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Annual Update 2003/2004 - Treatment of Genitourinary Disorders

As in previous months, the goal of this section is to present a balanced picture of the current status of therapies for genitourinary disorders in the clinical stage, summarizing in a few pages the most important advances in this area over the last year or so. For a number of reasons, certain groups of drugs that could well have been included in this annual review (such as Drugs for Diabetic Nephropathy) will appear in other upcoming updates (in this case, Treatment of Endocrine Disorders). Beginning this month, a table of oncolytic drugs corresponding to the particular therapeutic group being updated will be included at the end of the Annual Update in selected issues. For example, this month's Annual Update contains a table of drugs for the treatment of bladder, prostate, kidney and testicular cancers. The next Annual Update on Metabolic Disorders will feature a table of drugs for the treatment of bone cancer and osteosarcoma.

Treatment of Genitourinary Disorders by Condition

Condition	Phase	Drug	Source
Benign prostatic hyperplasia	L-2003	Dutasteride[3]	GlaxoSmithKline
	III	Silodosin[3]	Daiichi Pharmaceutical/Kissei/Watson
	II	BXL-628	BioXell
	II	Cetrorelix acetate[1,3]	Solvay/AEterna Zentaris
	II	GYKI-16084[3]	Ivax
	II	ML-4	Milkhaus
	II	RBx-2258 (SPM-969)	Ranbaxy/Schwarz Pharma
	II	Teverelix	Ardana Bioscience/AEterna Zentaris
	II	TF-505	Taiho
	II	TH-070	Threshold Pharmaceuticals
	I/II	NX-1207	Nymox
	I/II	QLT-0074	QLT
	IND Filed	RBx-9001	Ranbaxy
Erectile dysfunction	L-2003	Tadalafil[3]	Lilly Icos
	L-2003	Vardenafil hydrochloride hydrate[3]	Bayer/GlaxoSmithKline
	III	Alprostadil (cream)[2]	NexMed
	II	ABT-724	Abbott
	II	Alprostadil (cream)[2]	MacroChem
	II	Apomorphine hydrochloride (intranasal)[2]	Nastech
	II	Avanafil	Vivus/Tanabe Seiyaku
	II	GPI-1485	Guilford
	II	PT-141	Palatin Technologies
	II	VR-004 (inhaled apomorphine)	Vectura
	I/II	Apomorphine hydrochloride (nasal powder)[2]	Britannia
	I/II	NBI-69733	Neurocrine Biosciences
	I	ABT-670	Abbott
	I	DA-8159	Dong-A
	Clinical	Dasantafil	Schering-Plough
	Discontinued	EMR-62203	Merck KGaA
Erectile dysfunction, treatment-emergent	Discontinued	VML-670	Vernalis/Lilly
Glomerulonephritis	I	CYC-202	Cyclacel
Hyperoxaluria	I	IxOC-2	Ixion
Hypoactive bladder	II	TAK-802	Takeda
Hyponatremia	Prereg.	Conivaptan hydrochloride[3]	Yamanouchi
	II	SR-121463	Sanofi-Synthélabo
Interstitial cystitis	III	SI-7201 (NS-7201)	Seikagaku/Nippon Shinyaku
	II	Suplatast tosilate[1,3]	Taiho/Yamanouchi
	Discontinued	Resiniferatoxin	Icos
Nephritis	I	TJN-598	Tsumura
Nephritis, lupus	III	Tacrolimus[1,3]	Fujisawa
Nephritis, membranous	II	Eculizumab	Alexion
Nephropathy	Clinical	Nefecon™	Pharmalink/West Pharmaceutical Services
Nephrotoxicity, chemotherapy-induced	I	BNP-7787	BioNumerik/Baxter Oncology
Overactive bladder	L-2003	Oxybutynin chloride (transdermal patch)[2]	Watson
	R-2004	Trospium chloride+	Indevus/Pliva
	R-2003	Solifenacin succinate[3]	Yamanouchi/GlaxoSmithKline
	Prereg.	Darifenacin hydrobromide[3]	Novartis
	Prereg.	Temiverine hydrochoride hydrate	Nippon Shinyaku
	III	Fesoterodine[3]	Schwarz Pharma
	III	KRP-197/Ono-8025	Kyorin/Ono Pharmaceutical
	II	KW-7158	Kyowa Hakko
	II	NS-8	Nippon Shinyaku/Apogepha
	II	Talnetant	GlaxoSmithKline

Continuation

Treatment of Genitourinary Disorders by Condition

Condition	Phase	Drug	Source
Overactive bladder	II	YM-178	Yamanouchi
	II	ZD-0947	AstraZeneca
	I/II	DDP-200	Dynogen Pharmaceuticals
	I	Oxybutynin (gel)[2]	Antares Pharma
	I	Solabegron hydrochloride	GlaxoSmithKline
Premature ejaculation	III	Dapoxetine	PPD/Alza (Johnson & Johnson)
	II	DMI-7958 (LIF-301)	DMI BioSciences/Enhance Lifesciences
	II	NM-100061	NexMed
	II	VI-0134	Vivus
	I	Avanafil (VI-0162)	Vivus
Prostatitis	II	ML-4	Milkhaus
	II	Suplatast tosilate[1,3]	Taiho/Yamanouchi
Renal failure	II	*N*-Acetylcysteine[3]	Zambon
	II	NZ-419	Nippon Zoki
	I	SLV-320	Solvay
	I	XL-784	Exelixis
Renal failure (hepatorenal syndrome)	II	Tezosentan disodium[3]	Actelion
Ureterolithiasis	II	KUL-7211	Kissei
Urinary incontinence	III-Suspended	(*S*)-Oxybutynin	Sepracor
	II	C-3048	Merck & Co.
	II	Cizolirtine citrate[3]	Esteve
	II	FP-1097	FemmePharma
	II	NS-8	Nippon Shinyaku/Apogepha
	II	OPC-51803	Otsuka
	II	Oxybutynin chloride (vaginal ring)[2]	Barr
	II-On hold	TAK-637	Takeda
Urinary incontinence, stress	Prereg.	Duloxetine hydrochloride[3]	Lilly/Boehringer Ingelheim
	I	R-1484	Roche
	I	SOU-001 (AA-10020)	Sosei/Arachnova
Urinary incontinence, urge	Prereg.	Temiverine hydrochoride hydrate	Nippon Shinyaku
	III	Fesoterodine[3]	Schwarz Pharma
	II	KUC-7483	Boehringer Ingelheim/Kissei

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

Treatment of Genitourinary Disorders by Source

Source	Condition	Drug	Phase
Abbott	Erectile dysfunction	ABT-670	I
		ABT-724	II
Actelion	Renal failure (hepatorenal syndrome)	Tezosentan disodium[3]	II
AEterna Zentaris	Benign prostatic hyperplasia	Cetrorelix acetate[1,3]	II
		Teverelix	II
Alexion	Nephritis, membranous	Eculizumab	II
Alza (Johnson & Johnson)	Premature ejaculation	Dapoxetine	III
Antares Pharma	Overactive bladder	Oxybutynin (gel)[2]	I
Apogepha	Overactive bladder	NS-8	II
	Urinary incontinence	NS-8	II
Arachnova	Urinary incontinence, stress	SOU-001 (AA-10020)	I
Ardana Bioscience	Benign prostatic hyperplasia	Teverelix	II
AstraZeneca	Overactive bladder	ZD-0947	II
Barr	Urinary incontinence	Oxybutynin chloride (vaginal ring)[2]	II
Baxter Oncology	Nephrotoxicity, chemotherapy-induced	BNP-7787	I
Bayer	Erectile dysfunction	Vardenafil hydrochloride hydrate[3]	L-2003
BioNumerik	Nephrotoxicity, chemotherapy-induced	BNP-7787	I
BioXell	Benign prostatic hyperplasia	BXL-628	II
Boehringer Ingelheim	Urinary incontinence, stress	Duloxetine hydrochloride[3]	Prereg.
	Urinary incontinence, urge	KUC-7483	II
Britannia	Erectile dysfunction	Apomorphine hydrochloride (nasal powder)[2]	I/II
Cyclacel	Glomerulonephritis	CYC-202	I
Daiichi Pharmaceutical	Benign prostatic hyperplasia	Silodosin[3]	III
DMI BioSciences	Premature ejaculation	DMI-7958 (LIF-301)	II
Dong-A	Erectile dysfunction	DA-8159	I
Dynogen Pharmaceuticals	Overactive bladder	DDP-200	I/II
Enhance Lifesciences	Premature ejaculation	DMI-7958 (LIF-301)	II
Esteve	Urinary incontinence	Cizolirtine citrate[3]	II
Exelixis	Renal failure	XL-784	I
FemmePharma	Urinary incontinence	FP-1097	II
Fujisawa	Nephritis, lupus	Tacrolimus[1,3]	III
GlaxoSmithKline	Benign prostatic hyperplasia	Dutasteride[3]	L-2003
	Erectile dysfunction	Vardenafil hydrochloride hydrate[3]	L-2003
	Overactive bladder	Solabegron hydrochloride	I
		Solifenacin succinate[3]	R-2003
		Talnetant	II
Guilford	Erectile dysfunction, postprostatectomy	GPI-1485	II
Icos	Interstitial cystitis	Resiniferatoxin	Discontinued
Indevus	Overactive bladder	Trospium chloride[+]	R-2004
Ivax	Benign prostatic hyperplasia	GYKI-16084[3]	II
Ixion	Hyperoxaluria	IxOC-2	I
Kissei	Benign prostatic hyperplasia	Silodosin[3]	III
Kissei	Ureterolithiasis	KUL-7211	II
	Urinary incontinence, urge	KUC-7483	II
Kyorin	Overactive bladder	KRP-197/Ono-8025	III
Kyowa Hakko	Overactive bladder	KW-7158	II
Lilly	Erectile dysfunction, treatment-emergent	VML-670	Discontinued
	Urinary incontinence, stress	Duloxetine hydrochloride[3]	Prereg.
Lilly Icos	Erectile dysfunction	Tadalafil[3]	L-2003
MacroChem	Erectile dysfunction	Alprostadil (cream)[2]	II
Merck & Co.	Urinary incontinence	C-3048	II
Merck KGaA	Erectile dysfunction	EMR-62203	Discontinued
Milkhaus	Benign prostatic hyperplasia	ML-4	II
	Prostatitis, chronic nonbacterial	ML-4	II
Nastech	Erectile dysfunction	Apomorphine hydrochloride (intranasal)[2]	II
Neurocrine Biosciences	Erectile dysfunction	NBI-69733	I/II
NexMed	Erectile dysfunction	Alprostadil (cream)[2]	III
	Premature ejaculation	NM-100061	II
Nippon Shinyaku	Interstitial cystitis	SI-7201 (NS-7201)	III
	Overactive bladder	NS-8	II
		Temiverine hydrochoride hydrate	Prereg.
	Urinary incontinence	NS-8	II
	Urinary incontinence, urge	Temiverine hydrochoride hydrate	Prereg.
Nippon Zoki	Renal failure	NZ-419	II

Continuation

Treatment of Genitourinary Disorders by Source

Source	Condition	Drug	Phasç
Novartis	Overactive bladder	Darifenacin hydrobromide[3]	Prereg.
Nymox	Benign prostatic hyperplasia	NX-1207	I/II
Ono Pharmaceutical	Overactive bladder	KRP-197/Ono-8025	III
Otsuka	Urinary incontinence	OPC-51803	II
Palatin Technologies	Erectile dysfunction	PT-141	II
Pharmalink	Nephropathy	Nefecon™	Clinical
Pliva	Overactive bladder	Trospium chloride(+)	R-2004
PPD	Premature ejaculation	Dapoxetine	III
QLT	Benign prostatic hyperplasia	QLT-0074	I/II
Ranbaxy	Benign prostatic hyperplasia	RBx-9001	IND Filed
		RBx-2258 (SPM-969)	II
Roche	Urinary incontinence, stress	R-1484	I
Sanofi-Synthélabo	Hyponatremia	SR-121463	II
Schering-Plough	Erectile dysfunction	Dasantafil	Clinical
Schwarz Pharma	Benign prostatic hyperplasia	RBx-2258 (SPM-969)	II
	Overactive bladder	Fesoterodine[3]	III
	Urinary incontinence, urge	Fesoterodine[3]	III
Seikagaku	Interstitial cystitis	SI-7201 (NS-7201)	III
Sepracor	Urinary incontinence	(S)-Oxybutynin	III-Suspended
Solvay	Benign prostatic hyperplasia	Cetrorelix acetate[1,3]	II
	Renal failure	SLV-320	I
Sosei	Urinary incontinence, stress	SOU-001 (AA-10020)	I
Taiho	Benign prostatic hyperplasia	TF-505	II
	Interstitial cystitis	Suplatast tosilate[1,3]	II
	Prostatitis	Suplatast tosilate[1,3]	II
Takeda	Hypoactive bladder	TAK-802	II
	Urinary incontinence	TAK-637	II-On hold
Tanabe Seiyaku	Erectile dysfunction	Avanafil	II
Threshold Pharmaceuticals	Benign prostatic hyperplasia	TH-070	II
Tsumura	Nephritis	TJN-598	I
Vectura	Erectile dysfunction	VR-004 (inhaled apomorphine)	II
Vernalis	Erectile dysfunction, treatment-emergent	VML-670	Discontinued
Vivus	Erectile dysfunction	Avanafil	II
	Premature ejaculation	Avanafil (VI-0162)	I
		VI-0134	II
Watson	Benign prostatic hyperplasia	Silodosin[3]	III
	Overactive bladder	Oxybutynin chloride (transdermal patch)[2]	L-2003
West Pharmaceutical Services	Nephropathy	Nefecon(TM)	Clinical
Yamanouchi	Hyponatremia	Conivaptan hydrochloride[3]	Prereg.
	Interstitial cystitis	Suplatast tosilate[1,3]	II
	Overactive bladder	Solifenacin succinate[3]	R-2003
		YM-178	II
	Prostatitis	Suplatast tosilate[1,3]	II
Zambon	Renal failure	*N*-Acetylcysteine[3]	II

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

Treatment of Genitourinary Disorders

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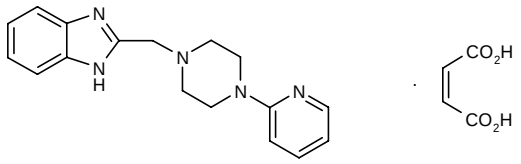
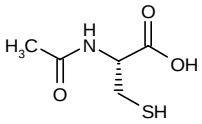
ABT-724/ABT-670



ABT-724

ABT-724 is a selective dopamine D4 receptor agonist in phase II clinical testing at Abbott for the treatment of erectile dysfunction (ED). Another compound, ABT-670, is in phase I clinical development for this indication.

N-Acetylcysteine



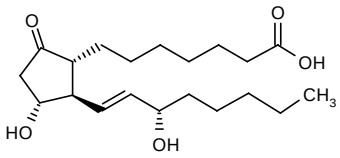
The antioxidant *N*-acetylcysteine is being evaluated for its potential in the treatment of chronic kidney disease/end-stage renal disease (ESRD). Phase II trials are under way at Zambon with the aim of registering the agent, administered as a prolonged infusion by extracorporeal circulation in conjunction with erythropoietin, for the management of anemia associated with ESRD in patients on hemodialysis.

A clinical trial conducted in 134 patients with end-stage renal failure being treated with hemodialysis 3 times weekly for at least 3 months randomized them to receive either placebo or 600 mg b.i.d. of *N*-acetylcysteine. After a median follow-up of 14.5 months, patients treated with *N*-acetylcysteine showed a lower incidence of cardiac events, ischemic strokes and peripheral vascular disease compared to those treated with placebo. Similar death rates due to any cause were found in each treatment group: 21.9% with *N*-acetylcysteine and 20.0% with placebo. The drug was well tolerated, as the most common adverse event was gastrointestinal discomfort (7.8% of patients) and no major adverse events were reported (1).

1. Tepel, M., van der Giet, M., Statz, M., Jankowski, J., Zidek, W. *The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure. A randomized, controlled trial*. Circulation 2003, 107(7): 992.

Original monograph – Drugs Fut 1995, 20(6): 559.

Alprostadil Cream



At least two cream formulations of alprostadil are in clinical development for use in ED: MacroChem's Topiglan® and NexMed's Alprox-TD®. NexMed's product has been available in China for several years under the trade name Befar®.

Following the lifting of the FDA hold on clinical trials of topical drugs utilizing MacroChem's patented SEPA® drug absorption enhancer for topical delivery through the skin and nails, including the company's Topiglan® alprostadil cream (1% alprostadil and 10% SEPA®), imposed in 2002 pending a review of questions surrounding a 26-week transgenic mouse (Tg.AC) carcinogenicity study of SEPA® conducted in 1999, Topiglan® entered a double-blind, placebo-controlled phase II study in subjects with mild to moderate ED in June 2003 in the U.K., which was subsequently expanded into the U.S. Phase I data for the new cream formulation showed it to be better tolerated than the first-generation gel. In an at-home trial of the gel, a 435-patient protocol-conforming subset of 550 men with moderate to severe ED achieved

statistically significant improvement in both primary endpoints —improvement in International Index of Erectile Funcion (IIEF) erectile function score and improvement in intercourse completion. Preliminary data from the phase II pharmacodynamic study demonstrated that the product did not meet the primary clinical endpoints. The randomized, double-blind study compared the efficacy of Topiglan® to placebo in men with mild to moderate ED using RigiScan® as a measure. Further analysis of the data will be conducted over the coming weeks (1-6).

Final data from a 2-year carcinogenicity study in rats showed no evidence of carcinogenicity associated with NexMed's NexACT® skin permeation enhancer in the animals tested. Doses of the NexACT® enhancer used in the study were up to 833 times the equivalent dose administered to patients in the phase III trials of Alprox-TD®, NexMed's proprietary cream treatment for ED that incorporates alprostadil with the NexACT® transdermal delivery technology. NexMed has completed two pivotal phase III studies of Alprox-TD® and reported positive topline results from these studies. Data indicated that the dose levels of Alprox-TD® tested were effective compared to placebo in each study and in the combined analysis of both studies. All doses showed a highly significant increase in IIEF Erectile Function domain scores. Side effects were mostly mild to moderate, localized and transient. The randomized, double-blind, placebo-controlled trials were designed to confirm the efficacy and safety of Alprox-TD® in over 1,700 patients with mild to severe ED at 85 sites. The studies included patients who had not previously taken ED medications, as well as patients who had little or no success with currently approved oral medications. Many of the patients also had diabetes, prostatectomies, hypertension and other serious medical conditions. NexMed continues to review the data for additional analyses of different populations, including those patients who can not take or have failed the marketed oral medications, and/or who have medical conditions such as hypertension, diabetes or cardiovascular complications. The company is also discussing possible stragetic marketing partnerships for Alprox-TD® (7-9).

1. *FDA lifts clinical hold on trials of MacroChem's SEPA-based drugs*. DailyDrugNews.com (Daily Essentials) April 15, 2003.

2. *MacroChem updates clinical progress*. DailyDrugNews.com (Daily Essentials) Jan 23, 2004.

3. *MacroChem expands phase II Topiglan trial into U.S.* DailyDrugNews.com (Daily Essentials) Sept 2, 2003.

4. *Topiglan enters new phase II study for erectile dysfunction*. DailyDrugNews.com (Daily Essentials) June 4, 2003.

5. *R&D highlights from the 3rd Annual Global Biotech Forum for Investing & Partnering: MacroChem*. DailyDrugNews.com (Daily Essentials) April 28, 2004.

6. *Phase II study of Topiglan fails to meet primary clinical endpoints*. DailyDrugNews.com (Daily Essentials) April 20, 2004.

7. *No evidence of carcinogenicity in NexACT rat study*. DailyDrugNews.com (Daily Essentials) June 2, 2003.

8. *Positive phase III topline results for Alprox-TD*. DailyDrugNews.com (Daily Essentials) June 17, 2003.

9. *NexMed updates pipeline progress*. DailyDrugNews.com (Daily Essentials) March 22, 2004.

Additional References

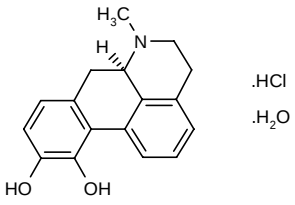
Deng, S. et al. *Topical application of alprostadil cream in combination with a local anesthetic for the treatment of premature ejaculation (PE)*. J Urol 2003, 169(4, Suppl.): Abst 957.

Padma-Nathan, H., Kim, E.D., Mcmurray, J.G., Thwing, D., Fendl, J., Yeager, J.L. *A novel topical alprostadil cream for the treatment of erectile dysfunction (ED): Combined analysis of two phase 3 pivotal studies*. J Urol 2004, 171(4, Suppl.): Abst 1198.

Padma-Nathan, H., Steidle, C., Salem, S., Tayse, N., Yeager, J., Harning, R. *The efficacy and safety of a topical alprostadil cream, Alprox-TD, for the treatment of erectile dysfunction: Two phase 2 studies in mild-to-moderate and severe ED*. Int J Impot Res 2003, 15(1): 10.

Steidle, C. et al. *A novel topical alprostadil cream for the treatment of erectile dysfunction (ED): Combined analysis of the phase 2 program*. J Urol 2003, 169(4, Suppl.): Abst 953.

Apomorphine Hydrochloride, New Formulations



Several pharmaceutical companies are developing novel formulations of apomorphine hydrochloride for the treatment of ED. Apomoprhine is a potent centrally acting dopamine agonist that promotes erectile fucntion by stimulating the D1/D2 class of dopamine receptors.

