) enzymes, is a single molecular entity isolated and purified from a common nonindigenous plant. Peplin holds global rights for PEP-005 Topical and all rights worldwide to other oncology applications of PEP-005 (1-10).

Peplin subsequently commenced its program of three phase IIa trials of PEP-005 Topical for the treatment of actinic keratosis and nonmelanoma skin cancer. The three separate studies will evaluate PEP-005 Topical in actinic keratosis and superficial and nodular forms of basal cell carcinoma, the most common form of nonmelanoma skin cancer. The three PEP-005 Topical phase IIa trials are multicenter, randomized, double-blind, parallel-group, vehicle-controlled studies to determine the safety of PEP-005 0.0025%, 0.01% and 0.05% gel in two alternative treatment regimens (day 1 and day 2 or day 1 and day 8 applications). The primary objective in each study is to determine the safety of PEP-005 0.0025%, 0.01% and 0.05% gel administered according to the two treatment schedules. The secondary objectives of each study will be to evaluate the efficacy of the PEP-005 gel administered according to the two treatment regimens, as well as to determine a recommended treatment regimen and evaluate patients for cosmetic outcome. Each study will enroll 60 patients. Subjects will be randomized on a 1:1 ratio to arm A (treatment on day 1 and day 2) or arm B (treatment on day 1 and day 8). Subjects will be randomized to receive one of the three active treatments or vehicle gel and patients will undergo follow-up for 3 months. The studies will be conducted by consulting dermatologists around Australia. Enrollment and treatment in the actinic keratosis trial have been completed and results are expected in the fourth quarter of 2005. The other trials in subjects with superficial and nodular basal cell carcinoma should report in the first quarter of 2006. The company also announced plans to conduct a U.S.-based phase IIa trial to study escalating doses of PEP-005 Topical on an area of skin with actinic keratosis. The open-label study would evaluate the safety and efficacy of escalating concentrations of PEP-005 Topical when applied on 2 consecutive days to a large area of skin incorporating an actinic keratosis lesion. This trial would recruit up to 30 patients at a single U.S. center. The trial is designed to evaluate both treatment area skin responses and the effect of the drug on actinic keratosis lesions. A primary outcome will be to establish a maximum tolerated dose when treating an area of skin. More advanced clinical studies are expected to start in the first half of 2006 (11, 12).

1. *INDs filed for topical PEP-005.* DailyDrugNews.com (Daily Essentials) March 26, 2004.

2. *Allergan to withdraw PEP-005 INDs, resubmission planned.* DailyDrugNews.com (Daily Essentials) April 29, 2004.

3. *Peplin Biotech reports 2003 year-end R&D highlights.* Peplin Biotech Web Site 2004, Feb 10.

4. *Allergan files INDs for PEP-005 Topical.* DailyDrugNews.com (Daily Essentials) July 12, 2004.

5. *PEP-005 shows high selectivity against leukemia.* DailyDrugNews.com (Daily Essentials) Aug 11, 2004.

6. *PEP-005 initiates human clinical trials.* DailyDrugNews.com (Daily Essentials) Sept 1, 2004.

7. *Allergan and Peplin discontinue PEP-005 collaboration.* DailyDrugNews.com (Daily Essentials) Oct 14, 2004.

8. *Peplin completes phase I study of PEP-005 Topical.* DailyDrugNews.com (Daily Essentials) Oct 26, 2004.

9. *Peplin to raise funds to support phase II studies of PEP-005 Topical.* DailyDrugNews.com (Daily Essentials) Nov 10, 2004.

10. *Peplin reports positive phase I results for PEP-005 Topical.* DailyDrugNews.com (Daily Essentials) Jan 12, 2005.

11. *PEP-005 Topical enters phase II.* DailyDrugNews.com (Daily Essentials) March 22, 2005.

12. *Peplin progresses PEP-005 Topical for actinic keratosis.* DailyDrugNews.com (Daily Essentials) July 5, 2005.

PH-10

Provectus has begun the process to start phase II trials for PH-10 (Xantryl™) to treat psoriasis and later eczema. Provectus expects to begin clinical studies for psoriasis in late 2005 and eczema in 2006. PH-10 has successfully completed preclinical and phase I studies in Denmark and the U.S. for the treatment of psoriasis. The same active ingredient (rose bengal) is also in early clinical trials in breast cancer patients as Provecta™ (PV-10) on the basis of its ability to selectively target and destroy cancer cells without harming surrounding healthy tissue (1-3).

1. *IND filing for Provecta.* DailyDrugNews.com (Daily Essentials) Aug 30, 2004.

2. *Provecta IND cleared.* DailyDrugNews.com (Daily Essentials) Oct 14, 2004.

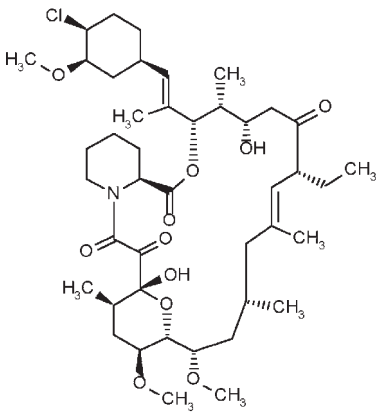
3. *Provectus prepares to study Xantryl in psoriasis and eczema.* DailyDrugNews.com (Daily Essentials) April 15, 2005.

PI-0824

PI-0824 has completed phase clinical I/II development at Peptimmune for the intravenous treatment of pemphigus vulgaris. The 19-amino-acid peptide works by selectively suppressing the production of autoantibodies to desmoglein

3, a self-adhesion molecule that holds skin cells together. This approach re-establishes a tolerant state in the subset of $CD4^+$ cells that recognize the immunodominant T-cell epitope of desmoglein 3 (DSg3), which can no longer stimulate pathogenic B-cells to proliferate and produce antibody. In October 2004, PI-0824 was granted orphan drug designation by the FDA for the treatment of pemphigus vulgaris.

Pimecrolimus



Novartis's pimecrolimus is a T-cell and mast cell inhibitor first introduced in 2002 in the U.S. and now available in approximately 90 countries as Elidel® topical cream for the short-term treatment of the signs and symptoms of atopic dermatitis and intermittent long-term treatment to prevent progression to flares in patients aged 3 months and older. It is also in phase III testing for the treatment of chronic hand dermatitis and atopic dermatitis in infants, and phase II trials for seborrheic dermatitis and inflammatory skin diseases. An eye drop formulation is being tested in phase II for dry eye and blepharitis, and an oral formulation is also in phase II trials for inflammatory skin diseases.

1. Bialynicki-Birula, R., Szepietowski, J.C., Kolodziej, T. *Pimecrolimus cream for the treatment of seborrheic dermatitis on the face.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P03.62 (Table XIII).

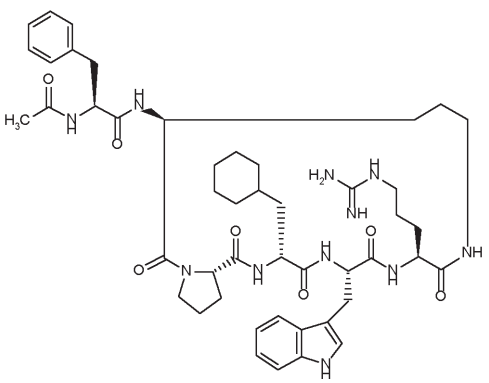
2. Cunha, P.R. *Pimecrolimus cream 1% in the treatment of seborrheic dermatitis in patients refractory to topical corticosteroids.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst FC07.3 (Table XIII).

3. Özden, M.G., Ilter, N., Gürer, M.A. *A new treatment choice for chronic hand dermatitis: 1% pimecrolimus cream.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P03.82 (Table XIII).

