4/233) discontinued due to protocol violations. The remaining five patients withdrew due to unsatisfactory compliance, lost to follow-up, and other reasons.

One hundred and fifty-eight patients were randomized in the double-blind crossover period. Six percent (10/158) of the patients discontinued the crossover period prematurely. Of these patients, four withdrew consent, one withdrew due to inadequate therapeutic response, and two were lost to follow-up. The remaining three patients withdrew due to unsatisfactory compliance, side effect and adverse experiences, and other reasons. Ninety-three percent (147/158) of the randomized patients completed the two-week double-blind crossover period. One patient (Patient , did not complete the crossover but continued into the open-label period. One hundred and forty-eight patients entered the open-label period.

The disposition of patients is summarized by study period below.

Disposition of Patients KU-620-002		
	No. and %	
Screening Period		
Number of Patients Entered	257	
Number of Patients Discontinued[a]	24	9%
Reason for Discontinuation		
Did Not Meet Criteria for Continuation	10	4%
Withdrew Consent	4	2%
Protocol Violation	3	1%
Lost to Follow-up	2	<1%
Local Side Effect	1	<1%
Other	4	2%
Dose-Titration Period		
Number of Patients Entered	233	
Number of Patients Discontinued	75	32%
Reason for Discontinuation		
Inadequate Therapeutic Response	48	21%
Local Side Effect	10	4%
Adverse Experience	2	<1%
Withdrew Consent	6	3%
Protocol Violation	4	2%
Unsatisfactory Compliance	2	<1%
Lost to Follow-up	2	<1%
Other	1	<1%
Double-Blind Crossover Period		
Number of Patients Randomized	158	
Number of Patients Discontinued	10	6%
Reason for Discontinuation		
Withdrew Consent	4	3%
Inadequate Therapeutic Response	1	<1%
Lost to Follow-up	2	1%
Unsatisfactory Compliance	1	<1%
Local Side Effect and Adverse Experience	1	<1%
Other	1	<1%
Number of Patients Completing 2 Weeks of Treatment[b]	147	93%

[a] Patients who discontinued during screening received one placebo injection.

[b] One patient did not complete the crossover period, but was not discontinued from the study.

from sponsor

8.2.4.2 Efficacy endpoint outcomes

This section will sequentially discuss the results in terms of the three major study times.

8.2.4.2.1 Screening period:

There was a screening period of one week. 24 (of 257) patients discontinued and one discontinued due to adverse event.

8.2.4.2.2 The Dose-Titration Period:

The dose-titration period was a time for educating the patients regarding injection of Alprostadil under the supervision of the investigator. The table below presents the distribution of doses administered during the dose-titration period and the response to those doses for the 233 patients who received alprostadil. Based on the Buckling Test, no patients responded to the placebo injection at the beginning of the dose-titration period. Of the patients who injected alprostadil, 73% (171/233) responded to at least one of the injections. No patient responded to placebo. Thirty-seven percent (307/822) of Alprostadil injections, overall, resulted in a response.

Dose-Titration Period
Response to Injection Based on the Buckling Test in the Investigator's Office
Study KU-620-002

Dose Category (µg)	No. Patients	Injection N=	Patients With a Response N (%)	Injections With a Response N (%)
Placebo	257	257	0	0
>0-2.5	22	26	2 (9)	3 (12)
>2.5-7.5	45	59	27 (60)	35 (59)
>7.5-10	205	216	60 (29)	68 (31)
>10-15	39	41	15 (38)	17 (41)
>15-20	177	187	48 (27)	57 (30)
>20-25	24	25	8 (33)	8 (32)
>25-30	127	130	50 (39)	51 (39)
>30-35	16	17	10 (63)	10 (59)
>35-40	101	121	52 (51)	58 (48)
All	233	822	171 (73)	307 (37)

adapted from sponsor

Patients could be counted in more than one dose category. The distribution of optimum doses is presented in the next table. Seventy-five patients discontinued during the dose-titration period and did not have an optimum dose assigned. Of these, 48 had inadequate response at 40 µg. The median dose for the 157 patients who had an optimum dose determined during the dose-titration period was 30 µg.

Distribution of Optimum Doses
Study KU-620-002

Dose (µg)	N=	%	Cumulative %
2.5	1	0.4	0.4
5.0	20	8.6	9.0
7.5	3	1.3	10.3
10.0	11	4.7	15.0
15.0	8	3.4	18.4
20.0	20	8.6	27.0
25.0	7	3.0	30.0
30.0	30	12.9	42.9
33.0	1	0.4	43.3
35.0	6	2.6	45.9
40.0	50	21.5	67.4
None Determined	76	32.6	100.0
Total	233	100.0	100.0

After the establishment of each patient's optimum dose of alprostadil, patients received an additional injection of alprostadil at their optimum dose in the investigator's office for the evaluation of selected efficacy variables. The table below summarizes the results of these selected efficacy variables.

Summary of Efficacy Variables at the Optimum Dose
Study KU-620-002

Efficacy Variable At Optimum Alprostadil Dose	
Response to Injection Based on Buckling Test	154/156 (99%)
Optimum Response to Injection Based on Buckling Test	131/156 (84%)
Response to Injection Based on Penile Angle	78/156 (50%)
Investigator Evaluation - Erection Sufficient for Intercourse	153/156 (98%)
Patient Evaluation - Erection Sufficient for Intercourse	151/156 (97%)
Penile Rigidity Score - Based on Patient Assessment	(N=155)
4	1 (1%)
5	4 (3%)
6	18 (12%)
7	41 (26%)
8	49 (32%)
9	29 (19%)
10	13 (8%)
Time to Erection (min)	
N=	156
Median	16.5
Duration of Erection (min)	
N	156
Mean	39.7
S.E.	1.56

8.2.4.2.3 Double-blind cross-over period:

The next table notes the number of patients with erections and the number sufficient for intercourse as assessed by the patient during the double-blind treatment period. Alprostadil was significantly ($p < 0.001$) more effective than placebo for both variables. Eighty-six percent (122/142) of the patients had an erection after injection with alprostadil compared to 15% (21/142) after injection with placebo. The majority of patients (73%; 103/141) had erections that were considered to be sufficient for intercourse after injection with Alprostadil compared to 13% (18/141) after injection with placebo. Similar results were observed for both treatment sequences.

Study KU-620-002
Double-Blind, Crossover Period
Response to Injection Based on Patient Assessment

Study Week	Treatment	Number of Patients with an Erection		Patients with an Erection Sufficient for Intercourse	
Week 1	Placebo	12/73	16%	9/72[a]	13%
	Alprostadil	57/69	83%	48/69	70%
Week 2	Placebo	9/69	13%	9/69	13%
	Alprostadil	65/73	89%	55/72	76%
Both	Placebo	21/142	15%	18/141	13%
	Alprostadil	122/142	86%*	103/141	73%*

One patient in each week reported an erection occurred but did not indicate if it was sufficient for intercourse.
**Significantly different from placebo ($p < 0.001$)*
adapted from sponsor's table

The median time to erection was 10 minutes in the Alprostadil group and > 60 minutes (censored) in the placebo group. The mean duration of erection was approximately eight minutes after injection with placebo and 59 minutes after injection with Alprostadil.

Distribution of Optimum Doses			
Dose (mg)	Patients N	%	Cumulative Percent
2.5	1	0.4	0.4
5.0	20	8.6	9.0
7.5	3	1.3	10.3
10.0	11	4.7	15.0
15.0	8	3.4	18.4
20.0	20	8.6	27.0
25.0	7	3.0	30.0
30.0	30	12.9	42.9
33.0	1	0.4	43.3
35.0	6	2.6	45.9
40.0	50	21.5	67.4
No Dose Determined	76	32.6	100.0
Total	233	100.0	100.0

[1] Doses were selected by the investigator during dose titration.

The median time to erection was 10 minutes for all patients injected with Alprostadil and greater than 60 minutes with placebo injections.

The mean maximum increase from pre-injection penile length was 3.9 cm (s.e. 0.12). The mean maximum increase in penile circumference was 2.9 cm (s.e. 0.09).

8.2.4.2.4 Open-Label Phase of Study (month 1 - 6):

At the conclusion of the last double-blind visit the patients were reinstructed in injection techniques and given a patient diary to complete during the interval before the next office visit. The patient was to record the results following every injection. The patients were given supplies and study drug sufficient for 9 injections and told to return to the study monitor at 30-day intervals with completed diary cards and unused supplies. Any change in dose was to be done in consultation with the investigator and recorded in the patient's diary. At the 30 day visits the investigators measured blood pressure, heart rates and reviewed the patient diary. A penile examination was included to evaluate any changes. At the 6 month visit this was repeated and each patient received a test injection of the drug at the current optimum dose. This injection was followed by blood pressure and heart rate measurements up to 1 hour post-injection and every 15 minutes until detumescence occurred. Penile circumference measurements were obtained during the same time period. Penile Buckling tests were conducted when the penis was at maximum circumference to verify the response to the study drug and a Poloroid photograph was taken.