Nastech reacquired all development and commercialization rights for intranasal apomorphine from Pharmacia following the Pfizer-Pharmacia merger. The move grants Nastech control of the apomorphine clinical development program for ED and female sexual dysfunction. Nastech was granted royalty-free, exclusive worldwide licenses to use intranasal apomorphine products for human sexual dysfunction using any and all Pharmacia-patented inventions and know-how, and inventions developed under their collaboration. In addition to ED, Nastech is also currently conducting a phase II trial in women with female sexual dysfunction, The company is in discussions with potential new partners for worldwide development and commercialization (1-3).

The results of a phase II clinical trial of intranasal apomorphine in men with sexual dysfunction were reported.

A total of 102 male subjects aged 50-82 years were included in this multicenter, double-blind, randomized, placebo-controlled clinical trial that assessed the safety profile of topical apomorphine at doses of 0.5-2.0 mg once daily for 7 days. Doses up to 1.75 mg/day were well tolerated, while doses up to 2.0 mg/day induced no significant changes in the systolic or diastolic blood pressure of the subjects. The adverse events reported with apomorphine included symptomatic hypotension (0-1.6%), nausea (2-6%), vomiting (2% with the 2.0 mg/day dose) and dizziness (1-5%). No evidence of Q-T_c prolongation or syncope was found with apomorphine (4).

Vectura is developing VR-004 as an inhaled, systemically acting product for the treatment of mild, moderate and severe ED. The active ingredient in VR-004, apomorphine hydrochloride, has previously been approved in Europe for the treatment of ED in a sublingual tablet form. VR-004 combines a proprietary formulation of apomorphine with Vectura's high-efficiency inhaler device Aspirair® to produce a dry powder inhaler (DPI) product for delivery via the lungs.

Vectura has completed a phase IIa trial of VR-004 for the treatment of ED, showing that VR-004 improved erectile performance with a rapid onset of action and was well tolerated. The placebo-controlled, escalating-dose study assessed 200-, 400- and 800-μg doses of VR-004 in 35 subjects with mild to moderate ED. Erectile performance, assessed in response to visual stimuli in a clinical setting, was improved at doses of 400 and 800 μg. At these doses, the proportion of patients achieving grade 3 or 4 erectile performance was 49% and 59%, respectively, compared to 31% on placebo. The response rate at 200 μg was 23%. Median onset times were 8 min for the 400- and 800-μg doses. The most rapid response occurred in some patients 3 min after they received 400 or 800 μg. Additional studies are planned for the near future. Vectura anticipates completing licensing discussions with third parties by the end of 2003 (5, 6).

VR-004 has been shown in a clinical study to be tolerated at doses up to and including 900 μg, and to be rapidly and efficiently absorbed following inhalation. Pharmacokinetic evaluations conducted over a 24-h period validated the concept of rapid lung absorption and elimination when VR-004 is delivered by inhalation. Maximum plasma concentrations were observed 1-3 min after dosing. Elimination of drug from plasma was relatively rapid, with a terminal half-life of approximately 60 min. All treatment-related adverse events were of mild to moderate severity, with the majority reported immediately after dosing and being transient in nature. No clinically relevant or significant changes in blood pressure, heart rate, electrocardiographic parameters or lung function tests were observed. Additional studies to assess the safety and efficacy of VR-004 will be initiated this year (7).

Britannia has also successfully completed a phase I study of its apomorphine nasal powder formulation for ED, showing that it may offer considerable improvement over currently marketed products. A phase II proof-of-principle study is planned for the near future (8). Britannia is seeking a codevelopment partner for this product.

A method has been claimed for the treatment of ED in psychogenic male patients, comprising the nasal administration of a pharmaceutical dosage formulation containing the dopamine D2 receptor agonist apomorphine. The claim further embodies the optional pre- or coadministration of an antiemetic agent for mitigating the symptoms of nausea —a side effect commonly associated with apomorphine therapy— and also the diagnosis of the aforementioned indication (9).

1. *Nastech reacquires intranasal apomorphine rights following Pfizer-Pharmacia merger*. DailyDrugNews.com (Daily Essentials) April 23, 2003.

2. *Intranasal apomorphine enters new phase II study in erectile dysfunction*. DailyDrugNews.com (Daily Essentials) June 6, 2003.

3. *Major step forward in Pfizer-Pharmacia merger*. DailyDrugNews.com (Daily Essentials) March 4, 2003.

4. *Nastech reports positive PYY obesity and apomorphine sexual dysfunction clinical trial data*. Nastech Pharmaceutical Press Release 2004, March 10.

5. *Phase IIa trial evaluates VR-004 delivered via lungs for ED*. DailyDrugNews.com (Daily Essentials) May 15, 2003.

6. *VR-004 shows efficacy in phase IIa erectile dysfunction trial*. DailyDrugNews.com (Daily Essentials) July 23, 2003.

7. *Second successful clinical study with VR-004 for erectile dysfunction*. DailyDrugNews.com (Daily Essentials) June 4, 2004.

8. *Landmark year at Britannia*. DailyDrugNewscom (Daily Essential2) Jan 28, 2004.

9. El-Rashidy, R. and Ronsen, B. (Pentech Pharmaceuticals, Inc.) *Apomorphine-containing dosage form for ameliorating male erectile dysfunction*. US 2003073715, US 6566368, WO 0335069.

Avanafil

Avanafil (TA-1790) is a potent, selective, orally active and rapid-acting phosphodiestersase type 5 (PDE5) inhibitor licensed by Vivus from Tanabe Seiyaku and currently in phase II clinical development in the U.S. and the E.U. for ED.

Vivus's double-blind, randomized, crossover phase II at-home study comparing the onset of action of avanafil and Pfizer's Viagra® (sildenafil) has shown comparable results. With each product, subjects had erections sufficient to achieve vaginal penetration on approximately 80% of attempts. These successful attempts occurred, on average, within 20 min after dosing. The results supported the rapid absorption and onset of action seen in the earlier in-clinic RigiScan® trial (see below), although avanafil did not outperform Viagra® as it did in the in-clinic study. A phase II dose-ranging trial and routine safety studies evaluating the interaction of avanafil with various drugs will be initiated in the first half of 2004 (1-3).

Vivus has commenced enrollment in another phase II trial designed to evaluate the safety and efficacy of avanafil. The at-home, double-blind, randomized, crossover study will enroll approximately 250 patients at

20 U.S. sites. Enrollment is anticipated to be completed by the end of 2004, with data expected in the first half of 2005 (4).

Patients with erectile dysfunction (n=80) enrolled in a multicenter, randomized, crossover study were given avanafil (50, 100 or 200 mg), placebo or sildenafil (50 mg) followed by visual sexual stimulation. Sexual stimulation was given 20-40, 60-80 or 100-120 min after dosing and responses to treatment were assessed by RigiScan®. The results, recently presented at the AUA meeting in San Francisco, showed that improvements in penile rigidity were similar after avanafil and sildenafil treatment. The mean duration of base rigidity above 60%, however, was highest with all avanafil doses after early visual sexual stimulation (20-40 min postdose). The longest mean duration of base rigidity above 60% after sildenafil treatment occurred when visual sexual stimulation was given after 60 min. Avanafil and sildenafil were well tolerated, with facial flushing the most common adverse event. These results suggest that avanafil might be favored by patients due to the achievement of a peak effect sooner than sildenafil (5).

Data from a proof-of-concept trial evaluating the effects of PDE5 inhibitors in men with premature ejaculation (PE) did not demonstrate an increase in the time to ejaculation. The placebo-controlled trial evaluated avanafil (known as VI-0162 for this indication) and sildenafil. Inhibition of PDE5 failed to significantly improve ejaculatory latency in this study even though results from previous studies had suggested that inhibition of PDE5 was associated with increased time to ejaculation in men with PE. Despite these results, the company plans to continue the development of VI-0162 for PE (6).

1. *At-home study of TA-1790 opens enrollment*. DailyDrugNews.com (Daily Essentials) July 22, 2003.

2. *Comparable results in phase II head-to-head study of TA-1790 and Viagra*. DailyDrugNews.com (Daily Essentials) Feb 11, 2004.

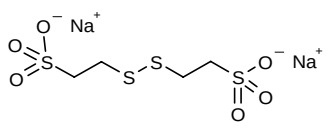
3. *Tanabe Seiyaku reports interim 2003 year-end R&D highlights*. Tanabe Seiyaku Web Site 2004, Feb 2.

4. *Enrollment underway in phase II trial of avanafil for erectile dysfunction*. DailyDrugNews.com (Daily Essentials) April 26, 2004.

5. Lewis, R.W., Hellstrom, W.J.G., Gittelman, M. et al. *Rigiscan evaluation of TA-1790, a novel PDE5 inhibitor for the treatment of men with erectile dysfunction*. J Urol 2004, 171(4, Suppl.): Abst 1196.

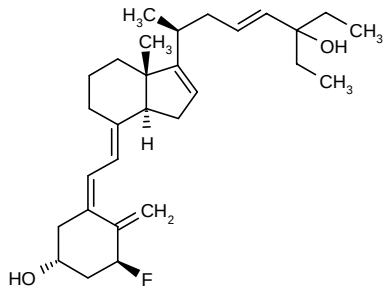
6. *Disappointing results for proof-of concept trial of VI-0162 in PE*. DailyDrugNews.com (Daily Essentials) July 21, 2003.

BNP-7787



The chemoprotective agent BNP-7787 (Tavocept™) is BioNumerik's lead product candidate, intended for preventing common and serious side effects of taxane- and platinum-based chemotherapy, particularly nerve and kidney damage. The company is conducting a phase I clinical trial in patients with solid tumors to determine the safety and efficacy of BNP-7787 in reducing or preventing the development of cisplatin-induced nephrotoxicity, as well as its possible protective effects against cisplatin- and/or paclitaxel-related neurotoxicity. Phase III clinical trials are under way in the U.S. and Japan to evaluate its efficacy in reducing or preventing the severe neurotoxicity associated with paclitaxel chemotherapy in patients with metastatic breast cancer, and a European phase III trial is also testing its efficacy in patients with non-small cell lung cancer treated with paclitaxel and cisplatin. Baxter Oncology holds rights to the product for all territories outside the U.S., Canada and Japan.

BXL-628



BioXell has completed enrollment in a double-blind, randomized, placebo-controlled phase IIa trial of its lead compound BXL-628 in benign prostatic hyperplasia (BPH). More than 160 patients were enrolled in under 6 months. The 3-month study is being coordinated by the Division of Urology of the San Raffaele Hospital in Milan and involves 12 centers in Italy. The primary endpoint is reduction in prostate size as measured by magnetic resonance imaging (MRI) scans, with secondary endpoints of reduced symptom severity and urinary flow rate. Results are expected in the first half of 2004. BXL-628 appears to inhibit the growth of prostate cells by impairing the activity of several growth factors that are involved in prostate growth and the pathogenesis of BPH. This inhibition is achieved without direct antiandrogenic activity, thereby eliminating the sexual dysfunction and other side effects associated with current therapies (1, 2).

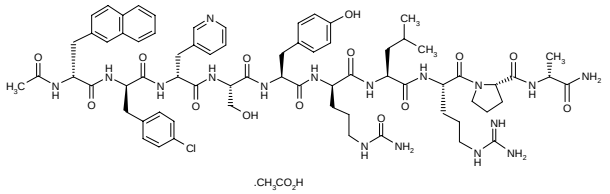
1. *Enrollment completed in phase IIa BPH study of BXL-628*. DailyDrugNews.com (Daily Essentials) Dec 2, 2003.

2. *BioXell commences phase II trial of BXL-628*. DailyDrugNews.com (Daily Essentials) March 31, 2003.

C-3048

C-3048 is in phase II clinical evaluation at Merck & Co. for use in urinary incontinence.

Cetrorelix Acetate



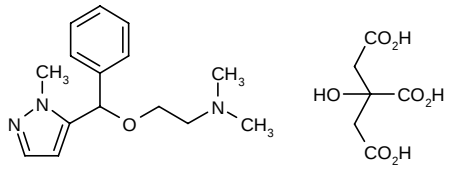
Cetrorelix acetate is a peptide-based luteinizing hormone-releasing hormone (LHRH) antagonist that blocks LHRH receptors in the pituitary and rapidly and dose-dependently decreases sex hormone levels (*i.e.*, testosterone in the testes and estrogen and progesterone in the ovaries). It is currently marketed worldwide, except in Japan where approval is expected this year, by AEterna Zentaris's licensee Serono as Cetrotide® for use in *in vitro* fertilization. Shionogi and Nippon Kayaku are the licensees for Japan. Solvay is the licensee for the new indications mentioned below, worldwide except for Japan.

Earlier this month, AEterna Zentaris, the recently unveiled new corporate name for AEterna Laboratories, updated the progress of various programs and expected milestones in the year ahead. In 2004, the company plans to place emphasis on the development of perifosine and cetrorelix. A pivotal program on cetrorelix with partner Solvay will begin in 2004 following the completion of 6 positive phase II trials in endometriosis, uterine myoma and benign prostatic hyperplasia (BPH) (1).

1. *AEterna Zentaris unveils new name, progress and plans*. DailyDrugNews.com (Daily Essentials) June 1, 2004.

Original monograph – Drugs Fut 1994, 19(3): 228.

Cizolirtine Citrate

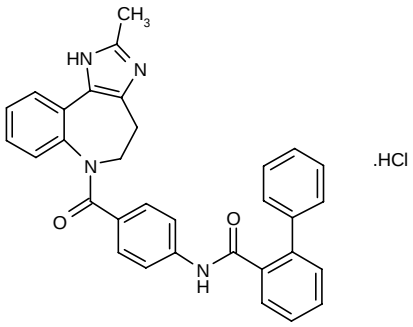


Esteve has completed two double-blind phase II trials of its proprietary molecule cizolirtine citrate, a substance P and calcitonin gene-related peptide (CGRP) modulator, in urinary incontinence. In the first trial, in which 135 patients were randomized to receive cizolirtine, oxybutynin or placebo, the primary efficacy endpoints (number of incontinence episodes and urgencies) were achieved in a statistically significant manner *versus* placebo. The second trial in 79 patients compared two different doses of cizolirtine and placebo. A dose-response relationship was observed, with the higher dose of cizolirtine showing statistically significantly better efficacy *versus* placebo. The trials represent the first time that a substance P and CGRP modulator has demonstrated clinical efficacy in urinary incontinence. Phase III trials are scheduled to begin in September 2004 (1).

1. *Cizolirtine completes phase II trials in urinary incontinence*. DailyDrugNews.com (Daily Essentials) June 1, 2004.

Original monograph – Drugs Fut 2002, 27(8): 721.

Conivaptan Hydrochloride

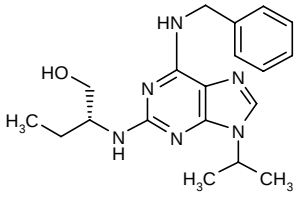


Yamanouchi has submitted an NDA for conivaptan hydrochloride (YM-087), an investigational drug to treat hyponatremia. YM-087 is an injectable dual V_{1a}/V_2 vasopressin receptor antagonist which restores blood sodium levels in patients with euvolemic and hypervolemic hyponatremia by increasing the excretion of free water without increasing the sodium output. If approved, YM-087 will be the world's first drug to treat this condition (1). Conivaptan is also in phase II clinical evaluation in the U.S. and Europe for the treatment of acutely decompensated chronic heart failure.

1. *NDA submission for YM-087 for hyponatremia*. DailyDrugNews.com (Daily Essentials) Feb 4, 2004.

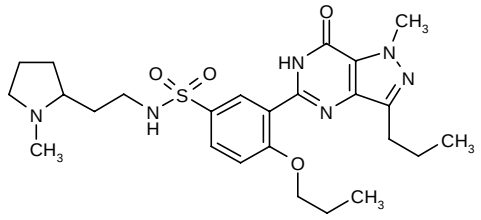
Original monograph – Drugs Fut 2000, 25(11): 1121.

CYC-202



Cyclacel's most advanced compound is CYC-202 ([*R*]-roscovitine), a small-molecule cyclin-dependent kinase (CDK) inhibitor, which has reached phase II clinical evaluation in breast and lung cancer patients. The company has also completed a phase I trial in healthy volunteers and is exploring the use of CYC-202 for glomerulonephritis, a renal cell proliferatory disease.

DA-8159



A PDE5 inhibitor from Dong-A, DA-8159 is undergoing phase I clinical evaluation as a potential new drug for ED.

A phase I and pharmacokinetic study of DA-8159 in healthy male volunteers indicated that the drug would have a rapid onset of action (t_{max} = 1-1.5 h) and a long duration of action ($t_{1/2}$ = 11-13 h). In this double-blind, placebo-controlled study, subjects received single ascending doses of 50, 100, 200 and 400 mg and multiple doses of 100 and 200 mg/day for 10 days. DA-8159 was well tolerated, with the most common adverse events (spontaneous erection and headache) seen primarily with repeated dosing at the 200-mg level. Steady-state plasma concentrations were achieved at 48 h after multiple dosing. Urinary excretion of unchanged drug was low, and multiple dosing did not lead to drug accumulation (1).

1. Padma-Nathan, H., Pacik, J.S., Ahn, B.O., Kang, K.K., Bahn, M.Y., Kim, W.B. *Phase I, double-blind, placebo-controlled study in healthy male subjects to investigate the safety, tolerability, and pharmacokinetics of DA-8159*. J Urol 2004, 171(4, Suppl.): Abst 884.

Additional References

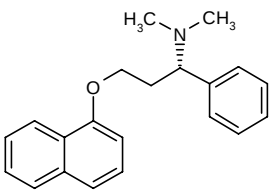
Amakye, D. et al. *DA-8159 - Phase I studies to investigate the safety and pharmacokinetics in healthy male caucasian subjects*. Clin Pharmacol Ther 2004, 75(2): Abst PII-132.

Cho, J.Y., Lim, H.S., Yu, K.S., Shim, H.J., Jang, I.J., Shin, S.G. *Sensitive liquid chromatography assay with ultraviolet detection for a new phosphodiesterase V inhibitor, DA-8159, in human plasma and urine*. J Chromatogr B Anal Technol Biomed Life Sci 2003, 795(2): 179.

Hong, K., Lim, H., Cho, J. et al. *Tolerability and single dose pharmacokinetics of a new PDE5 inhibitor, DA-8159 in healthy male subjects*. Clin Pharmacol Ther 2003, 73(2): Abst PI-70.

Kim, J. et al. *Simultaneous determination of a new phosphodiesterase-5 inhibitor DA-8159 and its active metabolite in human plasma by high performance liquid chromatography with tandem mass spectrometry*. Chromatographia 2003, 57(7-8): 447.

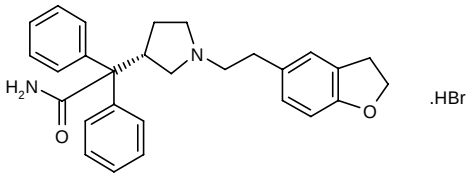
Dapoxetine



PPD has entered into an amendment to the dapoxetine license agreement with Alza, a wholly owned subsidiary of Johnson & Johnson. According to the amendment, certain sales-based payments will be abated for a period of time following NDA approval up to a maximum dollar amount. Alza will also make a cash payment to the company and agree to fix the amount of a milestone payment to be paid upon NDA approval. PPD acquired the patents for the compound in December of 2003 from Lilly for development in the field of genitourinary disorders. Dapoxetine is in phase III development for premature ejaculation and, if approved, would be the first prescription drug with a labeled claim for this indication (1).

1. *PPD amends dapoxetine license*. DailyDrugNews.com (Daily Essentials) Jan 13, 2004.

Darifenacin Hydrobromide



The FDA has issued an approvable letter to Novartis for darifenacin hydrobromide (Enablex®) for the treatment of overactive bladder. Darifenacin, a selective muscarinic M_3 receptor antagonist, works by selectively blocking an important receptor involved in the control of bladder muscle contraction. The drug was acquired by Novartis from Pfizer in 2003 through divestment prior to the merger of Pfizer and Pharmacia. The FDA has requested additional clinical work, after which Novartis anticipates launching the drug in 2004. European approval is also expected this year. Darifenacin has been studied in over 90 clinical trials involving more than 5,000 patients, with pivotal studies exploring key endpoints such as number of incontinence episodes per week, voluntary urination episodes per day, episodes of urgency and average volume of urine passed per micturition (1-5).

The population pharmacokinetics of darifenacin and its hydroxylated metabolite were described in a model using data from 337 healthy subjects enrolled in 18 phase I and II studies. Factors influencing absolute bioavailability of darifenacin were the formulation used, CYP2D6 genotype, CYP3A4 inhibitors, race and saturable first-pass metabolism. Clearance varied by time of day and by gender (6).

