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Endocrine Drugs

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Abstract

This *Annual Review* is dedicated to updated information on endocrine drugs. The following table lists 134 drugs under development in this area, some of which have been published in previous issues of the journal and others that have been marketed for an indication other than that discussed in the review. Information on the following 13 products is updated here: **alprostadil, AS-3201, etonogestrel, examorelin, fidarestat, mitiglinide calcium hydrate, NBI-6024, netoglitazone, NN-2211, pegvisomant, pramlintide acetate, raxofelast** and **reglitazar**.

Once again, we remind our readers that all of the information presented in this Review is available in electronic format in our drug discovery portal **Integrity**.

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Drug	Source	Indication/Action	Phase
Abarelix[1]	Sanofi-Synthélabo	Endometriosis	II/III
ACIDFORM	Universidade Estadual de Campinas	Vaginal spermicide	I
Acolbifene Hydrochloride	Schering-Plough	Postmenopausal syndrome	II
AERx Insulin	Aradigm/Novo Nordisk	Type 2 diabetes	II
AI-401	AutoImmune/Lilly	Type 1 diabetes	II
AIR-Insulin	Alkermes/Lilly	Type 2 diabetes	I
Albutropin	Human Genome Sciences	Growth hormone deficiency	I
Alprostadil[1,2]	Vivus	Female sexual dysfunction	II/III
Androsorb	Novavax	Female sexual dysfunction	II
AS-3201[1]	Dainippon	Diabetic complications	II
ATL-962	Alizyme	Antidiabetic	I
AZD-7545	AstraZeneca	Type 2 diabetes	I/II
Bay-27-9955	Bayer	Type 2 diabetes	II
Bazedoxifene Acetate[1]	Wyeth	Hormone replacement therapy	III
Bazedoxifene/Premarin	Wyeth	Postmenopausal syndrome	III
Betatropin	Restoragen	Type 2 diabetes	II
BMS-298585	Bristol-Myers Squibb	Type 2 diabetes	II
Bromocriptine Mesilate[2]	Ergo Science	Type 2 diabetes	Prereg
BVT-3498	Biovitrum	Type 2 diabetes	I
Cetrorelix Acetate	Zentaris	Uterine myoma	II
		Endometriosis	II
Chromax	Nutrition 21	Type 2 diabetes	Clinical
Cinacalcet Hydrochloride	Amgen/Kirin Brewery	Hyperparathyroidism	III
CKD-401	Chong Kun Dang Pharm.	Antidiabetic	III
Climara	Schering AG	Hormone replacement therapy	Prereg
CLX-0901	Calyx Therapeutics	Type 2 diabetes	II
CLX-0921	Calyx Therapeutics	Antidiabetic	I
CNT-2000 (American Ginseng)	Chai-Na-Ta	Antidiabetic	Clinical
CS-011	Sankyo	Type 2 diabetes	I
CS-917	Metabasis/Sankyo	Antidiabetic	I
Dexlipotam	Aventis Pharma/Asta Medica	Type 2 diabetes	II
	Aventis Pharma	Diabetic complications	II
DiaPep277	Peptor	Type 1 diabetes	II
DPP-728	Novartis	Type 2 diabetes	II
Elcometrine[1]	Population Council	Hormone replacement therapy	II
		Female contraceptive	II
Emfilermin	Serono	Female infertility	I
EML-16257	Merck KGaA	Type 2 diabetes	II
EML-16336	Merck KGaA	Type 2 diabetes	II
Estradiol/Nomogestrol Acetate	Merck KGaA	Hormone replacement therapy	Prereg
Estrasorb	Novavax	Hormone replacement therapy	Prereg
		Postmenopausal syndrome	III
Etonogestrel[1]	Organon	Male contraceptive	II
Examorelin[1]	Mediolanum	Growth hormone deficiency	II
Exendin-4	Amylin/Alkermes	Type 2 diabetes	III
Exubera	Aventis Pharma	Antidiabetic	Prereg
FE-200440	Ferring	Preterm labor	I
Fidarestat[1]	Sanwa/Kaken	Diabetic complications	Prereg
FK-614	Fujisawa	Type 2 diabetes	II
Flocalcitriol[1]	Taisho/Sumitomo	Thyroid disease	L-2001
Genapol-Stabilized Insulin	Aventis Pharma	Antidiabetic	I
Gestodene	Schering AG	Prevention of osteoporosis	III
		Hormone replacement therapy	III
GI-181771	Glaxo	Type 2 diabetes	I
Growth Hormone-Releasing Peptide	Atrix	Growth hormone deficiency	Clinical
GW-427353	Glaxo/Asahi Kasei	Type 2 diabetes	II
GW-516	Glaxo	Diabetic complications	I
		Type 2 diabetes	I
GW-544	Glaxo	Type 2 diabetes	I
Hexyl Insulin M2	Nobex	Antidiabetic	II
hGH	Cangene	Growth hormone deficiency	III

Continued

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Drug	Source	Indication/Action	Phase
hOKT3γ1 (Ala-Ala)	Columbia University/R.W. Johnson	Type 1 diabetes	II
Human Insulin	Flamel	Antidiabetic	I
IDR-90104	Institute for Drug Research	Postmenopausal syndrome	I/II
INGAP Peptide	GMP Companies	Antidiabetic	I/II
Inhaled Human Growth Hormone	Alkermes/Lilly	Growth hormone deficiency	I
INS-1	Taisho	Type 2 diabetes	II
		Female infetility	II
Insulin Detemir	Novo Nordisk	Antidiabetic	III
Insulin Glulisine	Aventis Pharma	Antidiabetic	III
Insulin Spiros	Lilly/Dura	Antidiabetic	II
Insulinotropin	Novo Nordisk	Type 2 diabetes	II
IoGen	Symbollon	Gynecological disorders	II
J-867	TAP	Gynecological disorders	II
		Endometriosis	II
		Hormone replacement therapy	II
J-956	TAP	Gynecological disorders	II
		Endometriosis	II
		Hormone replacement therapy	II
JTT-811	Japan Tobacco	Diabetic complications	II
KP-102LN	Kaken	Growth hormone deficiency	II
KRN-1493	Kirin Brewery	Hyperparathyroidism	II
KRP-297	Merck & Co./Kyorin	Type 2 diabetes	II
KUR-1246	Kissei	Preterm labor	II
LAF-237	Novartis	Type 2 diabetes	II
Leuprorelin Acetate[1]	Inhale	Endometriosis	I
Levonorgestrel/Ethinylestradiol	Barr	Oral contraeptive	III
	Agile Therapeutics	Female contraceptive	II
Lidorestat	Institute for Diabetes Discovery	Diabetic complications	II
LY-307161 SR	Lilly	Type 2 diabetes	II
LY-818	Lilly/Ligand	Type 2 diabetes	I
MBX-102	Metabolex	Antidiabetic	I
Meluadrine Tartrate	Mitsubishi Pharma	Tocolytic	III
Metformin GR	DepoMed/Biovail	Type 2 diabetes	III
Metformin Hydrochloride/Glipizide	Bristol-Myers Squibb	Type 2 diabetes	III
Methyltestosterone	Noven	Female sexual dysfunction	II
Mitiglinide Calcium Hydrate[1]	Servier	Type 2 diabetes	III
MLN-4760	Millennium/Abbott	Antidiabetic	I
NBI-42902	Neurocrine Biosciences	Gynecological disorders	I
NBI-6024[1]	Neurocrine Biosciences/Taisho	Type 1 diabetes	II
Nestorone	Population Council	Female contraceptive	II
		Hormone replacement therapy	II
Netoglitazone[1]	Mitsubishi Chem./Johnson & Johnson	Type 2 diabetes	II
NN-2211[1]	Novo Nordisk	Type 2 diabetes	II
NN-2344	Dr. Reddy's Res. Found./Novo Nordisk	Type 2 diabetes	II
NN-344	Novo Nordisk	Antidiabetic	I
NN-414	Novo Nordisk	Type 2 diabetes	II
NOX-700	Medinox	Type 2 diabetes	I
Ono-8815Ly	Ono	Tocolytic	I
Oral Insulin	Emisphere	Type 1 diabetes	I
Oralin	Generex	Antidiabetic	III
Org-30659	Organon	Contraceptive	II
P-57	Phytopharm	Type 2 diabetes	II
Pegvisomant[1]	Sensus	Acromegaly	Prereg
Pramlintide Acetate[1]	Amylin	Type 1 diabetes	Prereg
		Antidiabetic	Prereg
ProLease r-hFSH	Alkermes/Serono	Female infertility	I
PT-141	Palatin Technologies	Fenale sexual dysfunction	I
R-483	Roche	Type 2 diabetes	I
R-765	Roche	Type 2 diabetes	I
Ramipril[1,2]	Aventis Pharma	Type 2 diabetes	Clinical
Raxofelast[1]	Biomedica Foscama	Diabetic complications	II
Reglitazar[1]	Japan Tobacco/Pharmacia	Type 2 diabetes	II

Continued

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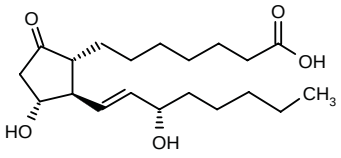
Drug	Source	Indication/Action	Phase
RF-1015	SuperGen	Type 2 diabetes	II
rhGAD65	Dyamid	Type 1 diabetes	II
Sildenafil Citrate[1,2]	Pfizer	Female sexual dysfunction	II
Somatokine	Insmed	Type 1 diabetes	II
SP-134101	Lipha	Type 2 diabetes	II
SR-58611A	Sanofi-Synthélabo	Type 2 diabetes	II
Tabimorelin	Novo Nordisk	Growth hormone deficiency	II
TAK-013	Takeda	Endometriosis	II
		Gynecological disorders	II
TAK-559	Takeda	Type 2diabetes	II
TAK-677	Takeda	Type 2 diabetes	II
Technosphere/Insulin	Pharmaceutical Discovery	Type 2 diabetes	II
Tesaglitazar	AstraZeneca	Type 2 diabetes	II
Testogel[2]	Unimed	Female sexual dysfunction	II
Testosterone Intravaginal Ring	Galen	Gynecological disorders	II
Testosterone PHBT	Columbia Laboratories	Hypogonadism	III
Testosterone Transdermal	3M Pharmaceuticals	Hormone replacement therapy	I
		Hypogonadism	I
TH-9507	TheraTechnologies	Type 2 diabetes	II
Tostrex	Cellegy	Hypogonadism	Prereg
		Female sexual dysfunction	II/III
Transdermal Testosterone	BioSante	Female sexual dysfunction	II
Trimegestone[1]	Aventis	Postmenopausal syndrome	Reg
Trimegestone/Premarin	Wyeth	Postmenopausal syndrome	III
	Wyeth	Hormone replacement therapy	III
TT-235	Mitsubishi Pharma	Tocolytic	I
Ulinastatin[2]	Mochida	Preterm labor	II
VML-670	Vernalis Research	Female sexual dysfunction	II

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

Alprostadil



Two proprietary topical formulations of alprostadil (prostaglandin E_1), a synthetic version of a naturally occurring vasodilator and a well-known drug for the treatment of male erectile dysfunction, are in clinical development for the treatment of female sexual arousal disorder (FASD): NexMed's Femprox™ cream and Vivus's Alista™.