4. Verros, C., Rallis, E., Moussatou, V., Papaconstantis, M., Papadakis, P. *Treatment of facial seborrheic dermatitis by topical application of pimecrolimus.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P03.61 (Table XIII).

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

PMX-53



A pilot study of topical PMX-53 (Promics) reported encouraging results. The study in 10 patients at the Royal Adelaide Hospital, South Australia, met the endpoints of safety and tolerability and demonstrated improvement in psoriasis lesion score in 90% of patients. PMX-53, a cyclic hexpeptide, acts by potently and selectively blocking the C5a receptor at an earlier stage in the immune and inflammatory process than currently available antiin-

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

Indication	Design	Treatments	n	Conclusions	Ref.
Dermatitis, seborrheic	Open	Pimecrolimus 1% cream top. b.i.d.	9	Pimecrolimus was safe, well tolerated and effective in patients with seborrheic dermatitis on the face	1
Dermatitis, seborrheic	Case report	Pimecrolimus 1% cream top.	2	Pimecrolimus was effective in the clearance of lesions, with rapid onset of action, and was well tolerated in patients with seborrheic dermatitis refractory to topical steroids	2
Dermatitis, hand	Open	Pimecrolimus 1% cream top. x 10 d (n=32) Placebo (n=16)	48	Pimecrolimus 1% cream was significantly effective in treating patients with chronic hand dermatitis	3
Dermatitis, seborrheic	Open	Pimecrolimus 1% cream top. o.d. x 10 d	11	Pimecrolimus 1% cream treatment resulted in complete remission in all patients with facial seborrheic dermatitis	4

flammatory drugs. The drug may have potential for reduced side effects and the ability to diminish the associated pain and tissue damage caused by inflammation. It also has the potential to act more effectively across a broader population base than available treatments. The topical gel formulation of PMX-53 has been cleared for phase Ib/IIa clinical evaluation of safety and tolerability in patients with mild to moderate psoriasis. PMX-53 has also completed an oral phase Ib/IIa trial in patients with chronic rheumatoid arthritis and may have application in a variety of other inflammatory diseases, including inflammatory bowel disease and ischemia/reperfusion injury (1, 2).

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

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

PN-105

PN-105 is a wound-healing agent in phase I trials at Wellstat Therapeutics for the treatment of skin lesions.

PN-106

Wellstat Therapeutics' PN-106 was last reported to be in phase II trials for the treatment of actinic keratosis.

Polyphenon® E, Ointment

Polyphenon® E is a defined and quantified extract from green tea developed as an ointment for the topical treatment of anogenital warts and actinic keratosis and currently in phase III and phase II clinical trials, respectively, at MediGene.

MediGene recently completed a phase II trial of Polyphenon® E ointment for the treatment of actinic keratosis. A total of 62 patients were enrolled in the double-blind, randomized, placebo-controlled study at 6 sites in Germany and Switzerland and treated daily for 4 months. After treatment with Polyphenon® E ointment, a significantly greater number of the remaining visible lesions were formerly subclinical in nature. Subclinical lesions are pre-existing actinic keratosis lesions that dwell under the top layer of skin. The subclinical lesions in trial patients were not visible at trial initiation. Their appearance and emergence through the skin represent an essential first step in a therapy for actinic keratosis. This observation demonstrates the immunomodulatory properties of Polyphenon® E, although the chosen treatment regimen and trial length were not sufficient for complete healing of all lesions. The dosage plan successfully applied in the treatment of genital warts could therefore not be transferred to the treatment of actinic keratosis. With further dose optimization, however, the company believes that the product still has great potential for the treatment of actinic keratosis (1-6).

1. *Results from European phase III trial of Polyphenon E Ointment.* DailyDrugNews.com (Daily Essentials) April 2, 2004.

2. *MediGene extends clinical development of Polyphenon E to actinic keratosis.* DailyDrugNews.com (Daily Essentials) April 13, 2004.

3. *Polyphenon E Ointment enters phase II trial for actinic keratosis.* DailyDrugNews.com (Daily Essentials) May 3, 2004.

4. *Enrollment completed in phase II actinic keratosis study of Polyphenon E.* DailyDrugNews.com (Daily Essentials) Oct 26, 2004.

5. *MediGene successfully completes pivotal clinical phase III trials of Polyphenon(R) E ointment for the treatment of genital warts.* MediGene Press Release 2004, Dec 7.

6. *MediGene announces phase 2 trial results of Polyphenon® E treatment of actinic keratosis.* MediGene Press Release 2005, June 30.

PSK-3841

Phase II trials are under way at ProStrakan with the topical antiandrogen PSK-3841 for the treatment of acne and alopecia.

Psoraxine®

Astralis's phase II study of its novel immunostimulatory product Psoraxine® (AS-210) for the treatment of psoriasis failed to meet the primary study endpoint upon completion of the treatment phase of the study, although its safety was confirmed. The randomized, double-blind, placebo-controlled study involved 120 patients with moderate to severe psoriasis who received repeated intramuscular injections of a second-generation version of Psoraxine® developed in collaboration with SkyePharma. The primary endpoint was a specified level of improvement of symptoms as measured in accordance with the PASI. Detailed analysis of the PASI data, as well as biopsy results, suggested that the product is active, but not at the level expected following 6 injections over 12 weeks of treatment. Astralis has identified several factors including the limited number of injections used and the formulation of the active components of the product that may have contributed to the unexpected results of the phase II trial.

Based on these analyses, the company remains committed to the development of Psoraxine® and is embarking on a program to improve the performance of its treatment. A first-generation version of Psoraxine® was studied extensively in Venezuela, where open-label studies involved nearly 3,000 patients, the majority of whom showed a positive response with few side effects. The first-generation version of Psoraxine® was based on a cellular extract from several species of the *Leishmania* parasite. The second-generation version of Psoraxine® being used in the U.S. trials is a purified protein fraction that is believed to act as an immunostimulator (1-4).

1. *Phase II Psoraxine trial underway.* DailyDrugNews.com (Daily Essentials) April 1, 2004.

2. *Enrollment completed for U.S. phase II Psoraxine study.* DailyDrugNews.com (Daily Essentials) Sept 27, 2004.

3. *Psoraxine phase II study fails to meet primary endpoint.* DailyDrugNews.com (Daily Essentials) March 21, 2005.

4. *Astralis announces presentation of phase II results at 66th Society for Investigative Dermatology Meeting.* Astralis Press Release 2005, May 6.

PTH(1-34), Nanovesicular Topical

Manhattan Pharmaceuticals intends to pursue a phase II trial for PTH(1-34) using IGI's Novasome® nanovesicular topical delivery technology following the merger with Tarpan Therapeutics. IGI previously signed a sublicense agreement with Tarpan for the clinical use of PTH(1-34) relating to the regulation of cell differentiation and proliferation for the treatment of skin disorders using IGI's Novasome® nanovesicular topical delivery technology. IGI's patented technology is suited to the topical application of PTH(1-34) because, as a nonionic, stable liposome preparation, it enhances the transdermal absorption of polypeptides. This results in enhanced product stability and controlled release in a nonirritating, deep-penetrating, moisturizing delivery system. Researchers recently reported positive results from a U.S. phase I/II trial evaluating the safety and efficacy of PTH(1-34) as a topical treatment for psoriasis. This double-blind, controlled trial in 15 patients comparing PTH(1-34) formulated in the Novasome® technology *versus* the Novasome® vehicle alone showed PTH(1-34) to be a potentially safe and effective treatment for plaque psoriasis. Following 8 weeks of treatment, the application of PTH(1-34) resulted in complete clearing of the treated lesion in 60% of patients and partial clearing in 85% of patients. Additionally, there was a statistically significant improvement in the global severity score. Ten patients continued in an open-label extension study in which the PASI was measured; PASI showed statistically significant improvement compared to baseline in all 10 patients (1-3).

1. *Phase II planned for PTH (1-34) after merger.* DailyDrugNews.com (Daily Essentials) Jan 17, 2005.

