CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-649

MEDICAL REVIEW(S)

NOV 27 1996

REVIEW OF ALPROSTADIL NDA
NDA 20,649

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1.1 Combined Medical and Statistical Review

1.1.1 NDA #20-649

1.1.2 Medical and Statistical Review

1.1.3 Submission January 7, 1996, received

1.1.4 Review completed October 23, 1996

1.2 Name of Drug

1.2.1 Generic name: Alprostadil alphadex (Alprostadil-alfadex/PGE_1) (Alpha-cyclodextrin) (SPM-691)

1.2.2 Proposed trade name: EDEX

1.3 Sponsor: Schwarz Pharma, Inc.

1.4 Pharmacologic Category: Prostaglandin - smooth muscle relaxant

1.5 Proposed Indication:

- Erectile Dysfunction

This drug is indicated for the intracavernous treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.

It is also indicated for use as an adjunct in the diagnosis of erectile dysfunction. The sponsor has submitted this data late and was advised to resubmit this data.

1.6 Dosage Forms and Route of Administration

Treatment:

Diagnostic:

1.7 NDA Drug Classification - 3S

1.8 Important Related Drugs

Several formulations of Alprostadil are marketed and include:

- Prostin VR - Pediatric sterile solution containing 500 µg of Alprostadil in 1 mL of dehydrated alcohol used as part of a 'tri-mix' solution for intracavernous injections; however, it is not approved for this indication. Prostin VR is approved for the palliative treatment of patent ductus arteriousus.

- Prostavasin - Schwarz Pharma AG - (Germany) freeze-dried formulation containing 20 µg of Alprostadil in a complex formation with alpha cyclodextrin.

1.9 Related Reviews: see pharmacology and biopharm review.

2 Table of Contents See page 1

3 Material Reviewed:

electronic versions submitted by sponsor
volume 1.1 - the entire NDA is well indexed.

Volumes Reviewed

Volume	Trial	Date
1,1		November 8, 1995
1.62,1.63,1.64, 1.74 (1-6),1.75 1.76, 1.78 (7-12)	KU 620-001	"
1.82 (1-6),	KU 620-002	"
1.88 (1-6) 1.94,1.96,1.107 (1-6)	KU 620-003	"
1.108	F 8653	"
1 and 3	Safety Update 33 volumes	March 15, 1966

4 **Chemistry/Manufacturing Controls**
See Chemistry Review - no clinically relevant issues.

5 **Animal Pharmacology/Toxicology**
See Pharmacology Review - no clinically relevant issues.

6 **Clinical Background**

Overview of sexual or erectile dysfunction:

This overview will include the definition, history, mechanism, diagnosis and treatments available for the treatment of erectile dysfunction. Erectile dysfunction, or impotence, is defined as the consistent inability to achieve or to maintain an erection of sufficient rigidity for vaginal penetration in sexual intercourse. Erectile dysfunction is a common sexual problem which affects an estimated one in ten men over the age of 21 and is an age-related disorder, with an incidence of 1.9% at 40 years of age and 25% at 65 years of age. A recent review of U.S. data suggests that 10 to 20 million American men have erectile insufficiency (Padma-Nathan et al 1987). The first approved therapy for the treatment of male erectile was Caverject, a prostaglandin E_1 developed by Upjohn.

Erectile dysfunction may be due to neuropathic, vasculogenic (including either arterial or venous insufficiency), psychogenic, hormonal, anatomic causes or, as in most cases, a combination of all of these problems. Men with diabetes may have some impariment of erectile function in 25 - 75% of cases. Although the diagnosis of erectile dysfunction is more easily determined today and possible organic causes identified, it is still difficult to define the exact contribution of psychogenic versus organic components. It is also difficult to identify on an individual basis the appropriate dose for intracavernous injection for each patient.

There are three phases involved in the vascular response which is responsible for an erection. These are: (1) an increase in the arterial inflow, (2) a sinusoidal relaxation and (3) filling of the corporeal bodies from the increased arterial flow, and a decrease in the outflow from or trapping of blood within the corpora bodies. Failure to trap blood within the corpora is a common cause of vasculogenic organic impotence. These patients fail to increase the intracorporeal pressure greater than the systolic blood pressure and/or have a rapid decrease in intracorporeal pressure after cessation of saline infusion during a test cavernosometry. In one study 68% (30/44) of men who failed to achieve an erection after intracorporeal papaverine injection had a vasculogenic cause of their erectile problems (Rajfer, et al, 1988). Most of these were caused by corporeal venous leakage.

A major component of penile erectile dysfunction is the impaired relaxation of the smooth muscle component of the corpus cavernosum. The corpora cavernosa are the bodies within the penis which entrap increased arterial blood to increase the rigidity of the organ with relaxtion of the smooth muscle in the corpora (see diagragm in appendix). Relaxation of the smooth muscle in the corpora is elicited by acetylcholine mediated by a chemical substance derived from the endothelium. In 1982 Virag first introduced the concept of papaverine as a smooth muscle relaxant in the penile smooth muscle. This was demonstrated by Brindley in 1983 with phenoxybenzamine. In the early years of intracavernous penile injections the major components used were either papaverine alone or in combination with phentolamine. By 1985 Lilly Pharmaceutical had added a disclaimer in their papaverine label contradicting its use for the treatment of erectile dysfunction possibly due to reports of prolonged erections or priapism, which constitute an emergency in most cases.

More recently the injection of vasoactive medications directly into the corpora cavernosa represents a dramatic change in both the diagnosis and treatment of this problem. Agents reported to be effective with intracavernous injections include papaverine alone (Virag 1982) or combinations of papaverine with phentolamine (Zorgniotti & Lefleur 1985), phenoxybenzamine (Brindley 1983), and alprostadil (prostaglandin E_1; PGE_1) (Ishii et al 1986, Lue, 1992). Prior to the approval of Caverject (prostaglandin E_1) in 1995 only one agent, a combination of papaverine and phentolamine, was licensed for the treatment or diagnosis of erectile dysfunction and this agent was licensed only in Austria and France. Many practitioners currently continue to combine several of the products as a "cocktail" or "tri-mix".

By 1986 several investigators studied the use of prostaglandin E_1 as a more effective smooth muscle relaxant. Prostin, available in hospital formularies for the treatment of patent ductus arteriosus, was initially utilized for this injectable treatment. This probably resulted in uneven dilutions and acidic pH of the final solution. The penile cavernosal tissue has the ability to

well as prostaglandins may have either contractile or relaxation effects on the smooth muscle.

Intracavernosal injection of vasoactive agents is particularly useful in patients who have neurogenic impairment, such as spinal-cord injury or diabetes mellitus, and in those with vascular insufficiency. Intracavernosal injection is also useful in patients with psychogenic impotence, and these patients often respond well because their vascular systems are usually normal (Krane et al 1989). Patients with severe corporal veno-occlusive dysfunction or those with severe arterial insufficiency are the least likely to respond to intracavernosal therapy, and intracavernosal self-injection therapy is not appropriate for patients with poor manual dexterity, poor visual acuity, or morbid obesity.

Intracavernosal injection therapy provides an attractive alternative to surgery. It is reliable, safe, and effective in the majority of men with erectile dysfunction. In more than 70% of men, functional erections are produced within 10 minutes of injection (Bénard & Lue 1990). The intracavernosal injection technique is easy to learn for the majority of patients or their partners and, because its effects are reversible as well as relatively rapid and "natural" in onset, satisfaction and compliance are high (Stevenson 1988).

Pharmacologic agents used for Erectile Dysfunction:

- **Papaverine Hydrochloride** is a benzylisoquinoline alkaloid with a major action to relax corporal smooth muscle.

- **Phentolamine Mesylate** is an alpha-adrenergic antagonist and may have a direct, nonspecific relaxant effect on vessels. It is thought not to produce a rigid erection by itself since it does not involve direct corporal smooth muscle relaxation. It is usually combined with papaverine. Current research is reevaluating the use of phentolamine as a single agent.

Prostaglandins:

- Prostaglandins are endogenously produced eicosanoids with smooth muscle relaxant properties which relax both the smooth muscle and helicine arteries. Prostaglandin E1 (PGE_1) has a strong relaxing effect on the smooth muscle of the corpus cavernosum and the helicine and cavernosal arteries. PGE_1 is thought to have an inhibitory effect on the alpha adrenergic receptors of the corpora cavernosa.

arteries. PGE_1 is thought to have an inhibitory effect on the alpha adrenergic receptors of the corpora cavernosa.

Other prostaglandins include: prostaglandin F_{2a} (PGF_{2a}), prostaglandin I_2 (PGI_2; prostacyclin; epoprostenol). Only PGE1 has been developed for the treatment of erectile dysfunction.

Prostaglandins (Alprostadil) approved or under investigation:

Sponsor:	IND/NDA	Drug:
Upjohn	IND NDA #20-379 intracavernous injection	CAVERJECT
Pharmacal	IND	none
Vivus	IND NDA 20-700 (pending) intraurethral	MUSE
Schwarz	IND NDA 20-649 (under review) intracavernous injection	EDEX

Nitric oxide delivery systems:

• Nitric oxide delivery systems are thought to be important mediaries in the process of smooth muscle relaxation. Nitric oxide synthase (NOS) activity decreases nitric oxide formed by the conversion of L-arginine into L-citrulline by the enzyme nitric oxide synthase.

Phosphodiesterase Inhibitors (PDE)

• UK-92,480 (sildenafil/Pfizer) selectively inhibits the type V cyclic guanosine monophosphate specific phosphodiesterase (PDE) enzyme which is the predominant PDE isoenzyme in human corpora cavernosa. It enhances the effects of endogenous and exogenous substances such as nitric oxide and the nitro-vasodilators, which also elevate cGMP. Through enhancing the second messenger, cGMP, UK-92,480 is expected to relax corpous cavernosal and vascular smooth muscle .

Use Of Prostaglandins As Diagnostic Test:

As part of an adequate impotence work-up a vasoactive penile injection (intracavernous) test is done in the office by the urologist or andrologist. If there is a prompt and sustained rigid erection it is unlikely there is a significant arterial or venous problem. In addition some Andrologists would include in this

- Intracavernous injection of 10 ug of prostaglandin E_1 and observe for 15 minutes
- **Good erection lasts >45 minutes,** phenylephrine injection to prevent priapism available.
- Partial erection, add manual genital stimulation in a private room
- If erection adequate the patient may proceed to home injection with adequate training. (Lue,1993)

Doses of current drugs used for penile intracavernosal injections are:

Prostaglandin E_1 - 10 ug
Mixture or cocktail of Papaverine, Phentolamine and Prostaglandin PGE_1 (PPP) 0.25 cc - 0.5 cc
(unapproved regimen)

Most patients enrolled in self-injection programs respond to Alprostadil in doses of 20 µg or less and approximately 50% of the patients selected a 20 µg dose for self-injection. The duration of erections usually range from 0.5 to 4 hours (mean - 1.2 hours). In some but not all studies there is a linear correlation between Alprostadil dose and duration of erection. Recommended dose of PPP for patients with neurogenic history is 0.1 cc and 0.25 cc for patients without a neurogenic history.