NexMed has reported clinical results from 2 U.S. safety trials of Femprox™ cream for the treatment of FSAD. Femprox™ combines the NexACT® transdermal penetration-enhancing technology with alprostadil. In these single-blind, placebo-controlled, dose-escalating studies, 64 healthy women aged 21-60 were divided into 8 groups of 8 women each. Each volunteer received a single dose of placebo or different doses of Femprox™. Results indicated that Femprox™ was safe and well tolerated at all doses. No serious adverse effects were reported and no abnormalities in blood pressure or heart rate were observed. These results confirm earlier findings (1).

NexMed has completed testing of 98 patients in its phase II at-home study of Femprox™ cream for FSAD. The multicenter, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of Femprox™ in premenopausal women with FSAD (2, 3).

Treatment has begun in Vivus's U.S.-based phase II/III at-home trial for Alista™ for FSAD. The multicenter, double-blind, placebo-controlled trial will evaluate the safety and efficacy of Alista™, including onset and duration of sexual response. In a previous in-clinic study, topically applied Alista™ significantly increased sexual arousal, satisfaction with the level of sexual arousal, and overall level of sexual satisfaction compared to baseline and placebo. Alista™ is a proprietary formulation of alprostadil which is applied locally to female genitalia. Alista™ is believed to increase blood flow to the female genitalia, thereby promoting engorgement and other natural processes that occur during sexual stimulation (4-7).

1. *NexMed's Femprox safe and well tolerated in phase I trials*. DailyDrugNews.com (Daily Essentials) May 4, 2001.

2. *Phase II study of Femprox in FSAD completed*. DailyDrugNews.com (Daily Essentials) April 4, 2002.

3. *Enrollment completed in phase II at-home study of Femprox*. DailyDrugNews.com (Daily Essentials) Jan 31, 2002.

4. *Treatment initiated in at-home phase II/III trial of Alista for FSAD*. DailyDrugNews.com (Daily Essentials) April 5, 2002.

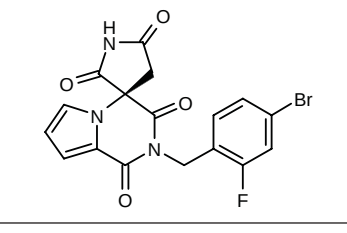
5. *Alista enters phase II evaluation for FSD*. DailyDrugNews.com (Daily Essentials) Jan 24, 2001.

6. *Patient dosing completed in phase II study of Alista for treatment of FSD*. DailyDrugNews.com (Daily Essentials) Aug 27, 2001.

7. *Alista associated with positive results in female sexual dysfunction*. DailyDrugNews.com (Daily Essentials) Dec 5, 2001.

Original monograph - Drugs Fut 1987, 12(6): 541 (published as lipoalprostadil).

AS-3201



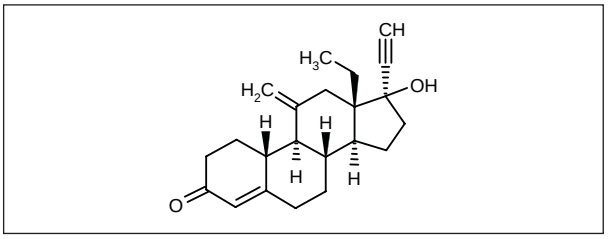
The aldose reductase inhibitor AS-3201 (Dainippon) is in phase II clinical evaluation for the treatment of diabetic complications.

In preclinical trials, researchers investigated the effect of the aldose reductase inhibitor AS-3201 on the decreased sciatic nerve (SN) motor nerve conduction velocity (MNCV) in streptozotocin-diabetic rats. One day following injection of streptozotocin, plasma glucose concentrations increased. After 1 week, the sorbitol and fructose levels in the SN increased by 8-10 times, followed by a gradual decrease in the SN MNCV. After 3 weeks, the MNCV of the diabetic rats was significantly lower than that of the nondiabetic control rats. When given orally, AS-3201 at a daily dose of 0.3-1.0 mg/kg/day for 3 weeks dose-dependently increased the MNCV in diabetic animals. Concomitantly, levels of sorbitol and fructose in the SN decreased. It was concluded that AS-3201 improved impaired MNCV in diabetic rats by normalizing sorbitol and fructose levels in tissues (1).

1. Matsumoto, T., Nakamura, K., Ono, Y., Kuromiya, K., Komiya, M. *Effect of aldose redactase inhibitor, AS-3201 on decreased nerve conduction velocity in diabetic rats*. Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-596.

Original monograph - Drugs Fut 2000, 25(2): 131.

Etonogestrel



The progestogen etonogestrel (Organon), the biologically active metabolite of desogestrel, is currently available as a long-acting contraceptive s.c. implant (Implanon®) for women. Organon is reportedly investigating etonogestrel + testosterone implants for male contraception.

Healthy male volunteers (n=28) were given either 1 or 2 s.c. implants of etonogestrel for a period of 24 weeks plus testosterone 400 mg on day 1 and at week 12 in a randomized study. Spermatogenesis was suppressed in all subjects, although more consistently in those receiving 2 implants. The treatment produced no significant alterations in body weight, hemoglobin, hematocrit or HDL cholesterol levels (1). These results are summarized in Table I.

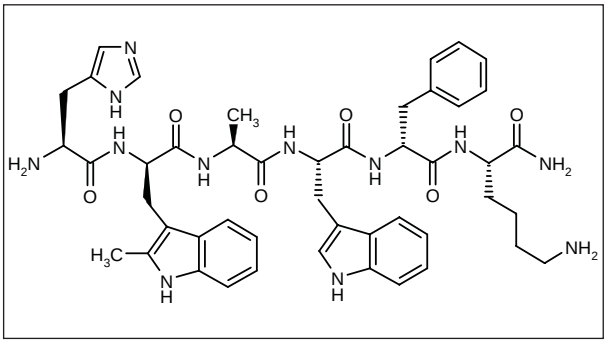
1. Anderson, R.A., Kinniburgh, D., Baird, D.T. *Suppression of spermatogenesis by etonogestrel implants with depot testosterone: Potential for long-acting male contraception*. J Clin Endocrinol Metab 2002, 87(8): 3640.

Original monograph - Drugs Fut 1978, 3(9): 664.

Table I: Clinical study of etonogestrel (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized	Etonogestrel, 1 s.c. implant for 24 wk + Testosterone, 400 mg @ d 1 and wk 12 Etonogestrel, 2 s.c. implants for 24 wk + Testosterone, 400 mg @ d 1 and wk 12	28	Spermatogenesis was suppressed in all subjects, although more consistently in those receiving 2 implants of etonogestrel. Treatment produced no signficant alterations in body weight, hemoglobin, hematocrit or HDL cholesterol	1

Examorelin



Examorelin (Hexarelin®, EP-23905) is a peptidyl growth hormone (GH) secretagogue developed at Europeptides and licensed to Mediolanum that is in phase II development for GH disorders.

In vitro experiments in excised rat jejunal segments demonstrated that Hexarelin and EP-51389 have poor intestinal permeability and that the passage of hexarelin is primarily through the transcellular passive pathway (1).

The cause of the low oral efficacy of Hexarelin and the means by which its absorption may be improved were investigated in rat, dog and Caco-2 cell models. Degradation of the drug, possibly by trypsin, in the rat ileum was inhibited by chymostatin, Pefabloc, EDTA and EGTA. Degradation by pancreas substitute drugs was inhibited by Pefabloc. EDTA, sodium caprate, palmitoyl carnitine, chitosan, MG C6-C10/oleic acid/MCT oil and biosomes increased Hexarelin intestinal epithelial permeability *in vitro* (2).

A study in 6 young (26-32 years of age) female volunteers examined the effects of glucagon (0.017 mg/kg i.m.) and Hexarelin (2 μg/kg i.v.) alone and in combination on somatotroph and corticotroph secretion. Glucagon administration alone significantly increased growth hormone (GH; 11.6 ± 3.4 μg/l *vs*. 3.3 ± 0.7 μg/l), adrenocorticotropin (ACTH; 11.6 ± 3.3 pmol/l *vs*. 4.1 ± 0.3 pmol/l) and cortisol (613.5 ± 65.6 nmol/l *vs*. 436.9 ± 13.3 nmol/l) levels as compared to baseline. Hexarelin also significantly increased the levels of these hormones (55.7 ± 19.8 μg/l *vs*. 3.7 ± 1.9 μg/l, 5.7 ± 1.1 pmol/l *vs*. 3.4 ± 0.6 pmol/l, 400.2 ± 31.4 nmol/l *vs*. 636.4 ± 32.2 nmol/l, respectively). The GH AUC value following Hexarelin administration was significantly higher (1637.3 ± 494

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, single-blind	Part I: (n=7) Ghrelin, 1 μg/kg i.v. Examorelin, 1 μg/kg i.v. Pegvisomant, 1 μg/kg i.v. Placebo Part II: (n=6) Ghrelin, 1 μg/kg i.v. + Examorelin, 1 μg/kg i.v. Ghrelin, 1 μg/kg i.v. + Growth hormone releasing hormone, 1 μg/kg i.v.	13	Treatment with ghrelin was more effective than the other drugs in stimulating GH secretion in healthy volunteers	4
GH deficiency, cardiomyopathy	Open	Examorelin, 2 μg/kg i.v. s.d.	26	Examorelin significantly increased left ventricular ejection fraction in normal subjects and patients with GH deficiency, and also significantly increased GH levels in healthy subjects and in patients with dilated cardiomyopathy, but not in those with GH deficiency	5
Acromegaly	Open	Examorelin, 1.5 μg/kg i.v. bolus Arginine, 20 g/m^2 over 30 min		In patients who had achieved safe GH levels through irradiation, the GH response to arginine was minimal, but the response to examorelin was maintained	7
Healthy volunteers	Randomized, open, crossover	hCRH, 2 μg/kg i.v. s.d. Examorelin, 2 μg/kg i.v. s.d. Somatomedin C, 20 μg/kg s.c. s.d. → hCRH, 2 μg/kg i.v. s.d. Somatomedin C, 20 μg/kg s.c. s.d. → Examorelin, 2 μg/kg i.v. s.d.	6	Somatomedin C increased circulating insulin-like growth factor I levels without altering the ACTH and cortisol responses to hCRH or examorelin in healthy volunteers	8
Healthy volunteers	Open, crossover	Examorelin, 1.5 μg/kg s.c. b.i.d. → 100 μg i.v. b.i.d. Examorelin, 1.5 μg/kg s.c. t.i.d. → 100 μg i.v. t.i.d. Placebo	6 6	GH secretion was enhanced to the same extent by b.i.d and t.i.d. examorelin administration, while secretion of PRL, ACTH and cortisol was not affected in healthy volunteers	9

μg/l/120 min *vs*. 479.1 ± 115.7 μg/l/120 min), while the AUC values for ACTH (208 ± 41.3 pmol/l/120 min *vs*. 426.3 ± 80.9 pmol/l/120 min) and cortisol (18,875.5 ± 1626 nmol/l/120 min *vs*. 28,338.5 ± 2430.7 nmol/l/120 min) were significantly lower than those obtained after glucagon administration. Combined Hexarelin and glucagon resulted in a less than additive effect on ACTH (564.02 ± 76.5 pmol/l/120 min) and cortisol (35,424.6 ± 5548.1 nmol/l/120 min) secretion and a synergistic effect on GH secretion (3243.8 ± 687.5 μg/l/120 min) (3).