2. *Manhattan Pharmaceuticals, Inc. to merge with Tarpan Therapeutics, Inc..* Manhattan Pharmaceuticals Press Release 2005, Jan 5.

3. *Manhattan Pharmaceuticals acquires Tarpan Therapeutics.* Manhattan Pharmaceuticals Press Release 2005, April 4.

Rambazole™

Barrier Therapeutics has reported positive phase IIa data for oral Rambazole™ in the treatment of psoriasis. Rambazole™ is a novel retinoic acid metabolism-blocking agent (RAMBA). A review of initial phase IIa trial data from 10 patients with moderate to severe psoriasis demonstrated a reduction in the PASI score by an average of 50% in patients treated with 1 mg once daily for 8 consecutive weeks. These PASI scores were measured at week 10, 2 weeks after stopping treatment. There were no serious treatment-related adverse effects reported. The study is ongoing and is expected to include a total of 17 patients upon completion. Barrier plans to initiate U.S. phase IIb trials with Rambazole™ in psoriasis. Studies to date suggest that Rambazole™ is more selective and more active than first-generation RAMBA-based product candidates. The company is developing an oral formulation of Rambazole™ for the treatment of psoriasis and severe acne, as well as a topical formulation for psoriasis, acne and wrinkles. In addition to the European phase IIa study in psoriasis, a similar study is ongoing in acne (1).

1. *Positive data for oral Rambazole in psoriasis.* DailyDrugNews.com (Daily Essentials) Jan 14, 2005.

Recombinant α_1-Antitrypsin, Gel

ProMetic Life Sciences has reported results from two clinical trials designed to demonstrate the safety and efficacy of recombinant α_1-antitrypsin (rAAT) in a topical gel formulation. Both studies were conducted by Arriva-ProMetic, a joint venture of Arriva and ProMetic Life Sciences. One placebo-controlled phase II trial was performed in Canada in patients with atopic dermatitis, while a second phase II trial was conducted in the U.K. in pediatric patients suffering from a different and more severe dermatological disorder. In both studies, the rAAT gel applied for up to 1 month was well tolerated. Results of the U.K. study were encouraging, with improvement in 3 of the 5 patients treated, each patient receiving both placebo and rAAT topical gel treatment. The U.K. trial may be repeated with a

Table XIV: Clinical studies of recombinant α_1-antitrypsin (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Dermatitis, atopic	Randomized Double-blind	Recombinant human α_1-antitrypsin 2% gel top. b.i.d. x 5 d (n=6) Placebo (n=6)	12	Five-day administration of recombinant human α_1-antitrypsin 2% gel was well tolerated in patients with atopic dermatitis	2

larger number of patients, with the same or an optimized formulation. However, the results of the atopic dermatitis trial demonstrated that patients receiving the rAAT gel did not show a statistically significant clinical outcome and the study did not achieve its primary or secondary endpoints. The joint venture partners are evaluating whether this could be related to the formulation (1).

A double-blind clinical trial evaluated the safety profile of a topical gel containing rAAT in 12 patients with atopic dermatitis. Each patient was randomized to apply placebo or an AP-102 gel containing 2% rAAT twice daily for 5 days to a skin area of 50-250 cm^2. No patients experienced serious or significant adverse events during the study treatment, and only one mild adverse event (transient pain at application site during the first study day) was reported (2) (Table XIV).

1. *ProMetic announces results of joint venture's clinical trials of recombinant α 1-antitrypsin in two dermatological indications.* ProMetic Life Sciences Press Release 2004, Oct 7.

2. Gratton, D., Cantwell, J., Pemberton, P., Barr, P., Barabe, J., Sundin, D. *A study of the safety and tolerability of recombinant human α 1-antitrypsin (rAAT) gel in subjects with atopic dermatitis.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst FC07.15.

Sorafin™-AD

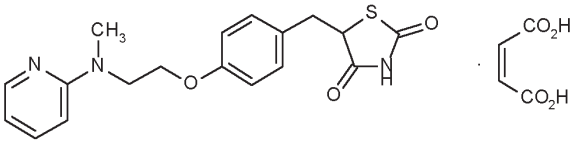
Sorafin™-AD, a combination of the steroid mometasone furoate and auranofin (synthetic gold), is in phase II clinical development at Psiron for the treatment of atopic dermatitis. Preclinical studies have shown that auranofin acts as a steroid-sparing agent, allowing reduced steroid concentrations without affecting efficacy. Psiron plans to commercialize the product through outlicensing.

STA-5326

Synta has closed a fourth private financing round for USD 80 million and the company is now well positioned to carry out its aggressive clinical development plans and advance new drugs from its discovery engine into the clinic. Synta has 7 clinical studies ongoing across its 3 small-molecule development programs. STA-5326 is a first-in-class, small-molecule oral compound that selectively inhibits IL-12. STA-5326 has successfully completed two phase I studies, and is in multiple phase II studies for patients with Crohn's disease and psoriasis (1).

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

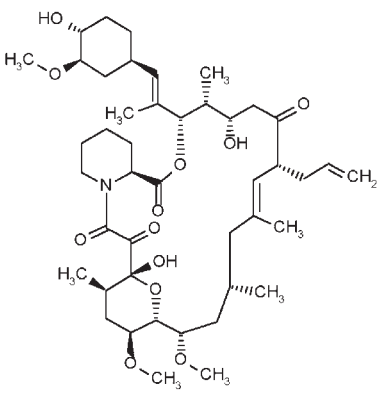
Rosiglitazone Maleate



Rosiglitazone maleate (Avandia®) is a thiazolidinedione peroxisome proliferator-activated receptor γ (PPARγ) agonist marketed by GlaxoSmithKline and Bristol-Myers Squibb for the treatment of type 2 diabetes. The drug is also under development for a variety of other indications, including psoriasis (phase III), rheumatoid arthritis and Alzheimer's disease (phase II).

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

Tacrolimus, Gel/Cream



The immunosuppressant tacrolimus (FK-506), marketed by Astellas Pharma as Prograf® for transplant rejection and myasthenia gravis and as Protopic® for atopic

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

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Randomized Open Multicenter	Tacrolimus 0.3% gel top. b.i.d. x 12 wks (n=33) Tacrolimus 0.5% cream top. b.i.d. x 12 wks (n=36) Calcipotriol 0.005% ointment top. b.i.d. x 12 wks (n=32)	101	Tacrolimus 0.3% gel and 0.5% cream showed efficacy comparable to calcipotriol 0.005% ointment in adult patients with mild to moderate plaque psoriasis	1
Psoriasis	Randomized Double-blind	Tacrolimus 0.03% gel top. o.d. A.M. + Placebo P.M. Tacrolimus 0.03% gel top. b.i.d. Tacrolimus 0.1% gel top. o.d. A.M. + Placebo P.M. Tacrolimus 0.1% gel top. b.i.d. Tacrolimus 0.3% gel top. o.d. A.M. + Placebo P.M.	354	Once- and twice-daily regimens of tacrolimus were safe and demonstrated dose-dependent efficacy in patients with mild to moderate psoriasis	2

dermatitis, continues to undergo active clinical development worldwide for a variety of conditions in different formulations, including psoriasis (gel/cream; phase III in the U.S.), rheumatoid arthritis (oral; phase III in the U.S./phase II in Europe), lupus nephritis (oral; phase III in Japan) and asthma (inhalation; phase II in Europe). A cream formulation is also in phase III evaluation in the U.S. for atopic dermatitis, in addition to the approved ointment formulation. A supplemental NDA is under review in Japan for the use of oral tacrolimus in the treatment of ulcerative colitis.

1. Ortone, J.P. *Treatment with 0.3% tacrolimus gel or 0.5% tacrolimus cream is as efficacious as calcipotriol in adults with mild to moderate plaque psoriasis.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P06.69 (Table XV).