A normal rigid erection following diagnostic testing usually occurs between 5 and 45 minutes. Rigidity response by either investigator or patient refers to a response sufficient for intercourse using a scale of 0 to 100%. If the rigidity response is >75%, injectable therapy or the use of vacuum device is recommended. If the rigidity response is <50% with visual stimulation, one should consider further evaluation which should include use of the Doppler and cavernosometry.

Diagnostic Tools:

Any methodology recording the quality of penile erection has included the determination of the penile blood pressure, blood flow, temperature, circumference, and rigidity. Penile rigidity is defined as the mechanical stiffness the penis exhibits to external load, and is manifested both cirumferentially and axially. Penile rigidity is the result of increased cavernous blood vessels increasing the blood volume within the corporal bodies. These bodies are constrained within their specialized lining - the tunica albuginea.

Rigidity develops when expansion is sufficient to induce stress in this envelope. Measurement of penile rigidity is the most important determination of the quality of penile erection. Rigidity of the penis is

critical - stiffness is more important than circumferential expansion as measured by nocturnal penile tumescence (NPT). NPT, if normal, indicates that neural and vascular supply and the penile structures are intact. Measurement of buckling force, the stamp test, and snap-gauge cuffs do not measure quality or duration of penile rigidity.

Visual sexual stimulation (VSS) or direct visual stimulation has become an adjunct to any measurement of erectile function. If erectile dysfunction (ED) is of psychogenic origin visual sexual stimulation alone may result in an erection. In patients with vascular impotence the combination of VSS and injection will provide a more complete evaluation. These diagnostic techniques are limited to major academic centers.

Efficacy endpoints used in the studies provided by Upjohn in the development of Caverject were in terms of response based on clinical evaluation of erection following each injection, as well as RigiScan measures of response, duration, latency, maximum penile radial rigidity, and maximum penile circumference. Rigiscan measurements were not done in all of the Upjohn studies. The computer-controlled, battery-powered Rigiscan system is ideal for the recording of penile tumescence and rigidity in a multicenter trial although it is a conservative estimate of function. The instrument easily quantifies the number of erections, duration of erections, tumescence at the base, and the tip of the penis.

The following list defines the terms relevant to the efficacy measures based on RigiScan data that are generally accepted endpoints:

Start of Erection: the time when radial rigidity first reached >70% at tip or base of penis, and remained at that level for at least 10 consecutive minutes.

End of Erection: the time when radial rigidity first fell below 70% (at both tip and base of the penis) after radial rigidity was maintained as above.

Response to Injection (Erection) Using **RigiScan**: radial rigidity > 70% (at tip or base) for at least 10 consecutive minutes.Rigidity was recorded by RigiScan at either the tip or base of the penis.

Optimum Response: an erection with duration between **30 and 60 minutes.**

Latency: time from injection until the start of erection. Latency was censored (i.e., set at the latest monitoring time) if an erection did not occur during monitoring.

Duration: the time from the start to the end of the erection.

Maximum Penile Rigidity: maximum radial rigidity (%) following injection recorded by RigiScan at either the tip or base of the penis.

Maximum Penile Circumference: maximum circumference (cm) following injection

Optimum Dose: the lowest dose that produced an erection of ≥70% radial rigidity with a duration of 30 minutes or longer during RigiScan monitoring.

Clinical asssessment of erection response commonly uses the following 3-point scale:

- 1 = none (no response)
- 2 = partial tumescence (not likely to be sufficient for penetration)
- 3 = full rigidity (with likely ability to penetrate and have intercourse).

A response to injection based on clinical evaluation required a "full" erection. Partial erections and failure to achieve erection were considered to be non-responses.

Investigator Measurements used in the Schwarz Pharma Pivotal Trials:

The primary efficacy variable in the investigator's office was based on the Penile Buckling Test. A response was defined as a positive Buckling Test within 60 minutes after injection. The secondary variables were: (1) a response to injection based on the penile angle equal to 90° within 60 minutes after injection or an angle ≥75 ° but <90° but in the opinion of both the patient and the investigator, an erection sufficient for satisfactory intercourse, (2) a maximum penile angle, (3) penile rigidity based on patient's assessment on a 10-point visual analogue scale, (4) time to onset of erection and duration in minutes, (5) optimum response, (6) maximum increase from pre-injection size, (7) the maximum increase from the preinjection length, and (8) an investigator's and patient's assessment if the erection was sufficient for intercourse.

Primary variables during the self-injection phase at home were based on : patient assessment of response to injection as an erection sufficient for intercourse. The secondary variables included: (1) an erection based on patient assessment (yes or no), (2) time to onset of erection at home as recorded in the patient diary following each injection.and (3) the duration as recorded in the patient diary. The partner's assessment was recorded as satisfactory or unsatisfactory.

Safey issues associated with intracavernous treatment:

Important **safety** issues regarding penile intracavernous injections include Peyronie's disease and prolonged erections and/or priapism.

Peyronie's disease is an inflammatory process of unknown origin. These are firm, painless plaques or bands usually found on the dorsum of the penis. Pain is primarily with erection during sexual activity and the associated deviation of the penis with the erection due to the inelasticity of the plaque. Peyronie's disease has been associated with many things including e.g. vitamin E deficiency, beta blocking agents, increased blood levels of serotinin in carcinoid syndrome, as an autoimmune disease with possible HLA association (e.g., B8 , Cw7, DR3, DQW 2 haplotype), and as a response to vascular trauma or growth factors. In Peyronie's disease the normal collagen and elastic fibers are altered and become noncompliant in a circumscribed area which in turn alters the symmetry of the normal erection. The penile curvature may require surgical treatment. The disease may wax and wane making clinical studies difficult. Any definition of curvature may be considered as a form of Peyronie's disease. The mechanical trauma of repeated injections could clearly be a cause of collagen changes.

Priapism and/or prolonged erections are an important problem associated with any of the injection therapies used today. The sponsor has defined prolonged erections as those erections in the time period between 4 and 6 hours and priapism as those longer than 6 hours. Priapism is the persistence of an erection that does not result from sexual desire. Most andrologists become concerned when erections last between two and four hours. The treatment of priapism is standard in most textbooks and includes non-invasive and invasive treatments and should be managed by a specialist.

A last safety issue of intracavernous injections is related to the injection and needle. Following the injection it is important to apply pressure to the site to prevent hematoma or fibrosis with healing. A second potential issue is the possible breakage of the small needles; however, this has not been a major problem to date.

6.1 Relevant human experience

See reviews of NDA 20-379 for Caverject (Alprostadil/Upjohn & Pharmacia) for the treatment erectile dysfunction due to neurogenic, vasculogenic, psychogenic or mixed etiology. This was approved July, 1995.

6.2 **Important information from related INDs and NDAs**

IND -
IND -

6.3 **Foreign experience with Alprostadil for the treatment of erectile dysfunction.**

Applications for marketing authorization for Alprostadil for injection for the indication of erectile dysfunction has been approved by the authorities of Belorussia, France, Kasachstan, Russia. There are pending applications in Germany, Great Britain, Ireland, Italy, Pakistan, Poland and Switerland.

Alprostadil is also marketed for the intravenous treatment of peripheral vascular occulsive disease in countries outside the United States. The NDA for this indication was not approved by FDA.

6.4 **Human Pharmacology, Pharmacokinetics, Pharmacodynamics**

See Pharmacology and Pharmacokinetic review.

Five pharmacokinetic drug interaction studies were conducted for agents frequently used in the target population . This included glibenclamide, warfarin, digoxin, heparin, and acetyl salicylic acid. There was no influence on the profile of glibenclamide or warfarin and no clincal changes were noted with digoxin, heparin or acetyl salicyclic acid. The pharmacokinetic data obtained following intracavernous injection in erectile dysfunction patients were similar to those following intracavernous injection in healthy volunteers with a rapid distribution of Alprostadil from the site of administration.

6.5 **Other relevant background information (meetings, commitments)**

The first IND for Alprostadil alphadex for the Erectile Dysfunction indication from Schwarz Pharma was filed in May 93 and was acceptable. There have been no significant problems in the development of the drug.

7 **Description of Clinical Data Sources**

7.1 **Study Type and Design/Patient Enumeration, Demographics,** Extent of Exposure - see Cinical Review

7.2 **Post-Marketing Experience** - There is no post-marketing experience for the treatment of erectile dysfunction.

7.3 **Literature - see appendix for relevant bibliography**

Clinical Studies

A total of 1580 subjects were enrolled in the clinical development program; 1505 of these men were exposed to Alprostadil. The clinical data submitted included 13 intracavernous studies. These studies included 3 in the United States and 10 in Europe. There were eight uncontrolled clinical studies. The drug interaction studies will not be reviewed (See biopharmaceutics review).

The U.S. clinical program comprised three therapeutic studies with a total of approximately 910 patients. Each of these trials included a dose-titration period and a 48-week, open-label at-home treatment period. The four clinical studies included use data (F-8653, KU-620-001,002, and 003) for up to 48 months.

CLINICAL STUDIES

Uncontrolled Studies		
Protocol	**Number of Subjects / Site**	
F-8653	171 - Europe (48 months)	
F-8653 1	81 - Europe extension of 8653	
KU-620-003	595 - Europe	
CT-176	20 - Yugoslovia	
F-8408	189 - Germany	
Controlled Studies		
Pharmacokinetic Studies		
DA-229	24 - Germany	
F-8495	12 - Germany	
KU-620-004	19 - Germany	
Pharmacodynamic Studies		
F-8250	10 - Germany Papaverine vs Prostavasin	
F-8299	101 - Germany Papaverine vs Prostavasin	
F-8301	15 - Germany	
F-8495	12 - Germany	
F-8598	50 - Prostavasin vs Paperverine + Phentolamine	
Placebo-controlled Clinical Studies		
Protocol	**No. of Subjects**	**Months**
KU-620-001	117	12
KU-620-002	257	24

* placebo-controlled during the 2 week cross-over period

The following diagnostic trials were completed in April 1995 with a total of 158 patients.