The GH-releasing activity of ghrelin was compared to that of growth hormone-releasing hormone (GHRH) and Hexarelin in 7 healthy male volunteers. Subjects received ghrelin, GHRH and Hexarelin at a dose of 1 μg/kg i.v. or placebo; 6 subjects were given a combination of ghrelin and Hexarelin or ghrelin and GHRH in a further study. The GH response to ghrelin was greater than that for Hexarelin or GHRH. While the addition of ghrelin to Hexarelin had no effect, the combination of ghrelin and GHRH had a synergistic effect on GH secretion (4). The results of this study and some that follow are summarized in Table II.

Hexarelin 2 μg/kg i.v. was administered to healthy volunteers, patients with severe GH deficiency and patients with severe left ventricular dysfunction due to either dilated cardiomyopathy or ischemic cardiomyopathy in an evaluation of the drug's cardiac effects. Hexarelin significantly increased left ventricular ejection fraction in normal subjects and patients with GH deficiency, as well as in those with ischemic, but not dilated, cardiomyopathy. The drug also significantly increased GH levels in healthy subjects and in patients with cardiomyopathy, but not in those with GH deficiency (5, 6).

Growth hormone responses were assessed in blood samples from 19 acromegalic patients after infusion of 20 g/m^2 arginine and, on a separate visit, after i.v. administration of Hexarelin 1.5 μg/kg. Patients had achieved mean serum GH levels below 5 mU/l through surgery alone or primary or postoperative irradiation. In those patients who had achieved safe GH levels through irradiation, the GH response to arginine was minimal, but the response to Hexarelin was retained (7).

The effect of recombinant human insulin-like growth factor-I (rhIGF-I) 20 μg/kg s.c. on the ACTH and cortisol responses to human corticotropin-releasing hormone (hCRH) 2 μg/kg i.v. or Hexarelin 2 μg/kg i.v. was compared to that of placebo in 6 healthy female volunteers. rhIGF-I increased circulating IGF-I levels without altering the ACTH and cortisol responses to hCRH or Hexarelin (8).

The effects of s.c. Hexarelin 1.5 μg/kg b.i.d. or t.i.d. on 24-h GH, prolactin (PRL), ACTH and cortisol secretion were investigated in 6 healthy male volunteers. Growth hormone secretion was enhanced to the same extent by b.i.d. and t.i.d. Hexarelin administration, while no changes occurred in the secretion of PRL, ACTH and cortisol (9).

1. Roumi, M., Kwong, E., Deghenghi, R., Locatelli, V., Marleau, S., DuSouich, P., Beliveau, R., Ong, H. *Permeability of the peptidic GH secretagogues Hexarelin and EP 51389, across rat jejunum*. Peptides 2001, 22(7): 1129.

2. Westberg, C., Benkestock, K., Fatouros, A., Svensson, M., Sjöström, B. *Hexarelin – evaluation of factors influencing oral bioavailability and ways to improve absorption*. J Pharm Pharmacol 2001, 53(9): 1257.

3. Arvat, E. et al. *Interaction between glucagon and Hexarelin, a peptidyl GH secretagogue, on somatotroph and corticotroph secretion in humans*. Eur J Endocrinol 2000, 143(5): 601.

4. Arvat, E., Maccario, M., Di Vito, L. et al. *Endocrine activities of ghrelin, a natural growth hormone secretagogue (GHS), in humans: Comparison and interactions with Hexarelin, a nonnatural peptidyl GHS, and GH-releasing hormone*. J Clin Endocrinol Metab 2001, 86(3): 1169.

5. Broglio, F., Benso, A., Valetto, M.R. et al. *Growth hormone-independent cardiotropic activities of growth hormone-releasing peptides in normal subjects, in patients with growth hormone deficiency, and in patients with idiopathic or ischemic dilated cardiomyopathy*. Endocrine 2001, 14(1): 105.

6. Imazio, M., Bobbio, M., Broglio, F., Benso, A., Podio, V., Valetto, M.R., Bisi, G., Ghigo, E., Trevi, G.P. *GH-independent cardiotropic activities of Hexarelin in patients with severe left ventricular dysfunction due to dilated and ischemic cardiomyopathy*. Eur J Heart Fail 2002, 4(2): 185.

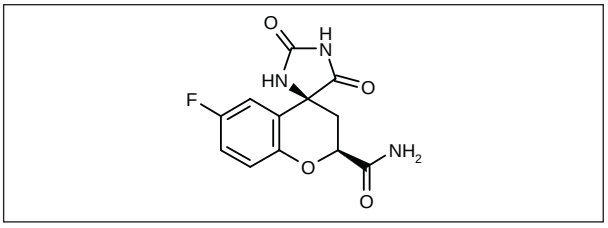
7. Murray, R.D., Peacey, S.R., Rahim, A., Toogood, A.A., Thorney, M.O., Shalet, S.M. *The diagnosis of growth hormone deficiency (GHD) in successfully treated acromegalic patients*. Clin Endocrinol 2001, 54(1): 37.

8. Gianotti, L., Ramunni, J., Lanfranco, F. et al. *Recombinant human IGF-I does not modify the ACTH and cortisol responses to hCRH and Hexarelin, a peptidyl GH secretagogue, in humans*. J Endocrinol Invest 2001, 24(2): 67.

9. Maccario, M., Veldhuis, J.D., Broglio, P., Di Vito, L., Arvat, E., Deghenghi, R., Ghio, E. *Impact of two or three daily subcutaneous injections of Hexarelin, a synthetic growth hormone (GH) secretagogue, on 24-h GH, prolactin, adrenocorticotropin and cortisol secretion in humans*. Eur J Endocrinol 2002, 146(3): 310.

Original monograph - Drugs Fut 1996, 21(4): 366.

Fidarestat



A potent aldose reductase inhibitor, fidarestat (SNK-860, Aldos®) is undergoing regulatory review in Japan for the treatment of diabetic neuropathy and is in phase II trials in the U.S. The product is being developed by NK Curex, a joint venture of Kaken and Japan Energy, in collaboration with Sanwa Kagaku.

Fidarestat has been used to explore the role of aldose reductase in diabetes-induced retinopathy in *in vitro* and *in vivo* experiments. Low and high doses of fidarestat partially and completely blocked diabetes-induced retinal sorbitol accumulation. This was associated with inhibition of increased retinal oxidative stress and vascular endothelial growth factor (VEGF) protein production. *In vitro* in bovine retinal endothelial cells, fidarestat reversed the increased production of reactive oxygen species and sorbitol and fructose concentrations in the presence of high glucose. It was concluded that aldose reductase plays a major role in retinal oxidative stress and VEGF overproduction in diabetes, and that fidarestat should be investigated further for its potential in the treatment of diabetic retinopathy (1).

The finding that inhibition of aldose reductase improves the hyperglycemia-induced increase in retinal vascular permeability and VEGF production prompted researchers to determine the effects of fidarestat on oxidative stress and VEGF production induced by hyperglycemia in cultured human retinal pigment epithelial cells. Hyperglycemia increased the levels of sorbitol, fructose, VEGF and oxidative stress-induced fluorescence measured in the treated cells, but these changes were significantly suppressed by fidarestat (2).

Experiments in human umbilical vein endothelial cells (HUVEC) cultured under conditions of high glucose showed significantly increased apoptosis and intracellular sorbitol levels. Exposure to fidarestat resulted in significant reductions in intracellular sorbitol levels, as well as HUVEC apoptosis (3).

Rat aorta vascular smooth muscle cells were cultured under conditions of normal and high glucose in the presence or absence of fidarestat. A significant increase in the proliferation of these cells and in oxidative stress and 3-deoxyglucose levels was seen under conditions of high glucose, effects which were significantly inhibited by fidarestat (4).

In *in vitro* experiments, fidarestat was found to inhibit the increase in sorbitol content in erythrocytes from healthy volunteers (IC_{50} = 18 nmol/l) and from diabetic patients. In diabetic rats, inhibition of erythrocyte sorbitol accumulation with fidarestat 0.25-2 mg/kg was correlated with inhibition of nerve sorbitol accumulation, indicating that the drug's effect on sorbitol pathway flux can be estimated from its effect on erythrocyte sorbitol (5).

The effects of fidarestat on the production of nerve growth factor (NGF) in rat sciatic nerve Schwann cells in the presence of varying glucose concentrations have been examined. The increase in NGF production seen under conditions of normal glucose and NT-3 stimulation was significantly attenuated in the presence of high glucose concentrations, and fidarestat reversed this inhibition. Fidarestat also normalized the increase in sorbitol levels (6).

The modulation of accelerated intimal hyperplasia with hyperglycemia by fidarestat (3 mg/kg for 1 week before and 4 weeks after endothelial denudation) was investigated in the carotid artery of hyperglycemic rabbits. The accelerated accumulation of endogenous nitric oxide synthase (NOS) inhibitors in endothelial cells and ET-1 within the vessel wall, as well as increased impairment of NO and cGMP production, were all prevented by fidarestat. Activation of the aldose reduction pathway is therefore implicated in these processes (7).

A study used a rat sciatic nerve crush model to compare the rate of neuronal regeneration in control rats, untreated diabetic rats and diabetic rats treated with 2 mg/kg/day fidarestat. Compared to untreated diabetic rats, treatment with fidarestat resulted in significant improvement in the levels of all proteins distal to the crush (which were lower than those measured in control animals) and normalized sorbitol and fructose levels in the sciatic nerve contralateral to the crush. This suggested that the aldose reductase inhibitor is effective against the impaired neuronal regeneration response in diabetic rats (8).

The effects of fidarestat on retinal vascular permeability in diabetic rats and VEGF production in human retinal pigment epithelial cells have been studied. The drug was administered by gavage (0.25-2 mg/kg/day) to diabetic rats for 15 months and was found to dose-dependently inhibit coadministered fluorescein leakage and retinal sorbitol accumulation. Increased VEGF production in retinal pigment epithelial cells incubated with 30 mM of glucose for 9 days was reversed by 0.1 and 1 μM fidarestat. Thus, the onset of diabetic retinopathy via VEGF production may involve polyol pathways, and fidarestat is suggested to suppress increased retinal vascular permeability via inhibition of retinal cell VEGF expression (9, 10).

