SECTION 1: BACKGROUND ON ERECTILE DYSFUNCTION

Erectile dysfunction (ED) is now the preferred term for impotence. It is defined as "the inability to achieve or maintain an erection sufficient for satisfactory sexual performance" (NIH consensus statement, 1992). Normal erections rely on a complex interaction of vascular, neurologic, psychological and endocrine factors. Although great advances have recently been made in all these areas, there are still important questions to be answered regarding the individual factors as well as their interactions with each other. In many patients, the etiology of erectile dysfunction is probably multifactorial.

Until the early 1980s, it was commonly believed that "psychogenic" causes were responsible for erectile dysfunction in 90% of the cases. Currently, most experts believe that vascular changes are the main etiologic factor in the largest proportion of patients. These changes can effect the flow of blood to and from the penis. Of these vascular changes, arterial disease often associated with generalized cardiovascular disease or risk factors is the most common cause of ED.

The Massachusetts Male Aging Study (MMAS) was a community based, random sample observational survey of noninstitutionilized men aged 40 to 70 years conducted from 1987 to 1989. In this important study, the combined prevalence of all degrees of erectile dysfunction was 52%. The age of the subject was the variable most highly associated with this condition. However, after adjustment for age, it was discovered that ED is directly correlated with heart disease, hypertension, diabetes and indices of anger and depression. Cigarette smoking was correlated with complete erectile dysfunction in men with heart disease and hypertension. The investigators concluded that erectile dysfunction is a major health concern highly associated with age and has multiple determinants including risk factors for vascular disease.

The penile erectile tissue, specifically the cavernous and arterial smooth muscle, plays a central role in the erectile process. In the flaccid state, the smooth muscles are in a contracted state allowing minimal blood flow for nutrition of the tissues. Sexual stimulation (processed by the CNS) triggers the release of neurotransmitters from the cavernous nerve terminals. This results in relaxation of the smooth muscles and: 1. Increased arterial blood flow in both diastolic and systolic phases; 2. Trapping of the incoming blood by expanding sinusoids; 3. Compression of the subtunical venular plexuses between the tunic albuginea and the peripheral sinusoids reducing venous outflow; 4. Stretching of the tunica to its capacity which further reduces venous outflow; and 5. An increase in intracavernosal pressure which results in an erection.

It is clear that a drug that relaxes the smooth muscles of the corpora carvernosa will facilitate penile erection. Two substances that are currently marketed relax smooth muscle by different mechanisms. Sildenafil has no direct relaxant effect on isolated corpus cavernosum but enhances the effect of nitric oxide (NO). Nitric oxide is released in the corpora with sexual stimulation. The enzyme guanylate cyclase, activated by NO, causes increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation. Sildenafil is a phosphodiesterase type 5 (PDE 5) inhibitor. Phosphodiesterase is responsible for the degradation of cGMP. Therefore, with the presence of sildenafil the levels of cGMP do not degrade and smooth muscle relaxation and increased blood flow to the corpora continues. Sildenafil should not be effective in the absence of sexual stimulation.

Prostaglandin E_1 (alprostadil) is available in several forms for the treatment of ED. Alprostadil induces erection by relaxation of the cavernosal trabecular smooth muscle and dilation of the

cavernosal arteries. This leads to expansion of the lacuna spaces and entrapment of blood within the penis thus causing erection. Sexual stimulation is unnecessary for the efficacy of this drug.

There has also been considerable research on drugs that work via the CNS to stimulate erections. Studies in animals have identified the medial preoptic area and the paraventricular nucleus of the hypothalamus as important areas for sexual drive and erection. There is some evidence in animals that dopaminergic receptors in these areas may promote sexual activity. There have been clinical observations that suggest that dopaminergic stimulation (i.e. apomorphine) increases libido and produces erection. The erections produced by apomorphine have been observed unaccompanied by sexual stimulation.

Many diagnostic studies have been used to further define the etiology of ED in an individual patient. The differential diagnosis of "psychogenic" versus "organic" erectile dysfunction can be difficult. The correct diagnosis may have important implications for the patient in terms of therapy. One of the most widely used approaches to differentiate between "psychogenic" and "organic" ED is Nocturnal Penile Tumescence (NPT) testing.

Nocturnal penile tumescence or sleep related erection is a recurring cycle of penile erections associated with rapid eye movement (REM) sleep in almost all normal men. Research in the 1970s suggested that NPT testing could be used to evaluate ED because the mechanism of these erections was presumed to rely on neurovascular responses similar to those of erotically induced erections. For this reason, patients that have a normal NPT test are presumed to have the capacity for spontaneous erotically-induced erections. In its most rigorous form, NPT testing is conducted for two or three nights in a row in a "sleep lab". Various aspects of the patient's sleep are monitored but in addition a device is placed on the patients penis that measures rigidity, number and duration of erections. Although there are criticisms of NPT testing, many investigators believe it is an important piece of information in identifying patients with psychogenic ED.

Two of the most important elements that must be examined when analyzing a clinical trial for ED are populations and efficacy measures. Inclusion and exclusion criteria will define the population and give clues as to how the trial results will apply to the general ED population or to a particular subgroup. The population of patients included in these trials is often defined by the severity and duration of their ED, regardless of the etiology ("psychogenic" or "organic"), and whether concomitant illness or medications are present. If populations are homogeneous then the results of the trial may not be applicable to the population as a whole, even if a significant treatment effect is observed in the study population.

Clinical trials for Uprima included only patients who had ED and a normal NPT test. Results from trials in this small, select population may not support claims of efficacy in the general ED population.

Efficacy measures in clinical trials for ED are generally of two types. The first are "objective" or "physiologic" external measures of erection, the second are patient (and partner) reports of events (sexual encounters). The "objective" measures often include a device that is attached to the patient's penis that measures erectile response to therapy, visual stimulation or both. Occasionally an observer records the quality of the erection in response to the intervention.

In Phase 3 trials, the "objective"methods are usually not appropriate so "self-report" measurements are used. The most common methods currently used in phase 3 trials are self-administered questionnaires and patient diaries. A commonly used questionnaire is the International Index of Erectile Function (IIEF). The IIEF consists of 15 items that assess sexual

function in five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. The most sensitive domain of the IIEF is the erectile function domain that is derived from six questions (1-5 and 15) of the IIEF. The score ranges from 0 to 30 and is derived by scoring 0 (poorest function) to 5(best function) on each of six questions. The ED domain of the IIEF is an important outcome measure in clinical trials for ED.

Patient diaries are another way of recording clinical data regarding sexual encounters during ED trials. Several investigators have "formalized" the diary concept into instruments with specific questions regarding sexual encounters. One of these "formalized" diaries is the "Sexual Encounter Profile" or SEP. The SEP consists of five questions that capture important data regarding the sexual encounter. Question 2 (Were you able to insert your penis into your partner's vagina?) records attaining an erection and Question 3 (Did your erection last long enough for you to have successful intercourse?) measures maintaining an erection. These are both important efficacy outcomes in clinical trials for ED.

The proportion of attempts at intercourse that are successful (that can be derived from diary data) are also an important measure of therapies for ED. One would expect to find strong correlation between the results of a self-administered questionnaire and the event data as recorded in the patient diary if the diary data is accurately recorded and the questionnaire well validated. If a therapy is effective, a robust improvement in erectile function should be measured by both the questionnaire and diary data.

The primary endpoint in the trials for Uprima was the proportion of attempts at intercourse that were successful.

Before the mid-1990s, there were four methods of treatment for erectile dysfunction. Yohimbine an indole alkaloid, was the most popular form of oral therapy. This drug has remained on the market based on the DESI review process and has never clearly been shown to be effective. External vacuum constriction devices both approved and unapproved were used by many patients. However, many were not satisfied with the devices because of the cumbersome procedures required to use them. Use of unapproved substances and off-label use of approved substances (papaverine, phentolamine, and prostaglandin E_1) as vasoactive intracavernous injections were used, but many patients had difficulty accepting penile injections. Finally, various forms of surgery were performed. The most popular and successful intervention was the implantation of hydraulic and nonhydraulic prostheses into the penis. Small proportions of patients were eligible and benefited from various types of penile revascularization surgery. Some of the above treatments are used today in selected populations. Three medical drug treatments are currently approved for ED and a brief summary of each follows.

CAVERJECT

In July 1995, CAVERJECT, an intracavernous injection, (alprostadil or prostaglandin E_1) was approved (NDA-20-379). This drug is administered initially in the clinician's office in order to titrate to the effective dose while observing for priapism. Dose titration should be initiated at 2.5micrograms of alprostadil. If there is a partial response, the dose may be increased by 2.5 micrograms to 5 micrograms and then in increments of 5 to 10 micrograms depending on the response. Doses over 60 micrograms are not recommended. In general, the lowest effective dose should be employed and the patient should stay in the physician's office until there is complete detumesence because of the risk of priapism (about 1%). The patient then self-administers the appropriate dose at home.

The inclusion criteria for the clinical trials were men aged 30 to 70 years with at least a 4-month history of ED of any etiology. The most common etiologies were vascular (45%), followed by mixed which included diabetes (15%). neurogenic(10%), psychogenic (10%), and endocrine(1%).

Trials for Caverject included ED patients with a variety of etiologies, representative of the ED population as a whole.

Caverject demonstrated about 70% efficacy in producing and maintaining erections sufficient for intercourse during the in-office and at-home phases whereas placebo injections produced only rare responses. In addition, 80% of the patients that entered the at-home phase completed their designated treatment period (4 weeks to 6 months).

The most common adverse event during the clinical trials was local pain (17%). The event of most concern was priapism (1.3%). It should be noted that in one of the central trials (n=237) in which blood pressure (BP) was evaluated soon after injection, there were no drug related BP changes. No symptoms associated with orthostatic hypotension were reported in this study. Four patients had dizziness and lightheadedness unassociated with orthostatic changes. In the other central trial (n=153), events related to possible orthostasis were not reported as a problem.

In November 1996, another formulation of alprostadil for intracavernous injection was approved (EDEX, NDA-20-649). Efficacy for EDEX was similar to CAVERJECT.

MUSE

MUSE (NDA-20-700) was approved in October 1996. This product is an intraurethral suppository that contains alprostadil. The mean time to maximum plasma alprostadil concentration after a 1000 microgram intraurethral dose is approximately 16 minutes. About 80% of alprostadil administered by MUSE is absorbed within 10 minutes and is rapidly cleared from the systemic circulation by the lungs. The alprostadil concentration is undetectable by 60 minutes. MUSE is available in four dosage strengths: 125 micrograms, 250 micrograms, 500 micrograms and 1000 micrograms. Dose titration under the supervision of a physician is recommended. Patients are titrated to the lowest dose sufficient for intercourse that does not result in significant adverse events, especially hypotension.

There were two identical double blind, dose-titration placebo controlled trials in men who had at least a 3 month history of having no erections sufficient for intercourse. Of the 1151 patients that began the trial, 996 (66%) successfully completed dose titration. These patients were then randomized to active or placebo at-home treatment. Eight hundred and seventy four patients completed the 3-month treatment period. Couples on active therapy were more likely to have one successful intercourse during the treatment period (65% vs.19%) than were couples on placebo. Therefore approximately 45% of the patients who were unable to have intercourse before treatment were able to have at least one successful intercourse with MUSE compared to 15% with placebo.

In the various US studies (n=2747), the proportions of various etiologies were vascular (25-47%), diabetes (12-23%), surgery or trauma (12-35%) and other (12-26%).
During the in-clinic titration phase of the two central trials, about 50% of patients reported some type of urogenital pain. Seven per cent withdrew at this stage because of adverse events. Symptomatic hypotension and syncope occurred in 3% and 0.4% of patients during the titration period. The overall incidence of hypotension was 8.1% and the incidence of syncope was 0.9%. in all studies (n=2700 approximately).

Trials for MUSE included ED patients with a variety of etiologies, representative of the ED population as a whole.

During the 3 month home-use portion of the studies, the incidence of dizziness was 1.9% on active drug versus 0.2% on placebo. Withdrawals for hypotension occurred after 1 to 44 doses (mean 4.6), suggesting that this is not simply a concern with the first dose or the first few doses. Of 22 cases of syncope that occurred in all studies, ten occurred after the first dose. A warning has been placed in the label regarding this problem. Physicians give initial doses in the office because of the concern for hypotension, the necessity of instructing the patients in the use of MUSE, and finding the lowest effective dose.

MUSE provides important perspective to Uprima, since it is an approved drug for ED that also caused hypotension and syncope. Approximately 50% of Muse related syncopal events (10 of 22) occurred after the first dose. MUSE is titrated for safety and efficacy in a physician's office, and is an intraurethral suppository that is rapidly metabolized.

VIAGRA

In March 1998, oral sildenafil (Viagra), a PGE_5 inhibitor was approved. In contrast to previous products, this medication requires sexual stimulation in order to be pharmacodynamically active. It is the first orally administered drug for ED. For most patients the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual intercourse. The dose may be increased to 100 mg or decreased to 25 depending on effectiveness or tolerability.

Approval of Viagra was based on 21 randomized, double blind, placebo controlled trials of up to 6 months duration using a variety of study designs. Patients in these trials generally were included if they had erectile dysfunction for 6 months or more. ED was broadly defined as the inability to attain or maintain a penile erection sufficient for satisfactory sexual performance). Patients in these trials had mild-to-moderate ED and included patients with organic (58%, including diabetics), psychogenic (17%) or mixed (24%) etiologies.

Trials for Viagra included ED patients with a variety of etiologies, representative of the ED population as a whole.