DIAGNOSTIC CLINICAL STUDIES

Protocol	Number of Subjects
KU-620-006	not available
KU-620-007	not available
F8598	not available

Studies KU-620-001 and KU-620-002 were conducted in the United States,and consisted of an open-label dose-titration period, a randomized, placebo-controlled double-blind crossover period in the patient's home, and a 48-week open-label extension period in the patient's home. During the dose-titration period, the investigator established each patient's individual optimum dose of Alprostadil necessary to produce an erection sufficient for sexual intercourse. This was a maximum of 20 µg in Study KU-620-001 and 40 µg in Study KU-620-002.

Following the dose-titration period patients were then randomized to a two-week crossover period in which they self-injected for one week either placebo or their optimum determined dose of Alprostadil and then crossed over to the alternate treatment for the second week. Patients had the option to enter a 48-week open-label extension period in which they self-administered alprostadil up to two times a week.

Studies KU-620-003 and F-8653 consisted of an open-label, dose-titration period and an open-label extension period (48 weeks for Study KU-620-003 and four years for Study F-8653) in the patient's home. During the dose-titration period of Study KU-620-003, the investigator established each patient's individual optimum dose of alprostadil necessary to produce an erection sufficient for sexual intercourse (a maximum of 40 µg). During the dose-titration period of Study F-8653, the investigator established each patient's individual optimum dose of alprostadil necessary to produce a full erection. The maximum dose was 20 µg. Patients had the option to enter the open-label extension period in which they self-administered alprostadil up to two times a week.

8.1 Trial #620-001

This study included only patients with erectile dysfunction (ED) due to primary vasculogenic or neurogenic causes, with or without a secondary psychogenic component or secondary hypogonadism.

8.1.1 Objectives

This study was designed to evaluate the safety and efficacy of intracavernosal injections of Alprostadil in nondiabetic patients with

erectile dysfunction (ED) and to assess the feasibility of self-injection of Alprostadil.

In addition the study was designed to evaluate the long-term efficacy and safety of intracavernosal injections of alprostadil in nondiabetic patients with erectile dysfunction (ED) of organic origin and to assess the long-term feasibility of self-injection of Alprostadil when administered by patients at home. A secondary objective was to assess the effect of alprostadil on the quality of patient and partner sexual activity at home.

8.1.2 Design

This multicenter study consisted of an open-label, dose-titration period in the investigator's office followed by a placebo-controlled double-blind cross-over period of 2 weeks and an open label period of 6 months or more.

8.1.3 Protocol

Protocol KU 620-001

Regimen	N=	Duration
screening	117	1 week
dose titration	117	10-21 days
double-blind cross-over	85	2 weeks
Open label	75 52	1-6 months 7-12 months

Study KU-620-001 consisted of four treatment periods: a screening visit in the investigator's office; an open-label, dose-titration period in the investigator's office during which one intracavernous injection of placebo and four injections of alprostadil at a dose range of 1.0 to 20.0 µg were given over 10 to 21 days. A two-week double-blind crossover comparison of placebo and the optimum dose of Alprostadil, self-injected by the patient at home (one or two injections per week), and an open-label, self-injection treatment period at home up to 24 months.

During the open-label, dose-titration phase in the investigator's office the patients received one intracavernosal injection of placebo and four intracavernosal injections of drug. All patients received intracavernosal injection therapy for the first time in this study. The initial dose of Alprostadil prior to titration was 5 µg. There was an interval between injections of at least 2 days. Dosing began at Visit 2 with an injection of placebo and an injection of 5 µg at Visit 3. If a patient experienced a response at 5 µg the titration was decreased until a no-effect dose was established. Patients were otherwise titrated up to their

optimum dose with a maximum allowable dose of 20 µg. The injection was administered over 5 to 10 seconds into the corpus cavernosum and pressure was applied to the area for three minutes to prevent hematoma. By the final visit the patient had been trained to prepare and self-inject the study drug and the optimum individual determined dose.

Patients continuing into the open-label extension period initially used Alprostadil at the optimum dose (1 µg to 20 µg) but could reduce the dose if it resulted in adverse effects such as penile pain or prolonged erection, or, after consultation with the investigator, they could increase the dose if it was determined that the current dose was ineffective.

This study included nondiabetic men only with ED due to primary vasculogenic or neurogenic causes, with or without a secondary psychogenic component or secondary hypogonadism. All patients received intracavernosal injection therapy for the first time in this study.

Blood pressure, heart rate and penile circumference measurements were recorded prior to each injection of study drug. After each injection these measurements were again recorded. Penile circumference was measured by a paper tape rule at mid-shaft of the penis. Penile axial loading tests (or Penile Buckling test) were conducted in the supine position. After the first measurement the test was performed at 10-minute intervals up to 60 minutes post-inecjtion and at 15-minute intervals beyond 60 minutes, if required. The test was negative if the penis buckled upon application of a 1.0 kg axial load and positive if sufficiently rigid to support the 1 kg axial load. A Polaroid photograph of the penis was taken at the initial positive Penile Buckling Test or no later than 30 minutes post-injection.

The double-blind, placebo crossover period at home started at visit 8 when patients were given blinded drug supplies of placebo or optimum dose that had been determined in the investigator's office. After each injection the patient was to assess the erection as satisfactory or unsatisfactory , the achievement of satisfactory intercourse and any adverse experiences that occurred. The partner completed the partner's portion of the diary. The patient returned any used and unusued drug supply at the end of the first week of the crossover. The results were reviewed before dispensing additional blinded study drugs for the second week. At the 8th visit the following evaluations were done: a complete physicial exmaination, including an examination of the flaccid penis for any changes including penile curvature,tunica plaques, or any intracavernosal nodules. In the investigator's office the patient then self-injected the optimum dose and a Penile Buckling test, a Polaroid photograph, and penile angle measurements were done at that time.

Primary efficacy variables included the following which are further discussed below:

• Penile rigidity following appliction of a 1.0 kg axial loading force (Buckling Test at the office) while the patient was in a supine position. The test was repeated once during each treatment period through the entire study and the results considered only for that time point.

• Erections considered as sufficient (Yes/No) for satisfactory sexual intercourse (home) as based on patient diary. Only the first injection of each study week was included in the statistical analysis.

Secondary efficacy variables in the investigators office and/or in the open label segment included the following:

- Time To Onset Of Erection
- Duration Of Erection
- Optimum Response To Injection
- Maximum Change From Pre-Injection Penile Circumference (cm)
- Erection Sufficient For Intercourse Based On Investigator Assessment
- Erection Sufficient For Intercourse Based On Patient Assessment
- Response To Injection Based On Penile Angle (≥ 90 degrees within 60 Minutes)
- Minimum Effective Dose
- Optimum Dose
- Time to Onset of Erection at Home
- Duration of Erection
- Partner Assessment of Intercourse

STUDY MEASUREMENTS

	Screen-Baseline	Open-Label Dose-Titration (Office)					Double-Blind Treatment Home	
Time (Days)	-7	Total 21 Days With ≥2 Days Between Visits					End of Week 1	End of Week 2
Visit No.	1	2	3	4	5	6	7	8
Event								
Physical Examination (including exam of penis)	X							X
History (with primary diagnosis of neurogenic or vasculogenic ED)	X							
Quality of Life	X							
Lab Evaluation and Urinalysis	X							X
Self-Injection Training		X	X	X	X	X		X
Penile Rigidity		X	X	X	X	X		X
Penile Circumference		X	X	X	X	X		X
Dose-Titration		X[a]	X[a]	X[a]	X[a]	X[a]		X[g]
Blood Pressure	X	X	X	X[b]	X	X		X
Polaroid Photograph		X	X	X[c]	X	X[c]		X[c]
Drug Dispensed		X	X	X	X	X[f]	X	X[g]
Diary						X	X	X[g]
Adverse Experiences		X[d]	X[d]	X[d]	X[d]	X[d]	X	X[d]

[a] Self-injected volumes consistent with Alprostadil alphadex doses of 0 to 20 mg administered in office with minimum of one-hour observation or until detumescence. Initial injection of 0.5 ml placebo vehicle on Day 1 (Visit 2). Investigator could decide not to increase dose based on the response observed at any visit (2-6). If so, at subsequent visit(s), the previous or a lower Alprostadil alphadex dose was administered.

[b] Supine blood pressure and heart rate taken prior to injection and 5, 10, 20, 30, 45, 60, and 60 minutes post-injection and every 15 minutes thereafter until detumescence.

[c] One Polaroid taken at the first positive Buckling Test or 30 minutes after injection in standing position.

[d] All reported AE's were to be followed until resolved.

[f] Dispense double-blind drug supply for 1 week.

[g] Verify response of optimum dose (determined during Visits 2-6).

[h] For patients going into 48-week, open-label Alprostadil alphadex treatment period at home.

adapted from sponsor's table

8.1.3.1 Population, procedures

117 men were enrolled in this study wiith a diagnosis of erectile dysfunction. The eligible patients met the following inclusion criteria:

1. Age between 18 to 75 years.

2. Presence of an erection problem consistent with impotence for at least six months.

3. A diagnosis of organic ED due to primary vasculogenic or neurogenic causes with or without a secondary psychogenic component or secondary hypogonadism (i.e., low serum testosterone) component.

Patients were excluded from the study for any of the following reasons:

1. Age younger than 18 years or older than 75 years.

2. Presence of a sexually transmitted disease, including a seropositive human immunodeficiency virus (HIV) test, within the past 60 days.

3. Poor manual dexterity or poor visual acuity precluding safe intracavernosal self-injection unless partner assisted.

4. Morbid obesity precluding safe intracavernous self-injection unless the partner was willing to perform the intracavernous injections.

5. A diagnosis of ED with a primary hormonal or psychogenic etiology.

6. A history of prior therapy by self-injection of vasoactive drugs (PGE_1, papaverine, papaverine/phentolamine) into the corpus cavernosum. This did not preclude diagnostic procedures.

7. A history of Peyronie's disease.

8. Concomitant use of a penile vacuum constrictive device.

9. Presence of a penile implant.

10. Lack of a stable relationship with a sexual partner.

11. A history of chronic alcohol or drug abuse within the last year.

12. Use of any investigational drug within the previous 30 days.

13. Concomitant use or use in the last seven days of the following medications: oral medication that may enhance penile erection, (i.e., trazodone, a-adrenergic receptor blocking agents or yohimbine); vasoactive medications applied topically to the penis; and monoamine oxidase inhibitors.

14. A history of uncontrolled hypertension.

15. Any disease or condition (cardiovascular, respiratory, immunologic, psychiatric, hematologic, hepatic, renal, neurologic or infectious) which, in the opinion of the investigator, might place the patient at increased risk.

The above criteria were essentially the same for all pivotal trials including 620-001 and 620-002.