A double-blind, parallel-group study assessed the effects of darifenacin on the warning time (defined as the time from the first sensation of urgency to micturition) of patients with overactive bladder. Sixty-seven patients with urgency for at least 6 months before inclusion and at least 4 times a day during a 2-week run-in period were randomized to receive placebo or darifenacin 30 mg once daily for 2 weeks. The mean warning time of patients

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

Indication	Design	Treatments	n	Conclusions	Ref.
Overactive bladder	Randomized Double-blind	Darifenacin, 30 mg o.d. x 2 wks (n=32) Placebo (n=35)	67	Darifenacin administered for 2 weeks was more effective than placebo in prolonging the warning time of patients with overactive bladder. Darifenacin was also associated with a higher percentage of patients improving their average warning time by at least 30% compared to baseline	7
Overactive bladder	Randomized Double-blind Multicenter	Darifenacin, 7.5 mg/d p.o. x 12 wks (n=108) Darifenacin, 15 mg/d p.o. x 12 wks (n=107) Darifenacin, 30 mg/d p.o. x 12 wks (n=115) Placebo (n=109)	439	Darifenacin effectively reduced symptoms of overactive bladder	8
Healthy volunteers	Randomized Double-blind Crossover	Darifenacin IR; 5 mg t.i.d. x 2 wks Darifenacin CR; 3.75 mg o.d. x 2 wks Darifenacin CR; 7.5 mg o.d. x 2 wks Darifenacin CR; 15 mg o.d. x 2 wks Placebo	129	Darifenacin was free of cognitive side effects in elderly volunteers	9
Injury, spinal cord, Overactive bladder	Randomized Double-blind Crossover	Darifenacin, 6 mg i.v. Placebo	8	Provocation tests conducted 30 min before and 30 and 90 min after administration of the study treatment revealed that darifenacin was effective in suppressing unstable bladder contractions caused by neurogenic detrusor overactivity in patients with spinal cord injury	10
Overactive bladder	Randomized Double-blind Multicenter Pooled/meta-analysis	Darifenacin CR, 7.5 mg p.o. o.d. x 12 wks (n=335) Darifenacin CR:, 15 mg p.o. o.d. x 12 wks (n=330) Placebo (n=655)	1049	Darifenacin was well tolerated and reduced incontinence in patients with overactive bladder	11

treated with darifenacin was 4.3 min longer than that of placebo-treated patients. The drug was also associated with a significantly higher percentage of patients improving their average warning time by at least 30% compared to baseline (47% *vs*. 20% with placebo). These results also confirmed that the warning time is a convenient endpoint to determine the efficacy of novel therapies for urgency or overactive bladder (7). These results and those from the following studies are summarized in Table I.

A multicenter, randomized, double-blind study has revealed the benefit of treating patients with overactive bladder with darifenacin. The 439 patients enrolled in the study, 85% of whom were female, were treated for 12 weeks with oral darifenacin 7.5, 15 or 30 mg/day or placebo. At the end of the study, it was found that the reductions in nocturnal awakenings and in incontinence episodes were significant with the proposed market doses of darifenacin compared to placebo. The median change from baseline in nocturnal awakenings per week was 3.6%, 22.1% and 22.7% with placebo, darifenacin 7.5 mg/day and darifenacin 15 mg/day, respectively. The median change from baseline in the number of incontinence episodes per week was 46%, 68.7% and 76.5% in the placebo, darifenacin 7.5 mg/day and darifenacin 15 mg/day groups, respectively (8).

In a randomized, double-blind, crossover trial, elderly volunteers were treated for 14 days with controlled-release darifenacin (3.75, 7.5 and 15 mg p.o. once daily), immediate-release darifenacin (5 mg p.o. t.i.d.) or placebo. Primary cognitive function tests revealed no significant differences between controlled-release darifenacin and placebo in the memory scanning sensitivity, choice reaction time and word recognition sensitivity of the subjects. Treatment-related adverse events were similar in all placebo and controlled-release darifenacin groups, and the most common were mild to moderate dry mouth and constipation (9).

A crossover trial included 8 male patients with spinal cord injury and used provocation tests to determine the effects induced by darifenacin on neurogenic detrusor overactivity. Each patient's bladder was filled at a rate of 15 ml/min in order to determine the volume at first unstable contraction, following which 50-100 ml were withdrawn and injected rapidly in order to induce such a contraction. The area under the pressure-time curve for each contraction was measured 30 min before and 30 and 90 min after receiving an intravenous dose of either placebo or 6 mg of darifenacin. The drug was significantly more effective than placebo in reducing the AUC for unstable contractions. This drug-induced suppression of unstable

provoked bladder contractions caused by neurogenic detrusor overactivity suggests a potential role for darifenacin in the management of patients with spinal cord injury (10).

Data from 3 multicenter, randomized, double-blind, placebo-controlled phase III trials in 1,049 patients were pooled to evaluate the efficacy of darifenacin in overactive bladder. Darifenacin (7.5 and 15 mg p.o. once daily) or placebo was given to the patients for 12 weeks. The number of incontinence episodes per week decreased significantly more with darifenacin (–68.4% with 7.5 mg, –76.8% with 15 mg) compared with placebo (–53.8-58.3%). Secondary efficacy parameters (*e.g.*, micturition frequency, bladder capacity, severity of urgency) also improved significantly with darifenacin. Dry mouth and constipation were the adverse events most commonly associated with darifenacin (11).

Pharmaceutical formulations containing the muscarinic M_3 receptor antagonist darifenacin or a pharmaceutically acceptable derivative thereof have been reported to be useful for the alleviation of urgency resulting from an overactive bladder. The claim further embodies the release of 10% or more darifenacin from a slow-release formulation to the lower gastrointestinal tract (12).

1. *Novartis acquires Enablex*. DailyDrugNews.com (Daily Essentials) May 13, 2003.

2. *Approvable letter issued for Enablex for overactive bladder*. DailyDrugNews.com (Daily Essentials) Oct 8, 2003.

3. *Novartis reports 2003 year-end R&D highlights*. Novartis Press Release 2004, Jan 22.

4. *Major step forward in Pfizer-Pharmacia merger*. DailyDrugNews.com (Daily Essentials) March 4, 2003.

5. *Novartis to acquire Pfizer incontinence drug*. DailyDrugNews.com (Daily Essentials) March 20, 2003.

6. Kerbusch, T., Wählby, U., Milligan, P.A., Karlsson, M.O. *Population pharmacokinetic modelling of darifenacin and its hydroxylated metabolite using pooled data, incorporating saturable first-pass metabolism, CYP2D6 genotype and formulation-dependent bioavailability*. Br J Clin Pharmacol 2003, 56(6): 639.

7. Cardozo, L., Prescott, K., Serdarevic, D., Skillern, L. *Can medication prolong warning time?* 33rd Annu Meet Int Continence Soc (Oct 5-9, Florence) 2003, Abst 74.

8. Khullar, V. *Darifenacin, an M3 selective receptor antagonist, reduces the frequency of nocturnal awakening, an important symptom of overactive bladder*. J Urol 2004, 171(4, Suppl.): Abst 491.

9. Wesnes, K., Lipton, R., Kolodner, K., Edgar, C. *Darifenacin, an M3 selective receptor antagonist for the treatment of overactive bladder, does not affect cognitive function in elderly volunteers*. Eur Urol Suppl 2004, 3(2): Abst 513.

10. Bycroft, J., Leaker, B., Wood, S., Knight, S., Shan, J., Craggs, M. *The effect of darifenacin on neurogenic detrusor overactivity in patients with spinal cord injury*. 33rd Annu Meet Int Continence Soc (Oct 5-9, Florence) 2003, Abst 190.

11. Chapple, C. *Darifenacin is effective in improving the major symptoms of overactive bladder: A pooled analysis of phase III studies*. Eur Urol Suppl 2004, 3(2): Abst 512.

12. Colli, E. et al. (Pfizer Ltd.) *Method of treatment*. WO 0351354.

Original monograph – Drugs Fut 1996, 21(11): 1105.

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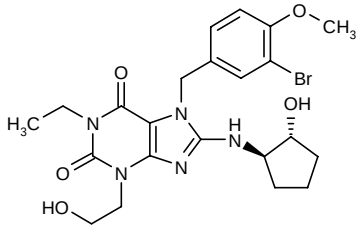
Haab, F. et al. *Darifenacin, an M3 selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder*. Eur Urol 2004, 45(4): 420.

Dasantafil



Dasantafil (Sch-446132) is a novel phosphodiesterase type 5 (PDE5) inhibitor in early clinical development at Schering-Plough for the treatment of male erectile dysfunction.

DDP-200

Dynogen has secured USD 50 million in its Series B venture capital funding which it will use to build its pipeline and advance its portfolio of preclinical- and clinical-stage development candidates. Dynogen's clinical candidates include DDP-200 for the treatment of overactive bladder. DDP-200 has completed phase I trials and is expected to enter a phase IIa study in the first half of 2004. The company has also entered into a research collaboration with Johnson & Johnson to study several neurological compounds for the treatment of overactive bladder (1).

1. *Series B financing supports efforts at Dynogen*. DailyDrugNews.com (Daily Essentials) April 21, 2004.

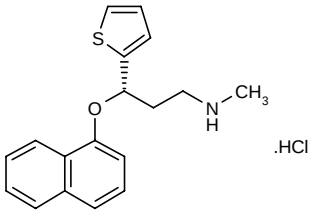
DMI-7958 (LIF-301)

A European phase IIa study of DMI BioSciences' investigational drug DMI-7958 in male volunteers suffering from premature ejaculation (PE) has met the endpoint, demonstrating substantial effect compared to placebo in men suspected of having primary

physiological PE. In the placebo-controlled, randomized, double-blind, crossover study, DMI-7958 was well tolerated with no serious adverse events. DMI-7958 is being codeveloped with the former Enhance Biotech, now Enhance Lifesciences, to treat PE on an as-needed basis (1). DMI-7958, known as LIF-301 (formerly LI-301) at Enhance Lifesciences, is a dual selective serotonin reuptake inhibitor (SSRI) and mu opioid receptor agonist for oral administration.

1. *Endpoint met in phase IIa study of DMI-7958*. DailyDrugNews.com (Daily Essentials) March 4, 2004.

Duloxetine Hydrochloride



Lilly's dual 5-HT and norepinephrine reuptake inhibitor duloxetine hydrochloride is nearing market launch for both stress urinary incontinence (SUI) and depression (Cymbalta™). Last fall, Lilly received the first approvable letter from the FDA for duloxetine for the treatment of SUI, as well as the second approvable letter for depression. Final FDA approval is contingent upon successful completion of additional acute preclinical and clinical pharmacology studies, satisfactory resolution of manufacturing issues and completion of label negotiations for the SUI indication, and resolution of manufacturing issues and the completion of label negotiations for depression. Pending more precise information following discussions with the FDA, Lilly expects U.S. approval for SUI in late 2004 or the first half of 2005. Lilly subsequently submitted its complete response to the approvable letter for depression, with approval and launch in the U.S. for this indication expected in the summer of 2004. The European Committee for Proprietary Medicinal Products (CPMP) also issued a positive opinion for duloxetine for the treatment of moderate to severe SUI in women. If approved, the product will be marketed throughout the E.U. by Lilly under the brand name Yentreve® and by Boehringer Ingelheim under the brand names Yentreve® and Ariclaim®. Marketing authorization by the European Commission is expected late in 2004. The positive opinion was based on a comprehensive data package of duloxetine from 10 studies that enrolled more than 2,000 women with SUI across 5 continents. Lilly and Boehringer Ingelheim signed a long-term agreement in November 2002 to jointly develop and commercialize duloxetine in most countries worldwide, although in the U.S. the collaboration focuses on SUI only (1-4).

Pharmacokinetic and metabolic data for [^{14}C]-duloxetine were obtained from an open-label, single-dose (20.2 mg, 100.6 mCi) study in 4 healthy volunteers over 13 days. The drug was safe, well tolerated and widely metabolized; unchanged drug represented only 3% of the total circulating radioactivity and was undetectable in urine. The half-life, t_{max}, C_{max} and AUC values were considerably greater for total radioactivity than for duloxetine. The total radioactivity recovered in urine and feces was 72% and 18%, respectively (5).

The pharmacokinetics of single doses of duloxetine (40 mg) were determined in 24 healthy female subjects, 12 older than 65 and 12 between the ages of 32 and 50. Plasma samples were also obtained from younger and older women with urinary incontinence who were treated with 20-80 mg/day. In these analyses, duloxetine clearance decreased with the increasing age of the subjects, but the safety profile of the drug was similar in older and younger women. Dose adjustments for elderly patients were therefore not recommended (6).

Results from a randomized, double-blind, crossover study in 12 healthy male volunteers indicated that duloxetine inhibits platelet serotonin and norepinephrine reuptake. In the study, subjects received duloxetine 80 mg/day or 60 mg b.i.d., desipramine 50 mg b.i.d. or placebo. Duloxetine appeared to have no effect on an intravenous tyramine pressor test (7). These results and those from some of the studies described below are depicted in Table II.

A randomized, placebo-controlled phase III clinical trial provided new data on the efficacy and safety of duloxetine in 494 women with SUI. The patients were randomized to receive either placebo or duloxetine (40 mg b.i.d.) for 12 weeks. The drug was significantly more effective than placebo in reducing the incontinence episode frequency (with a median decrease of 50% *vs.* 29%), increasing the voiding intervals (15 min *vs.* 4 min) and improving the patients' quality of life. The percentage of patients who showed a reduction of 50-100% in their incontinence episode frequency was 59.5% with duloxetine and 43.2% with placebo. Adverse events were also more frequent with duloxetine (76.2% *vs.* 59.3%), although most were mild or moderate, and the most common were nausea, headache, insomnia, constipation and dry mouth. The difference in the percentages of patients who completed the study (79% with duloxetine, 92% with placebo) was considered to be due to duloxetine-related adverse events. These results confirm the promising data from previous trials, and the authors suggested that duloxetine may become an alternative to pelvic floor muscle training (PFMT) and/or continence surgery in the treatment of SUI (8, 9).

A total of 1,913 women (mean age 52.5 years) with predominant SUI participated in 4 randomized, double-blind phase II or III clinical trials comparing the efficacy of duloxetine 40 mg twice daily with placebo. Treatment was for 12 weeks, following which patients in the phase III studies could continue treatment in an open-label extension phase. During the 12-week

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Double-blind Crossover	Desipramine, 50 mg b.i.d. x 7 d Duloxetine, 60 mg b.i.d. x 7 d Duloxetine, 80 mg q.d. x 7 d Placebo	12	Duloxetine inhibited platelet serotonin and norepinephrine reuptake in healthy volunteers	7
Incontinence, urinary	Randomized Double-blind Multicenter	Duloxetine, 40 mg b.i.d. x 12 wks (n=247) Placebo (n=247)	494	Duloxetine was well tolerated and significantly more effective than placebo in reducing incontinence episode frequency and increasing voiding intervals in patients with stress urinary incontinence; these changes were associated with a greater improvement in quality of life	8, 9
Incontinence, urinary	Pooled/meta-analysis	Duloxetine x 12 wks (n=958) Placebo (n=955)	1913	Duloxetine was effective in improving the number of dry days in women with both less severe stress urinary incontinence and with a more severe form of the disease	12
Incontinence, urinary	Randomized	Duloxetine x 12 wks (n=52) Pelvic floor muscle training x 12 wks (n=50) Duloxetine + Pelvic floor muscle training x 12 wks (n=52) Placebo (n=47)	201	Duloxetine combined with pelvic floor muscle training was more effective than duloxetine alone or muscle training alone in patients with stress urinary incontinence	13, 14

double-blind period, there were significant improvements for duloxetine compared with placebo for median percent decrease in incontinence episode frequency (52% *vs.* 33%), increases in mean time between voids and Incontinence Quality Of Life scores. The superior efficacy of duloxetine was evident at 4 weeks and was maintained for 1 year in the open-label studies. On the Patient Global Impression of Improvement, 74% and 82% of patients considered themselves better at 3 and 12 months, respectively (10).

A meta-analysis based on data from these studies assessed the safety of duloxetine 40 mg twice daily for 12 weeks. Duloxetine was safe and well tolerated, The most frequently reported adverse events, consisting of nausea, dry mouth, fatigue, insomnia, constipation, headache, dizziness, somnolence and diarrhea, were generally mild to moderate in severity and transient (11).

Initial analysis of the results from these studies showed that patients with a less severe condition had a similar rate of improvement as those with a more severe condition, despite smaller improvements in incontinence episode frequency and Incontinence Quality of Life scores. Analysis of the number of dry days per week in these patients showed that this was due to the fact that patients with less severe symptoms were more likely to be dry on most days (12).

The results of a trial in 201 women with SUI indicated that combination therapy with duloxetine and PFMT was more effective than either therapy alone. The study included women with at least 2 SUI episodes per day and either a urodynamic diagnosis of pure stress incontinence or a positive cough stress test, normal voiding frequencies and no symptoms of enuresis and urge incontinence. Patients were randomized in a double-blind fashion to 12 weeks of treatment with duloxetine plus imitation PFMT, PFMT, duloxetine plus PFMT or placebo plus imitation PFMT. A 57% change in incontinence episode frequency was seen in patients given either duloxetine alone or duloxetine with PFMT; this change was significantly greater than that seen with PFMT alone (35%) or placebo treatment (29%). However, the percent change in pad use and the Incontinence Quality of Life total score were improved more with combined treatment as compared to duloxetine alone and the other treatments (13, 14).

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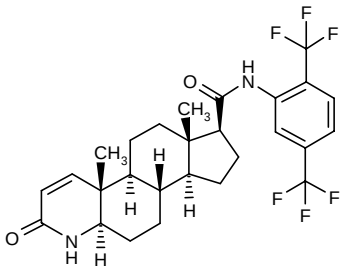
Dutasteride



GlaxoSmithKline launched dutasteride (Avodart® capsules, 0.5 mg) in the U.S. and the U.K. last year for the treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH) and reducing the risk of acute urinary retention and surgery in patients with moderate to severe symptoms of BPH. Dutasteride is an azasteroid that acts as a dual inhibitor of type I and II 5α-reductase, thereby further reducing serum dihydrotestosterone (DHT) levels in patients with BPH as compared to specific type II 5α-reductase inhibitors such as finasteride (1, 2).

GlaxoSmithKline has initiated an international trial to evaluate dutasteride in combination with the α-blocker tamsulosin in men with BPH. The COMBAT (COMBination of Avodart™ [dutasteride] and Tamsulosin) study will investigate the efficacy and safety of treatment with dutasteride and tamsulosin, administered once daily for 4 years, alone and in combination, on improving urinary symptoms and reducing the risk of disease progression in men with symptomatic BPH. Some 4,500 patients will be enrolled internationally. The study follows the landmark Medical Therapy of Prostatic Symptoms (MTOPS) study, which was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases. It showed that using finasteride, another 5α-reductase inhibitor, and doxazosin, an α-blocker, together was more effective than either drug alone at relieving symptoms and reducing the risk of BPH progression in approximately 3,000 men. The administration of doxazosin alone over time did not significantly reduce the risk of acute urinary retention nor the risk of having BPH-related prostate surgery. Furthermore, GlaxoSmithKline's own recent 36-week combination study (Symptom Management After Reducing Therapy) in men with symptomatic BPH demonstrated that dutasteride can be used in a 24-week combination with tamsulosin to achieve rapid onset of symptom relief in patients at risk of underlying disease progression. The symptom relief was maintained in the majority of patients after the α-blocker was removed from the combination (3).

The results of a multicenter, randomized, double-blind, placebo-controlled involving 99 healthy men suggested that dutasteride-induced suppression of DHT has no clinical or statistically significant effect on bone mineral density. Subjects were administered dutasteride (0.5 mg), finasteride (5.0 mg) or placebo for 52 weeks. During the treatment period and the 24-week follow-up, all parameters measured remained within normal ranges. After follow-up for 24 weeks, the only significant change in the lipid profile was an increase in triglyceride levels in both placebo and dutasteride study groups. However, these changes were not considered to be clinically relevant by the authors, as triglycerides were the most variable lipid parameter (4-6). The results from this study and some of those summarized below are depicted in Table III.

The effects of dutasteride on the intraprostatic levels of DHT were evaluated in a double-blind, randomized clinical trial in 46 patients with previously untreated prostate cancer. A daily dose of 5 mg of dutasteride administered for 17-82 days before radical prostatectomy was more effective than placebo in suppressing serum

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Double-blind	Dutasteride, 0.5 mg x 52 wks Finasteride, 5 mg x 52 wks Placebo	99	Dutasteride-associated dihydrotestosterone reduction had no effect on bone mineral density and bone metabolism compared with finasteride or placebo in healthy volunteers	4-6
Cancer, prostate	Randomized Double-blind Multicenter	Dutasteride, 10 mg o.d. x 7 d → 5 mg o.d. x 10-75 d (n=24) Placebo (n=22)	46	Dutasteride increased the levels of testosterone in serum and was more effective than placebo in reducing the levels of dihydrotestosterone in both serum and prostate. The drug also decreased the overall androgen content in the prostate	7
Prostatic hyperplasia, benign	Randomized Double-blind Multicenter	Dutasteride, 0.1-5.0 mg p.o. o.d. x 24 wks Finasteride, 5 mg p.o. o.d. x 24 wks Placebo	399	Dutasteride was more effective than placebo in reducing the levels of dihydrotestosterone in patients with benign prostatic hyperplasia	8
Prostatic hyperplasia, benign	Open	Dutasteride, 0.5 mg/d p.o. x 3 mo (n=120) Finasteride, 5 mg/d p.o. x 3 mo (n=120)	240	Dutasteride significantly improved American Urological Association Symptom Index (AUA-SI) score after 3 months of treatment in a greater proportion of patients with benign prostatic hyperplasia than finasteride. The onset of action was also faster with dutasteride	17
Prostatic hyperplasia, benign	Pooled/meta-analysis	Dutasteride, 0.5 mg/d Dutasteride, 0.5 mg/d + Tamsulosin, 0.4 mg/d Finasteride, 5 mg$ Placebo		Dutasteride was well tolerated in patients with benign prostatic hyperplasia	18

and intraprostatic levels of DHT. This reduction was associated with an increase in the levels of testosterone in both serum and prostate, but whereas the median concentration of DHT in the prostate had decreased from 6.49 ng/g tissue with placebo to 0.095 ng/g with dutasteride, that of testosterone had increased from 0.107 ng/g to 2.43 ng/g. This difference suggested that dutasteride also reduced the overall androgen burden in the prostate of these patients (7).