2. Pariser, D. et al. *Dosing concentration and application frequency of tacrolimus gel for treatment of mild to moderate psoriasis in adult and pediatric patients.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2736 (Table XV).

Original monograph – Drugs Fut 1989, 14(4): 746.

Additional References

Goodman, J.J. et al. *Tacrolimus pharmacokinetics in adult and psoriasis patients after topical administration of gel 0.03%, 0.1%, and 0.3%.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2797.

Rodríguez García, F. et al. *Serious generalized pustular psoriasis successfully treated with topical tacrolimus.* J Eur Acad Dermatol Venereol 2004, 18(Suppl. 2): Abst P03.89.

Talactoferrin Alfa, Gel

Talactoferrin alfa is a human recombinant lactoferrin (rhLF) in phase II development at Agennix as a gel for the treatment of diabetic foot ulcers. The product upregulates IL-18, stimulating $CD4^+$, $CD8^+$ and natural killer cells, as well as the production of GM-CSF (granulocyte-macrophage colony-stimulating factor), which is important in accelerating wound healing. An oral formulation is also in phase II trials for the treatment of cancer.

A pilot phase I/II clinical trial evaluated the potential benefits of talactoferrin alfa in 55 patients with diabetic neuropathic foot ulcers. In the first part of the study, twice-daily topical administration of talactoferrin alfa gel (1%, 2.5% or 8.5%) onto the ulcer for 30 days was well tolerated and did not result in drug-related adverse events or infections of the target ulcer. The second part of the study compared the effects of topical talactoferrin gel (2.5% or 8.5%) or placebo applied directly onto the ulcer twice daily for 12 weeks. The number of patients who achieved at least 75% healing was greater with talactoferrin (47% with the 2.5% gel, 53% with the 8.5% gel) compared to placebo (25%). At 20 weeks, the incidence of 100% healing in these groups was 33%, 27% and 19%, respectively. Again, no drug-related adverse events or laboratory abnormalities were found (1) (Table XVI).

1. Yankee, E. et al. *Recombinant human lactoferrin (rhLF) may promote healing of diabetic neuropathic ulcers.* 65th Annu Meet Sci Sess Am Diabetes Assoc (June 10-14, San Diego) 2005, Abst 32-LB.

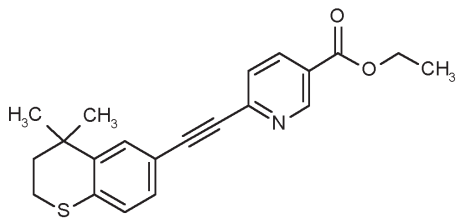
Table XVI: Clinical studies of talactoferrin alfa (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Ulcer, diabetic	Multicenter	Talactoferrin alfa 1% gel top. b.i.d. x 30 d Talactoferrin alfa 2.5% gel top. b.i.d. x 30 d Talactoferrin alfa 8.5% gel top. b.i.d. x 30 d Placebo	55	Topical application of talactoferrin alfa gel onto diabetic ulcers for 30 days was significantly more effective than placebo in promoting healing. No treatment-related adverse events or laboratory abnormalities were found	1

Table XVII: Clinical studies of tazarotene (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Randomized Double-blind Multicenter Pooled/meta-analysis	Tazarotene, 4.5 mg p.o. o.d. x 12 wks (n=348) Placebo (n=358)	706	Oral tazarotene induced significant improvements, which were rapid and sustained compared with placebo, in patients with difficult-to-treat psoriatic lesions on the elbows and knees	5
Psoriasis	Randomized Double-blind Crossover Multicenter Pooled/meta-analysis	Tazarotene, 0.4-6.3 mg p.o. o.d. (n=504) Placebo (n=383)	887	Oral tazarotene was safe and well tolerated compared with placebo and other systemic therapies in patients with moderate to severe plaque psoriasis	6

Tazarotene, Oral



Topical (cream and/or gel) formulations of the retinoid tazarotene are marketed by Allergan for the treatment of both acne and stable plaque psoriasis (Tazorac®), as well as adjunctive treatment for facial fine wrinkling, facial mottled hyper- or hypopigmentation and benign facial lentigines (Avage®). The company is currently seeking FDA approval for an oral formulation for the treatment of moderate to severe psoriasis.

Allergan has received a written response from the FDA regarding the company's request for formal dispute resolution on its oral tazarotene capsule NDA for psoriasis following the FDA's decision last year to issue a non-approvable letter. The FDA has outlined multiple potential options for improving oral tazarotene's risk-benefit profile. Allergan currently believes it can fund a pivotal clinical trial requested by the FDA and complete the study in a reasonable amount of time. The company also plans to provide some additional pharmacokinetic and toxicology data to the FDA. Allergan now plans to submit a development plan to the FDA (1-4).

The efficacy of tazarotene (4.5 mg p.o. once daily for 12 weeks) was evaluated in 706 patients with refractory psoriatic lesions of the elbows and knees in two multicenter, randomized, double-blind, placebo-controlled studies. The drug promoted significant, rapid and sustained improvements in the treated lesions as compared to placebo (5) (Table XVII).

A pooled analysis evaluated the safety of oral tazarotene (0.4-6.3 mg p.o. once daily) in over 1,100 patients with moderate to severe plaque psoriasis. Subjects were drawn from multicenter, double-blind, randomized, placebo-controlled trials, a crossover extension study, a multicenter noncomparative trial and a series of dose-response studies. The drug was safe and well tolerated as compared to placebo and other systemic therapies (6) (Table XVII).

1. *FDA Advisory Committee recommends against approval of oral tazarotene.* DailyDrugNews.com (Daily Essentials) July 16, 2004.

2. *Allergan receives written FDA response for oral tazarotene NDA.* DailyDrugNews.com (Daily Essentials) June 3, 2005.

3. *Non-approvable letter for oral tazarotene.* DailyDrugNews.com (Daily Essentials) Sept 29, 2004.

4. *Allergan reports Q1 R&D highlights.* Allergan Press Release 2005, April 27.

5. Kang, S., Menter, A., Walker, P.S. *Oral tazarotene and difficult-to-treat psoriatic lesions.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P597.

6. Walker, P.S., Gottlieb, A., Guenther, L., Menter, *A. Safety of oral tazarotene in moderate to severe plaque psoriasis.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P595.

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

Additional References

Koo, J.Y.M., Kowalski, J., Guenther, L., Walker, P. *Quality of life effect of oral tazarotene in patients with moderate to severe psoriasis as measured by the 12-item psoriasis quality of life questionnaire (PQOL-12).* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P578.

Koo, J.Y.M., Lowe, N., Sefton, J., Walker, P.S. *Duration of clinical improvement with oral tazarotene in plaque psoriasis.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P598.

Menter, A., Lew-Kaya, D., Beddingfield, F., Walker, P.S. *A long-term, open-label study of the safety and efficacy of oral tazarotene in moderate to very severe plaque psoriasis.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P6.

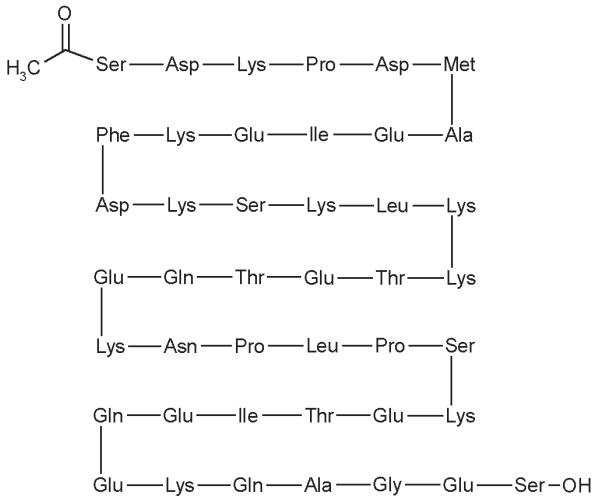
Tanghetti, E.A., Poulin, Y., Walker, P.S. *Oral tazarotene improves scalp psoriasis.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P607.