8.1.3.2 Endpoints

Efficacy was based on an "intent-to-treat" approach (i.e., the data from all patients who received at least one injection of study drug were included in summary statistics). However, due to limitations for the crossover design, the statistical analyses include only patients who received at least one injection during each study week of the double-blind crossover period.

All adverse experiences that were related to the penis were considered to be "local side effects." At the time of each injection, patients were specifically evaluated for the presence of penile pain (during injection, during erection, and after erection), prolonged erection, and bleeding. Erections were considered to be prolonged if the duration was greater than two hours. All adverse experiences that were not related to the penis were recorded as clinical adverse experiences.

The following endpoints were measured:
(Protocol 001 in volume 1.63)

Primary Efficacy Variables:

• Penile rigidity (yes or no) following application of a 1.0 kg axial loading force (Buckling Test) in the office with the patient supine. The penile angle was also measured following each injection

• Erections considered as sufficient (yes/no) for satisfactory sexual intercourse as based on patient diary. The response was based on Buckling Test with duration between 20 and 60 minutes. (see Appendix)

Secondary Efficacy Variables:

• Penile angle ≥90° or ≥75° and <90° and an erection considered sufficient for intercourse within 60 minutes after injection.

• Qualify of life questionnaires

• Based on a 10-point visual analogue scale (10 was defined to be like an erection the patient had when he was 18 or the best erection that the patient remembered).

• Time from injection to erection. Time to erection was considered >60 minutes if an erection did not occur.

• Time from the start of erection to the end of erection. Duration was set to 0 if an erection did not occur.

The measurements done by the investigators in the office also included response to injection based on Penile Buckling Test as noted above, quality of erection based on investigator evaluation,response to injection based on penile angle, optimum response, erection sufficient for intercourse based on investigator assessment, erection sufficient for intercourse based on patient assessment, time to onset of erection, duration of erection, maximum increase from pre-injection penile circumference, maximum penile angle, minimum effective dose and optimum dose. These variables were also used in protocols KU-620-002 and 003. With minor variations the same variables were used in F8653.

During the self-injection at home the investigators measured the response to injection {sufficient for intercourse, erection based on patient assessment (yes/no)}, time to onset of erection in minutes, duration of erection , and Quality of life. The quality of life evaluated frequency of sexual desire, orgasm rating, satisfaction, comfort, and quality of erections. The questionnaire also included the partner's evaluation (satisfactory or unsatisfactory).

8.1.4 Results

Summary Study KU-620-001

STUDY DESIGN non-diabetic	N= w/b/h/o	AGE	DOSE µG	RESPONSE
dose-titration	117* enrolled 114 - drug 3 - pbo	22-65	1 - 20 µg median opt dose 15 µg	87/114 responded to at least one injection
double-blind crossover	85 completed 6 disc.			
1-6 month open label extension	75 69/4/1/1	29-65		73/74 responded to at least one erection
7-12 month open label extension	52 49/1/1/1	33-64	median dose 12 µg	93% injections sufficient for intercourse
Investigators	Drs. S. Auerbach, I. Goldstein, J. Kaufman, L.Knoll, A. Seftel, J. Tuttle, and M. Witt.			

*32 withdrew prior to randomization

8.1.4.1 Patient Disposition, comparability

A total of 117 patients entered the study. Of these patients 32 withdrew prior to randomization. 114 of the patients received drug and 3 received

only placebo. The majority of these patients had erectile dysfunction of vasculogenic origin. The duration of dysfunction ranged from years. with a mean duration of 4.0 years. 82 (70%) of the men entered into this study had no previous treatment for erectile dysfunction. Most had received oral drugs prior to entering this study. 53% (62) of the patients used alcohol and 32 percent (38) were current smokers. There were 8 patients who had low testosterone defined as less than 280 ng/dL at the screening visit, four of whom discontinued during the dose-titration period.

79 patients who entered the open-label extension were issued study drug; however, only 75 patients injected study drug during the first six months of this period. These 75 men ranged in age from years (mean of 53.5 years) and 74 patients were evaluated for efficacy. Ninety-two percent (69/75) of the patients were white, 5% (4/75) were black, and 1% each (1/75) were Hispanic and "other" races. The majority of patients (79%; 59/75) had ED of vasculogenic origin. The duration of ED ranged from years, with a mean duration of 4.4 years.

The demographic characteristics for the 85 patients who were randomized into the double-blind crossover period were similar to those observed for the 117 patients who were enrolled into the study. There were no clinically significant differences among the centers in demographic characteristics.

Demographic and Other Pretreatment		
	N=117	
Previous Treatment of Erectile Dysfunction[a]		
None	82	70%
Oral Drug	25	21%
Vacuum Device	7	6%
Surgery	2	2%
Unknown	3	3%
Outcome of Previous ED Treatment		
Worsened	1	3%
Improved	5	16%
No Change	26	81%
Alcohol Use		
No	50	43%
Yes	62	53%
Unknown	5	4%
Current Smoker		
No	71	61%
Yes	38	32%
Unknown	8	7%
Previous Smoker		
No	11	9%
Yes	42	36%
Unknown	64	55%
Cardiovascular Risk Factors		
Hypertension	31	26%
Hypercholesterolemia	9	8%
Atherosclerotic Cardiovascular Disease	19	16%
Received Intracavernosal Injection(s) for Diagnostic Workup		
No	86	74%
Yes	31	26%

8.1.4.2 Efficacy endpoint outcomes

Efficacy was assessed at home for all patients who received at least one self-injection. Efficacy variables included an assessment of whether the patient had an erection, the patient's assessment of whether the erection was sufficient for intercourse, and the partner's assessment of the satisfaction of intercourse. The time from injection to the start of erection and duration of erection were also reported. The time to erection was summarized using medians and the duration of erection was summarized using means and standard errors. If a response was not achieved, duration was set to zero for summary purposes.

All summaries were presented by dose category and by study month. Each study month was based on 30-day intervals beginning at the end of the double-blind, crossover period. For patients who returned late for the Month 6 visit, diary data collected between the calculated six-month interval and the last visit were combined into a > 6 months category.

Efficacy was also assessed in the investigator's office for all patients who received the reinjection of the current optimum dose at the end of the six-month period or at the dropout visit. Efficacy variables that were summarized included response to injection based on the penile Buckling Test, response based on penile angle, time from injection to the start of erection, duration of erection, maximum increase from preinjection penile circumference, and patient and investigator assessments of whether the erection was sufficient for intercourse.

For both the Penile Buckling Test and the penile angle test, the number and percentage of patients with a response were presented by dose category. The time to erection was summarized using Kaplan-Meier medians. If a response (positive penile Buckling Test within 60 minutes after injection) was not achieved, the time to injection was considered to be greater than 60 minutes (i.e., censored). The duration of erection and the maximum increase from preinjection penile circumference were summarized using means and standard errors. Investigator and patient assessments of whether the erection was sufficient for intercourse were summarized using the percent of positive response at each dose.

At the time of each injection, patients were specifically evaluated for the presence of penile pain, prolonged erection, and bleeding. Erections were considered to be prolonged if the duration was greater than two hours. All reports of prolonged erections greater than four hours and all serious local side effects were also recorded as a clinical adverse experience. The number and percentage of patients with each local side effect or clinical adverse experience were summarized by dose category.

The incidence of clinically important changes (from preinjection) in postinjection vital sign measurements in the investigator's office were summarized by dose category. Frequency counts of patients with laboratory values outside predefined limits were summarized for each variable.

Almost all of the patients (99%; 72/74) had erections that were considered to be sufficient for sexual intercourse after at least one injection of alprostadil. In addition, most injections administered at home (93%; 2049/2210) resulted in erections that were considered to be sufficient for sexual intercourse.

The discussion will sequentially discuss the results in terms of the three major study times: dose titration period, the double-blind cross-over period and the Open label between 1 and 12 months.

8.1.4.2.1 The Dose-Titration period:

All 117 patients who enrolled in the study had at least one injection during the dose-titration period. Three patients discontinued after receiving the first (placebo) injection; therefore, only 114 of the 117 patients enrolled received alprostadil.

As noted above the response was defined as:

- Positive buckling test within 60 minutes after injection.
- Penile angle ≥90° within 60 minutes after injection.

The response measurements also included 117 placebo injections.

The penile measurement of ≥ 90° was a more strigent test than the buckling test.

The median dose for the 85 patients who completed the dose-titration period was 15 mg. Based on penile angle, 47% (54/114) of the patients responded (penile angle ≥90 within 60 minutes after injection) after at least one of the Alprostadil alphadex injections. No patient responded with a penile angle ≥90° after an injection with placebo.

Study KU-620-001
Response to Injection Based on the Buckling Test in the Investigator's Office Dose-Titration Period

Dose (µg)	No. Pts	No. Injs	Pts With a Response N (%)	Injections With a Response N (%)
Placebo	117	117	0	0
>0-2.5	19	33	8 (42)	13 (39)
>2.5-5	114	136	31 (27)	49 (36)
>5-10	97	124	36 (37)	56 (45)
>10-15	78	85	34 (44)	41 (48)
>15-20	66	68	40 (61)	41 (60)
Total	114	446	87 (76)	200 (45)

The responses based on the Buckling Test and on penile angle were concordant for 80% (444/555) of the injections administered during dose titration period. Nineteen percent (104/555) of the injections resulted in a positive Buckling Test with penile angle ≤90°, while only 7 injections

resulted in angle ≥90° with a negative Buckling Test. The sponsor believes that the penile angle of ≥90° was a more difficult criterion to achieve than the positive Buckling Test.

Number of Injections with a Response Buckling Test versus Penile Angle Dose-Titration Period				
Response to Injection		Buckling Test		
Penile Angle		No	Yes	Total
≤90°	No	348#	104	452
≥90°	Yes	7	96	103
	Total	355	200	555

Significant difference between response based on the Buckling Test and response based on penile angle (p<0.001).
#based on 11 placebo injections

The distribution of optimum doses as selected by the investigator during the dose titration is noted below. 32 patients did not have an optimum dose determined during this period.

Distribution of Optimum Doses (as selected by investigator during dose titration)			
Dose (mg)	Patients		Cumulative Percent
	N	%	
1.0	1	0.9	0.9
1.2	3	2.6	3.5
2.5	2	1.7	5.2
3.0	1	0.9	6.1
3.6	1	0.9	7.0
4.0	3	2.6	9.6
5.0	6	5.1	14.7
6.0	1	0.9	15.6
7.5	3	2.6	18.2
8.0	1	0.9	19.1
10.0	10	8.5	27.6
12.0	1	0.9	28.5
12.5	1	0.9	29.4
14.0	1	0.9	30.3
15.0	11	9.4	39.7
18.0	1	0.9	40.6
20.0	38	32.5	73.1
No Dose Determined	32	27.4	100.0
Total	117	100.0	100.0

The sponsor notes that 16 of the 20 patients whose primary diagnosis was erectile dysfunction of neurogenic origin completed the dose-titration period and had an optimum dose assigned as noted below.