Although 144 patients entered the open-label extension and were issued study drug only 139 patients injected study drug during the first 6 months of this period. Five patients had no reported injections during the extension period and were discontinued, one had spontaneous erections, 2 withdrew consent and 2 were lost to follow-up. 18% of the patients who entered the open label had diabetes mellitus (type I or II).

Study KU-620-002
Months 1 - 6
Summary of Erections Sufficient for Intercourse at Home, by Dose Category

Dose (µg)	Number of Pts	Number of Inj.	N (%) Pts with Erection Sufficient for Intercourse	Mean % Response Per Pt	N (%) Injections With Erection Sufficient for Intercourse
> 0 - 2.5	5	160	5 (100)	91.3	146 (91)
> 2.5 - 7.5	26	624	25 (96)	86.8	574 (92)
> 7.5 - 10	27	511	25 (93)	86.6	476 (93)
> 10 - 15	18	247	15 (83)	74.6	221 (89)
> 15 - 20	25	442	23 (92)	79.9	393 (89)
> 20 - 25	7	211	7 (100)	94.3	197 (93)
> 25 - 30	35	535	33 (94)	79.6	488 (91)
> 30 - 35	19	202	18 (95)	81.6	184 (91)
> 35 - 40	52	929	47 (90)	77.7	806 (87)
All Doses	139	3861	135 (97)	85.3	3485 (90)

Patients can be counted in more than one dose category.
The percent of injections resulting in an erection sufficient for intercourse for each patient (at a given dose) was used in the calculation. The value shown is the mean of the percent of responses for all patients. - adapted from sponsor

Study KU-620-002
Months 1 - 6
Summary of Erections Sufficient for Intercourse at Home, by Study Month

Study Month	N=	Number of Injections	N (%) of Patients with an Erection Sufficient for Intercourse	Mean % Response Per Patient	No. (%) of Injections With an Erection Sufficient for Intercourse
1	134	594	125 (93)	82.9	507 (85)
2	126	605	121 (96)	87.1	543 (90)
3	121	629	118 (98)	91.8	592 (94)
4	121	629	115 (95)	85.2	554 (88)
5	116	563	111 (96)	90.9	521 (93)
6	111	527	105 (95)	88.8	479 (91)
> 6	80	293	76 (95)	90.3	268 (91)

Patients can be counted in more than one month.
The percent of injections resulting in an erection sufficient for intercourse for each patient (for a given month) was used in the calculation. The value shown is the mean of the percent of responses for all patients. adapted from sponsor

The next table presents the duration of erections for each dose category at home for responders only. Including patients with no response, the mean duration of erection per patient was 65.4 minutes. The mean duration of erection among responders was 68.5 minutes. The median time to erection was 10 minutes for all patients and for responders only.

Study KU-620-002
Months 1 - 6
Summary of Duration of Erections (min) at Home by Dose Category: Responders Only

Dose Category (µg)	Number of Patients	Number of Injs	Mean Duration of Erection Per Patient (S.E.)	Mean Duration of Erection Per Injection (S.E.)
> 0 - 2.5	5	148	88.7 (14.34)	77.5 (3.41)
> 2.5 - 7.5	26	589	90.5 (15.20)	75.2 (2.24)
> 7.5 - 10	27	479	97.7 (15.13)	81.8 (2.55)
> 10 - 15	18	225	70.9 (18.31)	67.5 (4.00)
> 15 - 20	25	412	77.6 (10.74)	64.1 (2.13)
> 20 - 25	7	199	87.0 (21.25)	98.5 (3.82)
> 25 - 30	35	520	60.1 (5.27)	64.3 (1.54)
> 30 - 35	18	196	42.2 (5.31)	49.7 (2.28)
> 35 - 40	52	881	61.7 (6.13)	57.5 (1.30)
All Doses	139	3649	68.5 (3.65)	68.5 (0.79)

Time from start to the end of the erection based on patient assessment at home.
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
The value shown is the mean duration of erection for all injections given at a particular dose

Of the 139 patients who had at least one injection during the first six months of the open-label period, 109 reinjected the current optimum dose in the investigator's office at the end of Month 6 or at discontinuation. Eighty-four percent (92/109) responded (positive penile Buckling Test within 60 minutes after injection). Response based on penile angle (angle ≥ 90° within 60 minutes after injection, or ≥ 75° and < 90° but an erection considered sufficient for intercourse by both the patient and the investigator) was 51% (56/109).

At total of 106 patients completed the first 6 months of the 12 month open label exension. 33 patients discontinued during this phase of the study. Of these 8 withdrew consent, 7 had local side effects, 7 were lost to follow-up, 4 had adverse experiences, 2 had inadequate response, 2 had protocol violations, 1 had a compliance problem, 1 did not meet criteria to continue and 1 patient lost a partner.

8.2.4.2.5 Open-Label Extension (month 7 - 12):

A total of 101 patients entered the second six month open-label extension. Two of these patients did not inject Alprostadil during this period and ten others discontinued the study before the 12 months. A total of 89 patients completed Months 7 - 12.

65% of the patients (64/99) used the same dose at Month 6 as at Month 12 or at discontinuation. 18% of the patients lowered the dose and 17% had a higher dose. The average dose used was 23 µg. 81% (70.86) of the patients responded

with a positive Buckling Test within 60 minutes after Alprostadil injection in the in-office injection of their currently used dose. There were increases in sexual desire, sexual activity, sexual satisfaction and orgasm for both patients and partners from screening to Month 6 which were maintained through the 12th month using the Quality of Life Questionnaire.

8.2.4.3 Statistical Reviewer's Efficacy Analyses

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

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 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.

8.2.4.3.1 Dose-Titration Period

All 257 patients who enrolled into the study had at least one injection during the dose titration period. Twenty-four patients discontinued after receiving the first (placebo) injection; therefore, only 233 of the 257 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
		Number	%	Pairwise Comparison with Placebo
0 (Placebo)	257	0	0	
>0 - 2.5	22	2	9	< 0.001
> 2.5 - 7.5	45	27	60	< 0.001
> 7.5 - 10	205	60	29	< 0.001
> 10 - 15	39	15	38	< 0.001
> 15 - 20	177	48	27	< 0.001
> 20 - 25	24	8	33	< 0.001
> 25 - 30	127	50	39	< 0.001
> 30 - 35	16	10	63	< 0.001
> 35 - 40	101	52	51	< 0.001
All Alprostadil	233	171	73	< 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)	257	0	0	
>0 - 2.5	22	1	5	< 0.001
> 2.5 - 7.5	45	18	40	< 0.001
> 7.5 - 10	205	43	21	< 0.001
> 10 - 15	39	8	21	< 0.001
> 15 - 20	177	37	21	< 0.001
> 20 - 25	24	2	8	< 0.001
> 25 - 30	127	19	15	< 0.001
> 30 - 35	16	5	31	< 0.001
> 35 - 40	101	21	21	< 0.001
All Alprostadil	233	100	43	< 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.

8.2.4.3.2 Double-Blind Crossover Period

A total of 147 patients were randomized into the two-week double-blind crossover period. Of these, 145 patients received at least one injection during each study week. Two of these patients did not record any diary data following their injections. As some patients recorded incomplete data, all the analyses (given below) do not include all 145 patients. The analysis for **erection based on patients' assessment during self-injection** includes 142 patients. The analysis for **erection sufficient for intercourse based on patients' assessment during self-injection** includes 141 patients. The analysis for **duration of erection (in minutes) based on patients' assessment during self-injection at home** includes 139 patients.

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 based on Patients' Assessment during Self-Injection

Week	Treatment	Number of Patients	Responders		McNemar p-value for Tmnt Effect
			Number	%	
Week 1	Placebo	73	12	16	
	Alprostadil	69	57	83	
Week 2	Placebo	69	9	13	
	Alprostadil	73	65	89	
Combined Weeks	Placebo	142	21	15	
	Alprostadil	142	122	86	< 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:

Erections Sufficient for Intercourse

Week	Treatment	Number of Patients	Responders		McNemar p-value for Tmnt Effect
			Number	%	
Week 1	Placebo	72	9	13	
	Alprostadil	69	48	70	
Week 2	Placebo	69	9	13	
	Alprostadil	72	55	76	
Combined Weeks	Placebo	141	18	13	
	Alprostadil	141	103	73	< 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 Erections

Week	Treatment	Number of Patients	Duration of Erection		T-Test p-value for Tmnt Effect
			Mean	SE	
Week 1	Placebo	71	8.2	4.16	
	Alprostadil	68	57.5	6.92	< 0.0001
Week 2	Placebo	68	7.1	2.86	
	Alprostadil	71	60.5	6.43	< 0.0001
Combined Weeks	Placebo	139	7.6	2.54	
	Alprostadil	139	59	4.70	< 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.