Efficacy in most of the trials supporting approval of this product was based on the (IIEF). Information regarding the patient's ability to obtain and maintain erections can be obtained from the results of Question 3 (When you attempted intercourse, how often were you able to penetrate {enter} your partner?) and Question 4 (During sexual intercourse, how often were you able to maintain your erection after you had penetrated {entered} your partner?). These questions are scored form 0 to 5 [0= no sexual activity, 1=Almost never, 2= a few times (much less than half the time), 3= sometimes (about half the time), 4 = Most times (much more than half), 5 = almost always/always].

In the fixed dose trials, (n=1800), patients had a baseline score of about 2 on question 3 and 4 of the IIEF. Sixty-three per cent, 74% and 82% on the 25mg, 50 mg and 100mg of Viagra reported an improvement in these score compared to 24% on placebo. Titration studies (n=644) were similar. In some study reports, the proportion of successful attempts was reported. In general, for the placebo group, 20% of attempts were successful compared to 50 % in the Viagra group. The proportion of patients that had at least one success during the study was 60% for placebo and 85% for Viagra.

Viagra was administered to over 3700 patients during the clinical trials with data on 550 patients for longer than a year. Some of the adverse events that occurred more than 2% of the time and were more than placebo were: headache (16%), Flushing (10%), abnormal vision (3%) and dizziness (2%). Syncope occurred in one patient who received an 800-mg dose of Viagra in early trials. Viagra was otherwise uncommonly associated with symptoms of orthostatic hypotension or syncope.

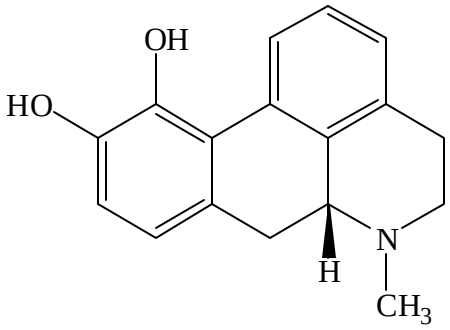
SECTION 2: CHEMISTRY, MANUFACTURING, AND CONTROLS

DRUG SUBSTANCE:

Chemical Name: 4-H-Dibenzo[de,g]quinoline-10,11-diol, 5,6,6a,7-tetrahydro-6-methyl-, hydrochloride, hemihydrate, (R)-
or…
6a,β-Apomorphine-10,11-diol hydrochloride hemihydrate

Compendial Name: Apomorphine hydrochloride **CAS Registry Number:** [41372-20-7]

Structural Formula:



• HCl • 1/2 H_2O

Molecular Formula: $C_{17}H_{17}NO_2 \cdot HCl \cdot \frac{1}{2}H_2O$ **Molecular Weight:** 312.79

APPLICATION SUMMARY:

In February 1996, TAP Holdings Incorporated (TAP) assumed sponsorship of IND [ ] for Uprima, from Pentech Pharmaceuticals. Uprima is not currently marketed in any other country by TAP and a submission of this NDA is not concurrently under review in any other country.

Uprima, Apomorphine hydrochloride hemihydrate, is a compendial active API and a dopamine receptor agonist, that induces penile erection. Chemically, it is structurally similar to dopamine and is synthesized via the dehydration of morphine followed by conversion of the free base to the HCl salt. The drug substance can be oxidized to a number of quinolindione compounds in aqueous solution that are an intense emerald green, yet, their high color intensity does not reliably reflect the quantitative amount of oxidized product present. Addition of anti-oxidants and adjustments of solution acidity to a pH of [ ] reduces the rate of apomorphine oxidation. Under storage conditions of 25°C and 60% relative humidity, the drug substance is stable for up to 18 months with a specification for assay of [ ]. The drug substance manufacturer is [ ].

Although clinical studies included 2, 4, 5, and 6 mg doses, TAP is pursuing marketing for only 2, 3, and 4 mg doses of the sublingual formulation in this application for the treatment of erectile disfunction. The 3 mg dose has not been studied in the clinic, however, in meetings with the Agency, the FDA stated that the 3 mg dose would be approvable provided both the 2 and 4 mg doses were safe and effective. The drug product manufacturers are [ ] and [ ]. The primary drug product packaging facility is [ ] and [ ] serves as a secondary packaging facility.

An original formulation (F1) was used in the first Phase III study followed by an optimized formulation (F2), with improved physical appearance and taste. [ ] The F2 formulation is the formulation proposed for marketing and it is comprised of apomorphine hydrochloride hemihydrate, mannitol, microcrystalline cellulose, hydroxypropyl methylcellulose, citric acid, ascorbic acid, edetate disodium, magnesium stearate, colloidal silicon dioxide, red iron oxide, entrapped cool mint orange flavor, and acesulfame potassium. Tablet discoloration during storage is primarily due to the presence of [ ] in the F2 formulation, which is [ ]. The incorporation of [ ] into the F2 formulation masks the discoloration caused by [ ]. Tablet discoloration does not represent a significant impurity profile and the active pharmaceutical ingredient assay remains within specification over the proposed 24 month expiration dating period (i.e., shelf-life) of the drug product. [ ] is added to the formulation [ ] of the active pharmaceutical ingredient. Over a period of 6 months during stability studies, the [ ] assay [ ] in the drug product tablets. The sponsor proposes no specification for [ ]. [ ] is also utilized in the drug product formulation [ ] which supports an [ ] environment further assisting in stabilization of the drug substance. All primary stability lots are comprised of the F2 formulation.

Drug product tablets proposed for marketing are to be manufactured in three shapes: 2mg (Pentagon), 3 mg (Triangle), and 4 mg (Round). As of the date of this summary, 28 stability lots have been provided for the 2, 3, and 4 mg tablets in the original round shape used for clinical studies. Two drug product lots manufactured at [ ] for the pentagonal and triangular shaped tablets have also been provided. Drug product tablet shapes, due to compression tooling differences, do appear to have a slight effect upon tablet hardness and dissolution. In general, however, dissolution profiles are similar to [ ] reference lots for the round tablets. Furthermore, a dissolution variance in the round tablet lots for the [ ]and [ ]manufacturing facilities is present and currently under further review.

Drug product specifications set the assay at release at [ ] and the assay for shelf-life at [ ]. The individual unknown related substances specification is set at not more than [ ] each, while the total related substances specification is set at not more than [ ]. Over the full 24 month stability time period at a storage condition of 25°C and 60% relative humidity, the drug product assay remains within shelf-life specifications and the impurity profile shows all lots with total related substances at not more than [ ].

The drug product is to be provided in foil/foil blisters and the storage statement provided in labeling is: "UPRIMA should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP controlled room temperature]. Protect from light and moisture." The sponsor proposes no post-marketing studies for the drug product.

SECTION 3: PHARMACOLOGY AND TOXICOLOGY

Introduction and history: Apomorphine is a dopaminergic agonist known to induce emesis and penile erection through central mechanisms. Apomorphine used as an emetic is a "grandfathered" drug, meaning it was used for this indication prior to the Food Drug and Cosmetic Act of 1938. As such, apomorphine was allowed to remain on the market without further regulatory approval if labeled for the same condition of use. Subcutaneous apomorphine is marketed in numerous European countries for the treatment of Parkinson's disease.

Mechanism of Action: Apomorphine is a dopamine agonist with affinity for both D_1 and D_2 receptor sites. Apomorphine acts centrally to enhance the neural signaling involved in the penile vascular response.

TOXICOLOGY

General Comments: The oral bioavailability of apomorphine is very low due to significant first-pass metabolism. Therefore, toxicology studies were conducted using subcutaneous dosing to permit evaluation of drug toxicity at plasma drug concentrations equal to and significantly greater than human therapeutic exposures. Toxicology studies evaluated the safety of daily dosing, while clinical use will be intermittent "as needed". In general, chronic daily dosing was well-tolerated in mice, rats and dogs. Drug-related toxicity findings are summarized below by species.

MOUSE

Toxicity was evaluated in two 3-month subcutaneous toxicity studies in male CD-1 mice.

Three Month Mouse Study # 96-2444 evaluated doses of 0.2, 0.8 and 2.0 mg/kg/day (1, 10 and 30 times human therapeutic exposures). Stereotypic behavior (disorientation, rearing) were observed in mice at doses $ 0.8 mg/kg. No significant drug-related toxicity was observed in the study and the no adverse effect level (NOAEL) was defined as 2 mg/kg/day .

Three Month Mouse Study # 96-2480 evaluated subcutaneous doses of 5, 14, 30 and 60 mg/kg/day (100, 225, 500 and 1000 times human therapeutic exposures). Drug-related mortality was observed at the two highest doses (3/20, 4/20 at 30 and 60 mg/kg/day) . Stereotypic rearing behavior was observed in all dose groups. Drug-related toxicity findings observed were :

1. Cornea - focal dystrophy at doses $ 14 mg/kg/day ($ 225 times human exposure).
2. Injection site – hypotrichosis, squamous hyperkeratosis, and skin erosion/ ulcers were observed at the injection site twice as frequently in high dose mice. The high dose produces systemic exposures 1000 times human, however, the actual dose administered at the injection site is 1.8 mg (60 mg/kg = 1.8 mg /30g mouse).

Conclusions: Daily subcutaneous administration of apomorphine to male mice for 3 months was not associated with systemic toxicity at doses up to 5 mg/kg/day (100 times human drug exposures). Local irritation was observed at the injection sites in high dose mice receiving 60 mg/kg (1.8 mg apomorphine locally).

RAT

Toxicity was evaluated in a 3-month subcutaneous toxicity study in male Sprague Dawley rats.

Three Month Rat Study # 6679-100 evaluated the toxicity of subcutaneous doses of 0.8, 2 and 8 mg/kg/day (10, 50 and 150 times human therapeutic exposures). The 8 mg/kg high dose was not well tolerated resulting in the death of 3 HD rats, tremors and physical trauma secondary to exaggerated behavioral effects, and a 30% decrement in body weight gain. The high dose group was terminated during week 9 of the study for animal welfare reasons. Stereotypic behaviors (gnawing, hyperactivity, circling) were observed at doses $ 2 mg/kg/day. Adrenal weights were increased in all apomorphine-treated groups. No tissue pathology was observed except for an increased frequency of hemorrhage, necrosis, fibrosis, and inflammation at the injection site in mid and high dose rats. The 2 and 8 mg/kg doses result in administration of 0.5 and 2 mg of apomorphine at the injection site of a 250 g rat.

Conclusions: The no adverse effect level in the rat was 0.8 mg/kg/day (10 times human therapeutic exposure). Significant toxicity as evidenced by death, tremors, vocalization, and decreased body weight gain was observed with the 8 mg/kg dose (150 times human exposure). As was observed in the mouse, local irritation was observed at the injection sites of mid and high dose rats administered $ 0.5 mg apomorphine locally.

DOG

Toxicity was evaluated in one- and six-month subcutaneous toxicity studies in beagle dogs.

One Month Dog Study #083-003 evaluated the toxicity of subcutaneous doses of 0.04, 0.1 and 0.4 mg/kg/day apomorphine administered for 28 days. These doses resulted in administration of 0.4, 1, and 4 mg/day of apomorphine and systemic drug concentrations (AUC) 2, 5 and 20 times human therapeutic exposures. Administration of apomorphine induced vomiting within one hour of dosing in all treated dogs. Salivation and changes in activity were observed in a dose-related fashion (hypoactivity /lethargy at low doses ; hyperactivity in high dose dogs).
Drug treatment had no significant effects on body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, or tissue pathology.
ECG, blood pressure and heart rate were monitored at 15 and 30 minutes and 4 hours after dosing on study days 1 and 24. The following dose-related effects were noted:

1. Increased heart rate, including runs of supraventricular tachycardia, were observed at all dose levels at 15 and 30 minutes after dosing on day 1 and day 24 as follows:
   Day 1 : 6 males and 1 female affected – 2 LD, 2 MD and 3 HD
   Day 24: 4 dogs affected – 1 LD, 1 MD, and 2 HD
   Heart rate had returned to normal by 4 hours after dosing on day 1.
2. No significant changes in blood pressure were observed on day 1 of dosing. On day 24, blood pressure was decreased and heart rate increased in a dose-related fashion in mid and high dose dogs (see NDA review pages 15-16).

The only other drug-related finding was an increased incidence of mild chronic inflammation at the injection site of high dose dogs.

Six Month Dog Study # 96-3309 evaluated the toxicity of subcutaneous doses of 0.04, 0.1, and 0.4 mg/kg apomorphine (0.4, 1, and 4 mg total dose producing 2, 5, 20 times human therapeutic exposures). Drug treatment produced vomiting, excess salivation, and circling behavior at all dose levels. Daily administration of apomorphine had no effects on body weight, ophthalmoscopy, ECG, clinical chemistry, urinalysis or organ weights. Blood pressure was monitored during month 5 of the study and mild, non significant decreases in blood pressure were observed in mid and high dose dogs. Mid and high dose dogs had significant increases in heart rate which were apparent by 5 minutes after dosing and were dose-related in duration (lasting 15

minutes in mid dose and > 30 minutes in high dose dogs). Mild decreases in white blood cell counts were observed in high dose dogs. There was no drug-related tissue pathology except an increased incidence of hemorrhage and inflammation at the injection site of mid and high dose dogs.

Conclusions: Behavioral effects (vomiting, salivation) were observed in all apomorphine treated dogs in both the one and six month studies. No drug-related changes suggestive of systemic toxicity were observed in body weight, hematology, clinical chemistry, ophthalmology, urinalysis, organ weight or histopathologic evaluations. Minimal vacuolization of the adrenal cortex was observed in all dose groups in the 6 month study including the vehicle controls, suggesting the finding was secondary to stress associated with daily injections. Injection site inflammation and hemorrhage were observed with increased frequency in dogs administered the mid and high doses ($ 1 mg apomorphine locally). Local irritation associated with clinical dosing should be easy to monitor with the sublingual dosage form.
Apomorphine decreased blood pressure and increased heart rate in dogs receiving doses $ 0.1 mg/kg (> 5 times human exposures). In the 28-day study, apomorphine was also associated with runs of supraventricular tachycardia within 30 minutes of dosing in dogs at all doses ($ 2 times human exposures). Clinical studies have been conducted to assess the cardiovascular effects of apomorphine in men.