Distribution of Optimum Doses Patients With Neurogenic Etiologies			
Dose (mg)	Patients		Cumulative Percent
	N	%	
3.0	1	5.0	5.0
4.0	2	10.0	15.0
5.0	1	5.0	20.0
7.5	2	10.0	30.0
10.0	1	5.0	35.0
12.0	1	5.0	40.0
15.0	1	5.0	45.0
20.0	7	35.0	80.0
No Dose Determined	4	20.0	100.0
Total	20	100.0	100.0

The sponsor also identified four of eight patients who had low serum testosterone at screening and completed the dose-titration period. The optimum doses for these patients included 5 mg for one patient, 10 mg for two patients and 15 mg for one patient. Three patients who had low serum testosterone at screening discontinued the study prematurely because of inadequate therapeutic response and one patient was discontinued because of a protocol entry violation which was a high glucose value and suspected diabetes.

In summary, 76% of the patients had a response to injection based on the Buckling Test in the investigator's office during the dose-titration period and 94% of the patients responded to his optimum dose based on the Buckling test within 60 minutes after injection. If the response was based on a Buckling test between 20 and 60 minutes only 68% had an optimum response. If the response to injection was based on penile angle of ≥90° only 43% responded. The patient and investigator evaluation of erection sufficient for intercourse was 94% and 93% respectively. The median time to erection was 20 minutes in 80 patients and the duration was 42.0 minutes. The maximum change from the pre-injection penile circumfereance was 2.6 cm (9.6 cm baseline to 12.2 cm).

8.1.4.2.2 **Double-blind cross-over period:**

85 patients were randomized in the second week to the double-blind cross-over period. 83 patients received at least one injection during each week. Two of these patients did not record any diary data following their injections and others had incomplete data. There was efficacy data on 81 patients and safety data on 84 patients. Patients used the dose selected from the previous dose-titration period. As shown below, when results from the two weeks were combined, 83% of the patients (67/81) had an erection after injection with active drug while 10% (8/81) had an erection after injection with placebo. 74% of the patients had erections that were considered to be sufficient for intercourse after injection with Alprostadil compared to 7% (6/81) after injection with placebo.

Study KU-620-001
Response to Injection Based on Patient Assessment
Double-Blind, Crossover Period

Study Week	Treatment	No. of Patients	No. (%) of Patients With an Erection	No. (%) of Patients With an Erection Sufficient for Intercourse
Week 1	Placebo	41	5 (12)	3 (7)
	Alprostadil	40	33 (83)	29 (73)
Week 2	Placebo	40	3 (8)	3 (8)
	Alprostadil	41	34 (83)	31 (76)
Comb	Placebo	81	8 (10)	6 (7)
	Alprostadil	81	67 (83)*	60 (74)*

** based on different from placebo p < 0.001 - adapted from sponsor*

The paired responses for each patient (placebo versus active drug) during the double-blind crossover period are shown below. The chart compares erections versus those considered by patient as sufficient for intercourse.

Study KU-620-001
Paired Responses to Injection for each Patient
Double-Blind, Crossover Period

Erection		Placebo	
		No	Yes
Alprostadil	No	14	0
	Yes	59	8

Erection Sufficient for Intercourse		Placebo	
		No	Yes
Alprostadil	No	21	0
	Yes	54	6

The median time to erection was 10 minutes in the alprostadil group and > 60 minutes (i.e., censored) in the placebo group. The mean duration of erection was approximately four minutes after injection with placebo and 57 minutes after injection with alprostadil.

8.1.4.2.3 The Open Label Period 1 - 6 months:

75 patients continued in the open label extension. One patient did not self-inject. The dose for each remained the dose determined during the dose titration period. Office visits and review of diary cards were made at 1, 2, 4, and at the end of 6 months. The primary cause of erectile dysfunction in patients that entered the open label study was vasculogenic (79%), and neurogenic (19%), and mixed (3%).

The primary objectives of the open-label extension of this study were to evaluate the long-term efficacy of intracavernosal injections of Alprostadil alphadex in producing erections sufficient for sexual intercourse during 6 months of self-injection at home and to determine the long-term safety and tolerability of Alprostadil alphadex treatment when administered by the patient at home.

The secondary objective of the open-label extension of this study was to assess the effects of long-term use of the study drug on the quality of patients' and partners' sexual activity at home.

At the 6 month office visit the patient diary was reviewed and each patient had a complete physical examination which included evaluation of the flaccid penis. The penis was then injected with the titrated dose and repeat measurements of blood pressure, heart rate, and penile circumference were done up to 1 hour and post detumescence. Penile Buckling Test, Penile Angle and poloroid photograph were also repeated. The patient and partner also completed a a Qualify of Life questionnaire. The percentage of injections that resulted in erections considered to be sufficient for intercourse was based on the patients' assessment.

The table below presents the number of patients and the number of injections with erections that were sufficient for intercourse by study month. All of the patients who self-injected responded to at least one of the injections. Ninety-nine percent (73/74) of patients stated that they had erections that were considered sufficient for intercourse after injection with Alprostadil alphadex, and 93% (2049/2210) of injections administered at home resulted in erections that were considered sufficient for intercourse. The median time to erection was 10 minutes and the mean duration of erection per patient was 65 minutes. Qualify of life, sexual satisfaction, activity and orgasm was improved for both patients and partners.

Study KU-620-001
Months 1 - 6
Summary of Erections Sufficient for Intercourse at Home, by Study Month

Study month	Number of Patients	Number of Injections	No. (%) of Patients with an Erection Sufficient for Intercourse	Mean % Response Per Patient	No. (%) of Injections With an Erection Sufficient for Intercourse
1	72	415	69 (96)	85.2	366 (88)
2	66	359	63 (95)	88.2	330 (92)
3	65	373	64 (98)	91.8	345 (92)
4	62	357	61 (98)	94.3	336 (94)
5	61	304	61 (100)	94.1	285 (94)
6	56	281	55 (98)	95.0	267 (95)
> 6	31	121	31 (100)	99.5	120 (99)

The next table includes the data regarding the duration of erections for each dose category at home for those patients who responded. The mean duration of erection per patient was 70.2 minutes. The duration of erection among all patients, including both responders and nonresponders, was slightly less at 65.0 minutes. The median time to erection was 10 minutes for all patients.

Study KU-620-001
Months 1 - 6
Summary of Duration of Erections (min) at Home by Dose Category: Responders Only

Dose Category (µg)	Number of Patients#	Number of Injections	Mean Duration of Erection Per Patient (S.E.)	Mean Duration of Erection Per Injection (S.E.)
> 0 - 2.5	10	272	61.0 (11.46)	61.7 (2.29)
> 2.5 - 5	17	410	79.9 (7.79)	75.2 (2.05)
> 5 - 7.5	10	137	108.3 (20.86)	92.4 (4.81)
> 7.5 - 10	15	161	88.2 (14.61)	84.9 (3.50)
> 10 - 15	24	395	88.9 (13.10)	80.9 (2.53)
> 15 - 20	31	713	64.5 (8.67)	60.4 (1.39)
All Alprostadil Doses	74	2088	70.2 (4.66)	71.4 (0.97)

#Patients could be counted in more than one dose category from sponsor

Of the 75 patients who had at least one injection during the first six months of the open-label period, 57 received an in-office injection of the current optimum dose at the end of Month 6. Fifty-seven patients received an injection in the investigator's office at the end of the 6-month period or at discontinuation. Patient response to injection based on the Penile Buckling Test was 96% (55/57) in the investigator's office; 96% of erections were considered sufficient for sexual intercourse by both the investigator and the patient. Response based on penile angle (angle ≥ 90 within 60 minutes) was 57% (31/54) following the in-office alprostadil injection.

Seventy-seven percent (58/75) of patients did not change dose categories from the optimum dose to the final dose at the end of the first six months of the open-label extension. Fifteen per cent (11/75) of patients decreased their dose, and 8% (6/75) increased their dose.

For the 74 patients who injected at home, Alprostadil alphadex was found to be very satisfactory and effective. All of the patients had erections after at least one injection at home; 93% (2049/2210) of injections resulted in erections that were considered sufficient for sexual intercourse. The mean duration of erection recorded by the patients at home was 65.7 minutes.

There were increases in the mean between screening and followup in patient and partner responses to questions concerning number of times they attempted or engaged in sexual intercourse during the previous 30-day period. For patients the mean increased from 4.7 times at screening to 6.9 at follow-up. This was similar for the partners. The increase in number of times patients felt sexual drive in the previous 30 days increased from 9.8 times to 17.1 while the partner's increased from 7.7 times at screening to 12.1 at follow-up. There was minimal increase in sexual activity (either intercourse or masturbation).

8.1.4.2.4 Open extension study months 7 - 12:

A total of 55 patients entered the second open extension study; however, 3 patients did not inject Alprostadil during this period and 3 others discontinued early. A total of 52 patients self-injected an average of 5 injections of the drug per month at home. 94% of the injections administered at home resulted in erections that were considered sufficient for intercourse. The median time to erection was 10 minutes and the mean duration of ereciton was 63 minutes. Eighty one percent of the patients had no change in dose throughout this 6 month period., The average dose was 12 µg. 49 patients completed months 7 - 12 of the 12 month open label extension.

Study KU-620-001
Months 7 - 12
Duration of Erections (min) at Home
by Dose Category including Responders Only

Dose Category (µg)	Number of Patients	Number of Injections	Mean Duration of Erection Per Patient (S.E.)	Mean Duration of Erection Per Injection (S.E.)
> 0 - 2.5	6	129	46.9 (12.48)	45.0 (2.01)
> 2.5 - 5	12	364	86.0 (9.01)	81.9 (2.25)
> 5 - 7.5	8	140	96.1 (15.36)	84.9 (2.77)
> 7.5 - 10	11	188	71.0 (10.90)	75.1 (2.84)
> 10 - 15	11	273	62.8 (10.95)	64.0 (2.20)
> 15 - 20	17	517	51.3 (6.68)	53.5 (1.40)
All Doses	52	1611	65.4 (4.51)	66.3 (0.95)

Time from start to the end of the erection based on patient assessment at home. Duration was set to zero for non-responders.
Patients can be counted in more than one dose category.
The mean duration of erection for each patient (for the injections he received at a given dose) was used in this calculation. The value shown is the mean of the means for all patients who received that dose that resulted in a response.
The value shown is the mean duration of erection for all injections given at a particular dose.
adapted from sponsor

Of the 52 patients who had at least one injection during Months 7 through 12 of the open-label period, 48 received an in-office injection of the current optimum dose at the end of Month 12 or at discontinuation. Of these patients 90% (43/48) responded based on a positive penile Buckling Test. Response based on penile angle (angle ≥ 90° within 60 minutes) was 60% (28/47) following the in-office alprostadil injection.