Vasudevan, J., Chandraratna, R. *Pharmacology of oral tazarotene.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P576.

Yu, D., Lee, E., Walker, P.S., Tang-Liu, D. *Simple and convenient dosing is possible with oral tazarotene.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P302.

Yu, D., Ni, J., Attar, M., Tang-Liu, D. *Pharmacokinetic profile of oral tazarotene.* J Am Acad Dermatol 2004, 50(3, Suppl.): Abst P573.

Thymosin Beta 4



Two phase II trials are planned to test RegeneRx Biopharmaceuticals' thymosin beta 4 (TB4) for the treatment of chronic pressure ulcers and venous stasis ulcers. The studies will be conducted in the U.S. by RegeneRx (chronic pressure ulcers) and in Europe by partner Sigma-Tau (venous stasis ulcers), both under a U.S. IND. The randomized, double-blind, placebo-controlled trials are designed to test several doses of TB4. The drug will be topically administered to each patient over a period of several weeks. The studies should be completed and analyzed within approximately 1 year from enrollment of the first patient. These trials are part of a portfolio of complementary clinical trials planned by RegeneRx, designed to evaluate TB4's effect on wound healing for specific types of dermal and ocular wounds. The company has also been cleared to initiate a phase II trial in epidermolysis bullosa, for which TB4 has been designated an orphan drug, and plans also include a study in diabetic lower extremity ulcers. TB4 is a naturally occurring peptide present in virtually all human cells. It represents a new class of wound-healing drug that promotes endothelial cell differentiation and keratinocyte cell migration, angiogenesis in and around wounds, and downregulates a number of inflammatory cytokines and chemokines. A key mechanism of action is TB4's ability to regulate the cell-building protein actin. It has been reported that TB4 directly influences the production of laminin-5. Furthermore, TB4 can inhibit or prevent apoptosis in ocular and cardiac tissues. Researchers at the National Institutes of Health (NIH) and other academic institutions throughout the U.S. have published numerous scientific articles indicating that TB4 is effective in accelerating dermal, corneal and myocardial wounds in several animal models, under a variety of conditions. Published data show that TB4 promotes angiogenesis, stimulates cell migration and increases collagen deposition in treated wounds in laboratory animals (1-8).

1. *Orphan drug designation for Thymosin beta 4 for epidermolysis bullosa.* DailyDrugNews.com (Daily Essentials) June 11, 2004.

2. *Sigma-Tau plans phase II European trial of TB4 for venous stasis ulcers.* DailyDrugNews.com (Daily Essentials) June 29, 2004.

3. *RegeneRx files to begin phase II study of TB4 for chronic pressure ulcers.* DailyDrugNews.com (Daily Essentials) Sept 28, 2004.

4. *RegeneRx seeks to begin new phase II study of TB4 for venous stasis ulcers.* DailyDrugNews.com (Daily Essentials) Dec 23, 2004.

5. *RegeneRx cleared to initiate phase II clinical trial with TB4 for chronic pressure ulcers.* RegeneRx Biopharmaceuticals Press Release 2004, Nov 2.

6. *TB4 to be studied in phase II trial for venous stasis ulcers.* DailyDrugNews.com (Daily Essentials) Jan 20, 2005.

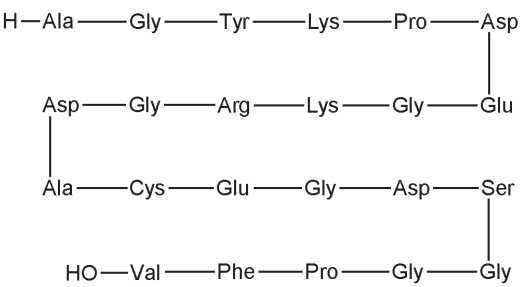
7. *RegeneRx closes on first tranche of $ 5.86 million private placement.* RegeneRx Biopharmaceuticals Press Release 2005, Jan 3.

8. *New phase II study to test TB4 for epidermolysis bullosa.* DailyDrugNews.com (Daily Essentials) March 4, 2005.

T4N5 Liposome Lotion

T4N5 liposome lotion (Dimericine®) is currently in phase III clinical development at AGI Dermatics for the prevention of skin cancer in patients with xeroderma pigmentosum and in phase II clinical trials for the prevention of skin cancer in renal transplant patients who have elevated rates of skin cancer due to the use of immunosuppressive drugs which inhibit DNA repair of UV damage. The compound encapsulates the DNA repair enzyme T4 endonuclease V in a liposome engineered to deliver the enzyme into cells of the skin.

TP-508



TP-508 (Chrysalin®), a synthetically manufactured peptide which represents a portion of the human enzyme thrombin and mimics the molecule's role in tissue repair, is currently undergoing phase III clinical trials at OrthoLogic (following its acquisition of Chrysalis last year) for the acceleration of fracture repair. A phase I/II trial was

previously conducted in diabetic foot ulcers with a saline formulation, and the company is currently evaluating various gel formulations for this indication. A phase I/II safety trial is also under way in spinal fusion and an IND application is being prepared to test a sustained-release microsphere formulation in cartilage defect repair.

TRX4

A new phase I trial is under way for TolerRx's TRX4 monoclonal antibody in subjects with psoriasis. The single-escalating-dose study in 30 patients with moderate to severe psoriasis is designed to establish the safety, pharmacokinetic and pharmacodynamic profile of TRX4. European investigators completed an investigator-sponsored study with TRX4 in new-onset type 1 diabetes patients, and the 6- and 12-month follow-up data are expected in the first half of 2005. TRX4 is a humanized monoclonal antibody that binds to a receptor found on all mature T-cells called CD3. TRX4 is believed to alter the function of T-cells and to have a favorable effect on T-regulatory cells. TolerRx is developing TRX4 for the treatment of patients with autoimmune diseases, including type 1 diabetes and psoriasis. Following the completion of Series D financing, the company plans to move TRX4 into a pivotal trial in type 1 diabetes (1, 2).

1. *TRX4 evaluated in new phase I study for psoriasis.* DailyDrugNews.com (Daily Essentials) Aug 5, 2004.

2. *TolerRx completes Series D financing.* DailyDrugNews.com (Daily Essentials) April 1, 2005.

TS-022

TS-022 is in phase I trials at Taisho for the topical treatment of atopic dermatitis.

Vibriolysin

Vibriolysin (Vibrilase™) is an enzyme developed by BioMarin that digests burned skin (eschar) without having any effects on healthy tissue. An open-label phase Ib clinical trial evaluated the efficacy and safety of topical vibriolysin (100, 250 or 500 U/g) given once daily for 3 days to 19 conscious patients with partial-thickness burns covering 1-2% of total body surface area. Data from this trial were presented during the 12th Congress of the International Society for Burn Injuries, which was held in Yokohama last year in August. Following treatment with vibriolysin, the average time to complete debridement of wound eschar was 2.9 days, while the average time to 90% epithelialization was 16.4 days. Some patients showed short-term pain after topical administration of vibriolysin, but the treatment was generally safe and well tolerated. These results confirm those of a previous double-blind, randomized, placebo-controlled phase Ia clinical trial where an 8-day treatment with topical vibriolysin (100, 250 or 500 U/g once daily) induced no contact sensitization or irritation in 118 healthy volunteers. The company plans to outlicense this program (1, 2).

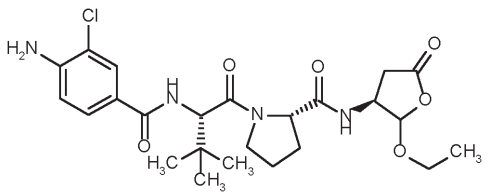
1. *BioMarin Pharmaceutical reports 2003 year-end R&D highlights.* BioMarin Pharmaceutical Press Release 2004, Feb 3.