8.2.4.4 Safety comparisons

The safety comparisons are summarized by treatment periods.

Dose-titration and double-blind treatment periods:
Three patients reported serious adverse experiences following injections of alprostadil during the dose-titration and double-blind periods. One of

these patients reported a kidney infection on Day 4 of the dose-titration period, and two patients reported serious adverse experiences that occurred more than 14 days after the last administration of study medication. Another one of these patients was reported to have a cardiac arrhythmia 28 days after the first 20-µg alprostadil injection during the dose-titration period of the study. Subsequently, this patient experienced cardiac arrest and death on Day 58. The third patient reported an inguinal hernia on Day 43 following the double-blind period of the study.

The Open Label Period:

There were a total of 119 of the 139 patients (86%) who reported local side effects or clinical adverse experiences during the 6 month open label period. Seventy-eight percent of the patients (108/139) reported local side effects related to the penis. Nine patients discontinued due to adverse experiences.

Study KU-620-002
Months 1 - 6
Summary of Local Side Effects

	All Alprostadil Patients (N = 139)
No. (%) of Patients With Local Side Effects	
Penile pain during injection	55 (40)
Penile pain during erection	62 (45)
Penile pain after erection	60 (43)
Penile pain, other	10 (7)
Any penile pain	83 (60)
Prolonged erection (total)	54 (39)
≤ 2 hours	2 (1)
> 2 - ≤ 4 hours	54 (39)
> 4 - ≤ 6 hours	5 (4)
> 6 hours	1 (<1)
Hematoma, local	0
Bleeding, local	21 (15)
Ecchymosis, local	9 (6)
Fibrotic nodules, spots, plaques	9 (6)
Cavernous body fibrosis	4 (3)
Penile angulation	10 (7)
Peyronie's disease	2 (1)
False injection	4 (3)
Swelling of foreskin or glans penis	2 (1)
Erythema	4 (3)
Injection site inflammation	1 (<1)
Numbness, localized	1 (<1)
Penis disorder	6 (4)
Verruca	1 (<1)

Patients who had more than one occurrence of an event are counted only one.
e.g., "penile aching," "burning," "penis felt bursting."
Penile pain during injection, during erection, after erection, or other penile pain.
adapted from sponsor's table

Prolonged erections of greater than 2 hours were reported by 54 (39%) of the patients in the open label extension of 1 - 6 months. 344 (8.6%) of the total 4010 injections administered during the first 6 months of the extension period were associated with prolonged erections. Most of the erections lasted no longer than 4 hours. Five patients (4%) experienced erections lasting longer than 4 hours but less than 6 hours (see table below). None of the patients discontinued due to prolonged erections.

Patients with Prolonged Erections (PE) ≥4 hours

Investigator/patient #	Patient age - etiology	Final Dose
Castellanos*	50 - neurogenic	15 µg and 5µg
Eid	54 - vasculogenic	2.5µg
Eid	66 - neurogenic	35 µg
Gittelman	50 - mixed	7.5 µg and 2.5 µg
Rajfer	69 - neurogenic	20 µg

*36 times at doses up to 15 µg and experienced 21 prolonged erections, 10 of which lasted longer than 4 hours. His last injection at Day 200 was 5 µg without a prolonged erection.

**23 out of 29 prolonged erections. nine erections lasted longer than 6 hours. The patient reduced his dose to 2.5 µg for 11 injections - 5 of these injections resulted in prolongered erections.

The main causes of erectile dysfunction in diabetic patients are the vascular and neurologic complications associated with the natural history of the disease. Of the patients who entered the open-label extension (months 1-6) only 18% (25/139) of the patients had diabetes mellitus (type I or II). The sponsor has compared the distribution of optimum dose chosen for diabetic and non-diabetic men during the dose titration period by the investigators (KU-620-002 and KU-620-003). There were a total of 197 diabetic men and 583 non-diabetic men in both of these studies. The mean defined optimum dose was similar (26.4 vs 25.2 µg respectively). There were 100 diabetic men (n=197/51%) and 177 non-diabetic men (n=583 30%) that did not have an optimum dose defined. Although there are a greater number of diabetic men that do not have an optimum dose defined during the titration phase there is no data that suggests that diabetic men are at greater risk and the defined dose is similar.

8.2.4.4 Discontinued patients

A total of 24 men (n=257) discontinued during the screening period. One discontinued due to a local side effect. 75 patients (n=233) discontinued during the dose-titration period and did not have an optimum dose assigned. Of these, 48 had an inadequate response at 40 µg. In contrast the median dose for the 157 patients who had an optimum dose determined during the dose titration period was 30 µg.

During the open label extension (months 1-6) 33 patients (24% of a total 139 patients) discontinued for the following reasons: 8 withdrew consent, 7 were lost to follow-up, 7 had local side effects, 4 had adverse

experience, 2 with inadequate response, 2 with protocol violation, 1 because of compliance, 1 did not meet criteria to continue and 1 lost a partner. Four patients discontinued with serious clinical adverse events, e.g., myocardial infarction, prostate cancer, and lung cancer and one patient discontinued due to leg pain. In addition, one patient receiving placebo discontinued because of penile pain.

Patients Who Discontinued During Open-label 1-6 Months					
Inv	Patient	Dose (mg)	N= Inj	Days on Study Drug	Reason for Discontinuation
Borges		9.5	40	252	Local Side Effect - Peyronie s
		30	17	112	Local Side Effect - Pain After Erection
		32.8	46	276	Local Side Effect - Pair During and After Injection
Castellanos		20	11	35	Adverse exp - Myocardial infarction
		40	39	180	Adverse Exp - prostate cancer
Gittelman		35	14	77	Local Side Effect - Pain after Erection
Murdock		30	11	66	Adverse Experience - Leg Pain
Rajter		40	24	192	Local Side Effect - Pain During and After Injection
		40	29	129	Adverse Experience - Lung Cancer
		40	10	58	Local Side Effect - Pain During Erection
Reid		10	9	71	Loss of Sensitivity with intercourse

There was one reported death in Study 002. This was a 71 year old diabetic white male who experienced a cardiac arrhythmia on Day 28 during the dose-titration period. He had secondary diagnosis of borderline LAD, frequent VPCs, irregular heartbeat and a previous myocardial infarction in 1972. He had a cardiac arrest and death on the 68th day of the dose-titration period. (Gittelman patient

8.2.5 Reviewer's Comments

8.2.5.1. Efficacy summary

The median dose for the 157 patients who had an optimum dose determined during the dose titration period was 30 µg. The optimum dose by diabetic status appeared to follow the same pattern as was observed for the non-diabetic patients although larger number of diabetic men did not have an optimum dose determined. The remaining 158 patients were randomized to double-blind treatment of which 147 men completed treatment.

99% of the patients (154/156) had a response to the injection based on the Buckling Test combining all durations of the erections. 84% (131/156) of the patients responded to their individually optimum dose of Alprostadil based on the Penile Buckling Test with a duration within 60 minutes. The median time to erection was 16.5 minutes in the Alprostadil treated group and the duration was 39.7 minutes (n=156). 48

patients did not have an adequate response to 40µg. The maximum change from the pre-injection penile circumference was 2.9 (n=156). The maximum increase from pre-injection in penile length in the investigators office at the optimum dose was 3.9 (n=155).

In the double-blind portion of the study at home 86% (122/142) of the patients had an erection after injection with Alprostadil compared to 15% (21/142) after injection with placebo. The majority of the patients (73% or 103/141) had erections that they considered to be sufficient for intercourse. The median time to erection was 10 minutes. The mean duration of the erection was approximately 7.6 minutes with placebo and 59 minutes after injection with Alprostadil.

The adequacy of the erection sufficient for intercourse was evaluated by both the patient and the investigator. 98% of the erections were considered sufficient for intercourse based on the investigator's evaluation (153/156). When this was based on the patient's evaluation 97% (151/156) were considered sufficient for intercourse.

During the open label 1 - 6 months, 90% of the injections resulted in erections sufficient for intercourse (3485/3861) and 97% of the patients had at least one erection that was considered sufficient for intercourse (135/139). This percentage continued into the second open label extension with 98% of the patients (97/99) having at least one erection considered to be sufficient for intercourse and 95% of the injections resulting in an erection sufficient for intercourse (2653/2796). The average dose in the open-label extension period was 23 µg.