REPRODUCTIVE TOXICITY

Male Rat Fertility Study # 96-4083
Male rats were administered 0.2, 0.8 and 2 mg/kg/day apomorphine subcutaneously for 4 weeks prior to mating and throughout a two week mating period. Female rats were not dosed. Drug treatment had no effect on mating or fertility indices, sperm parameters (count, motility , morphology), or fetal viability (pre/post implantation loss, number of corpora lutea/ live fetuses). The no adverse effect level for reproductive effects was defined as 2 mg/kg/day (30 times human exposures).

Sperm assessments (counts, motility, morphology) were also performed in the 3-month rat toxicity study. Subcutaneous administration of 0.8 and 2 mg/kg/day to male rats for 3 months had no effect on sperm parameters, testicular weights, or testicular histology.
Apomorphine had no effects on testicular weights or histopathology in the dog toxicity studies, however, sperm assessments were not performed.

Conclusions: Apomorphine had no effects on mating, fertility, or sperm parameters in male rats dosed with up to 2 mg/kg/day, subcutaneously (> 30 times human exposures).
Reproductive effects of apomorphine in pregnant animals (i.e., teratogenicity, developmental toxicity) have not been evaluated.

GENOTOXICITY

Apomorphine hydrochloride has been demonstrated to be genotoxic in four *in vitro* assay systems as follows:

1. Ames Assay : Apomorphine produces frameshift mutations in salmonella tester strains TA1537 and TA98 . Mutations were observed in the presence and absence of metabolic activation (Mutation Research 137: 17-18, 1984).
2. Chromosomal Aberrations Assay: Apomorphine and 18 of 19 of its alkaloids induced chromosome aberrations in Chinese hamster lung cells in the presence and absence of metabolic activation (J. Pharmcobiol-Dyn 15: 501-512, 1992).

3. Chromosomal Aberrations Assay: Apomorphine (with and without metabolic activation) induced chromosome aberrations in Chinese hamster ovary (CHO) cells.
4. Mouse Lymphoma Thymidine Kinase Assay: Apomorphine induced mutations at the thymidine kinase locus in mouse lymphoma cells when incubated in the presence of metabolic activation.

Glutathione supplementation decreased the cytotoxicity of apomorphine but did not eliminate the genotoxic effects in CHO or mouse lymphoma cells.

Apomorphine was not mutagenic in two *in vivo* genotoxicity assays, the Mouse Micronucleus Assay and Unscheduled DNA Synthesis Assay in Rat Hepatocytes.

Conclusions: Apomorphine was genotoxic in four *in vitro* assays. Apomorphine was not associated with genotoxicity in the *in vivo* assays.

CARCINOGENICITY

26-Week Subcutaneous Carcinogenicity Study in P53- Knockout Transgenic Mice
P53 transgenic mice (n = 15/sex/dose) were administered apomorphine daily for 6 months as follows:
Males- untreated , vehicle controls , positive (benzene) controls , 2, 7, and 20 mg/kg/day**;**
Females - untreated , vehicle controls, positive (benzene) controls, 4, 14, 40 mg/kg/day.
These doses produced systemic drug exposures(AUC) in mice 25, 75 and 200 times the human therapeutic exposures.

The only drug-related tumor finding in the study were injection site sarcomas in all groups receiving daily subcutaneous injections, including vehicle controls. The incidence rates were 22/30 , 27/30, 26,/30, 24/30 for vehicle controls, low, mid, and high dose groups, respectively. The pathology report argues that since the incidence rates of neoplasm in apomorphine treated groups were not different from vehicle controls, the sarcomas are the result of chronic irritation secondary to the repeated subcutaneous administration of an irritating vehicle.

Conclusion: Administration of apomorphine to P53-transgenic mice was not associated with an increased incidence of non-neoplastic pathologic findings or systemic tumors. The significance of the injection site sarcomas cannot be assessed due to the confounding positive tumor findings in vehicle controls.

22-Month Subcutaneous Carcinogenicity in Male Sprague Dawley (SD) Rats
Male SD rats (n = 70/dose) were administered 0, 0.1, 0.3, 0.8, and 2.0 mg/kg/day apomorphine . Dosing was terminated in the 2 mg/kg group after six months of dosing due to signs of significant toxicity suggesting the dose exceeded the maximum tolerated dose (exaggerated behavioral effects resulting in physical trauma and a 14% decrease in body weight gain relative to controls). The 2 mg/kg groups was maintained untreated for 16 months until terminal sacrifice. The study was terminated after 22 months due to increased mortality in the vehicle control group. Apomorphine treatment had no significant effect on survival. The primary statistical analyses for non-neoplastic and neoplastic findings were made between the vehicle control, 0.1, 0.3, and 0.8 mg/kg/day groups. These doses of apomorphine resulted in plasma drug exposures (AUC) in rats that were 3, 15 and 38 times greater than human therapeutic exposures. The drug-related findings are summarized in the tables below.

Non-neoplastic findings: Mammary gland hemosiderosis, retinal atrophy, and glandular dilatation of the stomach were observed with increased frequency in all apomorphine treated groups.

Incidence of Non-Neoplastic Findings in Apomorphine Treated Male Rats (n= 70/dose)

Tissue/Finding	Untreated	Vehicle	0.1 mkd	0.3 mkd	0.8 mkd	2 mkd[a]
Mammary gland hyperplasia	13	14	13	14	23	17
Hemosiderosis	11	5	25**	19**	21**	22**
Eyes, Retinal atrophy	2	7	10*	9*	15**	4
Inflammation	0	1	5	3	12**	3
Stomach, glandular dilatation	5	8	15*	14*	16*	14*

a. 2 mg/kg group dosed for 6 months and then untreated for 16 months prior to sacrifice

* $P < 0.05$; ** $P < 0.01$ mkd = mg/kg/day

Neoplastic findings: Administration of apomorphine significantly decreased the incidence of pituitary adenoma and increased the frequency of fibroma at the injection site and testicular interstitial cell tumors at the highest dose of 0.8 mg/kg/day (38 times human exposures). No increase in neoplastic findings was observed in animals receiving the low or mid dose of apomorphine.

Neoplastic Findings in Apomorphine Treated Male Rats vs. Vehicle control

Tissue/Finding	Vehicle Gp 2	0.1 mkd Gp 3	0.3 mkd Gp 4	0.8 mkd Gp 5	P-value
Pituitary , Adenoma	42	47	41	31**	$P < 0.001$
Skin/fibroma	3/70	1/69	2/70	7/69	$P < 0.03$
Testes/ Interstitial cell tumor	0/70	0/69	3/69	9/70	$P < 0.001$

Neoplastic Findings in Apomorphine Treated Male Rats vs. Untreated control

Tissue/Finding	Untreated Gp 1	0.1 mkd Gp 3	0.3 mkd Gp 4	0.8 mkd Gp 5	P-value
Skin/fibroma	1/68	1/69	2/70	7/69	$P < 0.005$
Testes/ Interstitial cell tumor	3/70	0/69	3/69	9/70	$P < 0.003$

Conclusions: A hormonal mechanism of testicular tumor induction in the rat has been observed with other dopamine agonists and pharmaceuticals that decrease prolactin and increase LH. Decreases in prolactin and increased LH were demonstrated in hormonal assays conducted in conjunction with this study. The mechanism involved in induction of leydig cell hyperplasia and adenoma in the rats is not relevant to monkeys and man.

The skin tumors at the subcutaneous injection sites were observed in rats dosed daily with the highest dose. Clinically, apomorphine will be administered intermittently as a sublingual tablet. Therefore, the increased incidence of the testicular interstitial cell tumors and skin fibromas in high dose animals in the male rat carcinogenicity study are not indicative of clinical risk.

23-Month Subcutaneous Carcinogenicity Study in Female Sprague Dawley Rats

Female SD rats (n = 70 /dose) were administered 0, 0.3, 0.8 and 2 mg/kg/day apomorphine daily for 23 months. These doses resulted in plasma drug concentrations (AUC) in the female rat that are 3, 12, and 35 times human drug exposures. The study was terminated during week 100 due to increased mortality in the control group. Apomorphine treatment had no effect on survival.

Non-neoplastic findings: Retinal atrophy and glandular dilatation of the stomach were significantly increased in all apomorphine treated groups, as was observed in the male rat

carcinogenicity study. Additional findings in female rats included increased frequency of kidney and bladder inflammation, eosinophilic foci in the liver, and ovarian cysts in rats dosed with $ 0.8 mg/kg/day (> 12 times human exposures). Animals receiving the highest dose of 2 mg/kg/day also had increased hemorrhage at the injection site.

Incidence of Non-Neoplastic Findings in Apomorphine Treated Female Rats

Tissue/Finding	Untreated	Vehicle	0.3 mkd	0.8 mkd	2 mkd
Adrenal medulla, hyperplasia	4	5	3	4	9
Eyes, Retinal atrophy	6	9	19**	18**	36**
Liver, eosinophilic focus	4	7	9	17*	15*
Ovary, cyst	9/70 (13%)	10/70 (14%)	10/48 (21%)	12/41* (29%)	17/70 (24%)
Kidney, inflammation	2	3	7	7	10*
Bladder, inflammation	1 (1%)	0 (0%)	4/39* (10%)	3/36* (8%)	7/70* (10%)
Injection site, hemorrhage	0	4	0	0	15*
Stomach, glandular dilatation	8	8	16	26**	25**

* $P < 0.05$; ** $P < 0.01$; n = 70/dose unless specified.

Neoplastic findings: The sponsor concludes there were no drug-related increases in neoplastic lesions. The mammary adenoma findings were dismissed due to the lack of dose-response and because an incidence of 14% (10/70) observed in mid-dose rats is within the historical incidence for this tumor type. Lymphoreticular tumors are rare (<0.1%) . The sponsor dismisses the increase in the high dose group as "spurious". The subcutaneous sarcomas were observed at the injection site. The sponsor attributes their occurance as secondary to the trauma of repeated subcutaneous injections. However, the incidence was significantly increased in high dose female rats compared to the vehicle control or low dose group. Tumors may well be secondary to inflammation and hyperkeratosis induced by local irritative properties of apomorphine.

Neoplastic Findings in Apomorphine Treated Female Rats vs. Vehicle control

Tissue/Finding	Vehicle Gp 2	0.3 mkd Gp 3	0.8 mkd Gp 4	2 mkd Gp 5	P-value
Mammary Adenoma	3	4	10*	5	$P < 0.05$
Lymphoreticular, lymphoma[a]	0	0	0	2*	$P < 0.05$
Skin/ subcutaneous sarcoma	1	0	3	6 **	$P < 0.002$

a. large granular cell (LGL) lymphoma

Conclusions: Retinal atrophy and glandular dilatation of the stomach were significantly increased in rats of both sexes treated chronically with apomorphine at all dose levels ($ 3 times human AUC exposures).

Apomorphine is locally irritating as evidenced by consistent observations of inflammation, hemorrhage, necrosis, and fibrosis at the injection sites in mice, rats and dogs. In the

carcinogenicity studies, chronic dosing increased the incidence of sarcomas at the injection site in mice and female rats and fibromas at the injection site in male rats. In rats, the skin tumors were significantly increased only with the highest dose of apomorphine (> 35 times human exposures). The only tumor clearly increased as a result of systemic dopamine exposures were testicular interstitial cell tumors in male rats. These tumors are known to arise in male rats secondary to hormonal alterations in the hypothalamic-pituitary-gonadal axis. Apomorphine, a dopaminergic agonist, had the expected effects of decreasing prolactin and increasing luteinizing hormone secretion in male rats, thereby inducing leydig cell tumors. This effect has been previously observed with other dopamine agonists and pharmaceuticals. The mechanism involved in interstitial cell tumor induction in rats is not believed to be relevant in primates or man.

SECTION 4: PHARMACOKINETICS AND DRUG INTERACTIONS

1. SYNOPSIS

1.1. PHARMACOKINETICS

Absorption and Bioavailability: Apomorphine is rapidly absorbed with maximum plasma concentrations occurring within 40 – 60 minutes after placing the tablet under the tongue. The inter-subject variability for the pharmacokinetics of apomorphine was rather high with a coefficient of variation of 50-80% in C_{max} and 35-60% in AUC parameters. The bioavailability of apomorphine from sublingual (SL) tablets, relative to a subcutaneous injection was 16-18%. Following sublingual administration, apomorphine is rapidly cleared from plasma, with a terminal elimination half-life of about 2 to 3 hours.

***In vivo* tablet dissolution**: In some of the Phase 1 studies, incomplete dissolution of the tablets was detected. Only about 40-50% of the tablets dissolved completely in the subject's mouth during early Phase 1 studies. However, the *in vivo* tablet dissolution improved considerably in the later Phase 1 studies with 88-100% of the tablets dissolved completely. *In vivo* tablet dissolution was monitored in one Phase 3 study and tablet dissolution ranged from 88-93% by 10 minutes and >99% by 20 minutes.

Metabolism and Excretion: Apomorphine is extensively metabolized by sulfation, glucuronidation and N-demethylation. The major metabolite in plasma of subjects receiving apomorphine SL tablet is apomorphine sulfate. Most of the apomorphine dose is excreted in urine as sulfate (59%) and glucuronide (12%) conjugates of apomorphine and about 18% of the dose is excreted as norapomorphine and its conjugates in urine. Very little unchanged apomorphine (<2% of the dose) is excreted in urine. *In vitro* studies suggested that the principal isoforms that could N-demethylate apomorphine were CYP1A2, CYP3A, and CYP2C19.