2. *BioMarin announces positive data from phase 1b clinical trial of Vibrilase for serious burns.* BioMarin Pharmaceutical Press Release 2004, Aug 25.

VIC-Acne

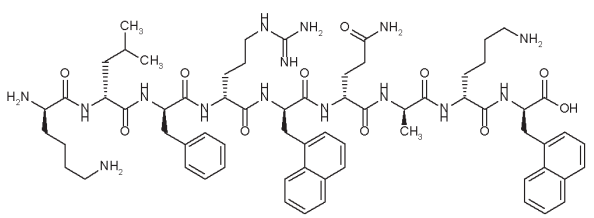
VIC-acne (BI-K0376), a novel antibiotic developed by Vicuron Pharmaceuticals, has completed phase I clinical trials for the topical treatment of acne. VIC-acne has shown activity against a large number of *Propionibacterium acne* strains, including some that are resistant to currently used broad-spectrum antibiotics, such as clindamycin and erythromycin. Vicuron plans to outlicense the compound for further development

VX-765



VX-765 is an oral caspase-1 (interleukin-1β-converting enzyme, or ICE) inhibitor in phase II trials at Vertex for the treatment of psoriasis.

XMP-629



Xoma's XMP-629 is a synthetic peptide derived from bactericidal/permeability-increasing protein (BPI), a

Table XVIII: Clinical studies of XP-828L (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Open	XP-828L, 5 g p.o. b.i.d. x 56 d	11	XP-828L was safe and effective in reducing the PASI score of patients with mild to moderate chronic stable plaque psoriasis	5

human host defense protein that is one of the body's early lines of defense against invading microorganisms. XMP-629 was found in preclinical studies to exert bactericidal activity against *P. acnes,* including strains resistant to other antibiotics such as erythromycin and clindamycin. Despite phase I clinical trial results demonstrating a reduction in acne lesions and no significant skin irritation or systemic absorption, the compound did not meet the primary endpoint in a preliminary phase II trial for the treatment of acne and the company is currently performing additional preclinical testing before determining the next steps for XMP-629.

XP-828L

XP-828L, Advitech's main platform, is a purified milk protein fraction with a patented growth factor composition that works at the immune system level by modulating proinflammatory Th1 cytokines. Advitech has completed a multicenter, double-blind, placebo-controlled, randomized clinical trial of oral XP-828L in 84 patients with mild to moderate psoriasis. The main objective of this study was to confirm the efficacy and safety of XP-828L. XP-828L (5 g/day p.o.) given for 56 days was significantly more effective than placebo in improving the symptoms of psoriasis, and 21.4% of patients treated with XP-828L showed a decrease in the severity of their disease by at least one level on the Physician's Global Assessment (PGA) scale. In a second study phase, which also lasted for 56 days, increasing the XP-828L dose from 5 to 10 mg/day was not associated with additional symptom improvements. No significant differences between study groups were found in the incidence of adverse events or in the patients' laboratory values. No treatment-related serious adverse events were found. Results of this study are expected during the second quarter of 2005. Advitech will then finalize the filing with the FDA and Health Canada with a view to launching the product at the beginning of 2006. The aim of this study was to confirm results obtained during an open study conducted last summer to determine whether the efficacy of XP-828L is dose-dependent. This multicenter, randomized double-blind, placebo-controlled study was conducted over a 112-day period. The study protocol involved two groups: a placebo group and a second group in which the patients received a single dose of XP-828L for 56 days. During the 56 days of the double-blind phase, the placebo group was then administered a double dose of XP-828L, while the second group remained on the initial single dose of XP-828L.In this trial, 7 of 11 adult patients with mild to moderate chronic plaque psoriasis who were given oral XP-828L (5 g p.o. b.i.d.) for 8 weeks showed improvements in their PASI scores of 9.5-81.3% at the end of the treatment period. Eight patients participated in an extension phase of the trial and continued receiving oral XP-828L for another 8 weeks. Four of the 7 patients who completed the extension phase achieved further improvements in their PASI scores compared to baseline. No evidence of clinically significant adverse events or laboratory abnormalities was found during the study. Advitech, in collaboration with the CHUL Research Center, also plans to conduct a research project to assess the potential of XP-828L for the treatment of inflammatory bowel diseases (IBD) using a transgenic rat model. Based on the results, a first clinical trial in patients suffering from IBD could take place in 2006 (1-6) (see Table XVIII).

1. *Good efficacy and safety profile found for XP-828L in mild-moderate psoriasis.* DailyDrugNews.com (Daily Essentials) Sept 3, 2004.

2. *Canadian approval for new trial of XP-828L for psoriasis.* DailyDrugNews.com (Daily Essentials) Nov 16, 2004.

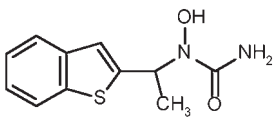
3. *Advitech and the CHULRC to test XP-828L for inflammatory bowel diseases.* DailyDrugNews.com (Daily Essentials) March 1, 2005.

4. *Advitech completes second study of XP-828L for psoriasis.* DailyDrugNews.com (Daily Essentials) June 20, 2005.

5. Poulin, Y. *Evaluation of the safety and efficacy of XP-828L in the treatment of plaque psoriasis: An open-label study.* 63rd Annu Meet Am Acad Dermatol (Feb 18-22, New Orleans) 2005, Abst P2830.

6. *XP-828L reported effective and safe in mild to moderate psoriasis.* DailyDrugNews.com (Daily Essentials) July 11, 2005.

Zileuton



Critical Therapeutics has completed a U.S. phase II study to assess the efficacy and safety of the tablet formulation of zileuton (Zyflo®) in patients with moderate to

severe acne. The multicenter, double-blind, placebo-controlled study randomized 101 patients to receive placebo or zileuton (600 mg p.o.) 4 times daily for 12 weeks. Compared to baseline, inflammatory lesions decreased by an average of 33.5% with zileuton and by 26.9% with placebo. The total number of lesions (*i.e.*, including both inflammatory and noninflammatory lesions) decreased by 25.3% with zileuton and by 16.4% with placebo. In a subset of patients with more severe acne, the number of inflammatory lesions also decreased more with zileuton (41.6% *vs.* 26.2%). Zileuton was safe and well tolerated, and induced significant reductions in total facial lesions after only 4 weeks of treatment. The drug blocks the activity of 5-lipoxygenase, the enzyme chiefly responsible for producing a range of inflammatory mediators known as leukotrienes, which are believed to play a central role in tissue inflammation related to asthma, acne and other diseases. Leukotriene B_4, which can be blocked by zileuton, has been shown to promote the production of sebum lipids. Key findings of a zileuton pilot study in acne included a 65% mean reduction of sebum lipids at 12 weeks and a mean reduction in inflammatory lesions of 71% at 12 weeks. There was also a significant reduction in the acne severity index as early as 4 weeks. Critical Therapeutics acquired the worldwide rights to develop and market zileuton for asthma from Abbott and has also acquired worldwide rights to other formulations of zileuton for multiple diseases and conditions, including asthma, acne, chronic obstructive pulmonary disease and nasal polyps. Zileuton tablets were approved in 1996 for the treatment of asthma in patients 12 and older. The product, however, has been commercially unavailable since early 2004 when commercial supply was depleted. The company was required to submit an sNDA as it is changing the manufacturing process and transferring production of the zileuton active pharmaceutical ingredient and the tablet formulation to third-party sites. Clinical supply of zileuton is currently available through an open-label phase IIIb study for patients who previously used and benefited from the drug and need it to control their asthma symptoms. Critical Therapeutics anticipates launching the product in the second half of 2005 (1-4).

1. *Phase II study set to open this month evaluating Zyflo for acne.* DailyDrugNews.com (Daily Essentials) Oct 13, 2004.