8.2.5.2 Statistical Reviewer's Conclusions (Trial # 620-002)

The 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 40 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.

8.3 Study KU-620-003

Study KU-620-003 consisted of a screening period, an open-label, dose-titration period and an open-label extension period of 48 weeks in the patient's home. Patients had the option to enter the open-label extension period in which they self-administered alprostadil up to two times a week. This study did not include a double-blind placebo-controlled cross-over period.

8.3.1 Objectives

This was a dose-titration safety and efficacy study of Alprostadil for injection (PGE_1-alpha-cyclodextrin) in the treatment of erectile dysfunction in both diabetic and nondiabetic patients. The primary objective was to evaluate the long-term efficacy and safety of intracavernosal injections of alprostadil in diabetic and nondiabetic patients with erectile dysfunction and to assess the feasibility of long-term 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.

8.3.2 Design

Study KU-620-003 included a screening period, an open-label, dose-titration period and an open-label extension period followed by 48 Weeks of open-label treatment. Patients could enter the second open-label extension period of 7 - 12 months for a total of one year.

8.3.3 Protocol

Study KU-620-003 consisted of three treatment periods: a one-week screening period in the investigator's office during which one intracavernous injection of placebo was administered; an open-label, dose-titration period in the investigator's office during which three to five intracavernous injections of alprostadil in a dose range of 1 µg to 40 µg were administered over five to 21 days to establish an optimum dose for each patient; and an open-label, self-injection alprostadil treatment period at home (approximately 24 months).

Patients continuing into the open-label extension period initially injected with their assigned optimum dose of alprostadil. Patients desiring to increase or reduce their dose during the open-label extension were told to consult with the investigator before changing the dose and to record all dose changes in the patient diary. Clinical trial reports included results through Month 12 of the open-label, self-injection home treatment period. This study is continuing.

Protocol 620-003

Regimen	N=	Duration
screening	595	1 week
dose titration	547	10-21 days
double-blind cross-over		2 weeks
Open label	327	1- 6 months 7-12 months

The investigators for this study were Drs. S. Auerbach, J. Bouillier, T. Burns, M. Duckett, B. Fallon, I. Goldstein, J. Kaufman, A. Melman, H. Padma-Nathan, R. Pelman, H. Ritter, Jr., R. Shabsigh, J. Smith, W. Stafford, H. Stevens, S. Thein, J. Tuttle, C. White, F. Witten, M. Wolff, J. Young, J.M. Zachary, and N. Zinner.

8.3.3.1 Population, procedures

This study included both diabetic and nondiabetic men, between the ages of 22 to 78 years with erectile dysfunction 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. Twenty five percent of the patients had diabetes mellitus, either type I or type II. All patients received intracavernosal therapy for the first time in this study.

8.3.3.2 Endpoints

Response to injection based on the Penile Buckling Test (positive penile Buckling Test within 60 minutes after injection) and response to injection based on penile angle (angle $\geq 90°$ within 60 minutes after injection, or angle $\geq 75°$ but $< 90°$ and in the opinion of both the patient and the investigator that the erection was sufficient for satisfactory intercourse) were summarized for the dose-titration period. For both variables, the number and percentage of patients with a response and the number and percentage of injections with a response are presented by dose category. The distribution of the optimum dose determined for each patient was summarized.

Efficacy at the optimum dose was assessed for all patients who were assigned an optimum dose during the dose-titration period. Efficacy variables that were summarized at the optimum dose included response to injection based on the penile Buckling Test, response based on penile angle, the time from injection to the start of erection, duration of erection, the maximum change from preinjection penile circumference and length, maximum penile angle, patient assessment of penile rigidity, and patient's and investigator's assessments of whether the erection was sufficient for intercourse.

At the optimum dose, the percent response based on the Penile Buckling Test and on the penile angle were summarized for each dose. 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 erection was considered to be > 60 minutes (i.e., censored at 60 minutes). The duration of erection and the maximum change from preinjection penile circumference were summarized using

means and standard errors. If a response was not achieved, duration was set to 0 for analysis purposes. The patient's and investigator's assessments of whether the erection was sufficient for intercourse were summarized using the percent positive response at each dose.

Efficacy was assessed at home for all patients who received at least one self-injection. Efficacy variables that were summarized include 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. For each variable, the number and percentage of patients with a response and the number and percentage of injections with a response were presented by dose category. The time from the injection to the start of erection and the 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.

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 clinical adverse experiences. The number and percentage of patients with each local side effect or clinical adverse experience were summarized by dose category.

8.3.4 Results

8.3.4.1 Patient Disposition

Five hundred ninety-five men, 22 to 78 years of age (mean, 57.7 years), participated in this study. Eighty-five percent (505/595) of the patients were white, 11% (63/595) were black, 3% (17/595) were Hispanic, and 2% (10/595) were "other" races. The majority of patients (82%; 485/595) had erectile dysfunction of vasculogenic origin. 25% (147/595) of the patients were diabetic, Type I or II. Two patients were defined as having erectile dysfunction of psychogenic origin and there were 42 out of 553 (7%) patients with low testosterone defined as a level less than ≤280 ng/dL.

The duration of erectile dysfunction ranged from 0.3 to 30 years, with a mean duration of 4.6 years. Of the 595 patients who entered the study, 547 continued into the dose-titration period, of whom 545 received an injection of alprostadil. Three hundred twenty-seven patients entered the open-label extension period and self-injected alprostadil at home.

8.3.4.2 Efficacy endpoint outcomes

Screening and Dose Titration Periods:

Of the 595 patients who enrolled in the study, 48 patients received only an initial placebo injection, and 547 patients received at least one injection of alprostadil during the dose-titration period.

Response to injection based on the Penile Buckling Test (defined as positive if within 60 minutes after injection) and response to injection based on penile angle (angle $\geq 90°$) within 60 minutes after injection, (or angle $\geq 75°$ but $< 90°$ and in the opinion of both the patient and the investigator that the erection was sufficient for satisfactory intercourse) were summarized for the dose-titration period. For both variables, the number and percentage of patients with a response and the number and percentage of injections with a response are presented by dose category. The distribution of the optimum dose determined for each patient was summarized.

Efficacy was assessed in the investigator's office for all patients who received the reinjection of the current optimum dose at the Month 6 visit or at their discontinuation 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 circumference and length, maximum penile angle, patient assessment of penile rigidity, and patient and investigator assessments of whether the erection was sufficient for intercourse. If a patient had more than one injection in the investigator's office, the last injection was used in the summary tables.

The distribution of doses administered during the dose-titration period and the response to those doses is noted in the table below. Based on the 542 patients with penile Buckling Test results, no patients responded to the placebo injection at the beginning of dose-titration. Of the patients who injected alprostadil, 69% (372/542) responded to at least one of the injections.

Study KU-620-003
Dose-Titration Period
Response to Injection Based on the Buckling Test in the Investigator's Office

Dose Category (µg)	No. of Patients	# of Inj	Patients Response N (%)	Injections With Response N (%)
Placebo	591	592	0 (0)	0 (0)
> 0 - 2.5	34	37	8 (24)	9 (24)
> 2.5 - 5	76	79	43 (57)	45 (57)
> 5 - 7.5	30	31	19 (63)	20 (65)
> 7.5 - 10	538	553	114 (21)	121 (22)
> 10 - 15	99	117	48 (48)	61 (52)
> 15 - 20	393	419	118 (30)	131 (31)
> 20 - 25	26	29	12 (46)	14 (48)
> 25 - 30	284	289	97 (34)	97 (34)
> 30 - 35	26	27	13 (50)	14 (52)
> 35 - 40	253	260	119 (47)	120 (46)
All Doses	542	1841	372 (69)	632 (34)

Response positive with Buckling Test within 60 minutes after injection.
Patients could be counted in more than one dose category. - table adapted from sponsor

Based on 546 patients with penile angle measurements, 62% (336/546) of the patients responded after at least one of the alprostadil injections.

Two hundred one patients (37%) did not have an optimum dose assigned. The median dose for the 346 patients who completed the dose-titration period and were assigned an optimum dose was 30 µg.

Of the 327 patients who had at least one injection during the first six months of the open-label period, 245 received an in-office injection of the current optimum dose at the end of Month 6 or at the time of discontinuation from the study. Of the patients who injected alprostadil in the investigator's office, 82% (210/245) responded (positive penile Buckling Test within 60 minutes after injection). Response based on penile angle was 76% (185/245) following the in-office alprostadil injection.