Of the 52 patients who injected during Months 7 through 12, 81% (42/52) had no change in dose, 13% (7/52) had decreases in dose, and 6% (3/52%) had increases in dose from the end of Month 6 to the end of Month 12.

Study KU-620-001
Months 7 - 12
Response to injections at Home

Month	PTS with Erections sufficient for intercourse n (%)		Injections sufficient for Intercourse n (%)	
7	51	95%	260	90%
8	49	98%	268	93%
93	47	100%	243	95%
10	50	100%	253	97%
11	46	95%	245	93%
12	47	100%	206	95%
>12	29	100%	100	95%

8.1.4.3 Statistical Reviewer's Efficacy Analyses

The statistical reviewer analyzed the following efficacy variables for this trial for the periods: dose titration period and double-blind crossover period.

Dose Titration Period :

- Response to Injection Based on Buckling Test in the Investigator's Office
- Response to Injection Based on Penile Angle in the Investigator's Office

Double-blind Crossover Period :

- Response to Self-Injection at Home -- Erection/Erection Sufficient for Intercourse
- Duration of Erection (in minutes) Based on Patient Assessment During Self-Injection at Home.

The Cochran-Mantel-Haenszel (CMH) test was utilized for pairwise comparisons of alprostadil dose categories with placebo for response to injection based on Buckling test in the investigator's office and response to injection based on penile angle in the investigator's office. McNemar's test was used to obtain an overall p-value for the treatment effect for response to self-injection at home -- erection/erection sufficient for intercourse. A t-test was utilized for the pairwise comparisons of alprostadil with placebo for the duration of erection (in minutes) based on patient assessment during self-injection at home.

8.1.4.3.1 Dose-Titration Period

All 117 patients who enrolled into the study had at least one injection during the dose titration period. Three patients discontinued after receiving the first (placebo) injection; therefore, only 114 of the 117 patients enrolled received alprostadil.

Response to Injection Based on Buckling Test in the Investigator's Office

The response to injection based on Buckling Test in the investigator's office during the dose-titration period is summarized in the following table. A response was defined as a positive Buckling Test within 60 minutes after injection.

Since there were a large number of different doses administered during the dose-titration period, the results are summarized using dose categories.

Buckling Test

Alprostadil Dose (µg)	Number of Patients	Responders		CMH* p-value Pairwise Comparison with Placebo
		Number	%	
0 (Placebo)	117	0	0	
>0 - 2.5	19	8	42	< 0.001
> 2.5 - 5	114	31	27	< 0.001
> 5 - 10	97	36	37	< 0.001
> 10 - 15	78	34	44	< 0.001
> 15 - 20	66	40	61	< 0.001
All Alprostadil	114	87	76	< 0.001

* CMH=Cochran-Mantel-Haenszel Test

There was no response to placebo. Each alprostadil dose category was statistically significantly different from placebo in terms of response to injection based on Buckling Test in the investigator's office.

Response to Injection Based on Penile Angle in the Investigator's Office

The response to injection based on penile angle in the investigator's office during the dose-titration period is summarized in the following table. A response was defined as a penile angle ≥ 90° within 60 minutes after injection.

Since there were a large number of different doses administered during the dose-titration period, the results are summarized using dose categories.

Penile Angle

Alprostadil Dose (μg)	Number of Patients	Responders		CMH* p-value
		Number	%	Pairwise Comparison with Placebo
0 (Placebo)	117	0	0	
>0 - 2.5	19	5	26	< 0.001
> 2.5 - 5	114	21	19	< 0.001
> 5 - 10	97	21	22	< 0.001
> 10 - 15	78	13	17	< 0.001
> 15 - 20	66	17	27	< 0.001
All Alprostadil	114	54	47	< 0.001

* CMH=Cochran-Mantel-Haenszel Test

There was no response to placebo. Each alprostadil dose level was statistically significantly different from placebo in terms of response to injection based on penile angle in the investigator's office.

8.1.4.3.2 Double-Blind Crossover Period

A total of 85 patients were randomized into the two-week double-blind crossover period. Of these, 83 patients received at least one injection during each study week. Two of these patients did not record any diary data following their injections.

Response to Self-Injection at Home -- Erection/Erection Sufficient for Intercourse

The following table gives the number of patients with an **erection (response)** based on patients' assessment during self-injection at home:

Erection

Week	Treatment	Number of Patients	Responders		McNemar p-value for Tmnt Effect
			Number	%	
Week 1	Placebo	41	5	12	
	Alprostadil	40	33	83	
Week 2	Placebo	40	3	8	
	Alprostadil	41	34	83	
Combined Weeks	Placebo	81	8	10	
	Alprostadil	81	67	83	< 0.001

Alprostadil was statistically significantly different from placebo in terms of patient's assessment of erection during self-injection at home.

The following table gives the number of patients with an **erection sufficient for intercourse (response)** based on patients' assessment during self-injection at home:

Erection Sufficient for Intercourse

Week	Treatment	Number of Patients	Responders		McNemar p-value for Tmnt Effect
			Number	%	
Week 1	Placebo	41	3	7	
	Alprostadil	40	29	73	
Week 2	Placebo	40	3	8	
	Alprostadil	41	31	76	
Combined Weeks	Placebo	81	6	6	
	Alprostadil	81	60	60	< 0.001

Alprostadil was statistically significantly different from placebo in terms of patient's assessment of erection sufficient for intercourse during self-injection at home.

Duration of Erection (in minutes) Based on Patient Assessment During Self-Injection at Home

The duration of erection (in minutes) based on patient assessment during self-injection at home during the double blind crossover period is summarized in the following table. The duration was defined as the number of minutes from the start to the end of erection. Duration was considered 0 if an erection was not achieved.

Duration of Erection (minutes)

Week	Treatment	Number of Patients	Duration of Erection		T-test p-value for Tmnt Effect
			Mean	SE	
Week 1	Placebo	40	3.4	2.33	
	Alprostadil	39	50.2	9.94	< 0.0001
Week 2	Placebo	39	4.6	2.70	
	Alprostadil	40	63.5	10.02	< 0.0001
Combined Weeks	Placebo	79	4.0	1.77	
	Alprostadil	79	56.9	7.05	< 0.0001

Alprostadil was statistically significantly different from placebo in terms of mean duration of erection based on patient assessment during self-injection at home.

8.1.4.4 Safety comparisons

The safety comparisons are summarized by treatment period.

8.1.4.4.1 Dose-titration and double-blind treatment periods:

The next table summarizes the number and percentage of patients that reported local side effects and/or clinical adverse experiences during the dose-titration and double-blind treatment periods. Overall, 50 (44%) of the 114 patients who received injections with Alprostadil (669 injections) reported at least one local side effect and/or clinical adverse experience compared to 10 (9%) of the 117 patients after injection with placebo (269 injections).

Four (4%) of the 114 patients who received Alprostadil injections reported adverse experiences not related to the penis compared to 2 (2%) of the 117 patients after injection with placebo. These included one patient each with a skin disorder, neuropathy, testis disorder, myocardial infarction, and fungal infection .

Number (%) of Patients with Local Side Effects and/or Clinical Adverse Experiences Study KU-620-001

	Alprostadil (N = 114) n (%)	Placebo (N = 117) n (%)
Local Side Effects	47 (41)	8 (7)
Clinical Adverse Experiences	4 (4)	2 (2)
Total	50 (44)	10 (9)

The most frequently reported local side effects for patients who received Alprostadil were penile pain (during injection, and during or after erection) and prolonged erection.

Study KU-620-001
Summary of Local Side Effects
Dose Titration and Double-blind Period

	Alprostadil			Placebo
	In Office (Dose-Titration) (N =114)	At Home (Double-Blind) (N=84)	Both (N =114)	(n=117)
No. of Injections	526	143	669	269
No. (%) of Patients With Local Side Effects				
Penile pain during injection	3 (3)	8 (10)	11 (10)	3 (3)
Penile pain during erection	15 (13)	11 (13)	21 (18)	2 (2)
Penile pain after erection	9 (8)	12 (14)	18 (16)	2 (2)
Penile pain, other*	3 (3)	4 (5)	5 (4)	0
Any penile pain**	22 (19)	20 (24)	33 (29)	5 (3)
Prolonged erection (total) > 2 - 4 hours > 4 - 6 hours > 6 hours	5 (4) 5 (4) 0 0	16 (19) 13 (15) 3 (4) 0	19 (17) 17 (15) 3 (3) 0	1 (<1) 1 (<1) 0 0
Hematoma, local	0	0	0	1 (<1)
Bleeding, local	3 (3)	2 (2)	5 (4)	2 (2)
Ecchymosis, local	3 (3)	0	3 (3)	2 (2)
Fibrotic nodules, spots, plaques	1 (<1)	0	1 (<1)	0
Cavernous body fibrosis	0	0	0	0
Penile angulation	2 (2)	0	2 (2)	0
Peyronie's disease	2 (2)	0	2 (2)	0
False injection	1 (<1)	0	1 (<1)	0
Blood in urine	1 (<1)	0	1 (<1)	0
Erythema	0	1 (1)	1 (<1)	0
Injection site reaction	1 (<1)	0	1 (<1)	0
Penis disorder	0	1 (1)	1 (<1)	0

* *"penile ache," "penile warmth," "burning," "sex hurts."*

** *Penile pain during injection, during erection, after erection, or other penile pain. adapted from sponsor*

Prolonged erections are subdivided between 2 - 4, 4 - 6, and >6 hours. Only one patient reported a local side effect that was rated severe and drug-related by the investigator. This was a prolonged erection of 4 hours and 41 minutes. The sponsor notes that the incidence of prolonged erections and pain after erection appeared to be somewhat higher in patients with neurogenic etiologies than in patients with non-neurogenic etiology { 5 patients of 20 (25%) with neurogenic etiology versus 14 of 94 (75%) with non-neurogenic etiology}. The table below

identifies the patients, etiology and final dose of patients with prolonged erections.

Patients with Prolonged Erections (PE)

Investigator/patient #	Patient age - etiology	Final Dose
Auerbach	57- vasculogenic	2.8 µg
Auerbach	54 - neurogenic	2.0 and 4.0 µg
Auerbach	53 - vasculogenic	10 µg
Goldstein	34 - neurogenic	10 µg
Goldstein	64 - neurogenic	10 µg discontinued
Goldstein	49 - vasculogenic	2.5 µg

Four patients reported local side effects that resulted in discontinuation. These effects consisted of penile curvature and Peyronie's Disease (two patients each).