2. *Phase IIIb study provides access to Zyflo prior to commercial availability.* DailyDrugNews.com (Daily Essentials) March 21, 2005.

3. *Critical Therapeutics submits sNDA for Zyflo.* DailyDrugNews.com (Daily Essentials) April 6, 2005.

4. *Zileuton shows efficacy in the treatment of inflammatory facial acne.* DailyDrugNews.com (Daily Essentials) July 21, 2005.

Original monograph – Drugs Fut 1993, 18(7): 616.

Annual Update 2004/2005 - Treatment of Head and Neck Cancer

Most head and neck cancers begin in the cells that line the mucosal surfaces in the head and neck area, *i.e.*, the mouth, nose and throat. Cancers of the head and neck are classified by the area in which they begin: oral cavity (lips, gums, buccal mucosa and hard palate), salivary glands, nasal cavity, pharynx (nasopharynx, oropharynx and hypopharynx) and larynx (1).

Head and neck cancer accounts for approximately 3-5% of all cancers in the United States. Head and neck cancer is more common in men and people over age 50. It is estimated that about 39,000 men and women will develop head and neck cancer in the U.S. in 2005 (2). Tobacco and alcohol use are the most important risk factors for head and neck cancer.

In the table that follows, drugs under active development for the treatment of head and neck cancer are shown. Eye cancer has also been included in this table; eye cancer includes intraocular melanoma and retinoblastoma (an eye cancer that most often occurs in children younger than 5 years of age). Approximately 2,000 new cases of eye cancer are estimated for 2005 (2) *(Source: Prous Science Integrity®)*.

References

1. *NCI website (www.cancer.gov)*

2. *Cancer Statistics 2005 (American Cancer Society, Inc., www.cancer.org)*

Itziar Escudero

Treatment of Head and Neck Cancer

Condition	Phase	Drug	Target	Source
Head and neck cancer	L-2005	SBN-1		SiBiono
	Reg	MedPulser (Drug Delivery Systems)		Inovio Biomedical
	III	Tirapazamine	DNA	Sanofi-Aventis
	III	Carboplatin[1]	DNA	National Cancer Institute
	III	Cetuximab[1]	EGFR	ImClone/Bristol-Myers Squibb/ Merck KGaA
	III	Gefitinib[1]	EGFR	AstraZeneca/ National Cancer Institute
	III	Ad5CMV-p53		Introgen
	III	Lapatinib	EGFR, HER2	GlaxoSmithKline
	III	Zinc sulfate[1]		National Cancer Institute
	II	Paclitaxel[1]	Tubulin	National Cancer Institute
	II	Gemcitabine[1]	Ribonucleoside diphosphate reductase	National Cancer Institute
	II	Irinotecan hydrochloride[1]	DNA topoisomerase I	National Cancer Institute
	II	Perifosine	PKB/Akt	AEterna Zentaris/National Cancer Institute
	II	MultiKine		Cel-Sci
	II	MG-98	DNMT2	MethylGene/MGI Pharma
	II	Nimotuzumab	EGFR	YM BioSciences/Center of Molecular Immunology/Biocon
	II	Sorafenib	Raf kinase, VEGFR, PDGFR, Kit, Flt3	National Cancer Institute
	II	FR-901228	HDAC	National Cancer Institute
	II	Bortezomib[1]	Proteasome	National Cancer Institute
	II	EF-5		National Cancer Institute
	II	SB-715992	Kinesin-like spindle protein (Eg5)	National Cancer Institute
	I/II	Bevacizumab[1]	VEGF	National Cancer Institute
	I/II	Combretastatin A-4 phosphate	Tubulin	OxiGene
	I/II	Erlotinib hydrochloride[1]	EGFR	National Cancer Institute
	I/II	SS(dsFv)-PE38	Mesothelin	National Cancer Institute/Enzon
	I/II	HuMax-EGFr	EGFR	Genmab

Continuation

Treatment of Head and Neck Cancer

Condition	Phase	Drug	Target	Source
	I/II	OncoVEX(GM-CSF)		BioVex
	I	Motexafin gadolinium		Pharmacyclics
	I	Erlotinib hydrochloride[1]	EGFR	National Cancer Institute of Canada
	I	Lonafarnib	Farnesyltransferase	National Cancer Institute
	I	M4N		Biocure
	I	VB4-845	EpCAM	Viventia Biotech
	I	ONYX-015		National Cancer Institute
	I	Fenretinide	RARβ, RARα	National Cancer Institute
Larynx cancer	III	Isotretinoin[1]	RAR	National Cancer Institute
	II	Ad5CMV-p53		National Cancer Institute
Pharyngeal cancer	III	Isotretinoin[1]	RAR	National Cancer Institute
Rhinopharyngeal cancer	III	Cevimeline[1]	Muscarinic M_1 receptors	Daiichi Pharmaceutical
	II	Capecitabine[1]	Pyrimidine nucleotides	National Cancer Institute
Oral cancer	II	Celecoxib[1]	COX-2	National Cancer Institute
Mouth cancer	I	Pelitinib	EGFR	National Cancer Institute
Lip cancer	III	Isotretinoin[1]	RAR	National Cancer Institute
Salivary gland cancer	II	Gemcitabine[1]	Ribonucleoside-diphosphate reductase	National Cancer Institute of Canada
	II	Carboplatin[1]	DNA	National Cancer Institute of Canada
Melanoma, intraocular	II	Interferon beta[1]		National Cancer Institute
	III	Sargramostim[1]		National Cancer Institute
	II	MDX-010	CD152 (CTLA4)	National Cancer Institute
	II	FR-901228	HDAC	National Cancer Institute
	II	Interferon beta[1]		National Cancer Institute
	II	Lenalidomide	TNF-α	National Cancer Institute
Retinoblastoma	III	Carboplatin[1]	DNA	National Cancer Institute

[1] Launched for another indication. DNMT: DNA methyltransferase; EGFR: Epidermal growth factor receptor; EpCAM: Epidermal cellular adhesion molecule; HDAC: Histone deacetylase; PDGFR: Platelet-derived growth factor receptor; PKB: Protein kinase B; RAR: Retinoic acid receptor; TNF: Tumor necrosis factor; VEGFR: Vascular endothelial growth factor receptor.

Annual Update 2004/2005 -Treatment of Skin Cancers

There are several types of skin cancer, depending on the cell type affected: squamous cell cancer affects the flat cells of the epidermis; basal cell carcinoma affects the round cells under the squamous cells; and melanoma affects the melanocytes. Other important forms of skin cancer include Kaposi's sarcoma, which commonly occurred among patients with AIDS prior to the introduction of protease inhibitors, and cutaneous T-cell lymphoma (CTCL). Merkel cell cancer develops on or just beneath the skin and in hair follicles (1).

Most of these forms of skin cancer are highly curable, but the most serious is melanoma, with approximately 8,000 estimated deaths for 2005 compared to 3,000 deaths expected in 2005 for the rest of nonepithelial skin cancer cases. Approximately 70,000 new cases of skin cancer will be diagnosed in the U.S. during 2005 (2).

The major risk factors for melanoma include a prior melanoma, family members with melanoma and moles. Other risk factors for all types of skin cancer include sun sensitivity (natural blond or red hair color), a history of excessive sun exposure, exposure to tanning booths and to diseases that suppress the immune system (2).

In the table that follows, drugs under active development for the treatment of skin cancer are shown. Cutaneous T-cell lymphoma was included in a previous review (Treatment of Hematological/Blood Cancers) (3) *(Source: Prous Science Integrity®)*.