Pharmacokinetics in Special Populations

Elderly Subjects: Apomorphine bioavailability was not different in the young and elderly subjects following sublingual administration.

Hepatic Impairment: The pharmacokinetics of apomorphine SL (2 mg and 4 mg) was found to be significantly different in subjects with all degrees of hepatic impairment compared to normal subjects. The mean C_{max} in subjects with mild, moderate and severe impairment classes was 16%, 36%, and 62% higher and the mean AUC_{∞} was 59%, 35%, and 68% higher, respectively, than the estimates for the normal hepatic function class. The upper bound of the 95% confidence intervals suggest that a 2- to 4-fold increase in the means for C_{max} and AUC is possible in subjects with hepatic impairment.

Renal Impairment: Although there was no significant change in mean C_{max}, the mean AUC_{∞} was significantly increased in subjects with moderate (52%) and severe (67%) renal impairment. The elimination half-life was also affected with a predicted increase of 0.24 hour for each 10 ml/min/1.73 m^2 drop in creatinine clearance.

1.2. DRUG INTERACTIONS

Anti-emetics: The pharmacokinetics of apomorphine was not found to be affected by two commonly prescribed anti-emetics, Zofran and Compazine.

Alcohol: Alcohol had little effect on the bioavailability of apomorphine and apomorphine likewise had minimal effects on the bioavailability of alcohol. When 0.3 g/kg ethanol was studied, there was a general trend towards greater drops in systolic and diastolic blood pressure measurements with apomorphine SL/ethanol than apomorphine SL alone or ethanol alone. There was a significant pharmacdynamic interaction between apomorphine SL and ethanol at 0.6g/kg dose, with greater mean maximum drop from baseline in systolic and diastolic blood pressure. Apomorphine SL increased the sedation effect induced by the alcohol at doses ranging from 0.15 to 0.6 g/kg. Coadministration of alcohol (0.3 – 0.6 g/kg) and apomorphine SL resulted in higher incidence of adverse events when compared apomorphine SL alone or ethanol alone.

1.3. PHARMACOKINETIC – CARDIOVASCULAR PHARMACODYNAMIC CORRELATIONS

Although, there was no relationship between blood pressure measurements and apomorphine C_{max} and AUC, most of the serious cardiovascular events including syncope in subjects from Phase 1 studies occurred approximately at the t_{max} of apomorphine SL. These subjects, in general, had Cmax values above the mean of their group indicating that peak plasma concentration of apomorphine is an important pharmacokinetic variable for the safety evaluation of apomorphine SL.

Upon cross study comparison, it is noted that both Cmax and AUC of apomorphine are not really distinguishable between 4 and 5 mg, and 5 mg and 6 mg doses. The variability in blood levels is notable given the safety concerns that have been seen particularly with higher doses of apomorphine. Patient safety at lower doses of apomorphine may be difficult to predict.

2. DRUG INTERACTION BETWEEN URPIMA$^{\delta}$ AND ETHANOL

During a multicenter, flexible dose (2, 4 or 6 mg), 6-month efficacy study of apomorphine SL (Study M96-471), one patient experienced a syncopal episode, accompanied by nausea and diaphoresis, after consuming a large amount of alcohol (a glass of vodka, a glass of rye and a can of beer) over approximately one hour, followed by a 6 mg apomorphine SL tablet one hour later. The patient had not previously experienced this type of reaction during 2 to 3 months of dosing with apomorphine SL and continued on study without any additional reported adverse experiences of this type. Since apomorphine SL use by patients might be temporally associated with consumption of alcohol, possible pharmacokinetic and pharmacodynamic interactions between apomorphine and ethanol were investigated.

Four drug interaction studies with alcohol (M97-745, M98-838, M98-891 and M97-762) were submitted in the NDA. These studies differed in the use of the doses of either apomorphine SL or alcohol and their design. The design of M98-838 and M98-891 was similar except for the dose of alcohol: M98-838 was with 0.3 g/kg dose and M98-891 was with 0.6 g/kg dose. The individual study summaries are described below.

2.1. STUDY M97-745

The objectives of this study were to evaluate the effect of single dose ethanol (0.6 g/kg, equivalent to 4 shots of vodka) on the pharmacokinetics of apomorphine and to evaluate whether a single dose of ethanol alters the cardiovascular effects of apomorphine SL.

This was a double-blind, placebo-controlled, two period crossover study. Each period was to consist of three days of treatment separated by four days of washout period. The study was planned to enroll 72 men in general good health and the subjects were to be sequentially assigned to 6 cohorts of 12 subjects each. Within each cohort, 6 subjects each were to be randomly assigned to Groups I and II and received the treatment as shown below:

Group	Number of Subjects	Regimens	
		Period 1	Period 2
I	36	A	B
II	36	B	A

Regimen A: Apomorphine SL 5 mg tablet once a day on first two days of the treatment period; ethanol beverage (0.6g/kg body weight) + apomorphine SL 5 mg tablet on third day of the treatment period.

Regimen B: Apomorphine SL 5 mg tablet once a day on first two days of the treatment period; Placebo beverage + apomorphine SL 5 mg tablet on third day of the treatment period.

The ethanol beverage (a dose of 0.6 g/kg) was prepared by diluting an appropriate amount of vodka (40% ethanol v/v ≅ 0.316 g/ml) to a final volume of 450 ml with orange juice. The ethanol or placebo beverage was consumed by subjects over 30 minutes and apomorphine SL was administered at 1 hour after beginning ethanol or placebo beverage ingestion.

Results

This study was prematurely terminated because of severe cardiovascular adverse events in subjects participating in the study. Thirty six subjects were enrolled by the time this study was terminated. No subjects completed the study prior to its termination. Thirty two (32) subjects received study medication. Ten subjects completed only Day 1 and one subject completed Day 2 receiving only apomorphine and never receiving either alcohol or placebo beverage on Day 3. Ten subjects ingested ethanol on Day 3 and received concomitant apomorphine SL while ten other subjects received placebo beverage followed by apomorphine SL on Day 3. One subject ingested the ethanol beverage but was not given apomorphine SL on Day 3.

Since the study was terminated prematurely and no subject received both ethanol and placebo beverage, it is difficult to draw any conclusions regarding the effect of alcohol on pharmacokinetics of apomorphine.

Apomorphine and ethanol concentrations in subjects experiencing serious adverse events

Two subjects experienced serious cardiovascular adverse events during this study. One subject experienced significant vomiting, diaphoresis and a one minute loss of consciousness approximately 40 minutes after taking his first 5 mg dose of apomorphine SL on Day 1 (no

alcohol was given during the first dose per protocol). Apomorphine concentrations were not measured on Day 1. The subject had significant hypotension (BP 71/37, pulse of 41) at the onset of this event; BP 64/45 with pulse not palpable one minute after onset; BP 78/45 with pulse 80 two minutes after onset; and BP 97/58 with pulse 84 ten minutes following the onset of this event. The subject required IV fluids and oxygen followed by a 0.5 mg bolus of atropine. He was then admitted to the hospital for cardiac monitoring and discharged the following day with no residual problems. The investigator considered this event to be life-threatening and definitely related to study drug.

A second subject experienced hypotension (BP 55/38) about 30 minutes following the Day 3 dose of apomorphine SL (5 mg); this subject had ingested the ethanol beverage approximately one hour prior to apomorphine dosing and was found to have the second highest apomorphine C_{max} value (2.12 ng/ml) at 30 minutes (t_{max}). This subject also had the highest blood ethanol concentration (441 µg/ml). He did not experience loss of consciousness. He was treated with IV bolus of 0.9% saline and was hospitalized for 2 days for further evaluation.

Two additional subjects also experienced hypotension after apomorphine dosing on Day 1 or 2, but no alcohol was given and apomorphine levels were not measured in these subjects.

The occurrence of hypotension in the second subject, at the time when the highest apomorphine and ethanol levels were present in his blood circulation suggests that there may be a significant pharmacodynamic interaction between alcohol and apomorphine.

2.2. STUDY M98-838

The objectives of this study were 1) to evaluate the effect of single dose of ethanol (0.3 g/kg) on the pharmacokinetics of sequential single doses of apomorphine SL (6 mg); 2) to evaluate the effects of single dose of ethanol on the cardiovascular effects of apomorphine SL; and 3) to evaluate whether apomorphine alters ethanol-induced psychomotor, sedative, and cardiovascular effects and to study the effect of apomorphine on the pharmacokinetics of apomorphine.

This was a double-blind, placebo-controlled, three period, six sequence crossover study conducted at two sites. Seventy (72) subjects (6 cohorts of 12 each), participated in the study. All subjects received the following three treatments in a randomized crossover fashion with a four day washout between each period:

A. Apomorphine SL 6 mg, Ethanol 0.3g/kg (equivalent to two shots of vodka)
B. Apomorphine SL 6 mg, Ethanol placebo
C. Apomorphine SL placebo, Ethanol 0.3g/kg (equivalent to two shots of vodka)

The following was the schematic of the study design

Sequence	Number of Subjects	Period		
		1	2	3
I	12	A	B	C
II	12	A	C	B
III	12	B	C	A
IV	12	B	A	C
V	12	C	A	B
VI	12	C	B	A

Each subject received either a single 6 mg dose of apomorphine SL or placebo tablet on Study Days 1 and 2 after an initial training period on the proper use of sublingual medication using placebo tablets. On study Day 2, the subjects were trained in the performance of the Digital Symbol Substitution Test (DSST) and Card Sorting (CS), the primary pharmacodynamic evaluations to be used to test for psychomotor events. On Study Day 3, subjects in regimen A and C received a single oral dose of ethanol (0.3 g/kg body weight) diluted to 450 ml of orange juice, over 30 minutes, while subjects in Regimen B received a placebo beverage. Within 10 minutes prior to study drug dosing, a breathalyzer test was performed. One hour after beginning ethanol or placebo ingestion, each subject received either a 6 mg dose of apomorphine SL or placebo tablet.

Blood samples for the determination of apomorphine and ethanol concentrations, measurements of supine and standing blood pressures and heart rates, Holter monitoring and the psychomotor battery and sedation assessments were performed periodically following study drug administration. Study Days 4 through 7 and 11 through 14 were out patient washout periods. The subjects crossed over between regimens on Study Days 8 through 10 and 15 through 17, with repeat pharmacokinetic, pharmacodynamic measurements and psychomotor and sedation assessments.

Supine and standing blood pressures and pulse were measured on study Day –1 and 30 minutes prior to and two hours post-dosing on Study Days 1 and 2, 8 and 9, and 15 and 16.
These measurements were also performed at –10, 25, 45, 60, 90, 120, 180, 240, and 300 minutes after apomorphine dose initiation on Study days 3, 10, and 17.
Psychomotor tests and sedation assessments were performed at 15 minutes prior to administration of apomorphine or placebo and at 120 and 180 minutes after ethanol dose initiation on Study Days 3, 19 and 17.

Results

Seventy-two (72) subjects were to be enrolled in the study. A total of 68 subjects were enrolled and 64 subjects completed all three periods. The mean age of these subjects was 35.0 (range: 21-59) years and mean weight was 167.4 (range: 139.1 – 205.3) pounds.
The most common protocol deviation was that standing vital signs were not measured due to adverse events.

Pharmacokinetic evaluation

The results of this study indicated that there was no statistically significant effect of ethanol on the pharmacokinetic parameters of apomorphine SL. A slight lowering of t_{max} and AUC of ethanol were noted when apomorphine was administered.

In most subjects, C_{max} of ethanol occurred in the blood sample collected just before the administration of the sublingual tablet. Thus ethanol levels were not at a maximum when the apomorphine levels reached peak concentrations (t_{max} =40 to 60 minutes). This may limit the chances of observing significant pharmacodynamic reaction between the two compounds.

Hemodynamic evaluations

The measurement of mean changes in vital signs from the study are presented in Table 1.

Table 1: Vital signs parameters: Maximum drop from baseline

Parameter	Treatment	N	Baseline Mean	Treatment Mean	Mean Change
Standing pulse	Apo SL + Ethanol	66	99.00	75.60	-23.40
	Apo SL alone	66	90.65	72.35	**-18.30***
	Ethanol alone	64	99.64	73.87	-25.77
Standing systolic Blood pressure	Apo SL + Ethanol	66	120.85	98.58	-22.27
	Apo SL alone	66	123.98	104.65	-19.33
	Ethanol alone	64	121.25	104.63	**-16.62***
Standing diastolic Blood pressure	Apo SL + Ethanol	66	73.69	59.48	-14.21
	Apo SL alone	66	75.71	63.63	-12.09
	Ethanol alone	64	72.97	63.44	**-9.53***
Supine pulse	Apo SL + Ethanol	66	73.75	57.53	-16.21
	Apo SL alone	66	68.36	55.99	**-12.38***
	Ethanol alone	64	71.98	55.70	-16.28
Supine systolic Blood pressure	Apo SL + Ethanol	66	120.19	104.98	-15.21
	Apo SL alone	66	120.30	107.13	-13.17
	Ethanol alone	64	119.12	105.14	-13.98
Supine diastolic Blood pressure	Apo SL + Ethanol	66	66.28	59.19	-7.09
	Apo SL alone	66	66.64	58.80	-7.84
	Ethanol alone	64	66.45	57.51	-8.94

* Statistically significant ($p<0.05$) versus apomorphine SL + ethanol

The following significant results were noted from hemodynamic evaluations:

- The analysis of maximum drop from baseline yielded four statistically significant differences in blood pressure and pulse rate.