Changes in blood pressure did not appear to be greater than those seen with placebo and did not appear to be dose related.

8.1.4.4.2 Open-label extension (1 - 6 months):

75 patients entered the first six months of the open-label extension. All were included in the safety analysis. One patient did not inject but was included in the safety evaluation. Overall, 55 (73%) of the 75 patients reported local side effects and/or clinical adverse experiences, after one or more injections with Alprostadil.

In this open-label period the most frequently reported adverse events were related to the injection with penile pain, prolonged erection and local bleeding. Penile pain occurred in 43% (32/75) of patients, but followed only 4.7% (108/2300) of injections. Penile pain was generally mild to moderate in intensity.

The incidence of penile pain did not appear to be dose related. The percentage of Alprostadil alphadex injections associated with pain was considerably lower than the percentage of patients who reported pain during the first 6 months of the extension period. Penile pain during injection, during erection, and after erection was reported by 19 (25%), 17 (23%), and 17 (23%) patients, respectively. However, only 1.7% (40), 2.3% (54), and 4.7% (108) of the total of 2300 injections were associated with these types of penile pain.

Prolonged erections (i.e., erection lasting longer than 2 hours) were reported by 31/75 (41%) patients after receiving Alprostadil alphadex; 219 (9.5%) of the total 2300 injections administered during the first 6 months

of the extension period were associated with prolonged erections. Most prolonged erections lasted no longer than 4 hours. Six patients (8%) experienced erections lasting longer than 4 hours, one of whom had an erection lasting longer than 6 hours. All of the events of prolonged erection lasting longer than 4 hours were considered related to the study drug. In all patients, the erection spontaneously detumesced. Most of these patients had their doses reduced as a result of prolonged erections. None of the events resulted in treatment discontinuation.

The incidence of injection-site bleeding was only 0.6% (14/2300) of injections. There was only one reported incidence of a hematoma, and no reports of Peyronie's disease or penile fibrosis. One patient experienced penile angulation.

The most frequently reported side effects in this open label period were penile pain related to the injection and prolonged erection. There were no reports of fibrosis or Peyronie's disease and there was one incident of penile angulation.

Two patients experienced serious adverse events during the first 6 months of the extension period.

- Patient [redacted] (Investigator - Kaufman) - a recurrence of prostate cancer.

- Patient [redacted] (Investigator - Kaufman) - a myocardial infarction. This patient had a history of coronary artery disease and controlled hypertension. On day 243 the patient experienced a myocardial infarciton of moderate intensity, 16 days after his previous injection. The patient had an angioplasty and resumed study participation one month later.

- One patient reported a serious clinical adverse experience (myocardial infarction) following a **placebo** injection during the double-blind, crossover period of the study. This was a 47 year old white man with a history of atypical chest pain secondary to chronic obstructive pulmonary disease and smoking. He experienced a myocardial infarction on Day 32 during the first week of the double-blind period of the study. (patient [redacted] - Knoll)

There did not appear to be any changes in laboratory parameters that are drug related.

8.1.4.4.3 Open Label Extension (7 - 12 months):

Study KU-620-001
Months 7 - 12
Summary of Local Side Effects at Home and In-Office

	Alprostadil Dose (µg)						All Patients n = 52
	>0-2.5 (N = 6)	>2.5-5 (N = 12)	>5-7.5 (N = 8)	>7.5-10 (N = 11)	>10-15 (N = 11)	>15-20 (N = 17)	
Local Side Effect	**Number (%) of Patients**						
Penile pain during injection	0	4 (33)	2 (25)	4 (36)	1 (9)	1 (6)	10 (19)
Penile pain during erection	1 (17)	1 (8)	1 (13)	2 (18)	0	1 (6)	6 (12)
Penile pain after erection	1 (17)	2 (17)	1 (13)	3 (27)	0	2 (12)	9 (17)
Penile pain, other[b]	0	0	0	1 (9)	0	2 (12)	3 (6)
Any penile pain	1 (17)	5 (42)	3 (38)	5 (45)	1 (9)	4 (24)	17 (33)
Prolonged erection (total)	1 (17)	5 (42)	5 (63)	5 (45)	3 (27)	3 (18)	19 (37)
> 2 - ≤ 4 hours	1 (17)	4 (33)	5 (63)	5 (45)	3 (27)	3 (18)	18 (35)
> 4 - ≤ 6 hours	0	2 (17)	1 (13)	0	0	0	3 (6)
> 6 hours	0	0	0	0	0	0	0
Hematoma, local	0	0	0	0	0	0	0
Bleeding, local	0	3 (25)	0	1 (9)	0	0	4 (8)
Ecchymosis, local	0	0	0	2 (18)	0	0	2 (4)
Fibrotic nodules, spots, plaques	2 (33)	1 (8)	1 (13)	0	0	1 (6)	5 (10)
Cavernous body fibrosis	0	0	0	0	0	0	0
Penile angulation	1 (17)	0	1 (13)	1 (9)	0	2 (12)	5 (10)
Peyronie's disease	0	1 (8)	0	0	0	0	1 (2)
False injection	0	0	0	0	0	1 (6)	1 (2)
Balanitis	0	0	0	2 (18)	0	0	2 (4)
Vein distended	0	1 (8)	0	0	0	0	1 (2)

Patients who had more than one experience are counted only once in the All Patients column.
Penile pain during injection, during erection, after erection, or other penile pain - adapted from sponsor's table

Clinical adverse experiences were reported for 25% (13/52) of the patient population. Three patients reported serious clinical adverse experiences during Months 7 through 12 of the open-label extension study. These included the recurrence of prostate cancer, myocardial infarction and arthritis (one patient each).

8.1.4.5 Summary of Discontinued Patients

Thirty-two patients discontinued the dose-titration period prematurely and did not have an optimum dose assigned.

Patients Who Discontinued During Dose Titration

Investigator	Patient	Dose (mg)[a]	Total No. Injections Received	Days on Study Drug[b]	Reason for Discontinuation
Auerbach		10	3	3	Local Side Effect - Dorsal Penile Curvature
		0	1	1[c]	Protocol Violation - Probable Diabetic with Low Testosterone
		20	5	18	Inadequate Therapeutic Response
		20	5	19	Local Side Effect - Peyronie's Band
		5	2	1	Withdrew Consent
		20	5	9	Inadequate Therapeutic Response
Goldstein		5	2	1	Local Side Effect - Peyronie's
		5	2	1	Local Side Effect - Penile Curvature
		20	5	22	Inadequate Therapeutic Response
		20	5	15	Inadequate Therapeutic Response
		20	5	15	Inadequate Therapeutic Response
Kaufman		20	5	17	Inadequate Therapeutic Response
		20	5	8	Inadequate Therapeutic Response
		20	5	13	Inadequate Therapeutic Response
		20	5	15	Inadequate Therapeutic Response
		20	5	13	Inadequate Therapeutic Response
		20	5	11	Inadequate Therapeutic Response
		20	5	11	Inadequate Therapeutic Response
Kaufman		20	5	19	Inadequate Therapeutic Response
		20	5	8	Inadequate Therapeutic Response
		20	5	13	Inadequate Therapeutic Response
		20	5	25	Inadequate Therapeutic Response
		20	5	10	Inadequate Therapeutic Response
Seftel		15	4	22	Withdrew Consent
		0	1	1[c]	Withdrew Consent
Tuttle		20	5	15	Inadequate Therapeutic Response
		20	5	16	Inadequate Therapeutic Response
		20	5	13	Inadequate Therapeutic Response
		0	1	1[c]	Lost to Follow-up
		20	5	12	Inadequate Therapeutic Response
		20	5	8	Inadequate Therapeutic Response
		20	5	8	Withdrew Consent

[a] Dose at discontinuation

[b] Relative to the first dose of Alprostadil alphadex.

[c] Patient did not inject Alprostadil alphadex. Days were calculated relative to the placebo injection.
adapted from sponsor's table

Four patients completed the double-blind crossover period, but did not enter the open-label period. Two of these patients did not enter because

of inadequate therapeutic response at the 20 µg dose, one patient withdrew consent, and one patient moved out of the area.

Patients Who Discontinued During Double-Blind Crossover					
Investigator	Patient	Dose (mg)	Total No. Injections Received	Days on Study Drug	Reason for Discontinuation
Auerbach		20	7	25	Withdrew Consent
Knoll		0	7	32	Adverse Experience - Myocardial Infarction

8.1.5 Reviewer's Comments

8.1.5.1 Efficacy:

After the establishment of the optimum dose for each patient the patients received this injection at the determined dose. 32 patients did not have an optimum determined dose. 32.5% (n=38) had a dose of 20 micrograms chosen. In the dose titration period the median optimum dose was 15 micrograms.

76% of the patients had a response to injection based on the Buckling Test in the investigator's office during the dose-titration period. 94% of the patients responded to their individual optimum dose of injection based on the Penile Buckling Test within 60 minutes after injection. If the response was based on a Buckling test between 20 and 60 minutes only 68% had an optimum response. If the response to injection was based on penile angle of ≥90° only 43% responded. The median time to erection was 10 minutes in the Alprostadil treated group in the double-blind period.

The maximum change from the pre-injection penile cirumference was 2.6 cm (9.6 cm baseline to 12.2 cm). The median optimum dose of alprostadil for the 85 patients who completed the dose-titration period was 15 µg. The median time to the onset of erection at the optimum dose was 20 minutes in 80 patients and the duration was 42.0 minutes. The mean duration of an erection was approximately 4 minutes after injection with placebo and 57 minutes after injection with Alprostadil.

• Patient Assessment of Intercourse

74% of the patients had erections that were considered to be sufficient for intercourse after injection with Alprostadil compared to 7% (6/81) after injection with placebo during the double-blind crossover period at home.

At the optimum dose during the dose titration period the patient evaluation of erections sufficient for intercourse was 94% (75/80) and the investigator evaluation of an erection sufficient for intercourse was 93% (74/80). Eighty three percent (67/81) of the patients had an erection after injection with Alprostadil compared to 10% (8/81) after injection with placebo in the double-blind period of the study. The majority of the patients (74%) had erections that were considered to be sufficient for intercourse after injection with Alprostadil while 7% (6/81) had erections sufficient for intercourse after placebo.

75 patients entered the first six months of the open-label extension. One patient did not inject but was included in the safety evaluation. All of the patients who self-injected responded to at least one of the injections. Ninety-nine percent (73/74) of patients stated that they had erections that were considered sufficient for intercourse after injection with Alprostadil alphadex, and 93% (2049/2210) of injections administered at home resulted in erections that were considered sufficient for intercourse.