A total of 399 men with BPH were enrolled in a clinical trial that compared the suppression of DHT levels induced by a 24-week treatment with dutasteride (0.1-5.0 mg/day), finasteride (5 mg/day) or placebo. At the end of the treatment period, 85.4% and 100.0% of the 48 patients who received a daily dose of 0.5 mg of dutasteride showed a > 90% and > 75% reduction in baseline DHT levels, respectively. In the 45 finasteride-treated patients, these reductions in baseline DHT levels were 2.2% and 49%, respectively (8).

In three randomized, double-blind phase III trials, over 4,300 men with lower urinary tract symptoms caused by BPH were treated with placebo or dutasteride 0.5 mg p.o. once daily for 2 years. Pooled analysis showed that dutasteride significantly improved patient quality of life beginning at 6 months (9). Regardless of the patients' baseline prostatic volume, the drug was significantly better than placebo in reducing prostatic volume, the risk of acute urinary retention and the risk of BPH-related surgery (10, 11). The analysis of the safety data revealed no significant differences in the incidence of adverse events between patients treated with dutasteride 0.5 mg/day or placebo who also received commonly prescribed concomitant medications, including cardiovascular drugs (*e.g.,* ACE inhibitors, β-blockers, calcium antagonists and diuretics) and PDE5 inhibitors (12). The incidence of new drug-related sexual adverse events was significantly higher with dutasteride than with placebo during the first 6 months of therapy, but then decreased over time. Drug-related gynecomastia was minimal and remained constant throughout the study. Overall, the incidence of sexual adverse events was similar to that historically reported for other 5α-reductase inhibitors (13). Dutasteride demonstrated long-term efficacy in patients from these trials who subsequently took part in a 2-year open-label extension. The risks of acute urinary retention and surgery related to BPH were low in the open-label phase of the study. The incidence of acute urinary retention and surgery was significantly lower in patients treated with dutasteride for 4 years compared to those who were given the drug for only 2 years (14). Total prostate volume steadily decreased with dutasteride, but the overall reduction was lower in patients treated for 2 years than in those who were given the drug for 4 years (–21.7% *vs.* –27.3%) (15). Dutasteride was associated with steady improvements in symptoms and peak urinary flow over 4 years. Greater improvements were seen in patients

receiving dutasteride throughout the study period compared to those who switched from placebo to dutasteride after 2 years of treatment (16).

A total of 240 patients with symptomatic BPH participated in a clinical trial that compared the benefits of dutasteride and finasteride in everyday clinical practice. After 3 months of treatment, the improvements in the American Urological Association Symptom Index scores of the patients were greater with dutasteride compared to finasteride (17).

Results from several studies including over 5,000 patients were reviewed to assess the safety and tolerability of dutasteride 0.5 mg/day in treating BPH. Overall, the drug was well tolerated, with a slight increase in sexual adverse events over placebo seen in large randomized trials. Total serum PSA concentrations were also reduced, but free-to-total PSA levels were not affected (18).

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Eculizumab

Alexion's complement C5 inhibitor eculizumab has been granted orphan drug status for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in both the U.S. and Europe. Eculizumab has completed a pilot program in PNH, and Alexion is now discussing the program with the FDA to finalize plans for the next stage of development. Eculizumab has also completed a pilot program for dermatomyositis and is in phase II trials for rheumatoid arthritis and membranous nephritis (1).

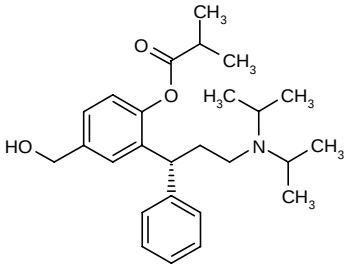
1. *Eculizumab granted U.S. and E.U. orphan drug designations for PNH*. DailyDrugNews.com (Daily Essentials) Dec 11, 2003.

EMR-62203

Earlier this year, Merck KGaA announced its plans to discontinue the development of EMR-62203, a PDE5 inhibitor which had reached phase II clinical evaluation for the treatment of ED (1).

1. *Merck to discontinue development of EMR-62203*. DailyDrugNews.com (Daily Essentials) March 29, 2004.

Fesoterodine



Phase IIb clinical studies of fesoterodine (SPM-907), an antimuscarinic agent with potential as a once-daily treatment for urge urinary incontinence/overactive bladder syndrome, were successfully concluded in 2003 (see below) and phase III testing in the U.S. and Europe was commenced at Schwarz Pharma.

The pharmacokinetics of fesoterodine were assessed in a clinical trial that enrolled 24 healthy male volunteers and randomized them to receive a single oral dose of 4, 8 and 12 mg. Both the C_{max} and the AUC of the drug increased with dose and maximum plasma levels were reached at 5 h after administration. The mean $t_{1/2}$ ranged from 7.3 to 8.9 h and the mean renal clearance from 249 to 264 ml/min (1).

The influence of ethnic origin on the pharmacokinetics of fesoterodine was assessed in a randomized, double-blind, placebo-controlled trial. The drug was safe and well tolerated and no variations in the pharmacokinetic parameters evaluated for the active metabolite SPM-7605 were noted between groups following the administration of a single oral dose (8 mg) to 16 healthy male Black African or Caucasian subjects (2).

The results from a double-blind, randomized, placebo-controlled trial evaluating multiple ascending oral doses of fesoterodine (4, 8, 12, 20 and 28 mg) or placebo, administered once daily for 3 days to healthy volunteers, have been reported. At doses of 12 mg and above, the compound increased residual urinary volume, indicative of relaxation of the detrusor muscle, the desired pharmacological effect in overactive bladder. Other antimuscarinic effects such as decreased salivary secretion and a mild to moderate increase in heart rate were also observed at higher doses, but the treatment was judged to be safe over the entire dose range. Pharmacokinetic analysis demonstrated that fesoterodine was rapidly metabolized to the active metabolite SPM-7605, which showed a profile indicating the feasibility of once-daily dosing (3) (see Table IV).

Phase IIb results for fesoterodine for the treatment of overactive bladder/urinary urge incontinence showed a significant dose-dependent reduction in symptoms. The compound was well tolerated and had a favorable efficacy/safety ratio (4).

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Double-blind	Fesoterodine, 4 mg p.o. o.d. x 3 d (n=6) Fesoterodine, 8 mg p.o. o.d. x 3 d (n=6) Fesoterodine, 12 mg p.o. o.d. x 3 d (n=6) Fesoterodine, 20 mg p.o. o.d. x 3 d (n=6) Fesoterodine, 28 mg p.o. o.d. x 3 d (n=6) Placebo (n=10)	40	Fesoterodine appeared to be safe in healthy volunteers at all doses studied. At higher doses, an increase in residual urinary volume and a reduction in salivary secretion were observed	3

2. Sachse, R., Cawello, W., Hammes, W., Horstmann, R. *Safety and pharmacokinetics of the novel bladder selective antimuscarinic receptor fesoterodine in populations of different ethnic origin*. 33rd Annu Meet Int Continence Soc (Oct 5-9, Florence) 2003, Abst 377.

3. Sachse, R., Cawello, W., Haag, C., Horstmann, R. *Pharmacodynamics and pharmacokinetics of ascending multiple oral doses of the novel bladder-selective antimuscarinic fesoterodine*. Eur Urol Suppl 2003, 2(1): Abst 111.

4. *Schwarz's year-end results exceed expectations*. DailyDrugNews.com (Daily Essentials) March 13, 2003.

Original monograph – Drugs Fut 2003, 28(7): 647.

Additional References

Sachse, R., Cawello, W., Haag, C., Horstmann, R. *Pharmacodynamics and pharmacokinetics of ascending multiple oral doses of the novel bladder-selective antimuscarinic fesoterodine*. Eur Urol Suppl 2003, 2(1): Abst 111.

FP-1097

A locally delivered agent for the treatment of urinary incontinence, FemmePharma's FP-1097 is in phase II clinical evaluation. It is expected to have high bioavailability in the pelvic region and affect local bladder receptors, and thus may be associated with reduced systemic side effects.

GPI-1485

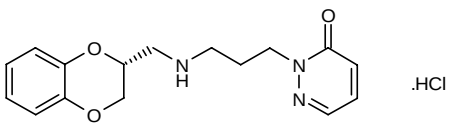
Guilford has begun a phase II trial of its novel neuroimmunophilin ligand GPI-1485 for the treatment of postprostatectomy erectile dysfunction (PPED). The multicenter, randomized, double-blind, placebo-controlled, 3-arm, 12-month study is designed to evaluate the safety, pharmacokinetics and efficacy of GPI-1485 in patients undergoing bilateral nerve-sparing radical retropubic prostatectomy for the treatment of prostate cancer. A total of 150 patients aged 40-55 years and 90 patients aged 60-69 years will be enrolled and randomized to receive either placebo, low-dose GPI-1485 or high-dose GPI-1485 orally 4 times a day. The primary endpoint will be a comparison of the effect of a postsurgical, 6-month course of treatment with GPI-1485 to placebo on erectile function as reported by patients aged 40-59 on the IIEF questionnaire. Secondary endpoints in the study include a similar comparison of erectile function in patients aged 60-69, an evaluation of the safety and pharmacokinetics of GPI-1485, a comparison of the time to first recovery of erectile function in each treatment group compared to placebo, and a comparison of Viagra® (sildenafil) use in each of the treatment groups and placebo group over an 11-month follow-up period. GPI-1485 represents a novel approach to the treatment of PPED by potentially promoting the protection and regeneration of peripheral nerves that may sustain injury during radical prostate surgery. Oral dosing in animals with GPI-1485 stimulated significant neuroprotective and neuroregenerative activity in preclinical models of PPED. Treatment at the time of injury maintained intracavernosal pressure at near normal levels for up to 28 days after injury. Delayed treatment up to 7 days after the peripheral nerve injury procedure promoted significant restoration of function, restoring intracavernosal pressure to between 90% and 100% of normal levels when measured at 1 month after injury. Another phase II trial of GPI-1485 for the treatment of Parkinson's disease is currently under way at U.S. sites (1-3).

1. *GPI-1485 enters phase II trial for postprostatectomy erectile dysfunction*. DailyDrugNews.com (Daily Essentials) Nov 20, 2003.

2. *NIH studies GPI-1485 in phase II Parkinson's trial*. DailyDrugNews.com (Daily Essentials) Feb 25, 2004.

3. *Guilford Pharmaceuticals reports 2003 year-end R&D highlights*. Guilford Pharmaceuticals Press Release 2004, Feb 17.

GYKI-16084



Ivax's GYKI-16084 (Uroflux™) has successfully completed a phase II trial for BPH. GYKI-16084 was well tolerated and did not induce cardiovascular or central nervous system adverse events (1).

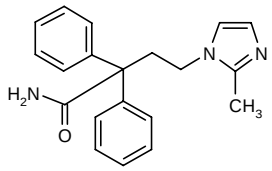
1. *Uroflux completes phase II trial for BPH*. DailyDrugNews.com (Daily Essentials) Feb 27, 2004.

Original monograph – Drugs Fut 1999, 24(10): 1072.

IxOC-2

Ixion's initial product, IxOC-2, is a medical probiotic that is comprised of live, active *Oxalobacter formigenes* delivered orally. This bacterium degrades oxalate in the intestinal tract, thereby preventing its absorption. In a phase I study in healthy volunteers, IxOC-2 proved to be safe and showed evidence of efficacy for reducing urinary oxalate levels. A phase I/II study in patients with primary hyperoxaluria is expected to be conducted this year.

KRP-197 (Ono-8025)

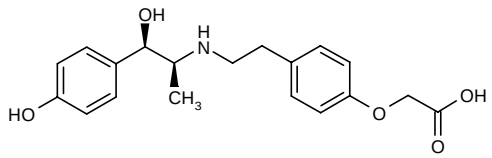


KRP-197 (imidafenacin, Ono-8025, Staybla®) is a potent anticholinergic agent which Kyorin and Ono Pharmaceutical are developing together for the treatment of overactive bladder (urinary incontinence and pollakiuria). The companies are conducting phase III clinical trials in Japan and it is also in phase I development in the U.K.

KUC-7483

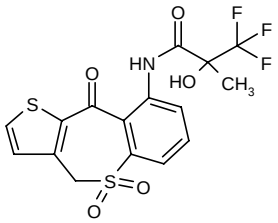
Kissei and Boehringer Ingelheim are codeveloping KUC-7483, a selective β_3-adrenoceptor agonist, as a novel therapeutic agent for the treatment of overactive bladder/urinary incontinence. The compound acts by relaxing the bladder and thereby increasing bladder capacity. Boehringer Ingelheim holds exclusive rights worldwide excluding Japan, Korea, China and Taiwan. Phase IIa trials are in progress in Europe for urge incontinence.

KUL-7211



KUL-7211, a β_2/β_3-adrenoceptor agonist, has advanced to phase II development at Kissei for the relief of colic caused by ureterolithiasis and for accelerating the excretion of calculi.

KW-7158



KW-7158 is a noncholinergic agent that acts on sensory nerves in the bladder and is therefore expected to have beneficial effects on the urinary urgency, frequency and incontinence associated with bladder overactivity. Phase II trials are under way in the U.S. and Europe and the product is in phase I clinical evaluation in Japan.

ML-04

Milkhaus is reportedly seeking licensees for ML-04 (HP-4), a patented oral form of human chorionic gonadotropin (hCG), for the treatment of BPH and prostatitis. ML-04 is completing phase IIb clinical trials in 546 patients being evaluated for changes in the symptoms of BPH as measured by the American Urological Association (AUA) Symptom Index. ML-04, which regulates genes affecting apoptosis and cell-regulatory proteins, is believed to act in prostatic hyperplasia at both the cellular and genomic levels, resulting in the restoration of normal cellular proliferation in prostatic tissue, thereby reducing both the irritative and obstructive symptoms associated with BPH. The company has conducted a multicenter, double-blind, placebo-controlled trial in 101 patients with moderate to severe BPH, where it improved the symptoms of the disease with minimal adverse events and improvement in sexual function. A larger phase IIb trial is under way. Milkhaus is also evaluating ML-04 as a regulator of cell growth and antiinflammatory agent in the treatment of nonbacterial chronic prostatitis/chronic pelvic pain syndrome. The final results from a phase IIa proof-of-concept trial of ML-04 conducted at Stanford University School of Medicine demonstrated its efficacy in the treatment of chronic nonbacterial prostatitis. Using the NIH Chronic Prostatitis Symptom Index (CPSI) as the primary endpoint, patients improved rapidly in the first 4 weeks of treatment, showing by week 12 an average reduction of more than 11 points from the baseline CPSI value of 24, representing an improvement of about 60%. When the treatment period was completed, symptoms began to return. However, when ML-04 was readministered, most patients experienced marked improvement (1-3).

1. *Milkhaus completes enrollment in expanded phase II trial with ML-04*. DailyDrugNews.com (Daily Essentials) May 6, 2003.

2. *Licensing opportunity from Milkhaus: ML-04 for BPH and prostatitis*. DailyDrugNews.com (Daily Essentials) May 12, 2003.

3. *ML-04 shows efficacy in chronic prostatitis*. DailyDrug News.com (Daily Essentials) March 17, 2003.

NBI-69733

Neurocrine Biosciences acquired the rights to develop PNU-142774 (now NBI-69733), a selective dopamine D2 receptor agonist, for indications related to male and female sexual dysfunction, from the former Pharmacia (now Pfizer) last year. As a condition to the closing of the Pharmacia-Pfizer merger, the Federal Trade Commission (FTC) required Pharmacia to divest PNU-142774 to enhance competition in the market for human sexual dysfunction. The compound has demonstrated high intrinsic activity in animal models of sexual dysfunction and Neurocrine plans to conduct a phase II proof-of-concept clinical study in the area of erectile dysfunction to determine its potential efficacy (1).

1. *Neurocrine Biosciences acquires compound for ED divested by Pharmacia*. DailyDrugNews.com (Daily Essentials) May 5, 2003.

Nefecon™

West Pharmaceutical Services has entered into a codevelopment and commercialization agreement with Pharmalink for the development of West's TARGIT™ oral drug delivery system with Pharmalink's Nefecon™ (PL-56), an antiinflammatory product candidate for the treatment of IgA nephropathy. The TARGIT™ system uses a combination of enteric polymer coatings on starch capsules for targeting the release of drugs within the terminal ileum or the colon. Such targeted oral delivery of Nefecon™ to the terminal ileum may be an effective treatment for IgA nephropathy. Nefecon™ is a patented treatment method which has shown significant clinical results. Product formulation work has already commenced and West and Pharmalink plan to pursue product commercialization through third-party marketing partners (1).

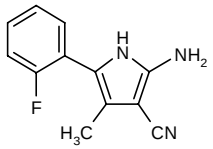
1. *West Pharmaceutical and Pharmalink to develop IgA-nephropathy treatment*. DailyDrugNews.com (Daily Essentials) Feb 26, 2004.

NM-100061

NexMed has reported positive results from an international pilot study of NM-100061, its proprietary product under development for the treatment of early ejaculation (EE). The 3-month, multicenter, double-blind, placebo-controlled study included a total of 89 patients, averaging 43 years of age and diagnosed with EE for 2.6 years. The primary endpoint was drug efficacy, as measured by simultaneously extending the ejaculatory latency time to over 2 min and improving the patients' overall sexual satisfaction ratio by a minimum of 20%. The primary endpoint was achieved, with a satisfaction rate for patients using the product of 84.8% *versus* 23.3% in the placebo group. Adverse events were local, mild and transient. NexMed plans to submit an IND to begin clinical development in the U.S (1). NM-100061 is a cream formulated using the company's NexACT® drug delivery technology.

1. *NM-100061 produces positive results in early ejaculation study*. DailyDrugNews.com (Daily Essentials) March 25, 2004.

NS-8



Nippon Shinyaku has granted the German company Apogepha exclusive development and marketing rights for NS-8 in Europe. NS-8, discovered and developed to date by Nippon Shinyaku for the treatment of overactive bladder (urinary incontinence and pollakiuria), is now in early phase II testing in Europe and phase I trials in Japan. The calcium-sensitive potassium channel opener increases bladder volume without affecting the cardiovascular system by selectively inhibiting the afferent micturition reflex. Given that its mechanism of action is different from existing anticholinergics, it is believed that NS-8 will cause less dry mouth and mydriasis (1).

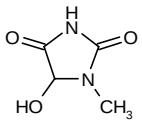
1. *Nippon Shinyaku grants Apogepha European rights for NS-8*. DailyDrugNews.com (Daily Essentials) Nov 7, 2003.

NX-1207

Nymox has concluded the first phase I and phase I/II U.S. trials of NX-1207, the company's investigational new drug for BPH. NX-1207 showed a good safety profile, with most patients experiencing rapid improvement in their symptoms. Clinical improvement measurements in both trials reached statistical significance. NX-1207 will be advanced into a more controlled pivotal phase II trial (1).

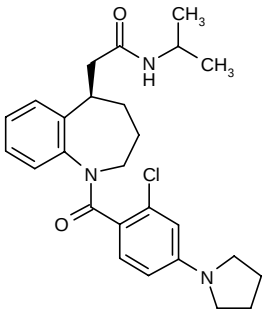
1. *NX-1207 produces significant clinical improvement in BPH*. DailyDrugNews.com (Daily Essentials) Feb 2, 2004.

NZ-419



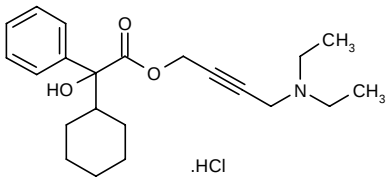
NZ-419 is an antioxidant developed at Nippon Zoki and last reported to be in phase II clinical studies for preventing the progression of renal failure.

OPC-51803



OPC-51803, a nonpeptide vasopressin V_2 receptor agonist, was developed at Otsuka as a potential new therapy for urinary incontinence. Phase II trials are under way.

Oxybutynin, New Formulations



Watson's Oxytrol™ (oxybutynin transdermal system) was introduced last year in the U.S. for the treatment of patients with overactive bladder and symptoms of urge urinary incontinence, urgency and frequency. Clinical trials in 1,000 subjects at more than 50 U.S. centers demonstrated that Oxytrol™ provides effective control of overactive bladder symptoms over a 3-4-day period. Oxytrol™ is a thin, flexible and clear patch that is applied to the abdomen, hip or buttock twice weekly and delivers 3.9 mg/day of oxybutynin consistently and continuously through the skin into the bloodstream, bypassing initial metabolism in the liver and the gastrointestinal tract. The product is also under regulatory review in Canada, where it will be launched by licensee Paladin and was just approved for marketing in Europe, where Watson has a marketing and supply agreement with UCB. In Japan, Oxytrol™ is in phase II development with Sankyo (1-8).

A placebo-controlled phase III clinical trial examined the effects of oxybutynin transdermal system at a daily dose of 3.9 mg in a population of 254 patients with urinary incontinence. The patients' perception of clinical improvement was established using a visual analogue scale for overall symptom severity, the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. After 12 weeks of treatment, the changes in these scores were related more with the relative reduction in the number of urinary incontinence episodes than with the absolute reduction in the number of such episodes compared to baseline (9) (see Table V).