In a study in rats with streptozotocin-induced diabetes, fidarestat completely restored the decreased blood flow to the sciatic nerve to normal, accompanied by inhibition of the reduction in NO production. The authors conclude that these actions may help explain its beneficial effects in diabetic neuropathy (11).

A total of 58 patients with type 2 diabetes were randomized to receive a daily dose of either 1 mg of fidarestat or 150 mg of epalrestat for 4 weeks. At the end of treatment, the erythrocyte sorbitol content of epalrestat-treated patients did not change significantly compared to baseline, whereas that of fidarestat-treated patients had decreased significantly to normal levels. Neither drug modified plasma glucose levels in these patients. Sorbitol accumulation is one of the possible causes of diabetic neuropathy, and its inhibition by fidarestat suggests the potential of the agent for the treatment of this disorder (12). The results of this study and the one that follows are summarized in Table III.

A 52-week, multicenter, double-blind, placebo-controlled study was undertaken to assess the effects of fidarestat on nerve function and subjective symptoms in 279 patients with type 1 or 2 diabetes and peripheral neuropathy. Fidarestat significantly improved nerve conduction velocity, as well as a variety of subjective symptoms. Adverse events were similar in the placebo and fidarestat groups (13).

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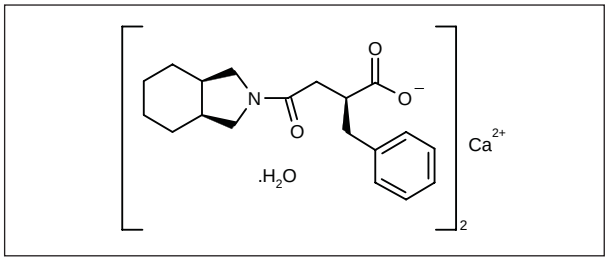
Original monograph - Drugs Fut 1996, 21(3): 261.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Diabetes mellitus type 2	Randomized, double-blind	Fidarestat, 1 mg o.d. x 4 wk (n=29) Epalrestat, 50 mg t.i.d. x 4 wk (n=29)	58	Fidarestat was safe and had no effects on glycemic control but was more effective than epalrestat in normalizing the high sorbitol levels present in the erythrocytes of patients suffering from type 2 diabetes	12
Diabetes mellitus type 1 and 2, peripheral neuropathy	Double-blind, multicenter	Fidarestat, 1 mg/d x 52 wk Placebo	272	Fidarestat significantly improved nerve conduction velocity as well as a variety of subjective symptoms in diabetic patients with peripheral neuropathy	13

Mitiglinide Calcium Hydrate



Kissei's antidiabetic agent mitiglinide (KAD-1229, S-21403) is currently in phase II clinical studies in the U.S.

Mitiglinide was being developed in the U.S., Canada, Mexico and Central and South America by Purdue Pharma until the companies decided to terminate their agreement last year and rights were transferred to Kissei Pharma USA, Kissei's U.S. subsidiary. Kissei has licensed mitiglinide in Europe, the Middle East, Africa, Oceania and some Asian countries to Servier, which is currently carrying out phase III trials with the drug. In Japan, Kissei is preparing double-blind comparative phase III studies with mitiglinide. Mitiglinide is different from conventional sulfonylurea agents in that the onset of action is rapid following dosing. In addition, the drug, which has a short duration of action, suppresses the postprandial hyperglycemia characteristic of diabetic patients and works to avoid hypoglycemia during fasting (1).

In studies in COS-1 cells, mitiglinide showed high specificity for the pancreatic beta-cell ATP-sensitive K^+ channel, indicating potential utility as an antidiabetic drug (2).

The mechanism of action of mitiglinide on Kir6.2/SUR1, Kir6.2/SUR2A and Kir6.2/SUR2B subtypes of ATP-sensitive potassium channels was investigated in *Xenopus* oocytes. The drug inhibited Kir6.2/SUR currents at the low-affinity site on Kir6.2 and the high-affinity site on SUR. Low-affinity inhibition was similar for all 3 types of channels, but high-affinity inhibition was greater for Kir6.2/SUR1 currents (IC_{50} = 4 nM) than for Kir6.2/SUR2A and Kir6.2/SUR2B currents (IC_{50} = 3 and 5 μM, respectively). Concentrations of 10 μM, but not 100 nM, blocked Kir6.2/SUR1-S1237Y and Kir6.2/SUR2 currents. Mitiglinide showed 1000-fold greater affinity for the pancreatic β-cell type than the cardiac and smooth muscle types of channel (3).

Glibenclamide, but not mitiglinide, exacerbated myocardial stunning in dogs induced by occlusion/reperfusion of the descending coronary artery. The difference in effect may be attributable to differences in binding properties of the drugs towards cardiac sulfonylurea receptors. Mitiglinide may be highly specific for pancreatic sulfonylurea receptors and may be a safer hypoglycemic agent than glibenclamide (4).

Mitiglinide has been compared to nateglinide and voglibose for its ability to reduce postprandial glycemia after a meal in rat models of mild, moderate or severe streptozotocin-induced diabetes. The animals were treated with mitiglinide (0.3, 1 or 3 mg/kg), nateglinide (25, 50 or 100 mg/kg) or voglibose (0.03, 0.1 or 0.3 mg/kg) orally just before an oral meal load. Mitiglinide proved to be the most effective hypoglycemic agent, affording significant and rapid decreases in blood glucose levels and reductions in the AUC for blood glucose in the mild and moderate models; a tendency for suppression of the meal-induced increase in blood glucose was also seen in the severely diabetic animals. Mitiglinide may thus be useful for preventing the postprandial hyperglycemia seen in type 2 diabetes (5-7).

Mitiglinide and gliclazide were compared for their hypoglycemic effects and insulinotropic actions in a dog model of diabetes. Mitiglinide was found to have a stronger effect on reducing the increase in plasma

glucose than gliclazide and, unlike the latter, it did not produce hypoglycemia. Mitiglinide demonstrated a rapid insulinotropic action. Thus, mitiglinide appears to have potential for attenuating hyperglycemia and for improving impaired insulin secretion in the early phase of type 2 diabetes (8).

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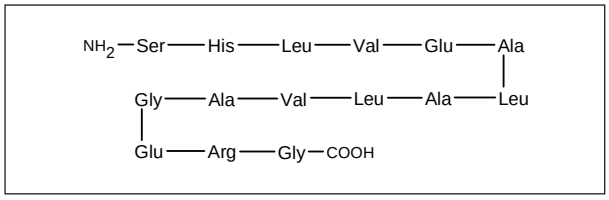
Original monograph - Drugs Fut 2000, 25(10): 1034.

NBI-6024



NBI-6024 is an altered peptide ligand (APL) designed specifically by Neurocrine Biosciences to generate an immune response that could result in preservation of β-cell function in patients with type 1 diabetes. The company has an agreement with Taisho, providing the latter with exclusive rights in Europe, Asia, North America and other markets.

Neurocrine Biosciences and Taisho have initiated the first of 2 pivotal phase IIb clinical trials of the therapeutic vaccine in adults and the adolescent/pediatric population with new-onset type 1 diabetes. The trial is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the safety, efficacy, tolerability and pharmacodynamic activity of 3 doses of NBI-6024 as compared to placebo. The primary endpoint of the trial is to assess the effect of repeated administration of NBI-6024 in preserving endogenous insulin secretion, as measured by C-peptide levels, in adult and adolescent patients. Each study will involve at least 30 centers and 300 patients. Adult patients will be dosed for up to 2 years and the pediatric/adolescent population will be treated for at least a year. These trials are designed to demonstrate a statistically significant and clinically relevant impact on delaying disease progression in patients with type 1 diabetes. Results from earlier phase I/II clinical trials in 50 adult patients with type 1 diabetes demonstrated that both single- and multiple-dose regimens of NBI-6024 were well tolerated, and no dose-limiting toxicities were reported (1, 2).

Phase I/II safety results also demonstrated that all s.c. doses of NBI-6024 were well tolerated in adolescent patients. In a multicenter, double-blind, randomized, placebo-controlled trial, 35 adolescents with insulin-dependent type 1 diabetes were administered a total of 5 doses of NBI-6024 of 0.1, 1 or 5 mg or placebo every 2 weeks for 8 weeks, or 1 or 5 mg of NBI-6024 or placebo every 2 weeks for 4 weeks, then every month for 2 months. Overall, the safety profile and incidence of adverse events for all dosing cohorts were similar to in the placebo group. The results of this study are summarized in Table IV.

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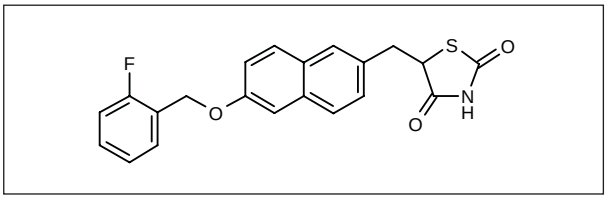
Original monograph - Drugs Fut 2002, 27(7): 645.

Table IV: Clinical study of NBI-6024 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Diabetes mellitus type 1	Randomized, double blind, multicenter	NBI-6024, 0.1 mg 1x/2 wk x 8 wk NBI-6024, 1 mg 1x/2 wk x 8 wk NBI-6024, 5 mg 1x/2 wk x 8 wk NBI-6024, 1 mg 1x/2 wk x 4 wk → 1x/1 mo x 2 mo NBI-6024, 5 mg 1x/2 wk x 4 wk → 1x/1 mo x 2 mo Placebo 1x/2 wk Placebo 1x/2 wk → 1x/1 mo x 12 mo	35	NBI-6024 was well tolerated in adolescent patients with insulin-dependent diabetes mellitus	3

Netoglitazone



Netoglitazone (RWJ-241947, MCC-555) is a new oral insulin sensitizer that modulates both peroxisome proliferator-activated receptors PPARα and PPARγ. Developed by Mitsubishi Pharma, it is licensed worldwide to Johnson & Johnson and has entered clinical trials.

The pharmacological activity of rosiglitazone and pioglitazone was compared with that of the development candidates netoglitazone, NNC-61-0029, reglitazar, KRP-297 and GI-262570 *in vitro* and in a mouse model of type 2 diabetes. All of the drug candidates showed peroxisome proliferator-activated receptor PPARα and PPARγ agonism *in vitro* and several demonstrated insulin-sensitizing activity superior to rosiglitazone and pioglitazone in mice (1).

The orally active insulin sensitizer netoglitazone has been assessed for its effects on serum lipoprotein levels in *db/db* mice following repeated oral administration at doses of 1, 3, 10 and 30 mg/kg over 2 weeks. Netoglitazone dose-dependently improved mean serum triglyceride, VLDL and VLDL-triglyceride levels in these mice compared to controls, with a significant reduction in all parameters and normalization of VLDL-triglyceride levels at the highest dose. No significant effect was seen on food consumption, which was increased in *db/db* controls. It thus appears that netoglitazone may be able to improve the abnormal lipoprotein metabolism seen in type 2 diabetes (2, 3).