Sixty percent of the patients (146/245) had an optimum response to injection (response with duration between 20 and 60 minutes). Most erections were considered to be sufficient for intercourse by both the investigator (87%) and the patient (86%). The mean patient assessment of penile rigidity, based on a 10-point visual analogue scale was 7.9 at the optimum dose. The median time to erection was 10 minutes, and the mean duration of erection was 38 minutes. The mean maximum penile angle was 78°. The mean maximum increase from preinjection penile length was 3.4 cm, and the mean maximum increase in penile circumference was 2.7 cm.

At the end of the dose-titration period, patients received an additional injection at their optimum dose for the evaluation0-point visual analogue scale, was 8.2, and all but 11 patients had a score of at least 5 (semi-firm erection). The median time to erection was 15 minutes and the mean duration of erection at the optimum dose was 39 minutes. The mean maximum penile angle was 80°. The mean maximum increase from preinjection penile length was 3.5 cm, and the mean maximum increase in penile circumference was 3.0 cm.

There were 21% more non-responders in the diabetic patients than the non-diabetic. Forty-seven percent (0-point visual analogue scale, was 8.2, and all but 11 patients had a score of at least 5 (semi-firm erection). The median time to erection was 15 minutes and the mean duration of erection at the optimum dose was 39 minutes. The mean maximum penile angle was 80°. The mean maximum increase from preinjection penile length was 3.5 cm, and the mean maximum increase in penile circumference was 3.0 cm.

There were 21% more non-responders in the diabetic patients than the non-diabetic group. Forty-seven percent (63/133) of the diabetic patients failed to respond to injection based on Penile Buckling test results while 26% of the nondiabetic patients were non-responders.

Open Label 1- 6 Months:

The table below presents the number of patients and the number of injections with erections that were sufficient for intercourse as assessed by the patient at home. Almost all of the patients (97%; 316/326) had erections that were considered to be sufficient for sexual intercourse after at least one injection with alprostadil. Most injections administered at home (89%; 6860/7699) resulted in erections that were considered to be sufficient for sexual intercourse.

Study KU-620-003
Months 1 - 6
Summary of Erections Sufficient for Intercourse at Home, by Dose Category

Dose (ug)	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
> 0 - 2.5	16	191	15 (94)	82.2	178 (93)
> 2.5 - 5	47	687	46 (98)	84.9	592 (86)
> 5 - 7.5	30	417	29 (97)	87.4	387 (93)
> 7.5 - 10	61	590	56 (92)	81.8	513 (87)
> 10 - 15	59	824	57 (97)	84.8	741 (90)
> 15 - 20	81	1171	75 (93)	80.4	1055 (90)
> 20 - 25	28	317	26 (93)	89.9	301 (95)
> 25 - 30	96	1015	92 (96)	84.7	922 (91)
> 30 - 35	34	210	28 (82)	74.8	183 (87)
> 35 - 40	133	2277	121 (91)	80.1	1988 (87)
All Doses	326	7699	316 (97)	85.1	6860 (89)

Patients can be counted in more than one dose category.
The percent of injections resulting in an erection sufficient for intercourse for each patient (at a given dose) was used in the calculation. The value shown is the mean of the percent of responses for all patients. Adapted from sponsor

The distribution of doses used at the end of the first 6 months of the open-label period ranged from 2 µg to 40 µg with a mean dose of 24.1 µg. 245 patients received an in-office injection of their current dose at Month 6 or at discontinuation. 82% of the patients (201/245) responded with a positive Buckling Test within 60 minutes after injection.

Open Label Beyond 6 Months:

A total of 238 patients entered the second extension. 7 of the patients did not inject during this period. One of the patients did not inject at home but did receive an injection in the investigator's office at Month 12. A total of 197 patients completed the second extension period. 230 of the patients averaged 4 injections of study drug per month at home. 98% (226/230) had at least one erection following injection that was considered sufficient for intercourse. The median time to erection among the responders was 10 to 13 minutes and the mean duration of the erection ranged from 65 to 70 minutes. The average average dose used was 24 µg per injection.

8.3.4.3. Safety comparisons

All 547 patients who received alprostadil injections during this study were included in the safety analysis. Overall, 403 (74%) of the 547 patients reported local side effects and/or clinical adverse experiences after one or more injections with Alprostadil. The most frequently reported local side effects were penile pain, prolonged erection, and local bleeding. No relation to dose was noted.

Clinical adverse experiences (including laboratory adverse experiences) were reported for 33% (179/547) of the patients while they were receiving alprostadil. The most frequently reported clinical adverse experiences in all periods occurred in the following body systems: body as a whole (10%), respiratory system disorders (8%), metabolic and nutritional disorders (4%), and musculoskeletal system disorders (4%). No single clinical adverse experience was reported by ≥1% of patients. Following the placebo injection, 3% (15/593) of the patients reported clinical adverse experiences.

A total of 25 patients reported serious clinical adverse experiences during this study; twenty-two following alprostadil injections and three following placebo injections. Forty-two patients discontinued as a result of local side effects or clinical adverse experiences; the most frequently reported was penile pain and prolonged erection.

Prolonged erections of longer than 2 hours occurred in 24% (134/547) patients and followed 8% of the injections (801/9927). 19 of these patients had erections lasting longer than 4 hours, two lasted for over 6 hours. Three patients had prolonged erections of unknown duration.

In the second open-label expension prolonged erections occurred in 31% of the patients (72/231) and followed 8% of the injections (459/5721). Two patients had erections that lasted > 4 hours. The longest lasted 5 hours 25 minutes. All of the erections spontaneously detumesced and none required medical intervention.

In the first extension there was one report of Peyronie's disease. Twenty four patients (4%) were reported to have penile angulation and ten patients (2%) were reported to have fibrotic nodules, spots or plaaques.

Tunica plaques were identified in 7% (16) of the patients in the second extension. 7 of the patients had associated penile angulation and two had both angulation and Peyronie's disease.

No deaths were reported in this study.

8.3.5 Reviewer's Comments

8.3.5.1 Efficacy:

This trial provides supportive data for the efficacy of intracavernous injection with Alprostadil. It differs from the previous trials in that it does not include a placebo controlled period. However, responses to the efficacy endpoints were similar. The median time to erection was 15 minutes and the duration was 39 minutes. The mean change from the pre-injection penile circumference was 3.0 cm and the mean maximum

increase from the pre-injection length was 3.5 cm. The mean dose of Alprostadil used in the dose-titration period was 30 µg and in the first 6 months of the open-label extension was 24.1 µg.

The evaluation of erections after drug injection sufficient for intercourse by both patient and investigator was 95% (investigator) and 94% (patient). During the open- label period 99% (316/326) of the men had at least one erection that was considered sufficient for intercourse and 89% of the injections administered at home resulted in erections considered sufficient for intercourse.

595 patients who entered into the screening period of which 48 patients discontinued. A total of 547 patients the dose-titration period and 69 patients discontinued. 132 patients completed the dose-titration period but did not continue into the open-label extension; of these 126 did not continue the open-label period because of inadequate response. A total of 346 men entered the open-label period (months 1-6).

The distribution of the patients was similar to the previous studies with the primary cause of erectile dysfunction being vasculogenic (82%) and 25% (147/595) were diabetic. A discussion of the diabetic men in this study is included with the previous study (KU 620-002).

A statistical review of this study was not done.

8.3.5.2

The safety profile of this study also appears similar to that of the previous protocols and included penile pain in 56% of the men (307 of 547) which was only related to injections in 19% of the cases. Prolonged erections (longer than 6 hours) occurred twice throughout the entire study. . Three patients had prolonged erections of unknown duration. No prolonged erection appeared to need medical intervention. Peyronie's disease and fibrotic nodules were infrequent (4 and 2%) throughout the study. There were no deaths.

8.4 Study F-8653

This study was an International Multicenter Study evaluating the Clinical Efficacy and Tolerability of Self-Medication by Injection of Prostaglandin E1 Into the Corpus Cavernosum in Patients With Chronic Erectile Dysfunction in Eight Centers. The study was conducted in Germany between January 1991 and April 1993. Data is available for up to 12 months. Open label extensions for each year are identified as 8653 I. II, and III with reports included through 48 months for a small number of patients. This study provides supportive data because it did <u>not</u> include a placebo-controlled portion of the study.

8.4.1 Objectives

The original primary study objective was to demonstrate responder-rates to Alprostadil injection in patients with erectile dysfunction.

The sponsor identified as secondary objectives the in-office evaluations of erection quality after Alprostadil injection using a combined 4 -grade scale and penile angle assessments.