A multicenter, double-blind, placebo-controlled study compared the efficacy and safety of transdermal oxybutynin and tolterodine tartrate in the treatment of overactive bladder. A total of 361 patients with urge or mixed urinary incontinence discontinued their baseline pharmacological therapy and after a washout period of 2 weeks were randomized to receive transdermal oxybutynin (3.9 mg/day), oral tolterodine (4 mg/day) or placebo for 12 weeks. Compared with placebo, both active treatments were effective in reducing the number of urinary incontinence episodes, reducing the micturition frequency and improving the quality of life of the patients. Tolterodine was associated with a higher incidence of treatment-related systemic adverse events, whereas transient application-site reactions (*e.g.*, erythema and pruritus) were more common with oxybutynin (10) (see Table V).

Schering AG signed an agreement with Barr Laboratories in April, whereby Schering will transfer its worldwide marketing and sales rights to the oxybutynin transvaginal ring for urinary incontinence, currently in phase II clinical trials. Barr, through its 2002 acquisition of Enhance Pharmaceuticals, had been developing the oxybutynin vaginal ring with Schering. Barr assumes all remaining development efforts and will pay Schering a milestone payment upon final FDA approval, as well as an ongoing royalty (11).

A phase I trial of Antares Pharma's oxybutynin topical gel product, in development for the treatment of overactive bladder, has been successfully completed. The German open-label study compared two doses of the oxybutynin gel in healthy female volunteers. Results showed that the gel delivers therapeutic doses of oxybutynin with a significant reduction of the main metabolite, *N*-desethyloxybutynin, which is believed to be responsible for several of the adverse effects of the oral drug. The product utilizes Antares Pharma's proprietary ATD™ gel technology designed to allow delivery of active substances across the skin. The oxybutynin formulation is a clear and odorless gel designed to be rapidly absorbed through the skin after once-a-day application on the abdomen, shoulders or thighs (12).

1. *Oxytrol available for overactive bladder*. DailyDrugNews.com (Daily Essentials) April 30, 2003.

2. *Oxytrol submission accepted for review in Canada*. DailyDrugNews.com (Daily Essentials) May 28, 2003.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Incontinence, urinary	Randomized Double-blind Multicenter	Oxybutynin [transdermal], 3.9 mg o.d. x 12 wks (n=124) Placebo (n=130)	254	The changes induced by 12-week treatment with oxybutynin in the patients' perception of clinical improvement (assessed using a visual analogue scale for overall symptom severity, the Incontinence Impact Questionnaire and the Urogenital Distress Inventory) showed that the relative reduction in the number of urinary incontinence episodes was more meaningful to the patients than the absolute reduction in the number of such episodes compared to baseline	9
Incontinence, urinary	Randomized Double-blind Multicenter	Oxybutynin [transdermal], 3.9 mg o.d. x 12 d (n=121) Tolterodine, 4 mg p.o. o.d. x 12 d (n=123) Placebo (n=117)	361	Compared with placebo, both transdermal oxybutynin and oral tolterodine were well tolerated and effective in reducing the number of urinary incontinence episodes, reducing micturition frequency and improving quality of life. Tolterodine was associated with a higher incidence of treatment-related systemic adverse events, whereas transient application-site reactions were more common with oxybutynin	10

3. *Watson and UCB enter marketing and supply agreement on Oxytrol*. DailyDrugNews.com (Daily Essentials) Sept 26, 2003.

4. *European CPMP issues positive opinion for oxybutynin transdermal patch*. DailyDrugNews.com (Daily Essentials) Nov 26, 2003.

5. *FDA approves Oxytrol for overactive bladder*. DailyDrugNews.com (Daily Essentials) March 3, 2003.

6. *Watson files Oxytrol MAA in Europe*. DailyDrugNews.com (Daily Essentials) March 14, 2003.

7. *Watson Pharmaceuticals' transdermal therapy for urge incontinence approved for marketing in the European Union*. Watson Pharmaceuticals, Inc. Press Release 2004, June 21.

8. *Watson Pharmaceuticals enters into licensing agreement with Paladin for Oxytrol® in Canada*. Watson Pharmaceuticals, Inc. Press Release 2004, Jan 8.

9. Dubeau, C.E., Luber, K.M. *Percent reduction in urinary incontinence episodes better reflects patient perception of clinical improvement than absolute change from baseline*. J Urol 2003, 169(4, Suppl.): Abst 1243.

10. Dmochowski, R.R., Sand, P.K., Zinner, N.R., Gittelman, M.C., Davila, G.W., Sanders, S.W. *Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence*. Urology 2003, 62(2): 237.

11. *Schering AG to transfer oxybutynin incontinence ring to Barr*. DailyDrugNews.com (Daily Essentials) April 13, 2004.

12. *Antares' topical oxybutynin product successfully completes phase I trial*. DailyDrugNews.com (Daily Essentials) March 19, 2004.

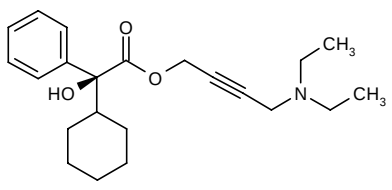
Additional References

Appell, R.A. et al. *Pharmacokinetics, metabolism, and saliva output during transdermal and extended-release oral oxybutynin administration in healthy subjects*. Mayo Clin Proc 2003, 78(6): 696.

Dmochowski, R.R. et al. *Oxytrol transdermal for the treatment of overactive bladder in the equal to or more than 70-year-old patient: Safety with up to 52 weeks of treatment*. J Am Geriatr Soc 2003, 51(4, Suppl.): Abst P551.

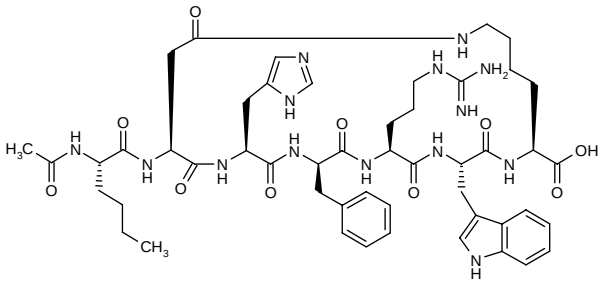
Zinner, N.R., Davila, G., Anderson, R.P. *Dose modulation using oxybutynin transdermal system for overactive bladder in older adults*. J Am Geriatr Soc 2004, 52(4, Suppl.): Abst P174.

(*S*)-Oxybutynin



Pending further review of the program, Sepracor has elected not to fund additional clinical studies of (*S*)-oxybutynin (esoxybutynin) at this time. The anticholinergic agent was in phase III clinical studies for urinary incontinence.

PT-141



Palatin Technologies has reported results of its phase IIb at-home study of PT-141 for the treatment of male erectile dysfunction (ED). The placebo-controlled, randomized, double-blind, parallel-group study examined the safety and efficacy of a range of intranasally administered doses (5, 10, 15 or 20 mg) of PT-141 given over 1 month in an at-home environment. A total of 271 patients aged 21-70 years were enrolled, all suffering from moderate to severe ED and having a history of responsiveness to Viagra® (sildenafil). The trial included patients with comorbidities such as diabetes, hypertension, hyperlipidemia and smoking. All had a baseline International Index of Erectile Function - Erectile Function (IIEF-EF) domain score of 6-21. Baseline scores were compared with scores reported after treatment. Treatment with PT-141 improved patients' erectile function, achieving both clinical and statistical significance for IIEF-EF domain scores, the primary efficacy endpoint for the study, at doses of 10 mg and above relative to placebo, and restoration of normal erectile function at all PT-141 doses relative to placebo. The improvement in the quality of erections as assessed by the Global Assessment Questionnaire score was highly significant for all doses of PT-141 relative to placebo, with improved erections in 17%, 49%, 67%, 66% and 66% of patients given placebo and PT-141 5, 10, 15 and 20 mg, respectively All doses of PT-141 were safe, with no reports of hypotension or syncope at any dose level. The 5- and 10-mg doses were well tolerated. Only 1 serious adverse event was reported (prolonged erection), gastrointestinal side effects being the cause of discontinuations in patients taking the higher doses A total of 30 patients were independently interviewed for their opinions on PT-141, with approximately 70% considering PT-141 to be at least as effective as sildenafil. The quality of erection achieved with PT-141 was perceived to be comparable or superior to sildenafil in 83% of patients. Patients also claimed that PT-141 had a longer duration of action, with a more rapid onset than sildenafil, and many patients claimed that being able to feel the drug working was a positive differentiator compared to sildenafil. A specific range of doses was identified to advance PT-141 towards a pivotal phase III trial. PT-141 is a melanocortin (MC) receptor agonist being developed for the treatment of male and female sexual dysfunction. Its mechanism of action may offer significant benefits over current products because it acts on the pathway that controls sexual function without acting directly on the vascular system (1-4).

Two phase I and II placebo-controlled clinical trials evaluated the effects, safety and pharmacokinetic profile of single doses of intranasal PT-141 (4, 7, 10 and 20 mg) in 32 healthy adult subjects and 24 adult patients with ED responsive to sildenafil. Dose-dependent increases in plasma PT-141 levels were seen, as was a significant erectile response in both study populations. Compared with placebo, the erectogenic response associated with PT-141 was significant at doses of 7 mg and above. In healthy volunteers, the mean duration of tip rigidity of at least 60% was between 41.1 and 126 min with PT-141 doses of 7-20 mg compared to only 5.3 min with placebo. In ED patients, the mean value of this parameter was 18.5 min with placebo and 26.0 and 53.8 min for the 7- and 20-mg PT-141 doses, respectively. The onset of first erection after intranasal PT-141 administration was 30-35 min in both study populations. The most common drug-related adverse events were flushing, nausea, feeling hot and taste disturbance. All adverse events were mild or moderate and required no treatment or intervention (5).

1. *At-home phase IIb study begins for ED treatment PT-141*. DailyDrugNews.com (Daily Essentials) May 15, 2003.

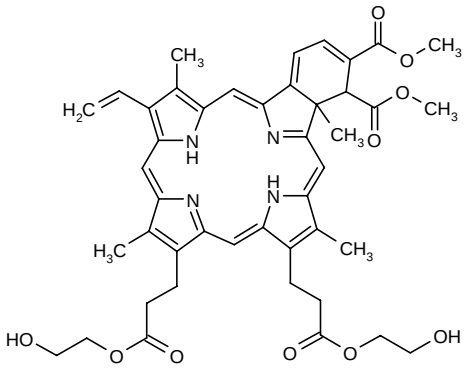
2. *Enrollment completed in phase IIb at-home study of PT-141*. DailyDrugNews.com (Daily Essentials) July 29, 2003.

3. *Positive results reported from phase IIb study of PT-141*. DailyDrugNews.com (Daily Essentials) Nov 5, 2003.

4. Wessells, H., Padma-Nathan, H., Raifer, J. et al. *At-home efficacy of an intranasally administered melanocortin receptor agonist, PT-141, in men with erectile dysfunction (ED).* J Urol 2004, 171(4, Suppl.): Abst 1197.

5. Diamond, L.E., Earle, D.C., Rosen, R.C., Willett, M.S., Molinoff, P.B. *Double-blind, placebo-controlled evaluation of the safety, pharmacokinetic properties and pharmacodynamic effects of intranasal PT-141, a melanocortin receptor agonist, in healthy males and patients with mild-to-moderate erectile dysfunction*. Int J Impot Res 2004, 16(1): 51.

QLT-0074



A third-generation photodynamic therapy from QLT, QLT-0074 (lemuteporphin) is in phase I/II clinical

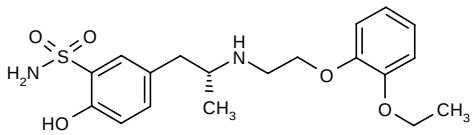
evaluation for benign prostatic hyperplasia, phase II clinical studies for androgenic alopecia and phase I clinical trials are planned in moderate to severe acne.

RBx-2258 (SPM-969)

RBx-2258 (SPM-969, Parvosin, pamirosin) is in phase I clinical testing at Schwarz Pharma for the treatment of BPH (1). Schwarz licensed this uroselective α-blocker for the U.S., Europe and Japan from Ranbaxy in late 2002. The compound has reached phase II trials in India and is scheduled to enter phase IIb studies in Europe and the U.S. this year.

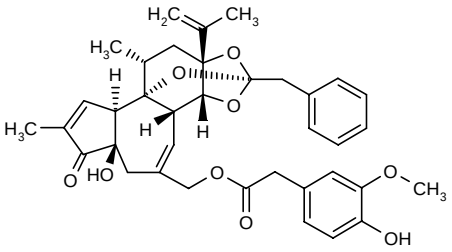
1. *Schwarz's year-end results exceed expectations*. DailyDrugNews.com (Daily Essentials) March 13, 2003.

RBx-9001



Ranbaxy filed an IND for its second new chemical entity for BPH, RBx-9001, last year in India. The first is RBx-2258 (see above).

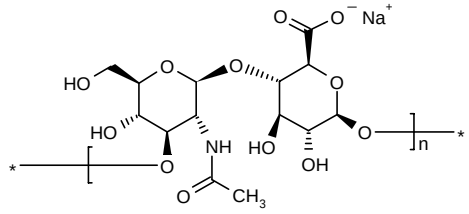
Resiniferatoxin



Data from patient follow-up of a phase II clinical study evaluating resiniferatoxin (RTX™), a vanilloid receptor agonist that acts as a neuronal desensitizing agent, for the treatment of interstitial cystitis indicated that it was not effective in relieving patients's symptoms and Icos will not pursue its development for this indication (1).

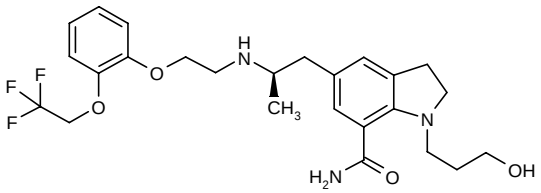
1. *Icos reports 2003 highlights*. DailyDrugNews.com (Daily Essentials) Feb 18, 2004.

SI-7201 (NS-7201)



A hyaluronic acid medical device for the treatment of interstitial cystitis, Seikagaku's SI-7201 (NS-7201) is in phase III testing in the U.S. and preclinical testing in Japan. Following intravesical injection, SI-7201 coats the deficient glycosaminoglycan (GAG) layer on the bladder surface to protect it from irritants in the urine. A joint development agreement in Japan was concluded in 2002 with Nippon Shinyaku.

Silodosin



Silodosin (KMD-3213, KAD-3213) is a highly selective α_{1A}-adrenoceptor antagonist that relaxes smooth muscles in the prostate and bladder neck and is under development for the treatment of urinary dysfunction associated with BPH. Kissei has an agreement with Daiichi Pharmaceutical to codevelop and market the product and they have completed clinical development in Japan and are preparing an NDA submission. A phase II study has also been completed in the U.S. Watson was recently granted exclusive rights to develop and market the drug in the U.S., Canada and Mexico (1, 2).

1. *Kissei preparing to license two of its products*. DailyDrugNews.com (Daily Essentials) Nov 17, 2003.

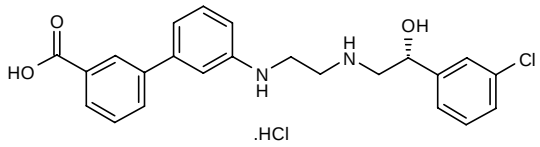
2. *Watson Pharmaceuticals announces agreement with Kissei for novel urology drug candidate*. Watson Pharmaceuticals, Inc. Press Release 2004, April 22.

Original monograph – Drugs Fut 2001, 26(6): 553.

SLV-320

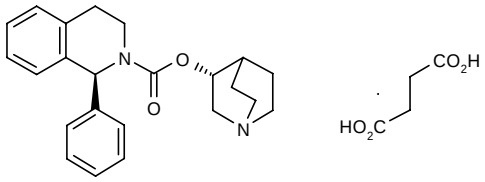
A selective adenosine A_1 receptor antagonist, SLV-320 is in the early stages of clinical development at Solvay for its potential in the treatment of congestive heart failure and renal failure.

Solabegron Hydrochloride



The β_3-adrenoceptor agonist solabegron hydrochloride (GW-427353, 427353) is undergoing phase I clinical testing at GlaxoSmithKline for type 2 diabetes and overactive bladder. The compound was licensed from Asahi Kasei.

Solifenacin Succinate



Yamanouchi's oral muscarinic antagonist solifenacin succinate (YM-905, Vesicare®) was approved for launch in its first market –The Netherlands– in late 2003 for the relief of the symptoms of urinary frequency, urinary incontinence or urgency associated with overactive bladder. In the U.S., Yamanouchi has received an approvable letter from the FDA and expects launch to begin this year in collaboration with partner GlaxoSmithKline. Phase III clinical studies are in progress in Japan (1-3).

The pharmacokinetics and safety of solifenacin were assessed in a double-blind, dose-escalating clinical trial that included 33 healthy men and women aged 65-80 years. Single doses of 10 or 20 mg of the drug or placebo were given to the subjects on day 1 and then once daily on days 5-19 of the study. The authors reported dose-dependent increases in the peak plasma concentration and the AUC for solifenacin in male volunteers, whereas no clear dose-effect relationship was found in female volunteers. The incidence of adverse events was 68% with solifenacin and 62% with placebo; the most common adverse events were dry mouth and constipation, and no clinically significant effects were detected in the laboratory values, vital signs or ECGs of the subjects. The results suggested that solifenacin was safe in elderly patients (4). The results from this and other clinical trials reported here are summarized in Table VI.

A multicenter, open-label clinical trial determined the safety and pharmacokinetics of a single oral dose of solifenacin 10 mg in 18 patients with mild, moderate or severe renal impairment and 6 healthy volunteers 41-80 years of age. Renal impairment was associated with significant increases in the systemic exposure and terminal half-life of solifenacin in these patients. Most adverse events were mild, and the events most often related to the drug were muscle cramps, dry mouth and pitting edema. No serious adverse events were found (5).

An open-label clinical trial compared the pharmacokinetic profile of a single dose of 10 mg of solifenacin in 8 patients with moderate hepatic impairment and 8 healthy volunteers 22-68 years old. Hepatic impairment was found to be associated with a 60% increase in the mean AUC for solifenacin (1042 ng·h/ml *vs.* 742 ng.h/ml) and a significant increase in the drug's half-life (106 h *vs.* 49.9 h) compared with healthy subjects. No serious adverse events or significant differences in vital signs, ECGs or laboratory parameters were reported. The authors recommended that, despite the drug's good safety profile, because of the pharmacokinetic differences no more than 5 mg/day should be given to patients with moderate hepatic impairment (6).

The efficacy and safety of solifenacin succinate and tolterodine tartrate in the treatment of urinary incontinence were compared in a multicenter, double-blind, randomized phase II clinical trial enrolling 265 men and women with overactive bladder and idiopathic detrusor overactivity. Each patient first entered a 2-week placebo run-in period and was randomized to receive placebo, immediate-release tolterodine (2 mg b.i.d.) or solifenacin (2.5, 5, 10 or 20 mg once daily) for 4 weeks. Both tolterodine and solifenacin were more effective than placebo in reducing the micturition rate and increasing the volume voided per void of the patients, although the differences only reached statistical significance with solifenacin at doses of 5, 10 and 20 mg/day. Solifenacin also reduced the mean number of incontinence episodes and urgency episodes per 24 h in a dose-dependent manner, although the differences compared to placebo and tolterodine were not significant. The incidence of adverse events among solifenacin-treated patients also increased with dose; the 5- and 10-mg doses were well tolerated, while the 20-mg dose was associated with a higher incidence of dry mouth (38%), constipation (16%) and dyspepsia (16%). Based on these efficacy and safety results, the authors recommended the use of solifenacin at doses of 5 and 10 mg/day in future large-scale phase III clinical trials (7).

A multicenter, double-blind, randomized, placebo-controlled phase III study evaluated solifenacin (5 or 10 mg once daily) *versus* placebo for 12 weeks in 907 patients with symptomatic overactive bladder. Solifenacin was significantly more effective than placebo in improving all symptoms, including the primary endpoint of micturitions per 24 h. The most frequent adverse events were dry mouth, constipation and blurred vision, and a lower incidence was seen on the 5-mg dose. The rate of discontinuation due to these adverse events was very low (0.3% on solifenacin 5 mg and 2.0% on solifenacin 10 mg). Overall, the lower dose of solifenacin appeared to have the best risk/benefit profile (8-10).