References

1. NCI website (www.cancer.gov)

2. Cancer Statistics 2005 (American Cancer Society, Inc., www.cancer.org)

3. Drugs Fut 2005, 30(5): 535-40.

Itziar Escudero

Treatment of Skin Cancers

Condition	Phase	Drug	Target	Source
Melanoma	Prereg.	Oblimersen sodium	BCL2	Genta
	III	Temozolomide[1]	DNA	EORTC
	III	C-Vax	Melanoma carbohydrate antigens	CancerVax
	II	MEDI-522	Integrin $\alpha_v\beta_3$	MedImmune
	II	Antineoplaston A10		Burzynski Research Institute
	II	Temozolomide[1]	DNA	National Cancer Institute
	II	UCN-0[1]	PDK1, CDK1, 2, 4 and 6, CHK1 and 2	National Cancer Institute
	II	Perifosine	PKB/Akt	AEterna Zentaris/ National Cancer Institute
	II	TT-232	SSTR1 and SSTR2	Biostatin/Hungarian Academy of Sciences
	II	PI-88	VEGF, FGF2 and FGF1, heparanase	Progen
	II	Cilengitide	Integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$	National Cancer Institute
	II	Tasidotin hydrochloride	Tubulin	Genzyme
	II	Hu14.18-IL-2	Ganglioside GD2	Merck KGaA
	II	Ispinesib	Kinesin-like spindle protein (Eg5)	National Cancer Institute
	II	SB-485232		GlaxoSmithKline
	II	Dexosome vaccine (melanoma)	MAGE peptides	Anosys
	II	STA-4783	HSP70	Synta Pharmaceuticals
	I/II	Imexon		AmpliMed
	I/II	Ad2CMV-MART1	MART1	National Cancer Institute
	I/II	Imatinib mesilate[1]	Bcr-Abl kinase, Kit, PDGFR	National Cancer Institute
	I/II	P450 GDEPT		Oxford BioMedica
	I/II	GV-1001	Telomerase	GemVax

Continuation

Treatment of Skin Cancers

Condition	Phase	Drug	Target	Source
	I/II	MVA-BN-Tyr	Tyrosinase	Bavarian Nordic
	I/II	Interleukin-21		ZymoGenetics/Novo Nordisk
	I/II	RNA-loaded dendritic cell vaccine		Argos Therapeutics
	I	COL-3	MMP-2 and -9	National Cancer Institute
	I	Pegylated arginine deiminase	Arginine deiminases	Phoenix Pharmacologics
	I	NV-18		Novogen
	I	ALS-357		Advanced Life Sciences
	I	ZRx-101		ZelleRx
	I	IMC-GP75		ImClone
	I	ALVAC-IL-12		University of Alabama at Birmingham/Virogenetics
Malignant melanoma	Prereg.	Interferon alfa[1]		ViraNative/Viragen
	III	Peginterferon alfa-2b[1]		Schering-Plough
	III	GMK vaccine	Ganglioside GM2	Progenics
	II/III	Thymalfasin[1]		Sigma-Tau
	II	Thalidomide[1]	TNF-α	National Cancer Institute
	II	Depsipeptide	HDAC	National Cancer Institute
	II	AN-9	HDAC	Titan
	II	Kahalalide F		PharmaMar
	II	Melanoma pharmaccine	Melanoma antigens	Oxxon Pharmaccines
	II	SB-249553	MAGE-3	GlaxoSmithKline
	II	Bevacizumab[1]	VEGF	National Cancer Institute
	I/II	KW-2871	Ganglioside GD3	Kyowa Hakko
	I/II	OncoVEX(GM-CSF)		BioVex
	I/II	AP-12009	TGF-β2	Antisense Pharma
	I/II	ImmunoVEX-Trimelan	Melanoma antigens	BioVex
	I	Edodekin alfa		National Cancer Institute
	III	Temozolomide[1]	DNA	Schering-Plough
	III	HSPPC-96	HSPPC-96	Antigenics
	III	Anti-CTLA4 MAb	CTLA4	Medarex/Bristol-Myers Squibb
	III	Sorafenib	VEGFR, PDGFR, Kit, Flt3	Bayer/Onyx
	III	MDX-1379	gp100 antigen	Medarex
	II	Interferon beta[1]		National Cancer Institute
	II	Bosentan[1]	ET_A and ET_B receptors	Actelion
	II	Allovectin-7		Vical
	II	Flt3 ligand	Flt3	National Cancer Institute
	II	17-AAG	HSP90	Kosan
	II	PI-88	VEGF, FGF2 and FGF1, heparanase	Progen
	II	Tipifarnib	Farnesyltransferase	National Cancer Institute
	II	BNP-1350	DNA topoisomerase I	BioNumerik
	II	PaTrin-2	*O*-6-Alkylguanine-DNA-alkyltransferase	Kudos Pharmaceuticals
	II	CpG-7909	TLR9	Coley Pharmaceutical
	II	IDD-3	Melanoma antigens	IDM/Sanofi-Aventis
Metastatic melanoma	II	INGN-241	MDA7	Introgen
	II	Talabostat	DPP-IV, FAPα	Point Therapeutics
	II	SB-249553	MAGE-3	National Cancer Institute
	II	Volociximab	Integrin $\alpha_5\beta_1$	Protein Design Labs
	II	CP-675206	CTLA4	Pfizer
	II	GCAN-101		GammaCan
	I	PHP	Nitric oxide	Curacyte
	I	ABI-0071	Tubulin	National Cancer Institute
	I	ALVAC-B7.1		University of Alabama at Birmingham/Virogenetics
Skin cancer	Registered	Electroporation therapy		Inovio Biomedical
	II	T4N5 liposome lotion		AGI Dermatics
Merkel cell cancer	II	Antineoplaston A10		Burzynski Research Institute
	II	Antineoplaston AS2-1		Burzynski Research Institute
	II	Oblimersen sodium	BCL2	National Cancer Institute
	II	Imatinib mesilate[1]	Bcr-Abl kinase, Kit, PDGFR	National Cancer Institute
Squamous cell carcinoma	II	Gefitinib1	EGFR	M.D. Anderson Cancer Center
	II	Phenoxodiol	tNOX	Marshall Edwards

Continuation

Treatment of Skin Cancers

Condition	Phase	Drug	Target	Source
Basal cell carcinoma of the skin	II	PEP-005	PKC	Peplin
	I/II	Baceca	HDAC	TopoTarget
	I	CUR-61414	Smoothened receptor	Curis/Genentech
Kaposi's sarcoma	II	Thalidomide[1]	TNF-α	National Cancer Institute
	II	Bevacizumab[1]	VEGF	National Cancer Institute
	II	Halofuginone hydrobromide	Collagen type 1	National Cancer Institute
	II	Imatinib mesilate[1]	Bcr-Abl kinase, Kit, PDGFRα and β	National Cancer Institute
	I/II	Rebimastat	MMP-1, -2, -9 and -14	National Cancer Institute
	I	Valganciclovir[1]		National Cancer Institute
	I	Valproic acid[1]	HDAC1	National Cancer Institute

[1] Launched for another indication. CDK: Cyclin-dependent kinase; CHK: Checkpoint kinase; CTLA4: Cytotoxic T-lymphocyte-associated 4; DPP: Dipeptidyl-peptidase; EGFR: Epidermal growth factor receptor; ET: Endothelin; FAPα: Fibroblast activation protein-α; FGF: Fibroblast growth factor; GP: Glycoprotein; HDAC: Histone deacetylase; HSP: Heat shock protein; HSPPC-96: Heat shock protein peptide complex-96; MAGE: Melanoma antigen; MART1: Melanoma antigen recognized by T-cells 1; MDA7: Melanoma differentiation-associated gene-7; MMP: Matrix metalloproteinases; PDGFR: Platelet-derived growth factor receptor; PDK: Phosphoinositide-dependent kinase; PKB: Protein kinase B; PKC: Protein kinase C; TGF-β2: Transforming growth factor-β2; TLR: Toll-like receptor; TNF: Tumor necrosis factor; tNOX: Tumor NADH oxidase; VEGF: Vascular endothelial growth factor.