8. 4. 2 Design

F-8653 consisted of an open-label, dose-titration period and an open-label extension period for up to four years in the patient's home. During the dose-titration period of Study F-8653, the investigator established each patient's individual optimum dose of alprostadil necessary to produce an full erection. The maximum dose in this study 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. 4. 3 Protocol

This multicenter study consisted of an open-label, dose-titration period followed by a four-year, open-label, self-injection phase in the patient's home. The discussion will summarize results through Month 6 of this study.

The optimum dose for each patient was determined by titrating from a starting dose of 10 µg alprostadil to an individual optimum dose between 1 µg and 20 µg. Patients were allowed to perform up to two self injections of Alprostadil per week at their optimum dose at home. In addition to follow-up visits performed every two months, an in-office reinjection with the patient's optimum dose was performed at the Month 12 follow-up visit in the investigator's office.

The study was to include patients 22 to 71 years of age with ED due to primary vasculogenic, neurogenic, or hormonal causes, with or without secondary psychogenic components. Primary psychogenic origin of ED was allowed if unsuccessful sex therapy for six months was documented.

The investigators for this study were Drs. H. Porst, J. Buvat, D. Hauri, G. S. Krotowski, E. Meuleman, V. Michal, E. Wespes, and G. Wagner.

8.4.3.1 Endpoints

At each two-month follow-up visit, investigators reviewed and collected efficacy and safety information recorded by patients in their individual diaries.

The primary efficacy variable was the ability to perform coitus as a result of self-medication by injection of Alprostadil. The patient had to document the injection, the amount of drug injected, the duration of the erection achieved, and whether the erection was adequate for intercourse or not. Secondary efficacy variables included the evaluation of the quality of erection in the investigator's office, and measurements of penile blood flow using Doppler ultrasound. Generally, all patients were included in the statistical analysis. These analyses were not reviewed by the FDA statistician.

8.4.4 Results

8.4.4.1 Patient Disposition, comparability

One hundred seventy-one men enrolled into this study. Nine patients (nonresponders) dropped out of the study during the dose-titration period. The remaining 162 patients, who ranged from years of age (median, 54.0 years), entered the open-label extension period of the study. The majority of patients (51%; 83/162) had ED of arterial origin while 20% (32/162) had ED of neurogenic origin, 15% (25/162) had ED of venous origin, 9% (15/162) had ED of psychogenic origin, and 4% (6/162) had ED of mixed origins.

8.4.4.2 Efficacy endpoint outcomes

The 116 patients who completed the trial performed 6303 Alprostadil injections at home, of which 5750 resulted in achieved coitus after injection. The overall success rate of achieved coitus after Alprostadil injection over the course of 12 months was 91.3%.

The percentage rate of successful intercourse after injection in the intent-to-treat population was similar to that of the "completers" for the first two-month period (81.9%). The patients performed a mean of 8.3 injections of which 6.8 of these injections were satisfactory for coitus. Over the course of the following two-month periods, the rate of successful intercourse after injections in the intent-to-treat population was about 1% lower than for the patients completing the trial. The rate of successful intercourse after injection in the "completers" increased from a 81.8% success rate (based on achievement of coitus after injection) during the first two months to 94.5% during the last two months. Although the improvement could be due to drop-outs, increasing experience with injection technique is important.

In this study the maximum allowable dose for intracavernous injection was 20 µg of Alprostadil. The mean optimum dose chosen by patient and investigator was 13.9 µg and 13.3 µg at the end of the study. For this study, the optimum dose was defined as the average dose for the first two months. It is not clear why the mean optimum doses chosen in this

study appeared to be lower than in the previous studies done in the United States.

Eighty-one patients who had completed 12 months of self-injection treatment in Study F-8653, continued into this phase of the study (Months 13 to 24).

The 74 patients who completed the 24-month treatment period performed 3821 injections during Months 13 to 24 of the open-label extension. The mean number of injections per bimonthly period was 9.0. The total number of achieved coitus over Months 13 to 24 was 3594 with an overall success rate of achieved coitus after alprostadil injection was 94.1%.

8.4.4.3 Safety comparisons

Sixty-five patients (46%) reported adverse experiences (local and/or clinical). The most frequently reported local side effects were prolonged erections, painful erections, hematoma, subcutaneous injections, and fibrotic changes. There were no statistically significant changes over the 12-month duration of the study in clinical laboratory values.

Seventeen of the 171 patients experienced serious adverse experiences, one of which was fatal (myocardial infarction). Serious adverse experiences included myocardial infarction, bronchial carcinoma, impaired renal function, angina pectoris, bladder carcinoma, vertebral disk protrusion, tachyrhythmia, chronic hepatitis, labyrinth disorders, and one suspected allergic reaction. All of these serious adverse experiences were regarded as unrelated to treatment with the exception of the patient with the allergic reaction, which was probably drug related.

Twelve patients experienced adverse experiences that led to discontinuation. These adverse experiences included myocardial infarction, pain after injection, induration penis plastica, impairment of renal function, bronchial carcinoma, prolonged erection, dizziness and disorientation, fibrotic spot/angulation, carcinoma of the urinary bladder, and allergic reaction to alprostadil.

There were no other reported deaths in this study.

8.4.5 Reviewer's Comments

This study done in Germany provides supporting data regarding the efficacy and safety of Alprostadil injections for the treatment of erectile dysfunction over an extended period of time. The success rate as perceived by the patient was between 82% and 94%. Increasing education and experience with injections by patients

with physicians is important. This trial used a very short 3 day patient-physician titration and education period. The overall success of achieved coitus with injectable therapy over the 12 month period of the open-label study was 91%.

116 patients completed the first year and 74 patients completed the 24 month treatment period from the original 171 who were enrolled in the study. The patients who did not complete the study may have required doses of Alprostadil greater than 20 µg to achieve an erection.

The safety profile reflected in this study is consistent with that of the previous studies. There was one death due to a myocardial infarction not related to drug. All of the other servious adverse events were considered unrelated to drug.

Pain with erections was reported in 46 of 162 patients. Prolonged erections, lasting longer than 6 hours, occurred in 2 of 162 patients. None needed further treatment but resolved by themselves. Fibrotic changes were identified on examination in 11 patients during the 12 month period.

9 Overview of Efficacy

Sponsor's summary

- *The ability of alprostadil to produce erections sufficient for intercourse does not diminish with continued open-label therapy at home. Patients generally do not need to increase their dose of alprostadil with continued open-label treatment for up to two years.*

- *Quality-of-sexual-life (both patients' and partners') is substantially enhanced following treatment with alprostadil for up to two years.*

- *Patients are comfortable with intracavernosal self-injections.*

- *Older patients (≥ 55 years) generally require higher doses of alprostadil than do younger patients (< 40 years).*

- *Within the dose range studied (up to 40 µg), a lower percentage of diabetic patients responded than nondiabetic patients.*

- *Alprostadil is generally safe and well tolerated.*

- *With the exception of penile pain and prolonged erection, there was relatively low correlation between the dose of alprostadil administered and the incidence rates of specific local side effects.*

- *With the exception of fibrotic changes, the frequency of which was relatively low across all study periods, incidence rates for local side effects declined over time.*

- *Overall, age, race, etiology of erectile dysfunction, diabetic status, absence or presence of cardiovascular risk, or alcohol use do not appear to have a differential effect on local side effect incidence rates following administration with alprostadil. However, there appeared to be a relationship between a majority of these subgroups and the incidence of prolonged erections.*

- *Clinical adverse experiences are generally infrequent even following continued treatment with alprostadil for up to two years.*

- *Alprostadil is not associated with dose-related increases nor decreases in vital sign measurements (blood pressure, heart rate). Predefined changes in vital signs appear to be related to the injection process.*

- *Alprostadil is not associated with clinically relevant changes in clinical laboratory values.*

- *The recommended frequency of injection is a maximum of three times weekly, with at least 24 hours between each dose.*

A minimum-effective dose was determined in 71% of all patients. Seventy-five percent (75.5%) of patients in Study KU-620-001, 73.0% of patients in Study KU-620-002, and 68.4% of patients in Study KU-620-003 had a minimum-effective dose determined. In Study KU-620-001, which had a maximum allowable dose of 20 µg of alprostadil and excluded patients over 65 years of age and diabetics, the mean minimum-effective dose was 10.7 µg, whereas in the two studies (KU-620-002 and KU-620-003) that had a maximum allowable dose of 40 µg and included patients as old as 78 years of age and diabetics, the mean minimum-effective doses were 22.1 and 21.7 µg.