A multicenter, double-blind, randomized, placebo-controlled phase III clinical trial compared the efficacy and safety of solifenacin (5 or 10 mg p.o. once daily) and tolterodine (2 mg p.o. once daily) in 1,081 adult patients

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Double-blind	Solifenacin, 10 mg o.d. on d 1 & 5-19 (n=13) Solifenacin, 20 mg o.d. on d 1 & 5-19 (n=12) Placebo (n=8)	33	Solifenacin was well tolerated in elderly male and female healthy subjects. Most adverse events were mild, and the most frequent were dry mouth and constipation	4
Overactive bladder	Randomized Single-blind Multicenter	Solifenacin, 2.5 mg p.o. o.d. x 4 wks Solifenacin, 5 mg p.o. o.d. x 4 wks Solifenacin, 10 mg p.o. o.d. x 4 wks Solifenacin, 20 mg p.o. o.d. x 4 wks Tolterodine, 2 mg p.o. b.i.d. x 4 wks Placebo	265	Tolterodine and solifenacin were more effective than placebo in reducing the micturition rate and increasing the volume voided per micturition, although the differences only reached statistical significance with solifenacin at doses of 5, 10 and 20 mg/day. Solifenacin dose-dependently reduced the mean number of incontinence episodes and urgency episodes per 24 hours and was well tolerated at doses up to 10 mg/day	7
Overactive bladder	Randomized Double-blind Multicenter	Solifenacin, 5 mg o.d. x 12 wks (n=301) Solifenacin, 10 mg o.d. x 12 wks (n=299) Placebo (n=307)	907	Solifenacin was more effective than placebo in improving the symptoms of micturition frequency, urgency and urge incontinence in patients with overactive bladder. The drug was also well tolerated, although a better safety profile was found with a daily dose of 5 mg	8-10
Overactive bladder	Randomized Double-blind Multicenter	Solifenacin, 5 mg p.o. o.d. x 12 wks (n=279) Solifenacin, 10 mg p.o. o.d. x 12 wks (n=269) Tolterodine, 2 mg p.o. o.d. x 12 wks (n=266) Placebo (n=267)	1081	Solifenacin was more effective than tolterodine or placebo in improving the symptoms associated with overactive bladder, including frequency, urgency and urge incontinence. All study treatments were well tolerated, and the adverse events most commonly associated with the active drugs were dry mouth, constipation and blurred vision	11-13
Overactive bladder	Randomized Double-blind Multicenter Pooled/meta-analysis	Solifenacin, 10 mg o.d. x 12 wks Placebo		A large percentage of overactive bladder patients became continent after a 12-week treatment with solifenacin compared with placebo. The drug was also more effective than placebo in reducing the level of incontinence, with a >/=25% reduction in incontinence, the daily number of micturitions and urgency episodes, and it increased the volume voided per micturition	14-16
Overactive bladder	Randomized Double-blind Pooled/meta-analysis	Solifenacin, 5 mg x 12 wks (n=548) Solifenacin, 10 mg x 12 wks (n=1151) Tolterodine, 2 mg b.i.d. x 12 wks (n=250) Placebo (n=1124)	3073	Solifenacin effectively reduced urgency in patients with overactive bladder	17

(1,077 treated, 1,033 evaluated for efficacy) with symptoms of overactive bladder for at least 3 months before enrollment. Both muscarinic antagonists were more effective than placebo in reducing the daily number of micturitions reported by the patients, but only solifenacin significantly improved all the overactive bladder symptoms. After 12 weeks of treatment, the reduction in the mean number of urgency episodes per 24 h compared to baseline was significantly greater with solifenacin (52% and 55% with 5 and 10 mg, respectively) than with tolterodine (38%) or placebo (33%). Solifenacin was also more effective than both tolterodine and placebo in reducing urge and general incontinence and in increasing the mean volume voided per void. All study treatments were

well tolerated, and most adverse events were mild or moderate. The most common adverse events in all study groups were dry mouth (14.0%, 21.3%, 18.6% and 4.9%, respectively, on solifenacin 5 and 10 mg, tolterodine and placebo), constipation and blurred vision, and few patients discontinued the study due to adverse events (0.4% with placebo, 0.0% with solifenacin 5 mg, 0.7% with solifenacin 10 mg and 0.8% with tolterodine) (11-13).

Two randomized, double-blind, placebo-controlled clinical trials assessed the safety and efficacy of solifenacin in over 1,000 patients with overactive bladder. After 12 weeks of treatment, a dose of 10 mg given once daily was significantly more effective than placebo in reducing the number of micturitions, incontinence episodes and urgency episodes per 24 h. The volume voided in each micturition increased by 46.8 ml with solifenacin compared to 7.7 ml with placebo. Solifenacin was also significantly better than placebo in increasing the percentage of patients who became continent (53% *vs*. 31%) or who experienced a reduction in incontinence of > 50% (82% *vs*. 57%) or > 25% (88% *vs*. 66%). Solifenacin was well tolerated, and the most common adverse events associated with its administration were dry mouth and constipation (14-16).

A pooled analysis of 4 randomized, double-blind, placebo-controlled clinical trials including 3,073 patients with overactive bladder has shown that solifenacin succinate may significantly reduce urgency. The patients were treated with solifenacin (5 and 10 mg), tolterodine (2 mg b.i.d.) and placebo for 12 weeks. The change from baseline in the mean number of urgency episodes per day in these groups was –2.9, –3.4, –2.1 and –2.0, respectively. Overall, 62-66% of solifenacin-treated patients showed a reduction of at least 50% in urgency episodes. Age and gender had no significant effects on the efficacy of solifenacin, which also reduced urgency in patients unresponsive to previous treatments (17).

1. *Yamanouchi obtains marketing authorization for the treatment of urinary frequency and urinary incontinence, Vesicare®, in the Netherlands*. Yamanouchi Pharmaceutical Co., Ltd. Press Release 2004, Jan 20.

2. *Yamanouchi receives approvable letter for Vesicare*. DailyDrugNews.com (Daily Essentials) Oct 21, 2003.

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

4. Smulders, R.A., Krauwinkel, W. , van Zijtveld, J. *Pharmacokinetics, pharmacodynamics, and safety of YM905 in healthy, elderly subjects*. J Am Geriatr Soc 2003, 51(4, Suppl.): Abst P172.

5. Smulders, R., Smith, N., Krauwinkel, W., Balan, G. *The safety, tolerability, and pharmacokinetics of solifenacin succinate in patients with mild, moderate, and severe renal disease*. 33rd Annu Meet Int Continence Soc (Oct 5-9, Florence) 2003, Abst 303.

6. Kuipers, M., Smulders, R., Krauwinkel, W. *The safety, tolerability, and pharmacokinetics of solifenacin succinate in patients with hepatic impairment*. 33rd Annu Meet Int Continence Soc (Oct 5-9, Florence) 2003, Abst 308.

7. Chapple, C.R., Araño, P., Bosch, J.L., De Ridder, D., Kramer, A.E., Ridder, A.M. *Solifenacin appears effective and well tolerated in patients with symptomatic idiopathic detrusor overactivity in a placebo- and tolterodine-controlled phase 2 dose-finding study*. BJU Int 2004, 93(1): 71.

8. Cardozo, L., Kuzmin, I., Lisec, M.L., Millard, R.J., Van Viersen Trip, O.B., Ridder, A.M., Drogendijk, T.E. *YM905: Results of a randomised, double-blind placebo-controlled trial in patients with symptomatic overactive bladder*. Eur Urol Suppl 2003, 2(1): Abst 104.

9. Cardozo, L., Kuzmin, I., Lisec, M.L., Millard, R.J., Van Vierssen Trip, O.B., Ridder, A.M., Drogendijk, T.E. *A double-blind, randomised, placebo-controlled trial with YM905 in symptomatic overactive bladder*. J Am Geriatr Soc 2003, 51(4, Suppl.): Abst P74.

10. Cardozo, L., Kuzmin, I., Lisec, M.L., Millard, R.J., Van Vierssen Trip, O.B., Ridder, A.M., Drogendijk, T.E. *YM905 in symptomatic overactive bladder: Results of a phase 3A randomised, placebo-controlled trial*. J Urol 2003, 169(4, Suppl.): Abst DP47.

11. Chapple, C.R., Rechberger, T., Al-Shukri, S., Meffan, P.J., Everaert, K.E., Ridder, A.M., Hartmans, H.L. *A double-blind, randomised, placebo and tolterodine controlled trial with YM905 in symptomatic overactive bladder*. J Am Geriatr Soc 2003, 51(4, Suppl.): Abst P76.

12. Rechberger, T., Al-Shukri, S., Meffan, P., Everaert, K., Huang, M., Ridder, A., Chapple, C.R. *Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder*. BJU Int 2004, 93(3): 303.

13. Chapple, C., Rechberger, T., Al-Shukri, S., Meffan, P., Everaert, K., Ridder, A. *Results of a randomized phase 3 study comparing solifenacin succinate with tolterodine and placebo in patients with overactive bladder*. 33rd Annu Meet Int Continence Soc (Oct 5-9, Florence) 2003, Abst 121.

14. Kaufman, J., Knapp, P., Siami, P., Harris, R., Smith, N., Ridge, S., Tempel, D. *YM905 10 mg increases the proportion of male and female patients with overactive bladder who become continent*. J Am Geriatr Soc 2003, 51(4, Suppl.): Abst P168.

15. Gittelman, M., Chu, F.M., Klimberg, I., Fincher, R., Smith, N., Tempel, D., Ridge, S. *Two randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multicenter studies assess the efficacy and safety of daily oral administration of 10 mg YM905 versus placebo in male and female subjects with overactive bladder*. J Urol 2003, 169(4, Suppl.): Abst DP43.

16. Kaufman, J., Knapp, P., Siami, P., Harris, R., Smith, N., Ridge, S., Tempel, D. *YM905 10 mg increases the proportion of male and female patients with overactive bladder who become continent*. J Urol 2003, 169(4, Suppl.): Abst DP49.

17. Chapple, C., Jonas, U., Chancellor, M., Ridder, A. *New antimuscarinic agent, solifenacin succinate, reduces urgency episodes in overactive bladder: An analysis of over 3000 patients*. Eur Urol Suppl 2004, 3(2): Abst 508.

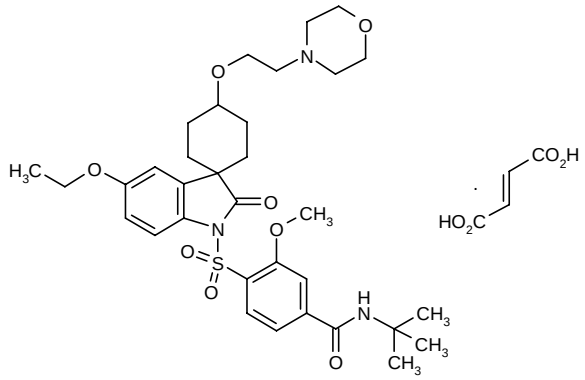
Original monograph – Drugs Fut 1999, 24(8): 871.

SOU-001 (AA-10020)

Sosei and Arachnova have completed a licensing deal involving the new therapeutic use of SOU-001 (AA-10020) for stress urinary incontinence. The pharmaceutical agent in SOU-001 is a drug licensed by Sosei from a Japanese company as part of Sosei's DRP® (Drug Reprofiling Platform®) and was previously developed up to phase II for intravenous use in a cardiovascular indication. Under Sosei and Arachnova's previous collaboration, SOU-001 was advanced into a phase Ib mechanism trial in volunteers, showing potential efficacy in increasing urethral pressure compared to placebo, without a significant increase in blood pressure. An optimized oral formulation may have the ability to enhance urethral sphincter action in patients with stress urinary incontinence and improve bladder control. Under the agreement, Arachnova will receive an upfront license fee and substantial developmental milestones together with royalties. Sosei takes exclusive worldwide development and marketing rights, and will share intellectual property with Arachnova. Sosei will continue with phase II efficacy trials, and may sublicense the project at a later date (1).

1. *Sosei and Arachnova in licensing agreement in stress urinary incontinence*. DailyDrugNews.com (Daily Essentials) March 1, 2004.

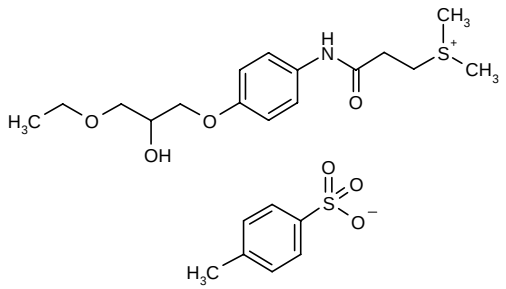
SR-121463



A vasopressin V_2 receptor antagonist, SR-121463 is a pure aquaretic compound in phase II development at Sanofi-Synthélabo for use in hyponatremia and cirrhotic ascites. Favorable phase IIb results were reported in the treatment of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and phase III trials with this compound are scheduled to begin this year for this indication (1).

1. *Sanofi-Synthélabo reports 2003 year-end R&D highlights*. Sanofi-Synthélabo Press Release 2004, Feb 16.

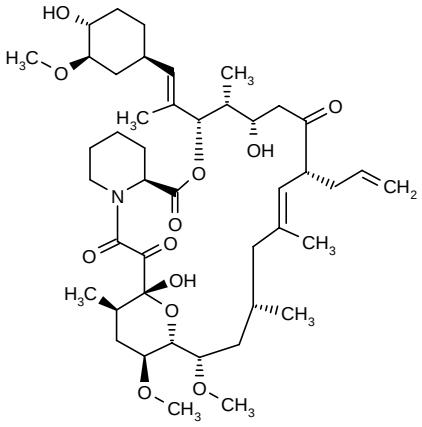
Suplatast Tosilate



Suplatast tosilate (IPD-1151T) is an antiinflammatory cytokine inhibitor currently marketed by Taiho in Japan for the treatment of bronchial asthma, allergic rhinitis and atopic dermatitis. It was licensed to Yamanouchi over a year ago for worldwide development outside Japan for interstitial cystitis and chronic nonbacterial prostatitis and was last reported to be in phase II clinical development for these indications.

Original monograph – Drugs Fut 1988, 13(11): 952.

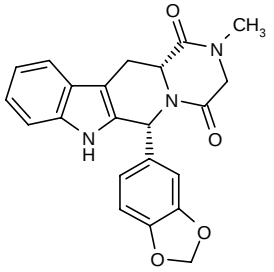
Tacrolimus



Among numerous other indications, Fujisawa's immunosuppressant tacrolimus, marketed as Prograf® for the treatment of organ transplant rejection and as Protopic® for the treatment of atopic dermatitis, is undergoing phase III clinical studies in Japan for the treatment of lupus nephritis.

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

Tadalafil



During 2003, tadalafil (Cialis®) was launched in 55 countries worldwide for the treatment of erectile dysfunction (ED). Commercial launches began in Europe, New Zealand and Australia in February, and finished in the U.S. and Canada in November. Tadalafil is marketed by Lilly Icos, a 50/50 joint venture between Icos and Lilly, in North America and Europe. Elsewhere, Lilly has rights to market the drug and pays a royalty to Lilly Icos for product sales in those territories. An oral PDE5 inhibitor, tadalafil has been tested in 22 clinical trials in more than 4,000 patients. Clinical studies showed that it improved erectile function up to 36 h after dosing and improved the ability to have sexual activity in some patients at 30 min after taking a dose. The drug was shown to be effective in treating ED in patients aged 27-87 years, including those with other underlying medical conditions such as diabetes or following radical prostatectomy for prostate cancer (1-9).

In a multicenter phase III study, 303 men who had undergone bilateral nerve-sparing radical prostatectomy 12-48 months prestudy were randomized to receive tadalafil 20 mg or placebo. Results showed that 62% of men who developed ED following bilateral nerve-sparing radical prostatectomy reported improved erections after taking tadalafil compared to 23% on placebo. Patients recorded that a majority of sexual attempts (54%) by men who took tadalafil resulted in successful vaginal penetration as compared to 32% on placebo. In a subgroup of 201 men who were able to experience some erection following radical prostatectomy, 71% experienced improved erections compared to 24% on placebo (10, 11). Data were also compiled from 11 randomized, double-blind, placebo-controlled, 12-week efficacy studies in 2,102 men with ED taking tadalafil 10 or 20 mg or placebo. Analysis showed that 82% of men attempted intercourse at least once between 4 and 36 h after taking tadalafil 10 or 20 mg over a 12-week period. The pattern of attempts was similar in the placebo group (10, 12). Both doses of tadalafil were effective from 30 min to 26 h postdose (10, 13). Moreover, treatment significantly improved measures of erectile function in patients with various levels of baseline ED (10, 14). In a retrospective analysis of data from 5 double-blind, placebo-controlled studies involving 12 weeks of treatment with tadalafil or placebo in a broad population of 887 men with ED, 67% of men who took tadalafil 20 mg and 56% of men who took tadalafil 10 mg experienced successful intercourse with their first dose, compared to 31% for the placebo group. After the first 4 doses, 86% of men who took tadalafil 20 mg and 72% of men who took tadalafil 10 mg achieved successful intercourse for the first time, compared to 48% of men on placebo. Among those men who had a successful intercourse attempt with their first dose, 88% of subsequent intercourse attempts were successful for those who took tadalafil 20 mg and 81% for those who took tadalafil 10 mg over the 12-week treatment period, compared to 64% for the placebo group (10, 15).

A double-blind, crossover study conducted in 49 healthy volunteers established that a 50-mg dose of sildenafil, but not a 10-mg dose of tadalafil, significantly enhanced the reduction in mean blood pressure induced by sublingual administration of nitroglycerin. The incidence of blood pressure changes that were potentially significant from a clinical point of view was higher with tadalafil or sildenafil than with placebo, suggesting that neither sildenafil nor tadalafil should be combined with nitrates in patients with ED (16). The results from this and other studies reported here are summarized in Table VII.

The long-term safety of tadalafil was assessed in 1,173 patients with ED who had previously been included in placebo-controlled studies on this drug. In this ongoing multicenter clinical trial, the patients were treated with an initial daily dose of 10 mg of tadalafil, which was later increased to 20 mg/day or decreased to 5 mg/day depending on the therapy's efficacy or safety profile. After 18 months of treatment, the most common adverse events reported were headache (15.3%), dyspepsia (11.0%), infection (10.1%), back pain (7.3%), rhinitis (6.5%), flu syndrome (6.2%), pain (6.1%) and surgical procedures (6.0%). Overall, tadalafil showed a good safety and tolerability profile, as only 5.4% of the patients discontinued the study due to adverse events (17, 18).

Two separate clinical trials revealed that the administration of tadalafil at daily doses of 10 or 20 mg had no adverse effects on spermatogenesis in 421 healthy men or men with mild ED. The percentage of patients who reported at least a 50% reduction in sperm concentration after receiving tadalafil or placebo for 6 months was not significantly different. The drug was well tolerated and induced no adverse effects on sperm count and motility or on the serum levels of reproductive hormones (19, 20).

The results of a series of 4 open-label studies in healthy men and women showed that tadalafil did not affect the pharmacokinetics of midazolam and lovastatin, while rifampicin decreased tadalafil exposure and ketoconazole and ritonavir increased tadalafil exposure (21).

Results of an international, randomized, double-blind-study indicated that men with ED prefer tadalafil over sildenafil. The 219 patients included in the trial were randomized to tadalafil (20 mg) or sildenafil (50 mg) for 12 weeks. Another 46 patients were randomized to receive tadalafil (20 mg) according to dosing instructions for either tadalafil or sildenafil for 12 weeks. At the end of these treatment periods, patients switched to the opposite therapy. At the end of the study, significantly more

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Double-blind Crossover	Sildenafil, 50 mg Tadalafil, 10 mg Placebo	49	Both sildenafil and tadalafil enhanced the blood pressure reduction induced by nitrate administration in at least one subset of healthy volunteers. The authors recommended that tadalafil should not be used concomitantly with nitrates	16
Erectile dysfunction	Open Multicenter	Tadalafil, 10 mg o.d. → 5 or 20 mg o.d. x 18 mo	1173	Tadalafil administered at daily doses up to 20 mg for 18 months was safe and well tolerated in the treatment of erectile dysfunction	17, 18
Erectile dysfunction	Double-blind Pooled/meta-analysis	Tadalafil, 10 mg x 6 mo (n=103) Tadalafil, 20 mg x 6 mo (n=111) Placebo (n=207)	421	Tadalafil was well tolerated and had no adverse effects on sperm count per ejaculate, percent normal sperm motility or morphology, or serum levels of reproductive hormones in healthy volunteers and patients with erectile dysfunction	19, 20
Erectile dysfunction	Randomized Double-blind Crossover Multicenter	Tadalafil, 20 mg x 12 wks Tadalafil, 20 mg [with tadalfil dosing instructions] Tadalafil, 20 mg [with sildenafil dosing instructions] Sildenafil, 50 mg x 12 wks Placebo	219	Tadalafil was preferred over sildenafil in men with erectile dysfunction, especially if administered following tadalafil dosing instructions	22
Erectile dysfunction	Randomized	Tadalafil, 20 mg p.o. q48 h x 1 mo Placebo	32	Chronic therapy with tadalafil improved endothelial function in patients with erectile dysfunction and this effect appeared to be sustained after discontinuation, although larger studies are needed in order to determine the clinical implications of this finding	23
Erectile dysfunction	Randomized Double-blind Multicenter	Tadalafil, 10 mg o.d. max. x 12 wks (n=103) Tadalafil, 20 mg o.d. max. x 12 wks (n=100) Placebo (n=50)	253	Tadalafil improved erectile function and was well tolerated in men with erectile dysfunction	24
Erectile dysfunction	Randomized Double-blind Pooled/meta-analysis	Tadalafil, 10 mg p.o. x 12 wks Tadalafil, 20 mg p.o. x 12 wks Placebo	1289	Tadalafil improved erectile function in patients with erectile dysfunction, irrespective of baseline severity	26
Erectile dysfunction	Double-blind Multicenter	Tadalafil, 20 mg x 12 wks (n=158) Placebo (n=46)	204	Tadalafil enhanced erectile function and was well tolerated in patients with erectile dysfunction	27
Erectile dysfunction	Randomized Double-blind Multicenter	Tadalafil, 20 mg o.d. [before sexual intercourse] x 12 wks placebo	207	Tadalafil was more effective than placebo in improving erectile function in patients with erectile dysfunction, as measured using the International Index of Erectile Function Erectile Function domain and Sexual Encounter Profile diary questions. The active drug also showed a good safety profile	28

patients chose tadalafil than sildenafil for use during a 12-week extension period that started after the second 12-week crossover period (73% *vs.* 27%). Most patients (67%) preferred taking tadalafil with tadalafil dosing instructions. Both sildenafil and tadalafil were well tolerated (22).