- For both standing systolic and standing diastolic blood pressure, the mean maximum drop from baseline was significantly greater for subjects receiving the apomorphine SL/ethanol regimen (-22.27 and –14.21 mm Hg, respectively) than subjects on ethanol alone (-16.62 and –9.53 mmHg, respectively) ($p\leq0.045$).

- Although not statistically significantly different, apomorphine SL/ethanol group had a greater mean maximum drop from baseline for both systolic and diastolic blood pressures than the apomorphine SL alone group. A significantly greater mean maximum drop in both standing and supine pulse rate from baseline was observed for the apomorphine SL/ethanol group when compared to apomorphine SL alone group ($p\leq0.011$).

- For the analysis of maximum drop moving from supine to standing, the apomorphine SL/ethanol subjects had a significantly ($p=0.013$) greater mean change from baseline for the maximum drop in diastolic blood pressure (-15.14 mm Hg) than subjects receiving ethanol alone (-9.83).

- For systolic blood pressure, there was a significantly greater mean drop from baseline in moving from supine to standing was observed in subjects on apomorphine SL/ethanol

regimen (mean change of -5.75 mm Hg) than apomorphine SL alone (mean change of 1.28 mm Hg).

Psychomotor and sedation assessments

There were no statistically significant differences among regimens for maximum decrease from baseline in the DSST and CS tests.
The mean changes in self-rated sedation scores following each treatment are reported in Table 2.

Table 2. Self-rated sedation scores:

Treatment	N	Baseline Mean	Treatment Mean	Mean change
Apomorphine + ethanol	67	0.37	1.93	1.57*
Apomorphine +placebo	66	0.31	1.56	1.25
Placebo + ethanol	64	0.29	1.27	0.98

*Statistically significantly different from placebo+ethanol group (p=0.002)

The sedation scale measured was as follows:
0 = Feeling wide awake and alert
1 = Feeling awake, but lethargic
2 = Feeling tired, not at full alertness
3 = Sleepy, prefer to be lying down
4 = Very sleepy, losing struggle to remain awake

All three regimens had increases from baseline for self-rated sedation scores (SRSS), suggesting an increased sedation. The mean maximum increase from baseline for apomorphine SL/ethanol (1.57) was significantly greater than that for ethanol alone (0.98). Apomorphine SL alone had a greater sedation effect than ethanol alone. Similar differences were observed in nurse-rated scores as well.

Safety evaluation
A summary table listing the treatment-emergent adverse events that were considered by the investigators to be related to study drug is attached (Attachment 1).

Treatment-related adverse events were reported more frequently by subjects in apomorphine SL/ethanol regimen (75%) than by subjects receiving apomorphine alone (59.7%) or ethanol alone (26.6%). Notably, the apomorphine SL/ethanol regimen resulted in a higher frequency of nausea, dizziness, pallor, sweating, vomiting and hypotension than apomorphine SL alone regimen indicating that ethanol potentates the occurrence of adverse events related to apomorphine use.

Two brief episodes of syncope occurred during the study. Both subjects were on apomorphine SL and both events were considered definitely related to the drug. Following are the details regarding the syncopal events:

- A 41 year old subject (6 mg apomorphine SL and ethanol placebo), at 30 minutes after apomorphine SL dosing, experienced dizziness, light-headedness, and pallor prior to a

syncopal event, that lasted two seconds. The subject was hypotensive (78/55) for 20 minutes. The investigator assessed this event to be definitely related to study drug.

- A 40 year old subject (6 mg apomorphine SL and 0.3g/kg ethanol), at 40 minutes following apomorphine SL dosing, experienced nausea, pallor, and diaphoresis prior to a syncopal event, that lasted two seconds. The other prodromal events lasted approximately 30 minutes.

Vital sign abnormalities

Several subjects had vital sign measurements that met predefined criteria for abnormally low values: pulse rate <40 beats /minute, systolic <80 mm Hg, diastolic <40 mm Hg.

Table 3. Number and percentage of subjects vital signs abnormalities

Parameter	Apomorphine SL+ ethanol n/N (%)	Apomorphine SL alone n/N (%)	Ethanol alone n/N (%)
Pulse			
Standing	0/67 (0.0)	0/66 (0.0)	1/64 (1.6)
Supine	0/67 (0.0)	0/66 (0.0)	0/64 (0.0)
Systolic Blood Pressure			
Standing	8/67 (11.9)	3/66 (4.5)	1/64 (1.6)
Supine	0/67 (0.0)	0/66 (0.0)	0/64 (0.0)
Diastolic Blood Pressure			
Standing	5/67 (7.5)	3/66 (4.5)	0/64 (0.0)
Supine	0/67 (0.0)	1/66 (1.5)	2/64 (3.1)

There was a slightly higher incidence of abnormally low standing systolic and diastolic blood pressures in subjects receiving apomorphine SL and ethanol compared to either apomorphine SL alone or ethanol alone regimens.

Approximately 21% of subjects in the apomorphine SL and ethanol group had abnormally high pulse rates (>130 beats/minute) compared to 1.5% in the apomorphine alone and 11% in the ethanol alone regimens.

Conclusions

- In general, there was a trend toward a greater drop in both systolic and diastolic blood pressure when ethanol was given with apomorphine SL. Although not statistically significantly different, the apomorphine SL/ethanol group had a greater mean maximum drop from baseline for both systolic and diastolic blood pressures than did the apomorphine SL alone group.

- The results indicate that apomorphine SL 6 mg dose potentiates the sedative effects induced by 0.3g/kg ethanol ingestion.

- The results also show that ethanol at the 0.3g/kg dose significantly increases the treatment-emergent adverse events (consistent with vasovagal symptoms) related to apomorphine SL.

2.3. STUDY M98-891

The objectives of this study were 1) to evaluate the effects of a single dose of ethanol (0.6g/kg) on the pharmacokinetics of sequential single doses of apomorphine SL (6mg); 2) to evaluate whether a single dose of ethanol alters cardiovascular effects of apomorphine SL; and 3) to evaluate whether apomorphine alters ethanol-induced psychomotor, sedative and cardiovascular effects or the pharmacokinetics of ethanol.

The design of this study is similar to that of Study M98-838 with exception of the alcohol dose. The present study used an alcohol dose of 0.6g/kg while Study M98-838 used a 0.3g/kg dose.

A total of 70 subjects were enrolled and 59 completed all three study periods. The mean age of the subjects was 34.5 (±10.7) years and weight was 162.1 (±16.7) pounds. Five subjects were prematurely discontinued by the investigator based on Holter ECG readings. Other patients withdrew for personal reasons or adverse events (probably not related to the drug).

Results

Pharmacokinetic evaluations

Coadministration of ethanol resulted in an increase of the mean C_{max} of apomorphine by about 23% and AUC by about 11-12%. The effect on C_{max} may be important in terms of known cardiovascular adverse events with apomorphine.
Administration of apomorphine SL (6mg) resulted in a slight (8%) but statistically significant decrease in the bioavailability of ethanol.

Pharmacodynamic evaluations

The analysis of maximum drop from supine to standing vital signs (orthostatic changes in comparison to baseline) showed two statistically significant differences.

- The apomorphine SL/ethanol group had a significantly greater (p=0.009) mean change from baseline in maximum drop in diastolic blood pressure (-15.38 mm Hg) than subjects receiving ethanol alone (-9.93 mm Hg).
- Apomorphine SL/ethanol subjects had a significantly (p=0.008) greater mean drop (smallest increase or largest decrease) in pulse rate (-18.87 mm Hg) than subjects receiving ethanol alone (-8.79 mm Hg).

The mean maximum drop in vital signs from baseline following each treatment is summarized in Table 4.

Table 4: Maximum drop in vital signs from baseline

Parameter	Treatment	N	Baseline Mean	Treatment Mean	Mean Change
Standing pulse	Apo SL + Ethanol	61	103.52	79.94	-23.58
	Apo SL alone	61	90.76	75.12	**-15.64***
	Ethanol alone	61	104.13	84.19	-19.94
Standing systolic Blood pressure	Apo SL + Ethanol	61	119.46	92.68	-26.78
	Apo SL alone	61	124.33	102.55	-21.77
	Ethanol alone	61	122.45	99.21	-23.23
Standing diastolic Blood pressure	Apo SL + Ethanol	61	73.61	56.74	-16.87
	Apo SL alone	61	74.07	61.49	**-12.58***
	Ethanol alone	61	74.23	63.68	**-10.55***
Supine pulse	Apo SL + Ethanol	61	78.63	62.98	-15.65
	Apo SL alone	61	71.26	57.88	-13.38
	Ethanol alone	61	77.27	61.59	-15.67
Supine systolic Blood pressure	Apo SL + Ethanol	61	118.93	103.06	-15.87
	Apo SL alone	61	117.22	106.36	**-10.86***
	Ethanol alone	61	117.67	102.98	-14.69
Supine diastolic Blood pressure	Apo SL + Ethanol	61	66.68	57.62	-9.07
	Apo SL alone	61	65.98	59.49	-6.49
	Ethanol alone	61	66.77	58.14	-8.64

* Statistically significant ($p<0.05$) versus apomorphine SL + ethanol

The analysis of maximum drop from baseline yielded four statistically significant differences in blood pressure.

- The mean maximum drop in standing diastolic blood pressure from baseline was significantly greater ($p\leq0.028$) for subjects receiving the apomorphine SL/ethanol regimen (-16.87 mm Hg) than for subjects receiving apomorphine SL alone (-12.58 mm Hg) or ethanol alone (-10.55 mm Hg).

- The mean maximum drop in supine systolic blood pressure from baseline was significantly higher ($p\leq0.028$) for subjects receiving the apomorphine SL/ethanol regimen (-15.87 mm Hg) than for subjects receiving apomorphine SL alone (-10.86 mm Hg).

- A significant difference between apomorphine SL/ethanol and apomorphine SL alone was observed for standing pulse rate ($p=0.005$), with the greater decrease observed in the combination regimen.

- Higher mean maximum drops in standing systolic and supine diastolic from baseline was also observed for the combination regimen than for apomorphine SL alone or ethanol alone regimens.

- Significant differences in systolic and diastolic blood pressure in the apomorphine SL/ethanol regimen compared to apomorphine SL alone or ethanol alone were observed approximately at the time of peak apomorphine (mean t_{max}: 0.8 h) and ethanol plasma concentrations (mean t_{max}: 1.6 to 1.8 h) indicating a clinically significant pharmacodynamic interaction between apomorphine and ethanol.

Psychomotor and sedation assessments

There were no statistically significant differences among three regimens for the maximum decrease from baseline for the DSST and CS tests. However, subjects on the apomorphine SL/ethanol regimen had a greater mean maximum increase in sedation scores from baseline (2.16) when compared to ethanol alone (1.48) and apomorphine alone (1.02).

Safety evaluation

Adverse events: Treatment related adverse events were reported more frequently by subjects in the apomorphine SL/ethanol regimen (75%) than by subjects receiving apomorphine SL alone (49.3%) or ethanol alone (42.9%, see Attachment 2). The combination of apomorphine and ethanol resulted in a higher frequency of the adverse events such as nausea, dizziness, pallor, hypotension and vomiting. Five subjects were withdrawn by the investigator due to an abnormal Holter monitor reading; four of the five were considered to be probably related to the study drug. Three of the events occurred after receiving apomorphine SL either with ethanol (one) or without ethanol (two). Four syncopal events occurred in three subjects in this study, all during apomorphine SL/ethanol placebo regimen. Only two events were considered by the investigator to be study drug related, as the other two occurred when blood was being drawn before apomorphine administration.

Vital signs abnormalities

The number and percentage of subjects with abnormally low values of vital signs are presented in Table 5.

Table 5. Number and percentage of subjects vital signs abnormalities

Parameter	Apomorphine SL+ ethanol n/N (%)	Apomorphine SL alone n/N (%)	Ethanol alone n/N (%)
Pulse			
Standing	0/64 (0.0)	1/65 (1.5)	0/63 (0.0)
Supine	0/64 (0.0)	0/65 (0.0)	0/63 (0.0)
Systolic Blood Pressure			
Standing	13/64 (20.3)	1/65 (1.5)	1/63 (1.6)
Supine	0/64 (0.0)	0/65 (0.0)	0/63 (0.0)
Diastolic Blood Pressure			
Standing	9/64 (14.1)	1/65 (1.5)	1/63 (1.6)
Supine	0/64 (0.0)	0/65 (0.0)	0/63 (0.0)

There was a significantly higher percentage of subjects with abnormally low standing systolic and diastolic blood pressure values in the apomorphine SL/ethanol regimen compared to apomorphine alone or ethanol alone. The higher incidence of abnormally low values in the combination regimen could be due to a drug interaction between apomorphine and ethanol.

Conclusions

- The combination of apomorphine SL and ethanol resulted in statistically significantly greater orthostatic decreases in diastolic blood pressure than the ethanol alone regimen.

- There was a significantly greater mean maximum drop in both systolic and diastolic blood pressure observed for apomorphine/ethanol regimen than apomorphine SL alone regimen. This indicates that ethanol potentiates the drop in blood pressure caused by apomorphine.

- Significant differences in systolic and diastolic blood pressure in the apomorphine SL/ethanol regimen compared to apomorphine SL alone or ethanol alone were observed approximately at the time of peak apomorphine and ethanol plasma concentrations. This indicates a clinically significant pharmacodynamic interaction between apomorphine and ethanol.

- Apomorphine SL significantly increased the sedation effects induced by alcohol.

- The presence of ethanol significantly increased the adverse events caused by apomorphine SL.

2.4. STUDY M97-762

The objectives of the study were to evaluate the effect of sequential doses of 6 mg apomorphine SL on the pharmacokinetics of a single dose of ethanol (0.15g/kg, equivalent to one shot of vodka), and to evaluate whether apomorphine SL alters ethanol-induced psychomotor, sedative, and cardiovascular effects.