A study characterized the effects of netoglitazone on plasma glucose and lipids in murine models of type 2 diabetes. Orally administered netoglitazone at doses of 10 and 30 mg/kg/day for 8 weeks to *db/db* mice significantly and dose-dependently lowered plasma glucose levels, triglycerides and HbA1c. Rosiglitazone 30 mg/kg/day had similar effects. In contrast, troglitazone (200 and 400 mg/kg/day) showed no significant effect on any parameter and pioglitazone (30 mg/kg/day) significantly reduced glucose levels only (4).

A study compared the metabolic effects of netoglitazone and glibenclamide, an oral sulfonylurea, in KKAy mice, an animal model characterized by hyperglycemia, hyperinsulinemia, hyperlipidemia and insulin resistance. Netoglitazone was given at doses of 1, 3, 10 or 30 mg/kg/day p.o. over 4 days and compared to a dose of 1 mg/kg glibenclamide. Whereas the sulfonylurea showed no significant effect on plasma glucose, insulin, triglyceride or free fatty acid levels, dose-dependent decreases in all parameters were obtained on netoglitazone, and at the highest dose the differences were statistically significant compared to controls. Neither of the treatments influenced total cholesterol levels (5).

The metabolic and adipogenic effects of netoglitazone and rosiglitazone were compared in male genetically obese insulin-resistant Zucker (*fa/fa*) rats. *In vitro* studies indicated that netoglitazone stimulates PPARγ receptors and adipocyte differentiation to a lesser degree than rosiglitazone. Animals treated with 30 mg/kg/day netoglitazone and 1 mg/kg/day rosiglitazone by oral gavage showed equivalent reductions in hyperinsulinemia, hyperlipidemia and muscle insulin resistance, whereas rosiglitazone was associated with more potent stimulation of adipose tissue growth than netoglitazone. These findings suggest that the therapeutic effects of the thiazolidinediones may not correlate with PPARγ-mediated stimulation of adipogenesis (6).

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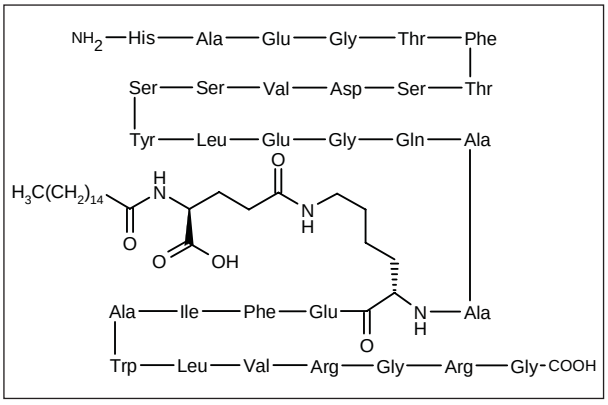
Original monograph - Drugs Fut 2002, 27(2): 132.

NN-2211



Novo Nordisk is developing the long-acting and metabolically stable GLP-1 (glucagon-like peptide-1) derivative NN-2211 for type 2 diabetes.

The effects of NN-2211 on glucose homeostasis and intake were assessed in diet-induced obese (DIO) rats. The animals received either saline or 150 μg/kg of NN-2211 s.c. b.i.d. for 14 days. An oral glucose tolerance test performed after 9 days of treatment demonstrated better results for NN-2211-treated DIO rats than for saline-treated rats. Overall, treatment with NN-2211 normalized blood glucose levels and reduced both body weight and food intake compared to control animals. The authors concluded that, besides its possible use for improving glucose homeostasis in obese humans, NN-2211 may also be effective for reducing weight (1). In another study, treatment with NN-2211 for 9 weeks normalized blood glucose levels and glucose tolerance in DIO rats. NN-2211 also reduced body weight due to a lower food intake. This suggested that the compound has dual beneficial effects on glycemic control and weight (2).

Synergistic effects were described for NN-2211 and ragaglitazar on glycemic control in diabetic rats. Ninety male diabetic ZDF rats were randomized to receive ragaglitazar (1 and 3 mg/kg p.o. once daily), NN-2211 (15 and 50 μg/kg s.c. b.i.d.) or a combination of these drugs for 4 weeks. The effects of a combination of NN-2211 and ragaglitazar on the 24-h glucose profiles and HbA1c levels of the diabetic rats were significantly greater than the additive effects calculated for the monotherapies. NN-2211 also tended to compensate for the effects on food intake and body weight induced by ragaglitazar, and the coadministration of both drugs induced focal pancreatic regeneration often associated with beta-cell neogenesis (3, 4).

A study compared the effects of NN-2211 and another GLP-1 analogue, exendin-4, given s.c. twice daily at respective doses of 200 and 100 μg/kg s.c. to female diabetic *db/db* mice, a model of type 2 diabetes. The results showed a longer lasting blood glucose-lowering effect and stimulation of β-cell proliferation on NN-2211 compared to exendin-4, which was attributed to the analogue's longer half-life. Results suggested that NN-2211, and to a lesser extent exendin-4, increased β-cell mass by stimulating the proliferation of existing β-cells rather than by stimulating β-cell neogenesis (5-7).

NN-2211 reduced blood glucose following an oral glucose load at a dose of 100 or 150 mcg/kg/day s.c. twice daily for 4 days in partially pancreatectomized rats. This was due to an increase in total β-cell mass, which appeared to involve increased proliferation or reduced apoptosis of remnant islets rather than increased neogenesis (8, 9).

A potential antiapoptotic role for NN-2211 was investigated using pancreatic islet cells isolated from neonatal rats. Apoptosis induced by free fatty acids was concentration-dependently inhibited by NN-2211, and to a lesser extent by GLP-1 (50 and 25% inhibition at 100 nM, respectively). The antiapoptotic effects of NN-2211 in this model were mimicked by cAMP and partially inhibited by wortmannin, but not by H98, indicating that the antiapoptotic actions of these hormones involve cAMP and PI_3 kinase but not protein kinase A (PKA) signaling (10). NN-2211 was also examined for its effects on cytokine-induced apoptosis in primary rat pancreatic islet β-cells. NN-2211 produced a concentration-dependent inhibition of cytokine (interferon-γ, TNF-α, IL-1)-induced apoptosis, with complete inhibition at the concentration of 1000 nM. Its effects were similar to GLP-1. Further experiments

Table V: Clinical studies of NN-2211 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind	NN-2211, 1.25 μg/kg s.c. s.d. → NN-2211, 1.25 μg/kg s.c. o.d. x 6 d [days 5-11 of the study] (n=1) NN-2211, 5.0 μg/kg s.c. s.d. → NN-2211, 5.0 μg/kg s.c. o.d. x 6 d [days 5-11 of the study] (n=2) NN-2211, 7.5 μg/kg s.c. s.d. → NN-2211, 7.5 μg/kg s.c. o.d. x 6 d [days 5-11 of the study] (n=4) NN-2211, 10.0 μg/kg s.c. s.d. → NN-2211, 10.0 μg/kg s.c. o.d. x 6 d [days 5-11 of the study] (n=4) NN-2211, 12.5 μg/kg s.c. s.d. → NN-2211, 12.5 μg/kg s.c. o.d. x 6 d [days 5-11 of the study] (n=4) Placebo (n=10)	30	Compared to placebo, NN-2211 in healthy subjects increased the incidence of adverse events, especially dizziness and adverse events related to the gastrointestinal system; a once-daily dose regimen was considered to be the best suited for humans	16
Diabetes mellitus type 2	Double-blind, crossover	NN-2211, 10 μg/kg i.v. Placebo	11	NN-2211 administered i.v. reduced fasting and postprandial plasma glucose levels by increasing insulin release, suppressing glucagon secretion and delaying gastric emptying in patients with type 2 diabetes	18
Diabetes mellitus type 2	Double-blind, crossover	NN-2211, 10 μg/kg s.d. s.c. Placebo	11	Compared to placebo, s.c. NN-2211 altered insulin secretion, reduced glucagon secretion and delayed gastric emptying in the fasting and fed states, reducing fasting and postprandial plasma glucose in patients with type 2 diabetes	19
Diabetes mellitus type 2	Randomized, double-blind	NN-2211, 0.045 mg o.d. x 12 wk NN-2211, 0.225 mg o.d. x 12 wk NN-2211, 0.45 mg o.d. x 12 wk NN-2211, 0.60 mg o.d. x 12 wk NN-2211, 0.75 mg o.d. x 12 wk Glimepiride, 2.7 [mean] mg o.d. x 12 wk Placebo	193	NN-2211 was safe and significantly improved glycemic control without inducing weight increase in patients with type 2 diabetes	21

indicated that their antiapoptotic effects involved cAMP/PKA and PI_3 kinase pathways (11). *In vitro* studies in neonatal rat islet cell cultures indicated that NN-2211 and GLP-1 stimulate β-cell proliferation in a cAMP/ PKA- and PI_3 kinase-dependent manner (12).

The effects of NN-2211 (200 μg/kg s.c. b.i.d.) on glycemia, body weight, insulin and lipid levels were investigated in obese prediabetic rats. The agent significantly reduced food intake and body weight and improved glycemic control. Insulin secretion was potentiated and basal insulin and fructosamine levels were reduced. Triglycerides, but not total cholesterol, were also reduced. β-Cell mass and proliferation were lower in the treatment group, suggesting good metabolic control as a result of NN-2211 treatment and thus a reduced need for β-cell expansion. It was concluded that NN-2211 may have potential in the early treatment of type 2 diabetes (13, 14).

The efficacy of NN-2211 in altering food intake and body mass was investigated in adult rhesus monkeys with spontaneous middle-age-onset obesity. NN-2211 (10 μg/kg b.i.d. 16 days) elicited a sustained attenuation of food intake to 38% below baseline with an accompanying reduction in weight. Complete recovery was achieved following the termination of NN-2211 treatment during the 1-month follow-up period (15).

The safety, tolerability, pharmacokinetics and pharmacodynamics of NN-2211 were assessed in 30 healthy volunteers randomly allocated to receive either placebo or s.c. NN-2211 at doses of 1.25-12.5 μg/kg. The half-life of NN-2211 was 11-13 h and drug exposure increased proportionally with increasing doses. Some accumulation was seen with repeated dosing. Overall, no significant effects on glucose or insulin were detected. Compared to placebo, subjects treated with NN-2211 had a higher incidence of adverse events, especially dizziness and gastrointestinal disturbances, but no serious adverse events were found; 3 patients withdrew from the study because of dizziness, fever and nausea. The authors concluded that the profile of NN-2211 supported once-daily dosing in humans (16). The results of this study and some that follow are summarized in Table V.