After placebo or tadalafil 20 mg was administered on alternate days to 32 patients with ED for 1 month, brachial artery flow-mediated dilatation was significantly improved in the tadalafil group. Placebo had no effect on endothelial function, while the effect in the tadalafil group was seen 2 weeks after treatment discontinuation (23).

The efficacy and safety of tadalafil 10 and 20 mg were compared to placebo treatment in a multicenter, randomized, double-blind phase III trial in 253 men with ED. Tadalafil improved erectile function and the rate of successful intercourse attempts in these patients and was well tolerated (24).

Seven patients with coronary artery disease received tadalafil (20 mg) or placebo in a randomized, double-blind, placebo-controlled, crossover study. Tadalafil had no significant effect on myocardial perfusion either at rest or after stress induction with adenosine (0.14 mg/kg/min) and dobutamine (10 μg/kg/min) (25).

Tadalafil (10 and 20 mg) was given to 1,289 patients with ED in a randomized, placebo-controlled trial. Tadalafil significantly improved erectile function irrespective of baseline severity. Adverse events included headache, dyspepsia and back pain (26).

In a multicenter, double-blind, placebo-controlled trial, 204 Brazilian patients with mild to severe ED were treated with tadalafil (20 mg) or placebo for 12 weeks. Tadalafil was well tolerated and enhanced erectile function (27).

A multicenter, double-blind, placebo-controlled clinical trial determined the efficacy and safety of tadalafil in 207 men from the U.S. and Puerto Rico with mild to severe ED. The drug was administered at a dose of 20 mg as required before sexual activity, once daily at the most, for 12 weeks. Men receiving tadalafil reported significant improvements in their IIEF-EF domain score, together with higher percentages of successful penetration and intercourse attempts. The percentage of patients with improved erections was found to be 79% with tadalafil *versus* 19% with placebo, as determined using the Global Assessment Question. Tadalafil also showed a good safety profile, the adverse events most commonly related to the drug being headache, back pain and dyspepsia, and the percentage of patients who discontinued the treatment due to adverse events was low (5% with tadalafil and 2% with placebo) (28).

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2. *U.S. approval for Cialis anticipated for second half of 2003*. DailyDrugNews.com (Daily Essentials) May 7, 2003.

3. *Lilly Icos submits complete response to FDA for Cialis*. DailyDrugNews.com (Daily Essentials) July 4, 2003.

4. *Lilly ICOS reports Q3 R&D highlights*. Lilly Icos Press Release 2003, Oct 22.

5. *Lilly Icos receives FDA approval for Cialis*. DailyDrugNews.com (Daily Essentials) Nov 25, 2003.

6. *Icos reports Q3 R&D highlights*. Icos Corp. Press Release 2003, Nov 4.

7. *Icos Corporation reports 2003 year-end R&D highlights*. Icos Corp. Press Release 2004, Feb 3.

8. *Lilly reports 2003 year-end R&D highlights*. Eli Lilly and Co. Press Release 2004, Jan 29.

9. *European label change for Cialis to include 36-hour efficacy claim*. DailyDrugNews.com (Daily Essentials) Feb 27, 2004.

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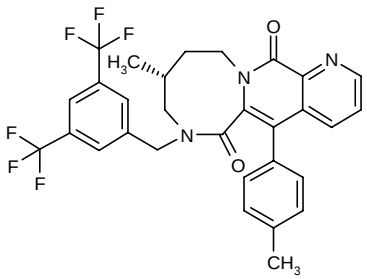
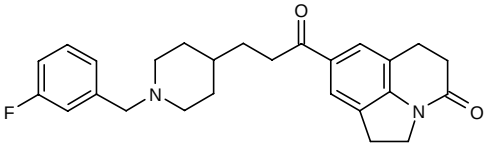
TAK-637



Takeda's TAK-637 is a potent and selective neurokinin NK_1 receptor antagonist being studied for its potential in the treatment of urinary incontinence, as well as depression and irritable bowel syndrome (IBS). The product had reached phase II trials for urinary incontinence in the U.S. and Europe and for the other two indications in the U.S., and phase I trials in Japan for urinary incontinence, before a hold was placed on the studies.

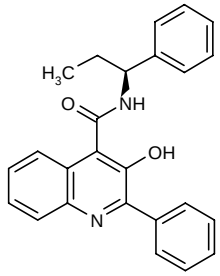
TAK-802



In a recent overview of the status of its new compounds in development, Takeda highlighted 9 proprietary compounds at various stages of development. One of these is TAK-802, an acetylcholinesterase (AChE) inhibitor in phase II testing in Japan for the treatment of hypoactive bladder (1).

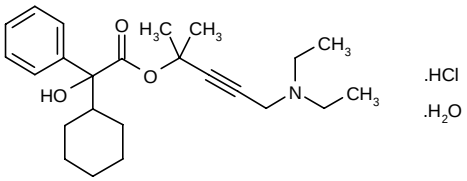
1. *Takeda Chemical Industries reports Q3 R&D highlights*. Takeda Chemical Industries Web Site 2004, Jan 27.

Talnetant



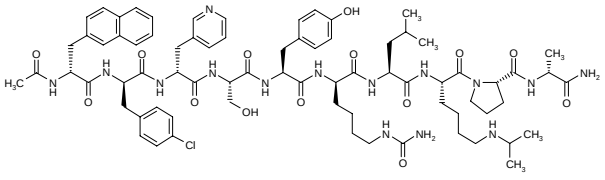
The selective NK_3 receptor antagonist talnetant (SB-223412) is undergoing phase II clinical studies at GlaxoSmithKline for its potential in the treatment of overactive bladder, as well as irritable bowel syndrome (IBS) and schizophrenia.

Temiverine Hydrochloride Hydrate



An anticholinergic agent with calcium-antagonist properties developed by Nippon Shinyaku for the treatment of pollakiuria and urinary incontinence, temiverine hydrochloride hydrate (NS-21, Urespas®) is in the preregistration stage in Japan.

Teverelix



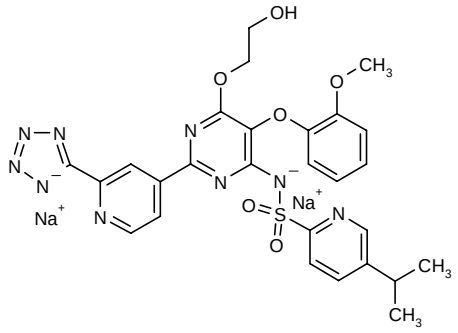
Ardana Bioscience recently initiated phase IIa clinical trials with its long-acting gonadotropin-releasing hormone (GnRH) antagonist teverelix (antarelix), licensed from AEterna Zentaris, for the treatment of both benign prostatic hyperplasia and prostate cancer (1-3). An immediate-release formulation is also in development for the prevention of premature ovulation in controlled ovarian stimulation and assisted reproductive technology. Teverelix may also be useful in the treatment of endometriosis and uterine fibroids and phase I trials in healthy female volunteers are in progress.

1. *Ardana acquires global rights to Teverelix*. DailyDrug News.com (Daily Essentials) April 7, 2004.

2. *AEterna Zentaris unveils new name, progress and plans*. DailyDrugNews.com (Daily Essentials) June 1, 2004.

3. *Ardana begins phase IIa clinical trials with the GnRH-antagonist teverelix LA in patients with prostate cancer*. Ardana Bioscience Press Release 2004, May 17.

Tezosentan Disodium



Actelion's dual endothelin receptor antagonist tezosentan disodium (Veletri®) is being evaluated in exploratory phase II studies in hepatorenal syndrome, a complication of liver cirrhosis that leads to renal failure and death, in addition to phase III trials in acute heart failure (1, 2).

1. *Ongoing discovery and development efforts at Actelion*. DailyDrugNews.com (Daily Essentials) May 16, 2003.

2. *Preclinical and clinical development efforts at Actelion*. DailyDrugNews.com (Daily Essentials) Nov 5, 2003.

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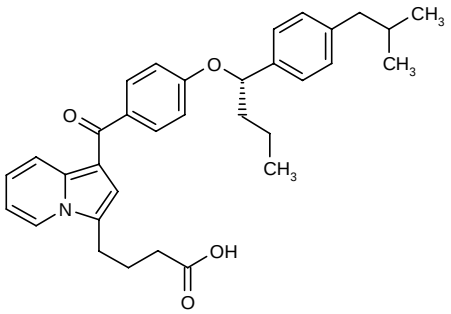
TF-505



The investigational 5α-reductase inhibitor TF-505 (previously referred to as FR-146687) is in phase II clinical trials at Taiho for use in benign prostatic hyperplasia.

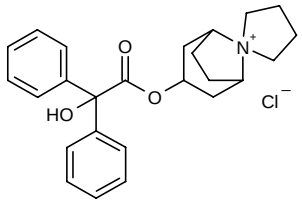
TH-070

TH-070 is Threshold Pharmaceuticals' product candidate for the treatment of BPH. An orally administered small molecule that inhibits glycolysis by inactivating hexokinase, the enzyme that catalyzes the first step in glycolysis, TH-070 kills prostate cells, which depend on glycolysis for their energy production, thereby reducing the size of the prostate. The company is currently conducting a phase II trial of TH-070 for the treatment of BPH, and plans to initiate a registrational program for this indication in 2005.

TJN-598

TJN-598 is a compound derived from a medicinal herb which suppresses the production of transforming growth factor (TGF-β_1) and tumor necrosis factor (TNF-α). It is in phase I clinical evaluation at Tsumura as a potential new treatment for chronic glomerular nephritis.

Trospium Chloride



The FDA has approved Indevus's trospium chloride (Sanctura®) for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency. Approval was based on a review of data from clinical studies conducted in the U.S. and Europe involving approximately 3,000 subjects. Sanctura® will be copromoted by a joint sales force of Indevus and Pliva through its specialty branded subsidiary Odyssey Pharmaceuticals, with launch expected in the third calendar quarter of 2004. Trospium, a quarternary ammonium compound, belongs to the muscarinic receptor antagonist class of anticholinergic compounds that relax smooth muscle tissue found in the bladder, thus decreasing bladder contractions. The product has been marketed in Europe for a number of years and Indevus licensed exclusive U.S. rights from Madaus in late 1999 (1-3).

Phase III data submitted with the NDA showed that trospium met the prespecified endpoints of reduction in frequency of urination and reduction in number of urge incontinence episodes. Trospium also reduced the severity of urgency. The 12-week, randomized, double-blind, placebo-controlled trial measured the effects of 20 mg of trospium *versus* placebo, given twice daily, on symptoms of overactive bladder in 523 patients at 51 U.S. sites. Patient entry criteria included urinary frequency of 10 or more toilet voids per day, symptoms of overactive bladder lasting at least 6 months, and an average of 1 or more incontinence episodes per day. Patients whose urinary frequency or urine loss was caused mainly by stress incontinence were excluded. Patients receiving trospium experienced statistically significantly fewer toilet voids per day (–2.37) at the end of the 12-week trial than did patients on placebo (–1.29). Trospium patients also experienced statistically significantly fewer episodes of urge urinary incontinence per day at the end of the 12-week trial than did placebo patients. This improvement began at 1 week and continued throughout the study. Trospium patients had 59% fewer incontinence episodes per day compared to baseline at the end of the study, whereas placebo patients had 44% fewer episodes at the end of the study. Volume voided per void increased in trospium patients beginning at week 1 and continuing through week 12, with an increase of 32.1 ml at week 12 compared to an increase of 7.7 ml in placebo patients. Trospium patients also experienced a significant improvement in average urgency severity beginning at week 1 and continuing through week 12 (4).

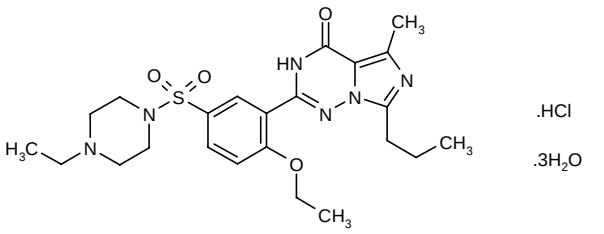
1. *Sanctura receives FDA approval*. DailyDrugNews.com (Daily Essentials) June 3, 2004.

2. *Indevus and Pliva enter U.S. copromotion deal for Sanctura*. DailyDrugNews.com (Daily Essentials) April 13, 2004.

3. *FDA accepts the NDA for trospium*. DailyDrugNews.com (Daily Essentials) July 4, 2003.

4. *Trospium NDA submitted for overactive bladder*. DailyDrugNews.com (Daily Essentials) April 30, 2003.

Vardenafil Hydrochloride Hydrate



Vardenafil hydrochloride hydrate (Levitra®) is a new PDE5 inhibitor for the treatment of ED. Codeveloped by Bayer and GlaxoSmithKline under a worldwide agreement, the agent was first launched in Germany last year and has now been approved in over 80 countries, including the U.S., the E.U. countries and, most recently, Japan. An extensive clinical trial program included more than 50 trials in more than 5,700 men. Phase III studies showed that vardenafil helped to achieve and maintain an erection sufficient for satisfactory sexual performance. It provided first-time success and reliable improvement of

erection quality for many men. Vardenafil also worked for men of varying ages, races and in those with coexisting medical conditions, such as diabetes, and in men who had had their prostate removed. Treatment led to a rapid response, allowing initiation of or response to sexual stimulation at the appropriate moment (1-5).

A national survey conducted recently on behalf of Bayer and GlaxoSmithKline reported satisfaction with vardenafil among men with ED who had taken the drug more than 3 times and among physicians who had recently prescribed vardenafil. Of the 240 patients interviewed, 94% reported positive levels of satisfaction generally based on efficacy, side effect profile, firmness of erection and onset. Of the 400 physicians polled, 92% registered high satisfaction with vardenafil, with the product's efficacy, side effect profile and rapid onset most often cited. Among men with ED, brand awareness of Levitra® is nearly 80% (6).

In a phase I study, 19 healthy male volunteers received a single dose of vardenafil 10 mg on day 1 and were then randomized in a double-blind, crossover fashion to vardenafil 10 mg or placebo given on days 5 and 8. Patients also received aspirin 162 mg/day on days 2-8. Evaluation of the main outcome of the study showed that vardenafil did not alter bleeding time when taken alone and did not alter bleeding time after 1 and 4 h when administered with aspirin (7). The results from this study and a number of those discussed below are shown in Table VIII.

The effects of ethanol, a high-fat breakfast and a moderate-fat evening meal on the pharmacokinetics of vardenafil were assessed in healthy male volunteers. Neither alcohol consumption nor the meals had any significant effect on the peak plasma concentration or half-life of vardenafil in healthy volunteers. Absorption was not affected by either alcohol or the moderate-fat meal, although it was delayed by 1 h with the high-fat meal. No significant differences were found in the safety profile of the treatments, and the most common adverse events reported were flushing and rhinitis with ethanol, and headache with the meals (8, 9).

A multicenter, open-label, flexible-dose study has shown that vardenafil is effective in improving erectile function in most men of diverse ethnic origin. A 10-week, multicenter study enrolled 136 African-American, 102 Hispanic and 153 Caucasian men with ED. Patients were given a starting dose of vardenafil of 10 mg orally, which at weeks 2 and 6 could be adjusted to 20 or 5 mg. At the end of the 10-week period, up to 89% of men reported improvement in erectile function based on the Global Assessment Question (GAQc) after taking vardenafil. Furthermore, over 80% of men across all ethnic origins reported successful penetration on their first attempt and 92% reported reliable results on subsequent attempts after taking vardenafil (10, 11).

Results from the double-blind, at-home ONTIME study have shown that some men with ED can achieve an erection in as little as 10 min with vardenafil. Men with ED were randomized to receive the drug (10 or 20 mg) or placebo and asked to start sexual activity immediately after dosing and to assess their erections using a stopwatch for the first 4 attempts. Time points from 5 to 25 min were tested comparing vardenafil with placebo to determine the earliest onset of action. Within 25 min, significantly more men taking vardenafil experienced an erection adequate for completion of successful intercourse compared with men taking placebo (50% for 10 mg, 53% for 20 mg, 26% for placebo). At all time periods under 10 min, a statistically significantly superior response was seen with both doses of vardenafil compared with placebo (49 of 232 for 10 mg *vs.* 32 of 235 for placebo; 56 of 241 for 20 mg *vs.* 35 of 235 for placebo). In a separate retrospective analysis of 2 studies, vardenafil was shown to provide a favorable window of opportunity of up to 12 h. In the analysis of 2 pivotal, randomized, double-blind, placebo-controlled phase III studies in 1,385 patients with ED, subjects were instructed to take vardenafil 60 min prior to sexual activity. Of the patients (34 of 347) who initiated sexual activity 8-12 h after taking vardenafil 10 mg, success rates of intercourse completion (SEP3) with vardenafil 10 mg and placebo were 79% and 54%, respectively. Findings also showed that 95% of patients treated with vardenafil 10 mg initiated sexual activity 45-75 min after dosing, where SEP3 rates with vardenafil 10 mg and placebo were 67% and 35%, respectively (12).

Vardenafil 10 mg or placebo was administered to 41 male patients with stable coronary artery disease in a multicenter, double-blind, crossover study. Exercise tolerance testing showed that vardenafil did not impair excercise capacity in these patients, and that the drug significantly increased the ischemic threshold. Hemodynamic parameters were similar in both treatment groups (13).

Men with stable angina (n=39) were randomized to receive vardenafil 20 mg or placebo in a multicenter, double-blind, crossover study. Treadmill exercise testing showed that vardenafil did not alter the patients' ability to exercise. Also, the ischemic threshold was similar in both treatment groups at exercise levels equal to those of sexual intercourse (14, 15).

The safety, tolerability and efficacy of flexible dosing of vardenafil were evaluated in a multicenter, open-label clinical trial in 390 patients with ED. A flexible dose of 5-20 mg of vardenafil administered for 10 weeks improved erection in 91.8% of these patients, as assessed using the IIEF-EF domain score, the GAQc and questions to the patients concerning penetration and erection maintenance. The good safety profile of vardenafil was confirmed by the finding that most drug-related adverse events were mild or moderate and transient (16).

Vardenafil 10 and 20 mg was evaluated in 452 men with ED and diabetes type 1 or 2 in a multicenter, randomized, double-blind, placebo-controlled trial. After 12 weeks, significant, dose-dependent improvements in erectile function scores and significant improvements in the rates of successful penetration and successful intercourse were seen. Most adverse events were mild to moderate in severity (17).