This was a double-blind, placebo-controlled, two-period crossover, single-center study. Each period consisted of three days of treatment separated by a four-day washout period. A total of 24 subjects were assigned to four cohorts of six subjects each. Within each cohort, three subjects were randomly assigned to Groups I (sequence A B) and II (sequence B A). During each period, subjects received a single 6 mg dose of apomorphine SL (regimen A) or placebo tablet (regimen B) on an outpatient basis on Study Days 1 and 2. Subjects were given training in the performance of the Digit Symbol Substitution Test (DSST) and Card Sorting (CS) to test for psychomotor effects. On Study Day 3 each subject received a single oral dose of ethanol, 0.15 g/kg body weight, over a 10 minute period. A single dose of 6 mg apomorphine SL tablet or placebo tablet was administered 15 minutes after the initiation of ethanol ingestion.

Blood samples for the determination of ethanol concentrations were obtained on Study Days 3 and 10 (third day of each period) at 0 (within 5 minutes prior to dosing), 10, 20, 30, 40 and 50 minutes, and 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 hours following ethanol dose initiation. Psychomotor tests (DSST, CS) and sedation assessments were performed prior to and at 30, 60, 90, 120, 180, 240, and 480 minutes after ethanol dose initiation.

Results

Pharmacokinetic evaluation

There was no statistically significant difference in t_{max}, C_{max} and AUC of ethanol between the two regimens indicating lack of apomorphine SL effect on ethanol (at 0.15 g/kg dose) pharmacokinetics.

Pharmacodynamic evaluations

No statistically significant mean differences between apomorphine SL and placebo group were noted for DSST and CS tests.
A statistically significantly greater increase in sedation for the apomorphine SL regimen (mean change 1.80) than placebo regimen (mean change 1.03) was observed.
Analysis of mean changes in vital signs measurements at each time point following study drug administration indicated that there were no significant differences between the two regimens.

Safety evaluation

Adverse events were reported by about 83% of subjects receiving apomorphine SL and by 26% of subjects receiving placebo SL tablet. The most frequently reported adverse events in the apomorphine SL regimen were nausea (43.5%), asthenia (39.0%), pallor (39.0%), vomiting (30.4%), and dizziness (26.1%). The most frequently reported adverse events in the placebo SL tablet regimen were asthenia (13%), and somnolence (13%).
No serious cardiovascular adverse events were reported in this study.

3. PHARMACOKINETIC-CARDIOVASCULAR PHARMACODYNAMIC CORRELATIONS

3.1. Relationship of blood pressure and pulse rate changes with apomorphine C_{max} and AUC in selected Phase 1 studies

Pharmacokinetic and vital signs data from seven Phase 1 studies with apomorphine SL (2, 4, 5 or 6 mg) were utilized to investigate the relationship of change from baseline in blood pressure and pulse rate with apomorphine C_{max} and AUC. There was no statistically significant correlation between change from baseline in systolic or diastolic pressure and AUC_{4h} or $C_{max.}$ The mean and maximum change in pulse rate from baseline
were statistically significantly correlated with C_{max} and AUC_{4h}. However, the results of this analysis indicated that only a small change in pulse rate would be expected from a large increase in C_{max} or AUC_{4h}.

3.2. Apomorphine C_{max} in subjects experiencing adverse cardiovascular events in Phase 1 studies

The relationship between apomorphine C_{max} and the adverse cardiovascular events observed in Phase 1 studies has been examined. A total of six subjects were identified for this analysis. Five of these subjects were from ethanol interaction studies. The apomorphine C_{max} values from those six subjects along with the mean C_{max} observed in these studies are presented in Table 6.

Table 6. Apomorphine and ethanol C_{max} values in subjects experiencing adverse cardiovascular events

Study	Sub No.	Cardiovascu-lar event	Regimen	Apo C_{max} (ng/ml)		Ethanol C_{max} (µg/ml)	
				Subject	Mean ± SD	Subject	Mean ± SD
M98-815	308	Syncope	Apo SL + Compazine	1.93	1.38 ± 0.72	n.a.	n.a.
M97-745	13	Vasovagal event and hypotension	Apo SL + EtOH Bev.	2.12	1.33 ± 0.85	441	342 ± 85
M98-838	70	Syncope	Apo SL+ Placebo Bev	3.28	1.47 ± 0.68	n.a.	n.a.
	72	Syncope	Apo Sl+ EtOH Bev	1.10	1.50 ± 0.87	182	122 ± 51
M98-891	268	Syncope Sinus pause	Apo SL+ Placebo Bev	1.96	1.76 ± 0.90 1.78 ± 0.82[a]	n.a.	n.a.
	251	Sinus pause	Apo SL + EtOH Bev	1.37	2.20 ± 1.29 1.99 ± 1.34[a]	245	411 ± 116 456 ± 129[a]

a. Mean ± SD for Lincoln site, n.a. = not applicable

Four of the six subjects from the above table had C_{max} values above the mean and two had lower C_{max} than the mean value. It should be noted that the two subjects who had lower C_{max} values of apomorphine were coadministered ethanol. Thus, the cardiovascular events in these two subjects may be due to the combined effects of apomorphine and ethanol. These results show that, in general, subjects who experienced cardiovascular events had higher apomorphine C_{max} values.

3.3. Relationship between abnormally low blood pressure values and apomorphine C_{max} in ethanol interaction studies M98-838 and M98-891

In Study M98-838, nine subjects had one or more abnormally low blood pressure measurements following administration of apomorphine (6 mg) and ethanol (0.3 g/kg) beverage. The sponsor reported that the mean C_{max} (1.54 ng/ml) for those nine subjects was similar to the mean C_{max} (1.50 ng/ml) for all subjects in that regimen. However, the apomorphine plasma levels must be viewed in conjunction with ethanol blood levels in these subjects because the cardiovascular effects may be due to the combination of apomorphine and alcohol. Four of the subjects with abnormally low blood pressure measurements had C_{max} values lower than the mean for the regimen while C_{max} for four other subjects were within one standard deviation above the regimen mean. One subject had a C_{max} of 2.66 ng/ml, greater than one standard deviation above the mean. Similar trends were also noted in Study M98-891, in which 15 subjects had abnormally low blood pressure values in Apomorphine + ethanol regimen compared to two subjects in apomorphine + placebo beverage regimen.

In general, these results suggest that the subjects who had severe cardiovascular adverse events or abnormally low blood pressure values had somewhat higher C_{max} values, although these were not unusually high values.

Apomorphine SL
Study M98-838
Report No. R&D/98/467
Page 99

Table 3. Summary of Related Treatment Emergent Adverse Events

COSTART term	Apomorphine SL+ Ethanol Subjects = 68 N(%)	Apomorphine SL Alone Subjects = 67 N(%)	Ethanol Alone Subjects = 64 N(%)
Total Subjects Any Sign/Symptom	51 (75.0)	40 (59.7)	17 (26.6)
Nausea	34 (50.0)	21 (31.3)	1 (1.6)
Dizziness	30 (44.1)	15 (22.4)	6 (9.4)
Pallor	21 (30.9)	18 (26.9)	1 (1.6)
Sweating	18 (26.5)	12 (17.9)	0 (0.0)
Vomiting	11 (16.2)	5 (7.5)	0 (0.0)
Headache	9 (13.2)	6 (9.0)	5 (7.8)
Hypotension	9 (13.2)	5 (7.5)	1 (1.6)
Asthenia	4 (5.9)	10 (14.9)	2 (3.1)
Somnolence	3 (4.4)	2 (3.0)	3 (4.7)
Yawn	3 (4.4)	6 (9.0)	2 (3.1)
Vasodilatation	3 (4.4)	3 (4.5)	0 (0.0)
Dyspepsia	2 (2.9)	0 (0.0)	0 (0.0)
Abdominal pain	2 (2.9)	2 (3.0)	0 (0.0)
Tinnitus	1 (1.5)	0 (0.0)	0 (0.0)
Syncope	1 (1.5)	1 (1.5)	0 (0.0)
Pruritus	1 (1.5)	0 (0.0)	0 (0.0)
Nervousness	0 (0.0)	1 (1.5)	0 (0.0)
Libido Increased	1 (1.5)	0 (0.0)	0 (0.0)
Hiccup	1 (1.5)	1 (1.5)	0 (0.0)
Tenesmus	1 (1.5)	1 (1.5)	0 (0.0)
Chills	1 (1.5)	1 (1.5)	0 (0.0)
Bradycardia	1 (1.5)	0 (0.0)	0 (0.0)
Anorexia	1 (1.5)	0 (0.0)	0 (0.0)
Tremor	1 (1.5)	1 (1.5)	0 (0.0)
Dry Mouth	0 (0.0)	0 (0.0)	1 (1.6)

Some subjects reported more then one symptom
Cross Reference: Statistical Table 14.3.1.4

Apomorphine SL
Study M98-891
Report No. R&D/98/593
Page 109

Table 3. Summary of Related Treatment Emergent Adverse Events

COSTART term	Apomorphine SL+ Ethanol Subjects = 64 N(%)	Apomorphine SL Alone Subjects = 67 N(%)	Ethanol Alone Subjects = 63 N(%)
Total Subjects Any Sign/Symptom	48 (75.0)	33 (49.3)	27 (42.9)
Nausea	31 (48.4)	23 (34.3)	2 (3.2)
Hypotension	24 (37.5)	9 (13.4)	9 (14.3)
Dizziness	22 (34.4)	12 (17.9)	6 (9.5)
Pallor	19 (29.7)	10 (14.9)	0 (0.0)
Vomiting	17 (26.6)	13 (19.4)	1 (1.6)
Asthenia	10(15.6)	7 (10.5)	5 (7.9)
Sweating	9 (14.1)	6 (9.0)	1 (1.6)
Headache	9 (14.1)	4 (6.0)	9 (14.3)
Vasodilatation	8 (12.5)	5 (7.5)	0 (0.0)
Somnolence	3 (4.7)	2 (3.0)	4 (6.4)
Dysphagia	1 (1.6)	0 (0.0)	0 (0.0)
Sinus Pause	1 (1.6)	2 (3.0)	1 (1.6)
Stomatitis	1 (1.6)	0 (0.0)	0 (0.0)
Edema	1 (1.6)	0 (0.0)	0 (0.0)
Euphoria	1 (1.6)	0 (0.0)	2 (3.2)
Ventricular Tachycardia	1 (1.6)	0 (0.0)	0 (0.0)
Rash	1 (1.6)	0 (0.0)	0 (0.0)
Lacrimation Disorder	1 (1.6)	0 (0.0)	0 (0.0)
Eye Disorder	1 (1.6)	1 (1.5)	0 (0.0)
Hiccup	1 (1.6)	1 (1.5)	0 (0.0)
Dyspepsia	1 (1.6)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	1 (1.5)	0 (0.0)
Syncope	0 (0.0)	2 (3.0)	0 (0.0)
Pruritus	0 (0.0)	0 (0.0)	1 (1.6)
Dry Mouth	0 (0.0)	0 (0.0)	1 (1.6)
Tremor	1 (1.6)	2 (3.0)	0 (0.0)
Eye Disorder	1 (1.6)	1 (1.5)	0 (0.0)
Urinary Tract Infection	0 (0.0)	1 (1.5)	0 (0.0)

Some subjects reported more then one symptom
Cross Reference: Statistical Table 14.3.1.4

SECTION 4: CLINICAL ASSESSMENT OF ETHANOL INTERACTION STUDIES

Study M97-745 (apomorphine and ethanol 0.6 g/kg (4 shots of vodka))

Safety analysis:
Extent of exposure : Ten subjects took one dose of apomorphine. Two subjects took 2 doses of apomorphine. Twenty subjects took 3 doses of apomorphine (ethanol or placebo beverage was taken 1 hour prior to dosing with the third apomorphine dose).

Deaths : There were no deaths in this study.

Serious adverse events : There were two serious adverse events during this study.

- A 41 year old subject experienced diaphoresis and "continuous vomiting" approximately 30 minutes after his first dose of 5 mg. He became hypotensive (60/43 mm Hg), experienced a one minute **loss of consciousness** and was administered IV fluids, oxygen (6 L/min) and atropine (0.5 mg IV). After 15 minutes, his blood pressure was 101/94 mm Hg and he was alert and oriented. After 1 hour, his blood pressure was 101/94 mm Hg. He was observed in a telemetry unit overnight and was discharged in stable condition the next day. The investigator believed that the event was definitely related to apomorphine.

- A 60 year old subject experienced "queeziness", nausea, light-headedness, pallor and "**significant hypotension**" (BP 55/38 mm Hg) approximately 30-45 minutes following the Day 3 dosing of apomorphine 5 mg and 0.6 mg/kg ethanol beverage. He did not lose consciousness. It should be noted that his blood pressure was documented as 55/38 mm Hg approximately 45 minutes after dosing of drug, and was 91/58 mm Hg approximately 90 minutes after dosing. The investigator reported the duration of hypotension as 2 hours 10 minutes. It is also notable that during this event his ECG demonstrated new inversions of the T waves in leads II, III and aVF. The machine-read ECG diagnosis was "cannot r/o inferior MI/ischemia". He was treated with 0.9% intravenous saline and 2 liters of oxygen via nasal cannula. He was hospitalized for 2 days. The investigator believed that the event was definitely related to apomorphine.

As a result of these two serious adverse events, the principal investigator, in agreement with the sponsor, chose to discontinue the study prior to completion.