The pharmacokinetics and safety of NN-2211 were assessed in healthy male subjects in a double-blind, randomized, dose-escalating study. Subjects were

administered single s.c. doses of NN-2211 of 1.25-20 μg/kg or placebo, and single i.v. and s.c. doses of 5 μg/kg. Following s.c. administration, NN-2211 was slowly absorbed, with peak levels reached at about 11 h after dosing. Pharmacokinetics were proportional to dose and the elimination half-life was 12 h. An absolute bioavailability of 55% was estimated in the subjects receiving i.v. and s.c. doses of 5 μg/kg. In subjects given an i.v. glucose tolerance test, insulin secretion significantly increased on NN-2211. The drug was well tolerated at doses up to 17.5 μg/kg, with nausea and vomiting seen at higher doses. The pharmacokinetic profile suggested the feasibility of once-daily administration of NN-2211 (17).

A double-blind, placebo-controlled, crossover study was undertaken to assess the activity of NN-2211 10 μg/kg s.c. in 11 patients with type 2 diabetes while fasting and after a meal. The drug reduced fasting and postprandial plasma glucose concentrations by increasing insulin release, suppressing glucagon secretion and delaying gastric emptying (18-20).

Five different daily doses of NN-2211 (0.045, 0.225, 0.45, 0.60 and 0.75 mg) and placebo were used to determine the dose-response relationship for glycemic control, effect on body weight and safety in 2 large studies in patients with type 2 diabetes. The reference comparators used were glimepiride and metformin. Results demonstrated that NN-2211 significantly improved glycemic control, to a similar degree as the reference drugs, and maintained or slightly decreased body weight. NN-2211 was both safe and well tolerated, as most gastrointestinal side effects associated with the drug were mild and transient, and the risk of hypoglycemia was very low (21-23).

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Pegvisomant

The European CPMP has recommended the approval of Pharmacia's Somavert® (pegvisomant, B2036-PEG) for the treatment of acromegaly. It is indicated for patients who have had an inadequate response to surgery and/or radiation therapy and who failed to respond to treatment with somatostatin analogues. Pegvisomant is a human somatotropin antagonist and an analogue of human GH that has been genetically modified to be a growth hormone (GH) receptor antagonist that blocks GH action rather than its secretion from tumors (1).

Pegvisomant has been designated an orphan medicinal product in the U.S., the E.U. and Japan. Pharmacia acquired pegvisomant through its acquisition of Sensus. Pegvisomant is also under priority review at the FDA (2).

The impact of pegvisomant-mediated GH receptor antagonism on somatotroph GH synthesis and secretion in pituitary cells has been investigated. A modest increase in these parameters was observed, providing further evidence for pituitary GH autoregulation. Both human- and rodent-derived somatotroph adenomas displayed transition to the sparsely granulated phenotype with pegvisomant and GH4 cells showed increased cell proliferation. Interference in GH signaling may play an important role in the treatment of the 2 subtypes of somatotroph adenoma (3).

The structure, function and impact of pegylation on the biological efficacy of pegvisomant have been evaluated in 293GHR cells. The unpegylated drug had a 4.5-fold greater affinity for GH-binding protein than GH but a similar affinity for the membrane receptor. Transcription assays demonstrated that pegylation significantly reduced membrane binding affinity and receptor antagonism by 39- and 20-fold, respectively. The high concentration of drug required for clinical efficacy is related to pegylation. It was suggested that pegvisomant binds to a receptor dimer and induces internalization but not signaling (4).

The inhibitory effect of pegvisomant (1 mg/kg s.c.) on GH signal transduction was investigated in 6-week-old male rats. The effect was maximal with a GH:pegvisomant ratio of 1:100, and with no JAK2 tyrosyl phosphorylation. Growth hormone-induced IRS-1, IRS-2 and Shc tyrosyl phosphorylation was inhibited by approximately 50% at equimolar concentrations of antagonist, and was almost abolished with a GH:pegvisomant ratio of 1:100 (5).

The therapeutic potential of downregulating the GH/IGF-I axis in the management of colon cancer has been investigated using pegvisomant and a syngeneic mouse model of colon cancer and hepatic metastasis. BALB/c mice injected with colon carcinoma CT-26 cells were treated with saline, pegvisomant 5 mg/day s.c., the topoisomerase I inhibitor irinotecan 100 mg/kg s.c. on days 7, 14 and 21, or a pegvisomant-irinotecan combination. The results showed significant reductions in both primary tumor size in the spleen and hepatic metastases in pegvisomant-treated animals. The GH antagonist was effective alone and potentiated the effects of irinotecan. Further studies of pegvisomant in colon cancer appear warranted (6).

The GH receptor antagonist pegvisomant (0, 1.25, 2.5, 5 and 10 mg/kg/day x 7) was administered to mice in order to study the effects of GH in regulating the expression of the hepatic and renal GH and IGF system. While body weight, food consumption and blood glucose were not changed, all doses decreased circulating IGF-I levels dose-dependently, and the highest doses decreased hepatic and renal IGF-I levels, also in a dose-dependent manner. All doses significantly increased hepatic GH receptor and GH-binding protein mRNA levels. At 2.5 and 5 mg/kg/day, pegvisomant significantly increased endogenous circulating GH and all doses resulted in increased circulating IGF-binding protein-4 (IGFBP-4) and hepatic IGFBP-4 mRNA levels. At high doses, renal GH and GH-binding protein mRNA levels were not changed, and in most pegvisomant groups, renal IGFBP-3 mRNA levels were not changed. The highest doses, however, significantly increased IGFBP-1, IGFBP-4 and IGFBP-5 (7).

The effects of pegvisomant (1 mg/kg) on GH signal transduction were investigated in the kidneys of streptozotocin-induced diabetic rats. A significant increase in the phosphorylation of JAK2, insulin receptor substrate-1 (IRS-1), Shc, ERK and Akt was observed. Pegvisomant demonstrated inhibitory effects on diabetic renal enlargement and reversed alterations in GH signal transduction in this animal model. Growth hormone receptor blockade may represent a new option for the treatment of diabetic kidney disease (8). A review of the potential use of GH receptor antagonists in the treatment of diabetic kidney disease reports that these agents are therapeutic in conditions where GH and insulin-like growth factors possibly play a pathophysiological role. Diabetic mice treated with pegvisomant from the onset of diabetes showed normalization of diabetes-associated renal hypertrophy and glomerular enlargement and a reduction in diabetes-induced increases in urinary albumin excretion. Regression of several diabetes-associated renal changes was also demonstrated (9).

The antitumor activity of pegvisomant (315 mg/kg/week) against 15 xenografted human meningioma tumors was evaluated in athymic mice during 8 weeks. The mean volume of tumors in treated animals was significantly less (198.3 ± 18.9 mm^3) as compared to the vehicle group (350.1 ± 23.5 mm^3). The serum IGF-I concentration was 257 ± 9.7 μg/l in treated animals compared with 319 ± 12.9 μg/l in vehicle-treated animals. Thus, downregulation of the GH/IGF-I axis reduces meningioma growth and induces, in some instances, tumor regression (10).

The effect of pegvisomant on pituitary tumor volume was determined in 131 acromegaly patients and retrospectively analyzed for associations with prior therapy. Patients received pegvisomant 10-40 mg/day s.c. with MRI at 6, 12 and 24 weeks and every 6 months until the end of the study. Pegvisomant had no effect on pituitary tumor growth in these patients, who had prior therapy consisting of either surgery with conventional external beam radiotherapy, surgery only, radiation only or no therapy (11). The results of this study and some that follow are summarized in Table VI.

Endogenous GH secretion and half-life were determined in blood samples taken over 10 h from 8 healthy men and 4 healthy women 72 h after administration of pegvisomant 1 mg/kg or saline in a double-blind, randomized, crossover trial. Growth hormone secretion was stimulated by depletion of systemic total IGF-I concentrations, and GH secretory burst amplitude was amplified and the basal/nonpulsatile rate of GH secretion was increased (12).

In a double-blind, placebo-controlled, crossover study in 10 healthy lean male volunteers, 3 days of fasting alone and in combination with pegvisomant increased GH concentrations and decreased serum free IGF-I concentrations. Fasting alone and pegvisomant alone and in combination significantly increased GH concentrations after a GH-releasing hormone test. After a GH-releasing peptide-6 test, fasting alone, but not pegvisomant alone, increased GH levels (13).

Six healthy male volunteers were given a standard meal and randomized to octreotide (50 μg s.c. t.i.d.) or pegvisomant (80-mg s.c. loading dose and 20 mg/day thereafter) for 7 days. Glucose tolerance and stimulated gut hormone release were assessed via an oral glucose tolerance test and after a standard mixed meal. While pegvisomant did not affect glucose tolerance or stimulate gut hormone responses, octreotide significantly increased fasting plasma glucose, reduced fasting plasma insulin and induced deterioraton in glucose tolerance. The release of cholecystokinin, gastrin, insulin and pancreatic polypeptide was also impaired by octreotide administration (14).

Cardiovascular risk factors were assessed in a 3-part study of pegvisomant treatment in 48 patients with acromegaly. The study consisted of a cross-sectional comparison of patients with healthy controls; a 12-week, placebo-controlled study of treatment with pegvisomant 10, 15 or 20 mg/day; and an open-label evaluation of treatment with pegvisomant 10-35 mg/day. Patients at baseline had higher C-reactive protein (CRP) and insulin levels than healthy controls; CRP levels were reduced by pegvisomant treatment (15).

Cardiovascular risk markers were evaluated after placebo and pegvisomant treatment in a double-blind, crossover study in healthy male, nonobese volunteers under fed and fasting conditions. No signficant changes in the major risk markers for cardiovascular disease were seen with pegvisomant treatment (80 mg s.d.) (16).

The control of tumor size and disease activity by combined treatment with octreotide (30 mg/month) and pegvisomant (40 mg/day) was evaluated in a male acromegalic patient. A rapid normalization of serum total IGF-I concentrations was observed within 2 months, which remained well controlled with levels around 35 nmol/l. No further increase in tumor size was apparent and a marked decrease in serum GH concentrations was noted. Abnormalities in the visual field were completely resolved and signs and symptoms of acromegaly were considerably improved (17).

Cortisol metabolism was studied in 7 patients with active acromegaly before and after receiving a mean of 46 weeks of treatment with pegvisomant. Pegvisomant reversed inhibition of 11β-hydroxysteroid dehydrogenase, corrected cortisol metabolism and reversed accelerated cortisol clearance in these patients (18).

Seven patients with acromegaly were treated with pegvisomant for 1 year (n=3) or 2 years (n=4) in 2 separate clinical trials. The patients had disease which was refractory to standard therapy. Serum IGF-I was normalized in all patients at a median dose of 20 mg/day. Improvements in soft tissue enlargement and general well-being were also observed. Pegvisomant was well tolerated and efficacy was maintained for more than 2 years (19).

Pegvisomant was ineffective in producing regression of retinal neovacularization in an multicenter, open-label phase IIa trial in 25 patients with diabetes mellitus type 1 or 2 and proliferative diabetic retinopathy. A pegvisomant loading dose of 100 mg s.c. was followed by self-administration of 20 mg/day for 12 weeks. Neovascularization in the study eye did not change in 16 patients and progressed in 9 at the end of the study (20).