Table VIII: Clinical studies of vardenafil hydrochloride hydrate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Double-blind Crossover	Vardenafil, 10 mg → Aspirin, 162 mg x d 2-8 → Vardenafil, 10 mg s.d. x d 5 and 8 Vardenafil, 10 mg → Aspirin, 162 mg x d 2-8 → Placebo x d 5 and 8	19	Vardenafil did not alter bleeding time in healthy volunteers when taken alone or when given with aspirin	7
Erectile dysfunction	Open Multicenter	Vardenafil, 10 mg → 5 or 20 mg on wk 2 & 6	391	Vardenafil significantly improved erectile function, irrespective of ethnicity, in men with erectile dysfunction. Treatment was associated with mild to moderate toxicity	11
Erectile dysfunction	Open Multicenter	Vardenafil, 10 mg o.d. x 10 wks Vardenafil, 10 mg o.d. x 6 wks → 20 mg o.d. x 4 wks Vardenafil, 10 mg o.d. x 2 wks → 20 mg o.d. x 8 wks	390	A flexible dose regimen of vardenafil administered at doses of 10-20 mg o.d. for up to 10 wks was well tolerated and improved erection rate, penetration success rate and erection maintenance success rate in patients with erectile dysfunction. Most adverse events were mild or moderate	16
Erectile dysfunction, Diabetes	Randomized Double-blind Multicenter	Vardenafil, 10 mg x 12 wks Vardenafil, 20 mg x 12 wks Placebo	452	Vardenafil was generally well tolerated and effectively improved satisfaction with erectile hardness, orgasmic function and sexual experience in male subjects with diabetes mellitus and erectile dysfunction	17
Erectile dysfunction	Randomized Double-blind Pooled/meta-analysis	Vardenafil, 5 mg x 12 wks Vardenafil, 10 mg x 12 wks Vardenafil, 20 mg x 12 wks Placebo	1479	Vardenafil at doses of 10 or 20 mg was significantly more effective than placebo in improving several erectile function parameters in all age groups of patients with erectile dysfunction, including erection hardness, sexual experience, ejaculation and intercourse satisfaction	18
Erectile dysfunction	Randomized Double-blind Multicenter	Vardenafil, 10 mg x 12 mo Vardenafil, 20 mg x 12 mo	1020	Vardenafil was highly effective and well tolerated over 12 months in patients with erectile dysfunction	19
Erectile dysfunction	Open	Vardenafil, 20 mg x 12 wk	176	Vardenafil was safe and effectively improved erectile function and satisfaction rate with hardness in Mexican patients with erectile dysfunction	20
Erectile dysfunction, Postprosta-tectomy	Randomized Double-blind Multicenter	Vardenafil, 10 mg o.d. x 12 wks Vardenafil, 20 mg o.d. x 12 wks Placebo	440	Vardenafil was more effective than placebo in improving erectile hardness, patient satisfaction, orgasmic function and sexual experience in patients with erectile dysfunction after nerve-sparing radical prostatectomy. The drug was safe and well tolerated, and most adverse events were mild or moderate and transient	21, 22
Erectile dysfunction, Hypertension	Pooled/meta-analysis	Vardenafil, 5 mg x	2718	The use of vardenafil with concomitant antihypertensive medication did not increase the incidence of cardiovascular events in patients with erectile dysfunction	23

Continuation

Table VIII Cont.: Clinical studies of vardenafil hydrochloride hydrate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Erectile dysfunction	Randomized Double-blind	Vardenafil, 10 mg → 5 or 20 mg o.d. x 12 wks (n=150) Placebo (n=148)	323	The mean IIEF-Erectile Function domain score measured at 12 wks was significantly higher in vardenafil- than in placebo-treated patients. Vardenafil was also associated with a higher percentage of patients reporting improved erections. At the end of the treatment, most patients were taking a daily vardenafil dose of 20 mg	24, 25
Erectile dysfunction, Depression, major	Randomized Double-blind Multicenter	Vardenafil, 10 mg [titrated to 5 or 20 mg 1x/4 wks x 12 wks] Placebo	280	Vardenafil significantly improved erectile function, depression, self-esteem and quality of life, and was effective and well tolerated in patients with erectile dysfunction and mild major depressive disorder	26
Erectile dysfunction	Randomized Double-blind Multicenter	Vardenafil, 10 mg o.d. x 4 wks [option to continue or titrate to 5 or 20 mg after each of 2 consecutive 4-wk intervals] x 12 wks Placebo	463	Vardenafil was well tolerated and produced rapid and reliable erections, irrespective of time from dosing, in patients with moderate to severe erectile dysfunction	27
Erectile dysfunction	Randomized Double-blind Multicenter	Vardenafil, 10 mg x 2 y (n=272) Vardenafil, 20 mg x 2 y (n=294)	566	Vardenafil provided clinically significant and sustained improvement in erectile dysfunction over 2 years of treatment, independent of prior sildenafil use. Vardenafil allowed successful completion of intercourse in nearly 90% of patients	28
Erectile dysfunction	Randomized Double-blind Multicenter	Vardenafil, 5 mg o.d. x 26 wks Vardenafil, 10 mg o.d. x 26 wks Vardenafil, 20 mg o.d. x 26 wks Placebo	805	Vardenafil administered for 26 wks was well tolerated and significantly improved satisfaction, erection hardness, sexual experience and ejaculation in men with erectile dysfunction	29-31

A retrospective analysis of the data obtained from two double-blind phase III clinical trials revealed that the beneficial effects of vardenafil on the erectile function of male patients were not age-dependent. A total of 1,479 men with ED for more than 6 months were randomized to receive either placebo or vardenafil (5, 10 or 20 mg) for 12 weeks. Compared to placebo, vardenafil at doses of 10 or 20 mg was significantly more effective in improving several erectile function parameters in all age groups, including erection hardness, sexual experience, ejaculation and intercourse satisfaction (18).

Vardenafil (10 or 20 mg) was given to 1,020 men with ED for 12 months in a multicenter, double-blind, randomized trial. Both doses significantly improved ED domain scores and mean success rate for maintaining erections to completion of successful intercourse, and the higher dose was more effective in both cases. The most frequently noted adverse events were headache, flushing and rhinitis, which led to discontinuation in 11% of patients (19).

A 12-week, open-label trial in 176 Mexican male patients with ED who were treated with vardenafil (20 mg) showed improvement in erectile function, intercourse completion and satisfaction rate with hardness (20).

Vardenafil 10 or 20 mg was given to 440 men with ED after nerve-sparing radical prostatectomy in a 12-week, multicenter, randomized, placebo-controlled phase III trial. Important aspects of the quality of life of the patients, including overall satisfaction and orgasmic function, increased significantly with vardenafil compared to placebo. Erections and the average intercourse success rate per patient were also improved with vardenafil compared to placebo, and adverse events were few and mild to moderate in severity (21, 22).

Data from 5 double-blind phase III trials in a total of 2,718 men with ED were analyzed to assess the cardiovascular safety of vardenafil 5, 10 and 20 mg. The use of vardenafil with concomitant antihypertensive medication did not increase the incidence of cardiovascular events. Blood pressure was lowered and heart rate increased in vardenafil-treated patients as compared with those given placebo (23).

The efficacy and safety of a flexible vardenafil dose regimen that may resemble real-world dosing were deter-

mined in 323 male patients with mild to severe ED. Patients were randomized to receive either placebo or vardenafil 10 mg as needed, with the possibility of increasing the daily dose to 20 mg (to increase efficacy) or reducing it to 5 mg (due to adverse events) after 4 and 8 weeks. The mean IIEF-EF domain score measured at 12 weeks was significantly higher in vardenafil-treated patients than in placebo-treated patients (24.2 *vs*. 15.6). The active drug was also associated with a higher percentage of patients reporting improved erections (86% *vs.* 36% with placebo). At the end of the treatment, most patients were taking a daily vardenafil dose of 20 mg All treatments were well tolerated, and the most common adverse events reported with vardenafil were headache, flushing and rhinitis (24, 25).

A multicenter, double-blind, randomized clinical trial evaluated the effects of placebo or vardenafil (10 mg, changed to 5 or 20 mg after 4 and 8 weeks of treatment) for 12 weeks in 280 men with ED and untreated mild major depressive disorder. Greater improvements were seen with vardenafil on the IIEF-EF domain scores, the Hamilton Depression Scale-D17 scores and the Rosenberg Self-Esteem Scale scores of the patients compared to placebo. The percentage of patients with successful penetration and erection maintenance increased significantly with vardenafil. The drug was well tolerated in these patients and was associated with adverse events that included headache, flushing and nasal congestion (26).

A multicenter, double-blind trial randomized 463 ED patients unresponsive to sildenafil to placebo or vardenafil (10 mg, changed to 5 or 20 mg after 4 and 8 weeks of treatment) for 12 weeks. Vardenafil was well tolerated and was associated with greater rates of success for vaginal penetration than placebo. In many vardenafil-treated patients, the drug effect was observed within 15 min after administration and lasted for more than 6 h. The most common adverse effects associated with vardenafil were headache, flushing, nasal congestion and dyspepsia (27).

In 566 men with ED taking vardenafil 10 or 20 mg for 2 years as part of a randomized, double-blind trial, efficacy was sustained and the treatment was well tolerated (28).

A multicenter, randomized, double-blind, placebo-controlled phase III study investigated the efficacy of vardenafil (5, 10 and 20 mg) in 805 patients with ED lasting for over 6 months prior to enrollment. Treatment with each dose as needed for up to 26 weeks improved erectile function scores and the success rates for penetration and maintenance of erections as compared to placebo. The drug also significantly improved the patients' satisfaction with erection hardness, sexual experience and orgasmic function. Vardenafil was well tolerated and had long-lasting effects on erectile function, Adverse events were mild to moderate and included headache, rhinitis and flushing (29-31).

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VI-0134

VI-0134 is in development at Vivus as an oral on-demand therapy for premature ejaculation. Phase II trials are in progress.

VML-670

Following the evaluation of data from an initial phase IIa study of VML-670, a potent and selective 5-HT_{1A} receptor agonist, for treatment-emergent sexual dysfunction, Vernalis decided to terminate its development. Although the study met certain secondary endpoints, the primary endpoint was not reached. The data were passed for review to Lilly, which had an option to further develop the product (1). The study was a multicenter, double-blind, placebo-controlled trial in male and female patients taking selective serotonin reuptake inhibitor (SSRI) antidepressants.

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XL-784

XL-784 (Exelixis) is a potent inhibitor of the ADAM-10 metalloprotease enzyme, a cell-surface protease which plays an important role in blood vessel formation and cell proliferation. XL-784 was specifically optimized to be MMP-1-sparing, thus potentially significantly improving its safety profile and enabling higher dosing in comparison to matrix metalloproteinase (MMP) inhibitors. In preclinical studies, orally administered XL-784 showed excellent pharmacokinetic properties and significantly inhibited the growth of human carcinoma xenografts. It also showed good activity in rat models of renal failure. Data from a phase I clinical trial of orally administered XL-784 in healthy volunteers showed single doses of the compound to be free of side effects and to have an attractive pharmacokinetic profile. The company plans to pursue a development path in renal disease this year, as well as to develop a new formulation suitable for chronic administration in patients with renal failure (1-4).

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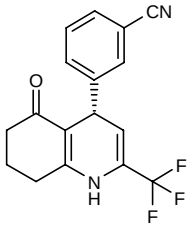
YM-178

Yamanouchi is conducting phase II clinical studies in Europe with YM-178, a β_3-adrenoceptor agonist for the treatment of overactive bladder.

ZD-0947



The potassium channel opener ZD-0947 is being evaluated in phase II clinical studies at AstraZeneca for use in overactive bladder.

Annual Update 2003/2004 - Treatment of Genitourinary Cancers

In developed countries, cancer represents one of the leading causes of death (1). In the U.S., cancer is the second leading cause of death after cardiovascular disease, accounting for 23% of all deaths. Approximately 500,000 people died from cancer in the U.S. in 2001, and 10% of these deaths were due to prostate cancer and 3% to bladder and kidney cancer (2). Prostate cancer represents the most common cancer and the second leading cause of cancer-related death. Nevertheless, since 1994 a 4% decrease in prostate cancer mortality has been detected in the U.S. (3).

In the table that follows, drugs under active development for genitourinary cancer (prostate, bladder, kidney and testicular cancer) are shown (*Source: Prous Science Integrity®*).

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Itziar Escudero

Treatment of Genitourinary Cancers

Condition	Phase	Drug	Target	Source
Bladder cancer	Prereg.	Aminolevulinic acid hexyl ester	RAR β and γ	PhotoCure
	III	Fenretinide		National Cancer Institute
	III	Vinflunine	DNA	Pierre Fabre
	II/III	Celecoxib[1]	COX-2	National Cancer Institute
	II/III	IDM-2		IDM
	II	Apaziquone	DNA	Spectrum Pharmaceuticals
	II	Gefitinib[1]	EGFR	National Cancer Institute/ AstraZeneca
	II	Halofuginone hydrobromide	Collagen I	Collgard
	II	Picoplatin	DNA	AnorMED/NeoRx
	II	S-8184	DNA	Sonus
	II	Tipifarnib	Farnesyltransferase	National Cancer Institute
	I/II	Aminolevulinic acid hydrochloride[1]		Dusa
	I/II	Gallium maltolate	Ribonucleoside-diphosphate reductase	Titan

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Treatment of Genitourinary Cancers

Condition	Phase	Drug	Target	Source
Bladder cancer	I/II	Mycobacterium cell wall complex		Bioniche Life Sciences
	I	Ad5CMV-p53		Introgen
	I	Gossypol	Bcl-xL, steroid 5α-reductase	Bioenvision
	Clinical	Hypericin	PKC	National Cancer Centre
Renal cell carcinoma	III	HSPPC-96	HSPPC96	Antigenics
	III	Sorafenib	Raf kinase	Bayer/Onyx
	III	Temsirolimus	mTOR	Wyeth
	III	Thalidomide[1]		National Cancer Institute
	II	Aplidine	VEGF, VEGFR1	PharmaMar
	II	Atrasentan	ETA receptor	National Cancer Institute
	II	Atvogen		HemispheRx
	II	Carboxyamidotriazole		National Cancer Institute
	II	DHA-paclitaxel	Tubulin	Protarga
	II	FR-901228	Histone deacetylase	Gloucester Pharmaceuticals/ Fujisawa/National Cancer Institute
	II	GTI-2040		Lorus Therapeutics
	II	Histamine dihydrochloride	Histamine receptor	Maxim
	II	MAb G250	G250/CAIX antigen	Wilex
	II	Methotrexate-human serum albumin conjugate	Dihydrofolate reductase	Erasmus University Rotterdam
	II	MG-98	DNA Methyltransferase I	MethylGene/MGI Pharma
	II	MVA-Muc1-IL-2	MUC-1	Transgene
	II	OSI-461	PDE2A and 5A	OSI Pharmaceuticals
	II	Thalidomide[1]		Celgene
	II	TTS-CD2		Active Biotech
	I/II	Kidney cancer vaccine		Genzyme Oncology
	I/II	MVA-5T4	5T4	Oxford BioMedica
	I/II	Oncomyc-NG	Myc	AVI BioPharma
	I/II	Phenoxodiol	NADH oxidase, Sphingosine kinase	Marshall Edwards
	I	FolateImmune	Folate receptor	Endocyte
	I	Innacell γδ		Innate Pharma
	I	Interleukin-21		ZymoGenetics
	I	NBI-3001	IL-4 receptor	Neurocrine Biosciences
	I	Pyridoxylated hemoglobin polyoxyethylene	Nitric oxide	Curacyte
	I	SB-485232		GlaxoSmithKline
	III	Bevacizumab	VEGF	National Cancer Institute
	III	SU-11248	VEGFR, PDGFR	Pfizer
	II	ABT-510		National Cancer Institute
	II	Bevacizumab	VEGF	Genentech
	II	Bexarotene	RXR	Ligand
	II	E-7010	Tubulin	Abbott
	II	Erlotinib hydrochloride	EGFR	National Cancer Institute
	II	Gemcitabine[1]	Pyrimidine nucleotides	National Cancer Institute
	II	Ixabepilone	Tubulin	National Cancer Institute
	II	Oblimersen sodium	Bcl-2	National Cancer Institute
	II	Ortataxel	Tubulin	Bayer
	II	Panitumumab	EGFR	Abgenix/Amgen
	II	SRL-172		SR Pharma
	I	CNTO-328	IL-6	Centocor

Continuation

Treatment of Genitourinary Cancers

Condition	Phase	Drug	Target	Source
Prostate cancer	L-2003	Dutasteride	Steroid 5α-reductase	GlaxoSmithKline
	R-2004	Docetaxel[1]	Tubulin	Aventis Pharma
	Prereg.	Histrelin acetate[1]	LHRH	Valera Pharmaceuticals
	III	APC-8015	Prostatic acid phosphatase	Dendreon
	III	Atrasentan	ETA receptor	Abbott
	III	Satraplatin	DNA	GPC Biotech/Spectrum Pharmaceuticals
	III	Thalidomide[1]		National Cancer Institute
	III	Toremifene[1]	ER	GTx
	III	Vinorelbine[1]	DNA	Pierre Fabre
	II/III	DN-101		Novacea
	II/III	(*R*)-Flurbiprofen		Myriad Genetics
	II	Abetafen	ER	Bioenvision
	II	Amonafide	Topoisomerase II	ChemGenex Therapeutics
	II	Antarelix	LHRH	AEterna Zentaris
	II	Anti-CTLA-4 MAb	CD152/CTLA-4	Medarex
	II	Antineoplaston A10		Burzynski Research Institute
	II	Arsenic trioxide[1]		National Cancer Institute
	II	Avorelin	LHRH	Mediolanum
	II	BLP-25	MUC-1	Biomira/Merck KGaA
	II	Bryostatin 1	PKC	National Cancer Institute
	II	CC-4047	TNF-α	Celgene
	II	CM-31747	Sigma receptors	Sanofi-Synthélabo
	II	CP-461	PDE2A and 5A	OSI Pharmaceuticals
	II	CTL-102		ML Laboratories
	II	D-63153	LHRH	AEterna Zentaris/Baxter Oncology
	II	Degarelix acetate	LHRH	Ferring
	II	DHA-paclitaxel	Tubulin	Protarga
	II	Diflomotecan	Topoisomerase I	Ipsen/Roche
	II	Doxercalciferol[1]		Bone Care International
	II	Eflornithine hydrochloride	Ornithine decarboxylase	National Cancer Institute
	II	Exisulind	cGMP PDE	National Cancer Institute/OSI Pharmaceuticals
	II	Fenretinide	RAR β and γ	National Cancer Institute
	II	FR-901228	Histone deacetylase	Gloucester Pharmaceuticals/ National Cancer Institute
	II	Genistein	EGFR	National Cancer Institute
	II	Globo H-KLH vaccine		Sloan-Kettering Institute
	II	GnRH Pharmaccine	LHRH	Aphton/GlaxoSmithKline
	II	GS-121	LHRH	Epic/Sicor
	II	GTI-2501	Ribonucleotide reductase	Lorus Therapeutics
	II	GVAX Prostate		Cell Genesys
	II	hLM609	Integrin αvβ3	MedImmune
	II	Irofulven	Caspase 8 and 9	MGI Pharma
	II	Ixabepilone	Tubulin	National Cancer Institute
	II	J591	PSMA	BZL Biologics
	II	Kahalalide F		PharmaMar
	II	Ledoxantrone	DNA	Pfizer
	II	MBT-0206	Tubulin	Munich Biotech

Continuation

Treatment of Genitourinary Cancers

Condition	Phase	Drug	Target	Source
Prostate cancer	II	MT-201	Ep-CAM	Micromet
	II	MVA-MUC1-IL-2	MUC-1	Transgene
	II	Oblimersen sodium	Bcl-2	Genta
	II	Onyvax P		Onyvax
	II	PCK-3145		Procyon
	II	Pentrix		AustCancer
	II	Pertuzumab	erbB2	Genentech/National Cancer Institute
	II	Prostvac	PSA	Therion/National Cancer Institute
	II	Reolysin		Oncolytics Biotech
	II	Rubitecan	DNA topoisomerase I	SuperGen
	II	Sabarubicin	DNA topoisomerase II	Menarini
	II	Squalamine	VEGF	Genaera
	II	Tesmilifene hydrochloride	ER, Histamine receptor	YM BioSciences
	II	Thalidomide[1]		Celgene
	II	Trabectedin	DNA	PharmaMar
	I/II	Bortezomib[1]	Proteasome, NF-κB	Millennium
	I/II	CN-787	PSA	Cell Genesys
	I/II	Combretastatin A-4 phosphate	Tubulin	OxiGene
	I/II	Gallium maltolate	Ribonucleoside-diphosphate reductase	Titan
	I/II	111In-DOTA-huJ591	PSMA	BZL Biologics/Millenium
	I/II	Izonsteride	Steroid 5α-reductase	Johns Hopkins University
	I/II	MLN-2704	PSMA	Millennium/Memorial Sloan-Kettering Cancer Center
	I/II	LEM-ETU	DNA topoisomerase II	NeoPharm
	I/II	Norelin	LHRH	YM BioSciences
	I/II	Oncomyc-NG	Myc	AVI BioPharma
	I/II	Pd-Bacteriopheophorbide		Yeda
	I/II	Perifosine	PLC	AEterna Zentaris/National Cancer Institute
	I/II	Phenoxodiol	NADH oxidase, Sphingosine kinase	Marshall Edwards
	I/II	Picoplatin	DNA	AnorMED
	I/II	Protaxel	DNA	Interpharma Praha
	I/II	Rebimastat	Matrix metalloproteinases	Bristol-Myers Squibb/Celltech
	I/II	Xcellerated T cells		Xcyte
	I/II	90Yttrium-DOTA-huJ591	PSMA	BZL Biologics/Millenium
	I	Abiraterone acetate	17α-Hydroxylase/C17-20 lyase	Cougar Biotechnology/BTG
	I	ABR-215050		Active Biotech
	I	AdCAIL-2		McMaster University
	I	Ad5CMV-p53		National Cancer Institute/ Introgen
	I	Ad5-PSA	PSA	University of Iowa
	I	AdV-tk		Advantagene
	I	Antarelix	LHRH	Ardana Bioscience/Teikoku Hormone
	I	Buffy coat interleukins		Cel-Sci
	I	CDglyTK		Henry Ford Hospital
	I	Gossypol	Bcl-xL, Steroid 5α-reductase	Bioenvision
	I	GPI-0100		Memorial Sloan-Kettering Cancer Center/Galenica
	I	Heat-activated doxorubicin liposomes	DNA	Celsion/Duke University
	I	Liposome encapsulated doxorubicin	DNA topoisomerase II	NeoPharm
	I	MDX-070	PSMA	Medarex
	I	Motexafin lutetium		National Cancer Institute

Continuation

Treatment of Genitourinary Cancers

Condition	Phase	Drug	Target	Source
Prostate cancer	I	Mycobacterium cell wall complex		Bioniche Life Sciences
	I	NBI-42902	LHRH	Neurocrine Biosciences
	I	OGX-011	Clusterin	OncoGeneX Technologies/Isis Pharmaceuticals
	I	Prostate cancer vaccine	PSMA	Cytogen/Progenics
	I	Rhodamine 123		University of Tennessee, Memphis
	I	UBITh	LHRH	United Biomedical
	IND Filed	Trilostane[1]	ER	Bioenvision
Testicular cancer	L-2003	Bleomycin sulfate	DNA	Bristol-Myers Squibb
	II	Ixabepilone	Tubulin	National Cancer Institute

[1]Launched for another indication. RAR: Retinoic acid receptor; COX-2: Cyclooxygenase type 2; EGFR: Epidermal growth factor receptor; PKC: Protein kinase C; HSPPC96: Heat shock protein peptide complex 96; mTOR: Mammalian target of rapamycin; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; ETA: Endothelin A; HDAC: Histone deacetylase; PDE: Phosphodiesterase; PDGFR: Platelet-derived growth factor receptor; RXR: Retinoid X receptor; IL-6: Interleukin-6; LHRH: Luteinizing hormone-releasing hormone; ER: Estrogen receptor; TNF: Tumor necrosis factor; PSMA: Prostate-specific membrane antigen; PSA: Prostate-specific antigen; PLC: Phospholipase C.