Other significant adverse events:
Three other subjects experienced prolonged hypotension:

- A 53 year old subject experienced an acute drop in blood pressure after his first dose of apomorphine on Day 1. His baseline BP of 117/80 mm Hg dropped to 98/65 mm Hg. He remained hypotensive for 1 hour 25 minutes. The next day, his blood pressure again dropped acutely after taking apomorphine. This time his baseline BP of 109/68 mm Hg dropped to a low of 76/53 mm Hg approximately 45 minutes after dosing. He remained hypotensive for 1 hour 5 minutes. The investigator believed the event was definitely related to apomorphine.

- A subject was reported to have had one episode of hypotension, on Study Day 1 that lasted 39 minutes. His baseline supine pressure was 117/71 mm Hg, dropping to a low of 71/41 mm Hg, and returning to normal."

- A 28 year old subject experienced a brief drop in pressure after his apomorphine dose on Day 2. His baseline BP of 110/53 mm Hg dropped to 99/59 mm Hg. On Day 3, however, he had a more significant drop in the blood pressure. Twenty-five minutes after ingesting the alcohol beverage, he complained of light-headedness, drowsiness, and queeziness. His blood pressure was noted to be 95/58 mm Hg sitting and 88/57 mm Hg standing. His pulse was 88 bpm sitting and 112 standing. The investigator reported that the orthostatic hypotension lasted 5 hours 5 minutes.

Overall adverse events:
Table 1 summarizes the events reported by all patients:

Table 1. All adverse events reported in M97-745

Adverse event	**Number of subjects (%)**
Nausea	11(34.4%)
Dizziness	11(34.4%)
Asthenia	10(31.3%)
Headache	6(18.8%)
Pallor	5(15.6%)
Vasodilation	4(12.5%)
Vomiting	4(12.5%)
Somnolence	3(9.4%)
Hypotension	3(9.4%)
Sweating	2(6.3%)
ECG abnormal	1(3.1%)
Postural hypotension	1(3.1%)
Syncope	1(3.1%)
Diarrhea	1(3.1%)
Dry mouth	1(3.1%)
Dyspepsia	1(3.1%)
Thirst	1(3.1%)
Paresthesia	1(3.1%)
Rhinitis	1(3.1%)
Dry eyes	1(3.1%)

Vital signs and physical findings:
Over all timepoints, there was a decrease in diastolic BP in the ethanol group compared to the placebo-beverage group. There was also a statistically significant difference in the mean maximum decrease from supine to standing BP between the ethanol and placebo-beverage group (Table 2).

Table 2. Maximum change in diastolic BP from supine to standing (mm Hg)

Treatment	N	Baseline mean change	Treatment mean change	Mean change	P-value for treatment difference
Ethanol	10	+9.10	-11.40	-20.50	0.013
Placebo	10	+9.70	+ 1.70	- 8.00	

Statistically significant differences between the ethanol group and the placebo-beverage group were noted in mean changes from baseline in the supine diastolic BP at multiple timepoints after dosing. Table 3 depicts this change at 45 minutes after dosing (approximate Tmax), and Table 4 depicts this difference at 2 hours after dosing.

Table 3. Decrease in supine diastolic BP (mm Hg) at 45 minutes

Treatment	N	Baseline mean	Treatment mean	Mean change	P-value for treatment difference
Ethanol	4	71.75	59.00	-12.75	0.033
Placebo	7	75.57	76.86	1.29	

Table 4. Decrease in supine diastolic BP (mm Hg) at 2 hours

Treatment	N	Baseline mean	Treatment mean	Mean change	P-value for treatment difference
Ethanol	6	71.00	65.00	-6.00	0.009
Placebo	10	74.00	75.60	1.00	

The sponsor believes that these differences were not indicative of a clinically meaninful trend.

> **Comment: The vital sign data, coupled with the adverse event reports, suggest an independent effect of apomorphine in causing a decrease in the diastolic BP. This is noted in both patients treated only with apomorphine and in those patients treated with apomorphine and alcohol beverage.**

The sponsor believes that there were no clinically meaningful changes in physical exam or ECG.

> **Comment: The post-dosing ECGs for one patient revealed acute T-wave inversions in leads II, III and aVF during the patient's hypotensive event.**

Sponsor's overall assessment;
The sponsor believes that several adverse events, "historically associated" with the use of apomorphine, were reported in this trial. These include nausea, vomiting, hypotension, bradycardia, dizziness, pallor and cardiovascular effects.

The sponsor prematurely terminated this study due to safety concerns following two serious adverse events.

The sponsor notes that in those patients with sufficient information for analysis, apomorphine mean C_{max} and AUC were increased in the alcohol-treated patients compared to the placebo beverage-treated patients. However, no conclusions can be drawn due to the premature study termination

Reviewer's overall assessment:
Apomorphine itself was poorly tolerated by these normal volunteers. Dosing of normal healthy volunteers with apomorphine SL 5 mg was associated with adverse events and serious adverse events. Two subjects required hospitalization due to protracted hypotension, one following apomorphine dosing alone and one following dosing with apomorphine and alcohol beverage. One of these patients (a 60 year old) had acute T wave inversions inferiorly on ECG. One

reported “continuous vomiting”. Two other patients also reported hypotension after dosing with apomorphine alone.

An analysis of the mean supine diastolic blood pressure changes revealed clinically meaningful decreases in the alcohol-treated group compared to the placebo beverage-treated group.

Although results of this trial cannot be used to draw definitive conclusions about an apomorphine-alcohol interaction, the events which transpired are suggestive of a problem.

Study M98-838 (apomorphine and ethanol 0.3 g/kg (3 shots of vodka))

Safety analysis:
Deaths: There were no deaths in this study.

Serious adverse events: Although there were no serious adverse events, two patients reported syncope (see narratives below).

Discontinuations due to adverse events: One patient discontinued due to an adverse event:

- A 22 year old male experienced loss of appetite and nausea approximately 55 minutes after his second dose of apomorphine. The nausea lasted six days and the anorexia twenty-two days. He took two more doses of apomorphine and then discontinued. The investigator assessed the reaction as probably related to apomorphine.

Other significant adverse events:
Two patients reported syncope:

- A 41 year old subject experienced dizziness, light-headedness and pallor approximately 30 minutes after a single dose of apomorphine SL 6 mg. He then experienced a syncopal event. During the event, his blood pressure was measured at 78/55 mm Hg. The syncope lasted for two seconds. The hypotension lasted for twenty minutes. The investigator assessed the event to be definitely related to apomorphine. The patient went on to complete the study.

  Reviewer comment: Hypotension lasted for 20 minutes in this patient.

- A 40 year old subject experienced nausea, pallor and diaphoresis approximately 40 minutes after taking apomorphine and ethanol beverage. The patient then experienced syncope. The syncope lasted two seconds. The other "prodromal" symptoms lasted thirty minutes. The investigator assessed the event as definitely related to apomorphine. The subject went on to complete the study.

Overall adverse events:
Table 1 summarizes the events reported by all patients:

Table 1. All adverse events reported in M98-838

Adverse event	**Apomorphine SL + Ethanol N(%)**	**Apomorphine SL Alone N(%)**	**Ethanol Alone N(%)**
Nausea	34(50.0%)	21(31.3%)	1(1.6%)
Dizziness	30(44.1%)	15(22.4%)	6(9.4%)
Pallor	21(30.9%)	18(26.9%)	1(1.6%)
Sweating	18(26.5%)	12(17.9%)	0(0.0%)
Vomiting	11(16.2%)	5(7.5%)	0(0.0%)
Headache	9(13.2%)	6(9.0%)	5(7.8%)
Hypotension	9(13.2%)	5(7.5%)	1(1.6%)
Asthenia	4(5.9%)	10(14.9%)	2(3.1%)
Somnolence	3(4.4%)	2(3.0%)	3(4.7%)
Yawning	3(4.4%)	6(9.0%)	2(3.1%)
Vasodilatation	3(4.4%)	3(4.5%)	0(0.0%)
Dyspepsia	2(2.9%)	0(0.0%)	0(0.0%)
Abdominal pain	2(2.9%)	2(3.0%)	0(0.0%)
Tinnitus	1(1.5%)	0(0.0%)	0(0.0%)
Syncope	1(1.5%)	1(1.5%)	0(0.0%)
Pruritis	1(1.5%)	0(0.0%)	0(0.0%)
Nervousness	0(0.0%)	1(1.5%)	0(0.0%)
Libido increased	1(1.5%)	0(0.0%)	0(0.0%)
Hiccup	1(1.5%)	1(1.5%)	0(0.0%)
Tenesmus	1(1.5%)	1(1.5%)	0(0.0%)
Chills	1(1.5%)	1(1.5%)	0(0.0%)
Bradycardia	1(1.5%)	0(0.0%)	0(0.0%)
Anorexia	1(1.5%)	0(0.0%)	0(0.0%)
Tremor	1(1.5%)	1(1.5%)	0(0.0%)

Reviewer's comments: The overall adverse events demonstrate the following:

1. **Incidence rates of nausea, dizziness, pallor, sweating, vomiting, headache, and hypotension increase when apomorphine is taken with ethanol.**
2. **Hypotension was reported by 13.2% of patients who took the two compounds together, whereas hypotension was reported in 7.5% of patients who took apomorphine alone.**
3. **A moderate amount of alcohol alone was tolerated significantly better than apomorphine alone.**

Vital signs and physical findings:
Analysis of vital signs revealed some clinically significant differences between the three Regimens, including comparisons between the apomorphine+ethanol group and ethanol alone. group

For example, there were significant differences in the maximum change-from-baseline in standing diastolic and systolic BP. Tables 2 and 3 depict these results:

Table 2. Maximum mean drops from baseline in standing systolic BP

Treatment	N	Baseline Mean	Treatment Mean	Mean Change	P-value, compared to ethanol alone
APO+Ethanol	66	120.85	98.58	-22.27	0.045
APO+Placebo beverage	66	123.98	104.65	-19.33	
APO placebo + Ethanol	64	121.25	104.63	-16.62	

Reviewer's comments:

1. **The mean maximum drop in standing systolic BP with apomorphine alone was 19.3 mmHg.**
2. **The difference between apomorphine+ethanol and ethanol alone was statistically significant.**

Table 3. Maximum mean drops from baseline in standing diastolic BP

Treatment	N	Baseline Mean	Treatment Mean	Mean Change	P-value, compared to ethanol alone
APO+Ethanol	66	73.69	59.48	-14.21	0.019
APO+Placebo beverage	66	75.71	63.63	-12.09	
APO placebo + Ethanol	64	72.97	63.44	- 9.53	

Reviewer's comments:

1. **The mean maximum drop in standing systolic BP with apomorphine alone was 12.1 mm Hg.**
2. **The difference between apomorphine+ethanol and ethanol alone was statistically significant.**

In terms of "markedly abnormal" vital signs following dosing, the sponsor defined "markedly high" pulse as >130 bpm, markedly low systolic BP as <80 mm Hg and markedly low diastolic BP as <40 bpm.

Table 4 describes the proportion of subjects with abnormally high standing pulse, abnormally low standing systolic BP and abnormally low standing diastolic BP.

Table 4. Numbers and percentages of subjects with abnormally high or abnormal low VS parameters.

Treatment group	N	Pulse>130 bpm N(%)	Systolic BP <80 N(%)	Diastolic BP <40 N(%)
APO+Ethanol	68	14(20.9%)	8(11.9%)	5(7.5%)
APO+Placebo beverage	67	1(1.5%)	3(4.5%)	3(4.5%)
APO placebo +Ethanol	64	7(10.9%)	1(1.6%)	0(0.0%)

Reviewer's comment:

1. **There were a significantly greater number of patients in the ethanol+apomorphine group who had abnormally high pulse, abnormally low diastolic BP and abnormally high systolic BP compared to either the apomorphine alone group, or the ethanol alone group.**
2. **Some patients in the apomorphine alone had markedly abnormal standing vital signs.**

Sponsor's overall assessment;
Ethanol did not affect the pharmacokinetics of apomorphine and apomophine did not affect ethanol pharmacokinetics.

In terms of sedation, all three groups reported sedation. The most sedation was noted in the apomorphine +ethanol group, but the sponsor believes that the mean differences were not clinically significant.

In terms of vital signs, there were "trends" suggestive of a possible interaction between apomorphine and ethanol, but the sponsor believes that the differences were small and not clinically significant.

Adverse events were reported more frequently by subjects in the apomorphine SL + ethanol regimen compared to the other treatment groups.

Overall, this study suggested that apomorphine could be safely administered with a moderate dose of ethanol.

Reviewer's overall assessment:
There were no effects on the pharmacokinetics of ethanol or apomorphine. However, the timing of dosing (tablet dosing 1 hour after alcohol ingestion) was not ideal for assessing an interaction at peak concentrations for each drug.

There is a clear trend in adverse events, sedation scores and vital signs suggesting that apomorphine SL+ethanol is not well-tolerated and is associated with an increase in sedation, frequency of adverse events, drop in blood pressure and increase in pulse rate compared to apomorphine or ethanol alone.

There is evidence that 6 mg of apomorphine was poorly tolerated. Cases of syncope, prolonged symptomatic hypotension, sedation, nausea vomiting, dizziness and pallor occurred at this dose.

There is evidence that apomorphine 6 mg has vasodilatory properties.

Some patients experienced a variety of symptoms concomitantly. For example, a patient could be queezy, clammy, diaphoretic, nauseated, sedated, lethargic, somnolent, pass out and vomit.

Study M97-762 (apomorphine and ethanol 0.15 g/kg (1 shot of vodka))

Safety analysis:
Extent of exposure : All 23 subjects took three doses of apomorphine.

Deaths : There were no deaths in this study.

Serious adverse events : There were no serious adverse events during this study.

Other significant adverse events:
A subject experienced hypotension after apomorphine dosing. There is no narrative description of this case.

Reviewer's comment: Four subjects required oxygen by nasal cannula.