Patients with active acromegaly (n=16) were administered pegvisomant 10-40 mg/day to study the effects of serum IGF-I normalization on serum IGF-11, IGFBP-1, IGFBP-2 and the molar ratio of IGF-I and II to IGFBP-3. Treatment with pegvisomant reduced serum IGF-I to the normal range in all patients and the decrease was correlated with a fall in fasting plasma insulin (FPI). Serum IGF-II was not changed. The IGF-I/IGFBP-3 molar ratio decreased and the IGF-II/IGFBP-3 molar ratio increased. The HOMA equation, which was used to calculate insulin, and the fall in IGFBP-1 indicated that improved insulin sensitivity caused the reduction of FPI and that IGF-II is independent of growth hormone (21).

Pegvisomant was studied in 109 patients with active acromegaly and soft tissue swelling. Patients included those who took part in a previous 12-week, double-blind, placebo-controlled study of pegvisomant 10-20 mg/day and 6 additional patients receiving 5-40 mg pegvisomant in an open-label study. In the initial study, pegvisomant 20 mg/day normalized serum IGF-I in 89% of patients and resulted in improvements in perspiration, fatigue, soft tissue swelling and total symptom scores. These changes were maintained for a median of 12 months. A dose-dependent reduction in ring size was found in the first study, which was maintained at last visit in the

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

Indication	Design	Treatments	n	Conclusions	Ref.
Acromegaly	Retrospective	Pegvisomant, 10-40 mg s.c. o.d. x 18 mo	131	Pegvisomant induced no changes in the pituitary tumor volume of the patients regardless of their previous therapy, therefore confirming that it is both safe and effective in the treatment of acromegaly	11
Healthy volunteers	Randomized, double-blind, crossover	Pegvisomant, 1 mg/kg s.c. s.d. Placebo	12	Pegvisomant treatment resulted in GH secretion, which was stimulated by depletion of systemic total IGF-I concentrations. GH secretory burst amplitude was also amplified and the basal/nonpulsatile rate of GH secretion was increased	12
Healthy volunteers	Double-blind, crossover	Pegvisomant, 80 mg s.c. s.d. Pegvisomant, 1 μg/kg i.v. [test given before and after 3 d of fasting] Growth hormone releasing peptide-6, 1 μg/kg i.v. [test given before and after 3 d of fasting] Placebo	10	Fasting and pegvisomant decreased serum free IGF-I and increased growth hormone concentrations and significantly increased GH concentrations after a GH-releasing hormone test. After a GH-releasing peptide-6 test, fasting alone, but not pegvisomant alone, increased GH levels	13
Healthy volunteers	Randomized, crossover	Pegvisomant, 20 mg/d s.c. x 7 d Octreotide, 50 mcg t.i.d. x 7 d	6	Octreotide, but not pegvisomant, led to deterioration in glucose tolerance and impaired stimulated gut hormone release in healthy male subjects	14
Acromegaly	Randomized, open, multicenter	Study 2: Pegvisomant, 10 mg/d x 12 wk (n=12) Pegvisomant, 15 mg/d x 12 wk (n=10) Pegvisomant, 20 mg/d x 12 wk (n=12) Placebo (n=14) Study 3: Pegvisomant, 10-35 mg x up to 18 mo [dose adjustment to achieve a normal IGF-I]	48	Patients at baseline had higher C-reactive protein (CRP) and insulin levels than healthy controls; CRP levels were reduced by pegvisomant treatment	15
Healthy volunteers	Double-blind, crossover	Pegvisomant, 80 mg s.d. s.c. Placebo	10	No signficant changes in the major risk markers for cardiovascular disease were seen with pegvisomant treatment	16
Acromegaly	Randomized, double-blind	Pegvisomant, 30 mg s.c. o.w. x 6 wk → 10 mg/d → 20 mg/d Pegvisomant, 80 mg s.c. o.w. x 6 wk → 10 mg/d → 20 mg/d Placebo	7	Pegvisomant reversed inhibition of 11β-hydroxysteroid dehydrogenase, corrected cortisol metabolism and reversed accelerated cortisol clearance in patients with acromegaly	18
Acromegaly		Pegvisomant, 20 mg/d (median dose) x 1 y (n=3) Pegvisomant, 20 mg/d (median dose) x 2 y (n=4)	7	Pegvisomant was effective in acromegaly normalizing serum insulin-like growth factor-I in all patients, improving soft tissue enlargement and general well being. The treatment was well tolerated and maintained efficacy for more than 2 years	19
Diabetes mellitus type 1 and 2, diabetic retinopathy	Multicenter	Pegvisomant, 100 mg s.c. (loading dose) → 20 mg/d x 12 wk	25	Pegvisomant was ineffective in producing regression of retinal neovascularization in patients with diabetic retinopathy	20
Acromegaly		Pegvisomant, 10-40 mg s.c. o.d.	16	Pegvisomat improved insulin sensitivity and normalized serum IGF-I levels in patients with active acromegaly	21

Continued

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

Indication	Design	Treatments	n	Conclusions	Ref.
Acromegaly	Randomized, double-blind	Pegvisomant, 5-40 mg s.c. o.d. x 12 wk Placebo	103	Pegvisomant normalized serum IGF-1 levels and improved symptom scores of active acromegaly and objective assessment of soft tissue swelling	22
Acromegaly	Double-blind	Study 1: (n=118) Pegvisomant, 10, 15 or 20 mg/d x 3 mo Placebo Study 2: (n = 109) Pegvisomant, 5-40 mg/d	227	Pegvisomant reduced serum IGF-I and significantly improved disease symptoms	23
Acromegaly, pituitary cancer	Multicenter	Pegvisomant, 10 mg o.d. s.c. → 40 mg o.d. s.c. [increased 5 mg each day]	160	Pegvisomant was an effective medical treatment for acromegaly	25

second study. The fall in serum IGF-I was positively correlated with the fall in total symptom score and the scores for perspiration and soft tissue swelling. In the open-label study, a decrease in serum IGF-I was maintained for a median of 18 months and improvements in total symptom score and ring size were maintained (22, 23).

An efficacy analysis of open-label studies in 160 patients with acromegaly treated with pegvisomant included 152 patients receiving daily s.c. injections for up to 18 months. At 6-, 12- and 18-month time points, mean serum IGF-I levels decreased by at least 50% on pegvisomant, and GH levels temporarily increased in parallel. Eighty-seven of 90 patients (97%) treated for at least 12 months achieved normal serum IGF-I levels. Although antibodies to GH were detected in some patients, there was no tachyphylaxis. Mean pituitary tumor volumes did not change significantly, except in 2 patients showing progressive increases. Pegvisomant was generally well tolerated, infections being the most frequent adverse event (33%). The investigators concluded that pegvisomant is an effective and safe treatment for acromegaly, especially in light of the limited efficacy of the current options of surgery, radiotherapy, dopamine agonists or somatostatin analogues. As fasting serum insulin and glucose levels also showed a significant decrease in patients treated with pegvisomant, it may also have potential beneficial effects on insulin resistance and type 2 diabetes in patients with or without acromegaly (24, 25).

Serum lipoprotein and insulin levels were evaluated in 20 acromegaly patients treated with pegvisomant begun at 10 mg/day and increased by 5 mg/day every 8 weeks until IGF-I levels were normalized. Pegvisomant was found to increase the reduced serum triglyceride and LDL levels seen in acromegaly patients and to improve insulin resistance (26).

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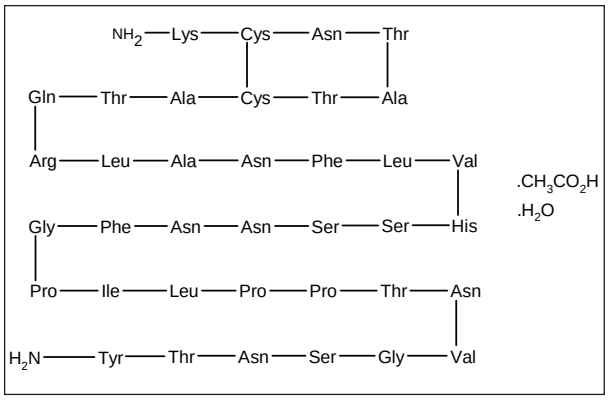
Pramlintide Acetate



Amylin has completed enrollment in a dose-titration study of pramlintide acetate (Symlin™), an analogue of human amylin, a hormone secreted with insulin by pancreatic β-cells, in patients with type 1 diabetes who are actively trying to improve their glucose control (1).

The double-blind, placebo-controlled, dose-titration study has enrolled some 250 subjects with type 1 diabetes over a period of 7 months. Subjects start with 1-month dose titration of placebo or pramlintide, coupled with insulin adjustments to safely optimize glucose control. Patients are then treated for 6 months at a steady-state dose of pramlintide or placebo, with additional insulin adjustments allowed. The results will be used for an NDA amendment, planned for submission in the first quarter of 2003. The FDA issued an approvable letter for pramlintide in October 2001 for the treatment of type 1 and insulin-dependent type 2 diabetes as an adjunct to insulin, although final approval is dependent on positive results from this dose-titration study and 4 small pharmacological studies already completed or under way. Amylin has also submitted marketing authorization applications for pramlintide in Europe and is currently working with the EMEA and Swiss regulatory authorities in their reviews (2-11).

In order to quantify the effect of a single dose of pramlintide on the postprandial glucose-lowering dose-response of insulin, streptozotocin-treated rats were injected with insulin lispro (0.1, 1 and 10 U/rat) with or without coadministration of 10 mcg pramlintide acetate, 2-3 weeks following the onset of diabetes. Insulin lispro dose-dependently reduced the 4-h mean plasma glucose levels and pramlintide augmented the maximal glucose-lowering effect of insulin lispro (12).