There were a small group of men (8) with low testosterone defined as ≤280 ng/dL. Only 4 completed the dose-titration portion of the study. Three of the patients with a low serum testosterone discontinued because of inadequate therapeutic response. This would suggest that low testosterone patients are not candidates for treatment in this way.

No men with a pure psychogenic diagnosis were included in this study although those with a mixed diagnosis were included.

8.1.5.2 Statistical Reviewer's Conclusions (Trial # 620-001)

Statistical reviewer's analyses indicated that this multicenter study, which included a dose-titration period followed by a double-blind placebo-controlled crossover period, showed that intracavernosal injection of alprostadil in doses ranging up to 20 µg is effective in the treatment of erectile dysfunction as judged by response to injection based on Buckling test in the investigator's office, response to injection based on penile angle in the investigator's office, response to self-injection at home -- erection/erection sufficient for intercourse and duration of erection (in minutes) based on patient assessment during self-injection at home.

8.1.5.3 Safety:

Thirty-two patients discontinued during the dose-titration period and did not have an optimum dose assigned. 55 (73%) of the patients reported at least one local side effect and/or clinical adverse experience. Only one was considered a serious adverse experience. Two patients discontinued due to adverse

experience and one patient died during the first open-label period. During the second open-label period 38 (73%) patients reported at least one local side effect, three of which were considered serious adverse experiences.

- Prolonged erections and priapism:

There were no injections associated with an erection longer than 4 hours in the dose titration or double blind period. There was one injection with placebo assoicated with a prolonged erection of >2 - ≤4 hours. A total of 19 (17%) patients had a prolonged erection. 3 (3%) were associated with an erection between 4 and 6 hours in the first six months of the open label period. The erections spontaneously detumesced in all three cases. In the open label 7 - 12 month extensions erections lasting more than 4 hours were experienced by only six of these patients, and an erection lasting more than 6 hours was experienced by only one patient.

8.2 Trial # 620-002

This second pivotal trial was a placebo-controlled safety and efficacy study of Alprostadil for injection (PGE_1-cyclodextrin) in the treatment of erectile dysfunction in both diabetic and non-diabetic patients, which was followed by 48 Weeks of open label treatment. It was planned to enroll 230 patients and it was expected that 25% of the 230 patients would have diabetes mellitus (either type I or II).

Protocol KU 620-002

Regimen	N=	Duration
Screening	257	1 week
Dose titration	233	10-21 days
Double-blind cross-over	158	2 weeks
Open label	139 101	1- 6 months 7-12 months

8.2.1 Objectives

The primary objectives of this study were to determine the efficacy of intracavernosal injection of Alprostadil alphadex to produce an erection sufficient for sexual intercourse and to evaluate the safety and tolerability of repeated injections of Alprostadil alphadex.

The secondary objectives included determining the distribution of optimum doses of Alprostadil alphadex and characterizing the erections produced by intracavernosal injection.

8.2.2 Design

This study was designed to evaluate the safety and efficacy of intracavernosal injections of Alprostadil in both diabetic and nondiabetic patients with erectile dysfunction (ED) and to assess the feasibility of self-injection of Alprostadil when administered by patients at home.

The design was similar to that of Study KU-620-001 except for the use of doses up to 40 µg and the inclusion of both diabetic men and non-diabetic men. All patients received intracavernosal injection therapy for the first time in this study.

Study KU-620-002 also consisted of the same four treatment periods as noted in the previous protocol. These periods included a screening visit in the investigator's office; an open-label, dose-titration period in the investigator's office during which three to five injections of Alprostadil in a dose range of 1 µg to 40 µg were given over 5 to 21 days to establish an optimum dose for each patient; a two-week, double-blind, crossover comparison of placebo and the optimum dose of alprostadil, self-injected by the patient at home (one or two injections per week); and an open-label, self-injection treatment period at home that was continued for up to 24 months.

8.2.3 Protocol

This multicenter study consisted of an open-label, dose-titration period in the investigator's office followed by a placebo-controlled, double-blind, crossover period at home. After patients received an initial injection of placebo during the screening period, the optimum dose for each patient was determined by titrating from a starting dose of 1 µg Alprostadil to a maximum dose of 40 µg. The dose was selected by the investigator with the patient during the dose titration period.

Patients were then randomized to a two-week, crossover period. During this period the patient self-injected for one week with either placebo or their optimum dose of Alprostadil and then self-injected with the alternate treatment for the second week. This included one or two injections per week. The inclusion and exclusion criteria were identical to those noted for the previous protocol (See page 19).

Response to injection based on Penile Buckling Test was the primary efficacy variable in the investigator's office. Patients who did not have a

positive Penile Buckling Test were not entered into the double-blind period of the study. Secondary efficacy variables included the response to injection based on penile angle, maximum penile angle, and determination of the minimum effective and optimum doses. The minimum effective dose was defined as the lowest dose resulting in a response to injection based on a positive Buckling Test within 60 minutes after injection. The optimum dose was defined as the dose selected by the investigator during dose titration for injection during the double-blind, crossover period.

Although patients received one or two injections during each study week of the crossover period, only the first injection of each study week was included in the statistical analysis. The second injection was excluded since the response to the first injection in a study week may have influenced the patient's decision to inject a second time that week, introducing a potential bias.

Both the number and percentage of patients and the number and percentage of injections with a response (erection and erection sufficient for intercourse based on patient assessment) are displayed for each study week and for the combined study weeks. The McNemar test was performed to evaluate differences between placebo and Alprostadil. A formal test for carry over effect was not performed. However, based on an inspection of weekly statistics, there was no apparent carryover effect (i.e., the results were very similar for the two treatment sequences).

All adverse experiences that were related to the penis were considered to be local side effects. At the time of each injection, patients were specifically evaluated for the presence of penile pain (during injection, during erection, and after erection), prolonged erection, and bleeding. Erections were considered to be prolonged if the duration was greater than two hours. All adverse experiences that were not related to the penis were recorded as clinical adverse experiences.

8.2.3.1 Population and procedures

The eligibility criteria other than inclusion of men with diabetes were identical to that of protocol 620-001.

8.2.3.2 Endpoints

The primary efficacy variable during the double-blind, crossover period was the patient's assessment of response to injection. A response was defined as an erection that was considered by the patient to be sufficient for intercourse. Secondary efficacy variables included the time to onset of erection, duration of erection, and partner assessment of intercourse.

The efficacy and safety analyses were based on an "intent-to-treat" approach. However, due to limitations of the crossover design, the analyses of the double-blind, crossover period include only patients who received at least one injection in each week of the double-blind, crossover period.

The following endpoints were measured:

- Positive Buckling Test within 60 minutes after injection.

- Response based on Buckling Test with duration between 20 and 60 minutes.

- Penile angle ≥90° or ≥75° and <90° and an erection considered sufficient for intercourse within 60 minutes after injection.

- Based on a 10-point visual analog scale (10 was defined to be like an erection the patient had when he was 18 or the best erection that the patient remembered).

- Time from injection to erection. Time to erection was considered >60 minutes if an erection did not occur.

- Time from the start of erection to the end of erection. Duration was set to zero if an erection did not occur.

8.2.4 Results

8.2.4.1 Patient Disposition, comparability

Summary of Study KU-620-002

STUDY DESIGN	N= w/b/h/o*	AGE	DOSE µG med opt dose	ERECTION after injection
Screening	257 190/43/18/6	23-74	placebo	
Dose titration diabetic or nondiabetic with ED of vasculogenic or neurogenic cause	233		0 - 40 µg median dose 30 µg	73%
Double-blind cross-over	158		2.5-40 µg and placebo	
Open label extension 1-6 months	139 98/26/12/3	35-74	2.5-40 µg dose	97% erection sufficient for intercourse
Open label extension 7 12 months	101 68/18/10/3	35-74	2.5-40µg	98% erection sufficient for intercourse
Investigators	Borges,Brosman, Castellanos, Eid, Fitch III, Gittelman, Kuglitsch, Lewis, McGill, Murdock, Rajfer, and Reid adapted from sponsor.			

* *w (white),b (black), h (Hispanic), o (other).*

A total of 257 men, ages 23 to 74 years (mean, 59.5 years), were enrolled in the study. Seventy-four percent of the patients (190/257) were white; 17% (43/257) were black, 7% (18/257) were Hispanic and 2% (6/257) were "other" races. The majority of patients (67%; 171/257) had ED of vasculogenic origin while 20% (52/257) had ED of neurogenic origin and 13% (34/257) had ED of both neurogenic and vasculogenic origin. The duration of ED ranged from years, with a mean duration of 4.1 years. Of the 257 patients, 177 (69%) had no previous treatment of ED. Forty-six percent (118/257) of the patients used alcohol. Eighteen percent (45/257) of the patients were currently smokers. Seventy-five (29%) patients had diabetes mellitus (type I or II). There were 22 (9%) patients who had low serum total testosterone (<280 ng/dL) at the screening visit. Low testosterone was defined as less than 280 ng/dL at screening. Cardiovascular risk factors (e.g., hypertension, hypercholesterolemia, and atherosclerotic cardiovascular disease) appeared to be comparable between the two pivotal trials.

82% of the 257 patients were not current smokers, 46% used alcohol less than an average of once per week . All 257 patients who enrolled in the study had at least one injection during the dose-titration period. Twenty-four patients discontinued after receiving the first (placebo) injection; therefore, only 253 of the 257 patients enrolled received Alprostadil. 24 discontinued during the screening period and 75 discontinued during the dose-titration period. The remaining 158 patients were randomized to double-blind treatment, of which 147 patients completed this period.

One hundred forty-four patients who completed the dose-titration and double-blind, crossover periods entered the 12-month, open-label extension period and were issued study medication. Only 139 patients injected study medication during the first six months. These 139 men ranged in age from years (mean, 59.5 years). Seventy-one percent (98/139) of the patients were white, 19% (26/139) were black, 9% (12/139) were Hispanic, and 2% (3/139) were "other" races. The majority of the patients (75%, 104/139) had ED of vasculogenic origin. The duration of ED ranged from years, with a mean duration of 4.1 years.

Of the 257 screened patients, 24 (9%) were discontinued from study participation after receiving a placebo injection. Seventy-five patients (32%; 75/233) who injected Alprostadil alphadex during the dose-titration period discontinued the dose-titration period prematurely. The most frequent reason for discontinuation during the dose-titration period was inadequate therapeutic response (21%; 48/233). Ten patients (4%; 10/233) withdrew due to local side effects, and two patients (<1%; 2/233) withdrew due to clinical adverse experiences. Six patients (3%; 6/233) withdrew consent for study participation, and 4 patients (2%;