Reviewer's Summary:

The sponsor, Schwarz Pharma, has provided two pivotal trials and two other trials supporting the treatment of male erectile dysfunction with prostaglandin E1 - the Alprostadil alphadex. The results of these studies are expected based on previous experience with the approved prostaglandin, Caverject (Pharmacia/Upjohn). The risks versus the benefits appear identical in both of these prostaglandins. Although injectable treatment is not a perfect method of treatment, it has been found to be a very acceptable method for men with erectile dysfunction.

During the dose-titration period, the investigator established each patient's individual optimum dose to produce an erection sufficient for sexual intercourse up to a maximum of 20 µg in 620-001 and 40 µg in study 620-002. The patients were then randomized to a two week crossover period in which they self-injected for one week either placebo or their optimum dose of Alprostadil and entered a 48 week open label extension period in which they self-administered the drug up to two times a week.

In Study KU-620-001, a total of 74 patients self-injected 3940 injections at home. In Study KU-620-002, a total of 139 patients self-injected 3899 injections at home. In Study KU-620-003, a total of 327 patients self-injected 7812 injections at home. The distribution of doses during open-label treatment at home was essentially the same as the distribution of doses at the end of dose titration.

In Studies F-8653 and the F-8653 I extension, 152 patients self-injected 6935 injections at home during the first year, and 81 patients self-injected 3594 injections at home the second year.

The identified changes in penile circumference, length, buckling pressure, and penile angle were all expected objective changes with the injection of the active drug. Placebo injections resulted in erections with a short duration when erections occurred.

Changes in Penile Circumference and Length

Study	Circumference	Length
001	2.6 cm	not done
002	2.9 cm	3.9 cm
003	3.0 cm	3.5 cm

The following chart is adapted from the Pharmacia/Upjohn NDA. One can note the similarity in penile circumference change using two types of measurements.

PENILE CIRCUMFERENCE AND CHANGE - RIGISCAN MEASUREMENTS

DOSE	STUDY 68	CHANGE	STUDY 69	CHANGE
0 - PLACEBO	8.1	0.1	8.4 (0.13)	0.2
2.5	9.6 (0.13)	1.8***	9.8 (0.22)	2.0 ***
5	10.1 (0.14)	2.0***	10.0 (0.19)	2.2***
7.5	10.1 (0.13)	2.1***		--
10	10.0 (0.15)	2.1***	10.4 (0.20)	2.4***
20			10.0 (0.19)	2.7***

*** P ≥ 0.001 FROM PLACEBO.

In Studies KU-620-001, KU-620-002, and KU-620-003, the median time to erection for the patients who responded to therapy at home was 10 - minutes, with a response occurring as early as one minute following injection. In Study KU-620-001, KU-620-002, and KU-620-003, the median duration of erection for the patients who responded to therapy at home ranged from 58 to 67 minutes.

The table below presents the median time to erection based on patient assessment after self-injection at home during two weeks of double-blind therapy.

Time to Erection (min) Based on Patient Assessment After Self-Injection at Home
Controlled Studies (Double-Blind, Crossover)

	KU-620-001		KU-620-002	
	Alprostadil	Placebo	Alprostadil	Placebo
N	80	80	140	140
Median	10.0	> 60.0	10.0	> 60.0

Includes only patients with a measurement for both alprostadil and placebo. Only the first injection of each study week was included.

The table below presents the mean duration of erection based on patient assessment after self-injection at home combined over two weeks of double-blind, crossover therapy. As shown, the mean duration of erection for patients who received Alprostadil was much longer than the mean duration for patients who received placebo.

Duration of Erection (min) Based on Patient Assessment After Self-Injection at Home Controlled Studies (Double-Blind, Crossover)

	KU-620-001		KU-620-002	
	Alprostadil	Placebo	Alprostadil	Placebo
N[a]	79	79	139	139
Mean[b]	56.9	4.0	59.0	7.6
S.E.	7.05	1.77	4.7	2.54

[a] *Includes only patients with a measurement for both alprostadil and placebo. Only the first injection of each study week was included.*

[b] *Patients who did not respond were assigned a value of zero for the calculation of mean duration.*

from sponsor

The median time to erection in the investigator's office at the optimum dose in the dose-titration studies ranged from 10.0 to 20.0 minutes. The median time to erection for Study KU-620-001 (20.0 minutes) was longer than median times for Studies KU-620-002 and KU-620-003 (12.0 and 10.0 minutes, respectively). The time to erection ranged from 3 to 20 minutes for the majority of responders.

The mean time to erection in the investigator's office during dose titration in 115 completers in Study F-8653 was 10.2 minutes. This value reflects the best response (best erection quality achieved with one to three injections in the investigator's office).

A comparison to the data from Caverject demonstrates similar duration of erections (not time to erection) as noted with the studies in this NDA.

COMPARISON OF THE DURATION (minutes) OF ERECTION BY DOSE (Caverject NDA)

DOSE µg	STUDY 68	STUDY 69
0	0 (5)	0 (7)
2.5	8.5 (44)	11.8 (45)
5	9.5 (51)	32.7 (57)
7.5	16.6 (50)	
10	18.2 (51)	30.8 (52)
20		43.6 (55)

The next table presents the number of patients with an erection sufficient for intercourse based on patient assessment after self-injection at home during double-blind treatment. Overall, patients treated with Alprostadil had a statistically significantly greater number of erections sufficient for intercourse than did patients who received placebo during double-blind therapy. The percentage of patients treated with Alprostadil

who had an erection sufficient for intercourse was similar for these two studies (74% in Study KU-620-001 and 73% in Study KU-620-002).

Those who self-injected Alprostadil during open-label therapy at home had erections sufficient for intercourse. The mean percent response per patient ranged from 85.1% to 88.9%. The percent of injections that was associated with a response ranged from 89% to 93%.

Number of Patients With an Erection Sufficient for Intercourse Based on Patient Assessment After Self-Injection at Home Controlled Studies (Double-Blind, Crossover)

Week	KU-620-001				KU-620-002			
	Placebo		Alprostadil[c]		Placebo		Alprostadil[d]	
	No. of Patients	No. (%) With a Response	No. of Patients	No. (%) With a Response	No. of Patients	No. (%) With a Response	No. of Patients	No. (%) With a Response
1	41	3 (7)	40	29 (73)	72	9 (13)	69	48 (70)
2	40	3 (8)	41	31 (76)	69	9 (13)	72	55 (76)
Total	81	6 (7)	81	60 (74)***	141	18 (13)	141	103 (73)***

[a] *Includes only patients with a measurement both for placebo and alprostadil. Only the first injection of each study week was included.*

[b] *Results from the first injection during each week.*

[c] *Patients could receive an alprostadil dose of up to 20 µg in Study KU-620-001.*

[d] *Patients could receive an alprostadil dose of up to 40 µg in Study KU-620-002.*

adapted from sponsor *Adapted from sponsor.*

Generally, the number of patients who had an erection sufficient for intercourse and the number of injections associated with a response increased slightly by month which probably reflects the value of education and experience. The percent of patients who responded (83% to 85%) and the percent of successful Alprostadil injections (84% to 88%) were generally lowest during the first month of home treatment.

The response to injections based on both penile angle and Buckling Test were also satisfactory. Penile angle, although simple, is not as sensitive a test as the Buckling test for rigidity of the penis. However, the responses were similar throughout all of the studies where it was done

Response to Injection Based on Penile Angle in the Investigator's Office at the Optimum Dose (End of Dose Titration)

KU-620-001		KU-620-002		KU-620-003	
N= Patients	N (%) With Response	N = Patients	N (%) With a Response	N = Patients	N (%) With a Response
79	34 (43)	156	78 (50)	334	282 (84)

[a] *Response = penile angle ≥ 90° within 60 minutes after injection in Study KU-620-001 of penile angle ≥ 90° or ≥ 75° and erection sufficient for intercourse according to the patient and the investigator in Studies KU-620-002 and KU-620-003.*

[b] *Optimum dose selected by the investigator during dose titration. If a patient received more than one injection at the optimum dose in the investigator's office, only the last injection is included adapted from sponsor's tables.*

97% to 99% of the patients who self-injected Alprostadil during open-label therapy at home had erections sufficient for intercourse. The mean percent response per patient ranged from 85.1 to 88.9%. The percent of injections that was associated with a response ranged from 89 to 93%. Generally, the number of patients who had an erection sufficient for intercourse and the number of injections associated with a response increased slightly by month. The percent of patients who responded (83% to 85%) and the percent of successful Alprostadil injections (84% to 88%) were generally lowest during the first month of home treatment.

There were 29 patients with low testosterone in trial 001 and 002. Low testosterone was defined as less than 280 ng/dL. In general hypogonadal men should be treated for the testosterone deficiency before injectable therapy for erectile dysfunction. In trial 001 four of the patients withdrew early. Although the treatment may have been effective in the other four men, the testosterone level in these men may not have been that abnormal.