Data from 3 clinical trials of preprandial pramlintide (120 μg b.i.d.) as adjunctive therapy in type 2 diabetes were pooled to analyze changes in HbA1c, body weight and insulin use. Compared with placebo, patients

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

Indication	Design	Treatments	n	Conclusions	Ref.
Diabetes mellitus type 2	Randomized	Pramlintide, 120 μg s.c. b.i.d. x 26 wk + Insulin x 26 wk Placebo + Insulin	523	Compared to insulin alone, addition of pramlintide to insulin treatment increased the percentage of patients with type 2 diabetes who reached glucose control, in conjunction with weight loss	13
Diabetes mellitus type 2		Pramlintide, 120 μg s.c. b.i.d. + Insulin Placebo + Insulin	428	Addition of pramlintide to insulin therapy improved glycemic and weight control in patients with type 2 diabetes	14
Diabetes mellitus type 1	Randomized	Pramlintide, 120-270 μg/d s.c. x 4 wk + Insulin x 4 wk Placebo + Insulin	1154	Addition of pramlintide to insulin treatment improved glycemic control (as shown by reduced severe hypoglycemia rates) compared to insulin alone in patients with type 1 diabetes	16
Diabetes mellitus type 1		Pramlintide, 30 μg s.c. t.i.d. + Insulin Pramlintide, 30 μg s.c. t.i.d. + Insulin Pramlintide, 60 μg s.c. q.i.d. + Insulin Pramlintide, 60 μg s.c. q.i.d. + Insulin Placebo + Insulin	889	Pramlintide administered as an adjuvant to insulin therapy was better than insulin alone in achieving good glycemic and weight control in patients with type 1 diabetes	17
Diabetes mellitus type 1	Randomized, double-blind, multicenter	Double-blind study: Pramlintide, 30 μg q.i.d. s.c. [increased to 60 μg @ 120 wk if decreases of HbA1c <1% @ wk 13] x 52 wk (n=243) Placebo x 1 y → Pramlintide, 30-60 μg s.c. q.i.d. x 1 y (n=237)	480	Pramlintide produced significant and sustained reductions in HbA1c levels which were not associated with weight gain in type 1 diabetes	19
Diabetes mellitus type 1	Randomized, double-blind, multicenter	Pramlintide, 30 μg t.i.d. x 4 wk (n=18) Placebo (n=6)	24	Pramlintide substantially reduced postprandial glucose, glucagon triglyceride excursions and insulin requirements in type 1 diabetes	20, 21
Diabetes mellitus type 1 and 2	Randomized, crossover	Pramlintide, 30 μg t.i.d. s.c. x 4 d Pramlintide, 60 μg t.i.d. s.c. x 4 d Placebo		Pramlintide delayed gastric emptying and lowered postprandial plasma pancreatic polypeptide levels to the same extent in patients with type 1 or type 2 diabetes	24
Diabetes mellitus type 2	Randomized, double-blind, multicenter	Pramlintide, 30 μg s.c. t.i.d. x 52 wk (n=122) Pramlintide, 75 μg s.c. t.i.d. x 52 wk (n=136) Pramlintide, 100 μg s.c. t.i.d. x 52 wk (n=144) Placebo (n=136)	538	Pramlintide reduced HbA1c levels without increasing insulin use or severe hypoglycemia. Significant reductions in body weight were also seen in all dose groups compared to placebo	27
Diabetes mellitus type 1	Randomized, double-blind, crossover	Study 1: Pramlintide, 25 μg i.v. over 5 h x 2 d + Insulin s.c. (n=9) Pramlintide, 50 μg i.v. over 5 h x 2 d + Insulin s.c. (n=9) Placebo x Insulin s.c. (n=18) Study 2: Pramlintide, 30 μg s.c. t.i.d. x 14 d (n=18) Pramlintide, 100 μg s.c. t.i.d. x 14 d (n=23) Pramlintide, 300 μg s.c. t.i.d. x 14 d (n=21)$ Placebo + Insulin (n=22)	120	Pramlintide prevented abnormal postprandial increases in plasma glucagon concentrations in patients with type 1 diabetes	28

receiving pramlintide in combination with insulin had better glycemic control and this was associated with significant weight loss (13, 14). The results of this study and some that follow are summarized in Table VII.

Analysis of pooled data from 3 randomized, placebo-controlled clinical trials conducted in patients with type 1 diabetes revealed that preprandial s.c. injections of pramlintide (30/60 μg t.i.d./q.i.d.) for 26 weeks added to preexisting insulin regimens significantly decreased plasma HbA1c levels without increasing either body weight or the risk of severe hypoglycemia. Pramlintide appeared to prevent the weight gain associated with glycemic

improvement in lean patients and induced weight loss in overweight patients. The authors concluded that the addition of pramlintide to insulin therapy might help to achieve near-normal glucose control in patients with type 1 diabetes via additional decreases in HbA1c and glucose levels (15-18).

A 1-year, multicenter, randomized, double-blind, placebo-controlled trial of pramlintide in 480 patients with type 1 diabetes was followed by a 1-year open-label extension in 236 patients. In the double-blind study, preprandial injections of placebo or pramlintide 20 μg q.i.d. (plus continuing insulin therapy) were administered until week 20, when patients in the pramlintide group with decreases in HbA1c of less than 1% at week 13 were rerandomized to pramlintide 30 or 60 μg q.i.d. In the open-label study, pramlintide doses of 30 and 60 μg q.i.d. were given. Pramlintide significantly reduced HbA1c levels and these levels were sustained throughout the randomized and extension phases of the study. The reduction in HbA1c was not associated with weight gain (19).

Pramlintide 30 μg t.i.d. was administered for 4 weeks to 24 patients with type 1 diabetes intensively treated with insulin pump therapy in a randomized, double-blind, placebo-controlled study. Pramlintide reduced postprandial glucose excursions by more than 80%, postprandial glucagon by approximately 90% and postprandial triglyceride excursions by approximately 75%. The time spent in the target glucose range increased by 32% and the time spent above the target range declined from 59% to 48% in a 24-h period. Patients treated with pramlintide showed a shift in their plasma glucose levels towards euglycemic ranges without any severe hypoglycemic events. Postprandial triglyceride excursions, a recognized cardiovascular risk factor, were also reduced. Two weeks after patients finished pramlintide therapy, daily glucose profiles and postprandial triglyceride excursions returned to levels similar to those recorded prior to initiation of therapy (10, 20-23).

A randomized, crossover study was conducted to compare gastric emptying in patients with type 1 (n=6) or type 2 (n=6) diabetes treated with pramlintide. Subcutaneous pramlintide 30 or 60 μg t.i.d. administered for 5 days equally delayed gastric emptying and lowered postprandial plasma pancreatic polypeptide to the same extent in patients with type 1 or type 2 diabetes (24).

A randomized, single-blind, placebo-controlled, crossover study enrolled 19 patients with type 2 diabetes treated with insulin lispro and the patients were randomized to receive either placebo or 60 μg of pramlintide at different times between 15 min before and 30 min after a mixed meal. The patients also received their usual dose of insulin lispro. Measurement of plasma glucose concentrations before and after each meal revealed that pramlintide injected at the time of the meal was more effective than insulin lispro in reducing postprandial glucose excursions (70% *vs*. 60%). Pramlintide treatment was well tolerated and induced no serious adverse events (25).

A randomized, single-blind, placebo-controlled, crossover study included 35 patients with type 1 diabetes treated with either regular insulin or insulin lispro. The patients were randomized to receive either placebo or 60 μg of pramlintide at different times between 15 min before and 60 min after a mixed meal. The patients also received their usual dose of regular insulin or insulin lispro. Measurement of plasma glucose concentrations before and after each meal revealed that pramlintide injected at the time of the meal was more effective than the patients' background insulin treatment in reducing postprandial glucose excursions (95% *vs*. 75%). The intensity of this effect decreased when pramlintide was administered 15 or 30 min after the meal (26).

A year-long, randomized, double-blind, placebo-controlled, dose-ranging study compared treatment of 538 patients with type 2 diabetes receiving insulin therapy with pramlintide 30, 75 or 150 μg s.c. t.i.d with meals. Pramlintide reduced HbA1c levels without increasing insulin use or severe hypoglycemia. Significant reductions in body weight were also seen in all dose groups compared to placebo (27).

Pramlintide was found to prevent postprandial increases in plasma glucagon concentrations in type 1 diabetic patients in 2 randomized, double-blind, placebo-controlled trials. The first study evaluated a 5-h i.v. infusion of pramlintide 25 or 50 mcg/h plus insulin injections in 18 patients, and the second was a 14-day study in 84 patients given s.c. pramlintide 30, 100 or 300 μg t.i.d. plus s.c. insulin for 14 days. In placebo-treated patients in both trials, plasma glucagon concentrations were elevated after a meal (28).

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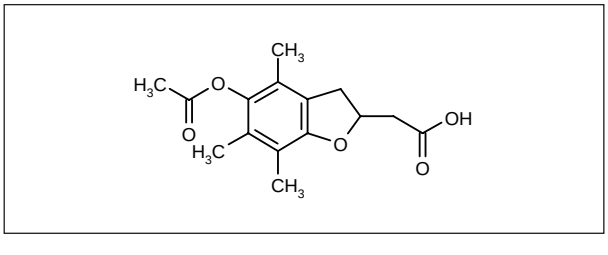
Raxolefast



Raxofelast (IRFI-016) is a vitamin E-like antioxidant which is undergoing phase II trials at Biomedica Foscama for the treatment of diabetic complications.

The involvement of lipid peroxidation in the pathogenesis of altered vascular endothelial growth factor (VEGF) expression in diabetes-related healing deficit was studied in female diabetic C57BL/KsJ *db/db* mice receiving raxofelast (15 mg/kg/day i.p.). A significant improvement in wound repair was observed via the stimulation of angiogenesis, reepithelialization, synthesis and maturation of the extracellular matrix. The drug also significantly reduced wound conjugated diene levels and increased the wound breaking strength. Inhibition of lipid peroxidation restored the defect in VEGF expression during the process of skin repair and normalized the VEGF wound content (1, 2).

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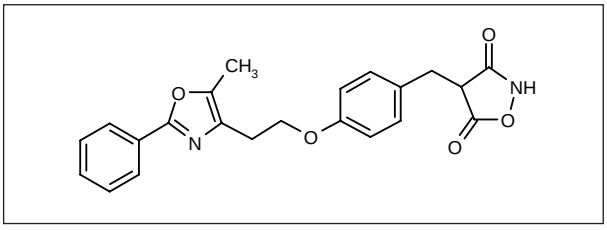
Reglitazar



The insulin-sensitizing agent reglitazar (JTT-501, PNU-182716) was originally synthesized at Japan Tobacco and subsequently licensed to Pharmacia worldwide except Japan and Korea. The compound has reached phase II clinical evaluation for the treatment of non-insulin-dependent diabetes mellitus.

The pharmacological activity of rosiglitazone and pioglitazone was compared with that of the development candidates reglitazar, NNC-61-0029, KRP-297, netoglitazone and GI-262570 *in vitro* and in a mouse model of type 2 diabetes. All of the drug candidates showed PPARα and PPARγ agonism *in vitro* and several demonstrated insulin-sensitizing activity superior to rosiglitazone and pioglitazone in mice (1).

Investigators found that reglitazar restored the reduced expression of the phosphodiesterase 3B gene in the adipose tissues of obese, diabetic KKAy mice. Reglitazar also reduced elevated levels of serum insulin, glucose, free fatty acids and triglyceride in these animals (2).

The effects of reglitazar on the hepatic gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) gene expression and phosphorylation of Akt were investigated in diabetic rat livers and cultured hepatocytes. The agent reduced the expression and activity of PEPCK mRNA in the liver and attenuated the cAMP-induced increase in mRNA expression in hepatocytes. Furthermore, the agent increased the expression of phosphorylated Akt in cultured hepatocytes. All observed effects were sensitive to wortmanin (3).

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