Men with erectile dysfunction of psychogenic etiology were not identified individually in 001 or 002. Two patients of 595 and 15 out of 162 patients were identified in 003 and 8653. There are insufficient numbers to identify changes specific to these patients. Previous data would suggest that patients with a psychogenic etiology will respond to lower doses of prostaglandin, but this has not been identified in these trials. There is a psychogenic component to many of the mixed etiologies of erectile dysfunction.

In trial 002 and 003 a large number of diabetic men were treated. There were 25 out of 139 men in 002 and 147 out of 595 in 003. The distribution of optimum doses at the end of dose titration (Studies KU-620-2 and KU-620-003) by diabetic men and nondiabetic appear similar. The mean chosen for the diabetic men was 26.4 µg (n=97) and the non-diabetic was 25.2 µg (n=406). However, a larger number of diabetic than non-diabetic did not have an optimum dose selected by the investigator during dose titration.

A large number of the men in trials 001, 002 and 003 were current smokers, (32%, 18% and 22% respectively). It should always be encouraged to add smoking cessation to any treatment for erectile dysfunction. The data was not reviewed to identify any differences in efficacy.

10 Overview of Safety

The major adverse events associated with intracavernous injection therapy relate to the local effects on the penis. Priapism and prolonged erections, penile pain and alterations in the penis are the most important adverse events that are associated with injection therapy. In addition penile angulation, Peyronie's disease, and nodules of the tunica may be a result of injection therapy. The most frequently reported local side effects were penile pain (52%; 356/691), and prolonged erection > 2 hours (37%; 253/691).

The table below presents the number and percentage of patients who reported local side effects following intracavernosal administration of Alprostadil and placebo during double-blind treatment. The most frequently reported local side effects were penile pain (31% Alprostadil [73/232], 9% placebo [21/233]), prolonged erection > 2 to ≤ 4 hours (17% Alprostadil [40/232], 2% placebo [4/233]), and local bleeding (6% Alprostadil [14/232], 3% placebo [7/233]).

Number (%) of Patients With Local Side Effects
Primary Data Base during the Double-Blind Period[a]

Local Side Effect	Placebo (N = 233)	Alprostadil (N = 232)
Penile Pain (Any)[b]	21 (9)	73 (31)
Penile Pain During Injection	10 (4)	33 (14)
Penile Pain During Erection	7 (3)	51 (22)
Penile Pain After Erection	6 (3)	48 (21)
Penile Pain, Other	2 (<1)	7 (3)
Prolonged Erection (Total)	4 (2)	40 (17)
> 2 - ≤ 4 hours	3 (1)	35 (15)
> 4 - ≤ 6 hours	1 (<1)	8 (3)
> 6 hours	0	0
Bleeding, Local	7 (3)	14 (6)
Ecchymosis, Local	1 (<1)	3 (1)
Hematoma, Local	1 (<1)	0
Penile Angulation	0	1 (<1)
Erythema	0	1 (<1)
Penis Disorder	0	1 (<1)
Urethral Disorder	0	1 (<1)
False Injection	1 (<1)	0

[a] Includes Studies KU-620-001 and KU-620-002.
[b] Patients can be counted in more than one subcategory.

Patients withdrew if they did not have a therapeutic response or if injection was associated with too much discomfort. The pain of prostaglandin injections is an issue that needs to be resolved. It is important to identify in future studies whether it is the temperature of the solution, the speed of the injection and whether it can be by the appropriate pressure placed on the injection site for 5 minutes after.

Priapism (or prolonged erections ≥ 6 hours) remains the single most important adverse event to be identified.

There were three deaths from myocardial infarctions in the clinical trials reviewed. They did not appear to be drug-related nor where they coincident with injections.

Safety Update

A comparison of the adverse experiences from the NDA and the Safety Update at 4 months does not reveal any major differences in the incidence of local side effects, or serious clinical adverse events. There were no differences in penile pain or hematoma. Fibrotic changes and tunica plaques in the penis remain a concern with the long term use of injectable therapy. There are no reports of broken needles.

11 **Labeling Review**

Responses to the proposed labeling submitted by the sponsor.

11.3 Indications and Usage

11.4 Contraindications

11.5 Warnings

11.6 Precautions

11.7 Adverse Reactions

11.8 Drug Abuse and Dependence

11.9 Overdosage

11.10 Dosage and Administration

11.11 How Supplied

12 Conclusions

This new drug application for the use of Alprostadil alphadex (SPM-691) is approvable.

13 Recommendations

It is recommended that the sponsor continue to study methods to reduce the pain and discomfort with this form of treatment for erectile dysfunction.

In the patient education package the sponsor should include the following information:

- A discussion of the impact of smoking on potency.

- A discussion of priapism and how it should be treated and the long term effects.

- The association of injections and penile pain and the importance of pressure at site of injection for five minutes - possibly preventing further problems.

- A discussion of the stability of the drug and how it should be stored especially with traveling.

- A discussion of partner issues including time and pain.

- A discussion of the importance of not treating your colleagues.

- Discussion of the importance of individual dosing regimes.

- A discussion of the lack of information on the use of drug combinations for intracavernous injection - particularly the lack of information.

Jean L. Fourcroy, M.D., Ph.D.
Medical Officer (HFD-580)

Heidi Jolson, M.D.
Deputy Division Director (HFD-580)

I concur with recommendation that this application is approvable. See Group Leader Memorandum dated 11/8/96 for discussion of outstanding issues. HJ

Baldeo K. Taneja, Ph.D.
Mathematical Statistician (Biomed).

Daniel N. Marticello, M.S.
(Concur -- Statistical Section)

S. Edward Nevius, Ph.D.
(Concur -- Statistical Section)

cc:
Archival NDA 20-649
HFD-580/Rumble, Fourcroy, Jolson, Rarick
HFD-715/Taneja, Marticello, Nevius, Division File, Chron.

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JUN - 2 1997

Safety Update Amendment NO. 026

Drug: ALPROSTADIL/EDEX
Sponsor: Schwarz Pharma
NDA 20-649
June 2, 1997

This safety update for EDEX (alprostadil) injection for the treatment of erectile dysfunction was submitted by Schwarz Pharma on May 13, 1997. This update included data from 11/1/96 -3/31/97. There have been three previous safety updates, March 15, 1996, August 7, 1996 and December 29, 1997 (amendment 023). The first two were included in the NDA review and the third was noted in the review of March 19, 1997.

There were no unexpected adverse experiences reported during this period associated with the use of this product. Two serious cases in IND studies during this period included one patient with a non-fatal mycocardial infarction and one patient with hyperglycemia. These were in Protocol KU-620-006/F9029 and may not be directly related to the drug. Ten additional complaints of penile pain associated with intracavernous injections were noted in this study; the total number of patients in this study is not available although 60 patients have been enrolled between November 1, 1996 and March 31, 1997.

There does not appear to be any new safety information that alters the proposed labeling of this drug.

Jean L. Fourcroy, M.D., PhD
Medical Officer

HFD-580/JFourcroy/HJolson/6/2/97

Noted: HJolson 6/2/97

JUN - 2 1997

Safety Update Amendment NO. 023

Drug: ALPROSTADIL/EDEX
Sponsor: Schwarz Pharma
NDA 20-649
March 19, 1997

This safety update for EDEX (alprostadil) injection for the treatment of erectile dysfunction was submitted by Schwarz Pharma on December 20 and received December 23. There have been two previous safety updates, March 15, 1996 and August 7, 1996. These were included in the NDA review. This safety update includes data on three completed studies not previously reviewed.

One of the studies is a multicenter evaluation with both office and open-label home treatment. The other two studies are office studies with further objective evaluation of alprostadil as a tool in the diagnosis of erectile dysfunction.

Submitted Studies - Amendment 023

Study	N =	Mean dose
F-8898 office/home OL	75	13.5 μg
KU-620-006 diagnostic	95	27.1 μg
KU-620-007 diagnostic	47	42.1 μg

None of the data in this submission alters the previous experience with this drug. The efficacy and dosing appears comparable to previous studies. There are no changes in the adverse experiences, e.g. those resulting in discontinuation, serious experiences or patient deaths. There does not appear to be any new safety information that alters the proposed labeling.

Jean L. Fourcroy, M.D., PhD
Medical Officer

HFD-580/JFourcroy/HJolson/3/19/97

Noted 6/2/97 HJ

NDA 20-649
Edex™ (alprostadil-α-cyclodextrin for injection)
Schwarz Pharma, Inc.

A combined Medical and Statistical Review was done.

See Medical Review.