Overall adverse events:
Table 1 summarizes the events reported by all patients:

Table 1. All adverse events reported in M97-745

Adverse event	Apomorphine Number of subjects (%)	Placebo Number of subjects (%)
Nausea	10(43.5%)	0(0.0%)
Pallor	9(39.1%)	0(0.0%)
Asthenia	9(39.1%)	0(0.0%)
Vomiting	7(30.4%)	0(0.0%)
Vasodilatation	6(26.1%)	0(0.0%)
Sweating	6(26.1%)	0(0.0%)
Dizziness	6(26.1%)	0(0.0%)
Somnolence	5(21.7%)	3(13.0%)
Headache	4(17.4%)	3(13.0%)
Yawning	3(13.0%)	1(4.4%)
Pain	3(13.0%)	1(4.4%)
Pharyngitis	2(8.7%)	0(0.0%)
Lacrimation disorder	2(8.7%)	0(0.0%)
Tinnitus	1(4.4%)	0(0.0%)
Libido decrease	1(4.4%)	0(0.0%)
Hypotension	1(4.4%)	0(0.0%)
Hiccup	1(4.4%)	0(0.0%)
Euphoria	1(4.4%)	0(0.0%)
Dry mouth	1(4.4%)	1(4.4%)
Abdominal pain	1(4.4%)	0(0.0%)

All adverse events were considered "mild" in severity.

Reviewer's comments:

1. **The incidence rates of "pallor", "vasodilatation" and "dizziness" are at least 25% in the apomorphine-treated group, but zero in the placebo group.**

2. **The rate of somnolence is 22% in the apomorphine group compared to 13% in the placebo-treated groups. This supports the SRSS results, which suggest a drug-alcohol interaction.**

Vital signs and physical findings:
Analysis over all timepoints in maximum drop from supine to standing BP yielded no statistically significant differences between drug and placebo.

Sponsor's overall assessment:
The sponsor believes that apomorphine does not affect the pharmacokinetics of ethanol. The sponsor believes that there were no meaningful differences in psychomotor behavior, sedation status and vital signs between apomorphine and placebo after alcohol intake.

Reviewer's overall assessment:
There were no effects on the pharmacokinetics of ethanol, but the results suggest a pharmacodynamic interaction.

Patients rated themselves as significantly more sedated after taking apomorphine than after placebo. The adverse event reports of somnolence and vasodilatation were also greater in the actively treated group.

Of note, the amount of alcohol used in this study was relatively modest (one "shot").

Four patients required oxygen therapy.

These events raise concern about a drug-alcohol interaction, even with very minimal alcohol intake.

SECTION 5: STATISTICAL

Summary of the Efficacy Results

The primary efficacy variable is the percentage of home-use attempts resulting in erection firm enough for intercourse as rated by the patient. For this variable, the results indicate that the 4 mg dose is statistically significantly different from placebo (in favor of the 4 mg dose) in all three of the clinical studies covered here which included that treatment group. The 2 mg dose is statistically significantly different from placebo (in favor of the 2 mg dose) in the 2 studies which included that treatment arm. The dose optimization treatment group, using the 2 or 4 mg dose, is also statistically significantly different from placebo (in favor of the 2/4 mg dose) in the one study that tested that regimen.

The results for the secondary endpoint, the percent of patients who were a treatment success, were not as consistent. The 4 mg dose is statistically significantly different from placebo (in favor of the 4 mg dose) in the two clinical studies with patients with ED with no major organic component, but there is not a statistical difference in the study of patients with controlled diabetes. The 2 mg dose is statistically significantly different from placebo (in favor of the 2 mg dose) in one of the two studies which included that treatment arm. Finally, the dose optimization treatment group is statistically significantly different from placebo (in favor of the 2/4 mg dose) in the one study which tested that regimen.

Summary of the Study Designs

Four clinical studies will be covered in this statistical summary: M97-658, M98-941, M97-763, and M97-804. All but M97-763 are 2-period crossover studies comparing a fixed dose of apomorphine SL to a blinded placebo treatment. Of the crossover studies, M97-658 and M98-941 include a patient population of men with erectile dysfunction with no major organic component, while M97-804 enrolled only patients with controlled diabetes. Study M97-763 is a parallel arm study with an apomorphine SL dose optimization regimen group compared to a blinded placebo group. The patient population in M97-763 is men with erectile dysfunction with no major organic component. Table 1 (attached) contains further details about each study.

The applicant has only requested approval of the 2, 3, and 4 mg doses. The 2 and 4 mg levels were included in some or all of the four clinical trials in this efficacy summary. All of the clinical trials assessed here also included treatment groups for higher doses of apomorphine SL that were not submitted for approval in the NDA (5 mg and/or 6 mg). These treatment groups are not included in efficacy analyses. Also, in the dose optimization group in Study M97-763, it was possible for subjects to increase to the 5 and 6 mg doses for some attempts. Attempts while using those higher doses are excluded from efficacy analyses.

The primary efficacy variable is the percentage of home-use attempts resulting in erection firm enough for intercourse as rated by the patient. The percentage is calculated for each subject, then averaged over all subjects to report the mean percentage per group per treatment period. For the crossover studies, within-subject comparisons between apomorphine SL and placebo are made using the Cochran-Mantel-Haenszel (CMH) test with patients as the strata. The parallel arm study allows for between-group comparisons using an ANOVA model with a factor for treatment.

A secondary efficacy endpoint, also covered in this summary, is the percent of patients classified as a treatment "success", defined as an erection firm enough for intercourse in 50 percent or more of the attempts. The analysis of the crossover studies uses Gart's methodology for paired data, while the analysis of the parallel arm study uses Fisher's exact test.

Summary of the Statistical Analyses

The sponsor performed the statistical analyses that were agreed upon in the protocol as being appropriate. For the crossover studies, an ANOVA model with effects for treatment, period, sequence, and patient within sequence was used to check the assumptions required for combining the data from the two treatment periods for the analyses. Only subjects who had at least one attempt in each treatment period were included in the analyses. The CMH test was used for the hypothesis tests comparing apomorphine SL to placebo. In the parallel arm study, an ANOVA model with an effect for treatment was used to test the between-group comparison of apomorphine SL to placebo.

The results of Study M97-658 indicate that both the 2 mg and 4 mg treatment regimens were statistically significantly different (p-value =0.012 and p-value ≤ 0.001, respectively) from the placebo treatment for the mean percentage of attempts resulting in an erection firm enough for intercourse. The mean was 45.2% for the 2 mg treatment vs. 37.5% for placebo, and 59.1% for the 4 mg treatment vs. 36.1% for placebo.

The results of the secondary variable, the percent of patients who were a treatment success, were mixed in Study M97-658. The 4 mg dose was statistically significant from placebo (p-value ≤ 0.001), with 64.6% successful on 4 mg versus 38.4% successful on placebo. However, the 2 mg dose was not statistically significant from placebo (p-value = 0.226), with 48.2% successful on the 2 mg treatment versus 41.4% successful on placebo.

In Study M98-941, both the 2 and 4 mg doses were statistically significant from placebo on both the primary and secondary endpoint (all four p-values ≤ 0.001). The mean percent of attempts firm enough for intercourse was 46.4% for the 2 mg dose versus 32.4 % for placebo. In the 4 mg treatment arm, the results were 53.3% of attempts on the 4 mg dose versus 30.7% on placebo. The percent of patients who were a treatment success was 49.3% for the 2 mg dose vs. 33.6% for placebo, while the 4 mg dose had 56.0% vs. 29.1% for placebo.

Study M97-804 was the crossover study with the patient population of subjects with controlled diabetes. The 2 mg dose level was not included in this study. The results showed that the 4 mg dose was statistically significantly different from placebo for the mean percent of attempts firm enough for intercourse (p-value = 0.020). Subjects had 25.5% of attempts firm enough for intercourse on the 4 mg dose versus 16.0% of attempts on placebo. The two treatments were not statistically different for the percent of treatment successes (p-value = 0.082).

Study M97-763 is the parallel arm study. In this study, the mean percentage of attempts resulting in an erection firm enough for intercourse was 47.5% for the dose optimization group, and 34.5% for the placebo group. The results of the ANOVA comparison of the dose optimization group to the placebo group indicate that this is a statistically significant (p-value ≤ 0.001) difference in favor of the dose optimization group. Similarly, the comparison of the percent of patients who were a treatment success also showed a statistically significant difference (p-value ≤ 0.001) in

favor of the dose optimization group, with 53.4% "treatment successes" in the dose optimization group versus 35.1 % in the placebo group.

Table 1: Summary of Randomized, Controlled Clinical Studies

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Type of Control	Design	Duration of Treatment
M97-658 (8/97 – 6/98)	35 (U.S. and Canada)	Enrolled: n=520 Apo SL 2 mg n=135 Apo SL 4 mg n=125 Apo SL 5 mg n=134 Apo SL 6 mg n=126	Placebo (vs. each dose in X-over design)	Dbl-blind, Randomized, Placebo-ctrl, Cross-over	4 weeks active + 4 weeks placebo (2-way X-over)
M97-763 (1/98 – 8/98)	53 (U.S. and Canada)	Enrolled: n=569 Apo SL dose opt. Regimen n=242 Apo SL 5 mg n=119 Apo SL 6 mg n=89 Placebo n=119	Placebo	Dbl-blind, Randomized, Placebo-ctrl, Parallel, Dose-optimizing regimen in one trmt. group	8 weeks (In dose optim. trmt. group, first 4 weeks on trmt. was dose optim., then fixed dose last 4 wks. on trmt.
M97-804 (2/98 – 1/99) Controlled Diabetic Pt. Popln.	18 (U.S.)	Enrolled: n=218 Apo SL 4 mg n=107 Apo SL 5 mg n=111	Placebo	Dbl-blind, Randomized, Placebo-ctrl, Cross-over	4 weeks active + 4 weeks placebo (2-way X-over)
M98-941	54 (U.S.)	Enrolled: n=495 Apo SL 2 mg n=166 Apo SL 4 mg n=168 Apo SL 5 mg n=161	Placebo	Dbl-blind, Randomized, Placebo-ctrl, Cross-over	4 weeks active + 4 weeks placebo (2-way X-over)

The primary efficacy variable for all 4 clinical studies is the mean percentage of attempts which resulted in an erection firm enough for intercourse. For each subject, the percent of attempts firm enough for intercourse is calculated for baseline and each treatment period, using all attempts during the period. The mean percentage is then calculated across all the subjects within each treatment arm.

Table 2: Mean Percentage of Attempts with Erection Firm Enough for Intercourse (Patient Rating)

Study	M98-941		M97-658		M97-763	M97-804
Dose Level	2 mg	4 mg	2 mg	4 mg	Dose Optimization (Attempts with 2 & 4 mg doses only)	4 mg
Baseline						
N	139	131	112	99	Optm. gp.: n=227 25.2%	85
Mean % Attempts	28.5%	26.7%	23.9%	27.8%	Plac. gp.: n=110 24.0%	4.5%
Uprima						
N	140	134	112	99	232	90
Mean % Attempts	46.4%	53.3%	45.2%	59.1%	47.5%	25.0%
Placebo						
N	140	134	112	99	114	90
Mean % Attempts	32.4%	30.7%	37.5%	36.1%	34.5%	16.0%
Difference [apo. – plac.] (SE) Mean % Attempts	14.1% (2.6)	22.7% (3.1)	7.8% (2.7)	23.2% (3.9)	13.0% (4.0)	8.8% (3.8)
p-value (apo. vs. plac.)	< 0.001	< 0.001	0.012	< 0.001	0.001	0.020
# Subjects Dropped from Analysis	9 discont. apo 14 discont. plac. 3 miss. data	20 discont. apo 12 discont. plac. 2 miss. data	8 discont. apo 15 discont. plac. 0 miss. data	15 discont. apo 10 discont. plac. 1 miss. data	4 discont. apo 2 discont. plac.	12 discont. apo 7 discont. plac. 0 miss. data
Design Comments	Cross-over CMH test with subject=strata		Cross-over CMH test with subject=strata		Parallel arm; Exclude data from Inv. Butterworth; ANOVA with F-test	Cross-over; Pts. With Controlled Diab.; CMH test with subject=strata
Source: Volumes; Figures and/or Tables; SAS Datasets (.sd2)	Vol. 3.108 Fig. 3; Table 10; Stat. Table 14.2.1.8; Takehome.sd2		Vol. 1.518, 1.519 Fig. 3; Table 9; Stat. Table 14.2.1.8; Takehome.sd2		Vol. 1.556, 1.559 Fig. 3; Stat. Table 14.4.1.2; Takehome.sd2	Vol. 1.615 Fig. 3; Table 9; Stat. Table 14.2.1.8; Takehome.sd2

A secondary efficacy variable for all 4 clinical studies is the percent of patients who are classified as a treatment success. A treatment success is defined as having at least 50% of attempts result in an erection firm enough for intercourse.

Table 3: Percent of Patients Who Are a Treatment Success (At least 50 % of attempts firm enough for intercourse)

Study	M98-941		M97-658		M97-763	M97-804
Dose Level	2 mg	4 mg	2 mg	4 mg	Dose Optimization (Attempts with 2 & 4 mg doses only)	4 mg
Baseline						
n/N	49 / 139	43 / 131	30 / 112	32 / 99	Optm. gp.: 71/227 31.3%	2 / 85
% Treatment Success	35.3%	32.8%	26.8%	32.3%	Plac. gp.: 28/110 25.5%	2.4%
Uprima						
n/N	69 / 140	75 / 134	54 / 112	64 / 99	124 / 232	21 / 90
% Treatment Success	49.3%	56.0	48.2%	64.6%	53.4%	23.3%
Placebo						
n/N	47 / 140	39 / 134	46 / 112	38 / 99	40 / 114	14 / 90
% Treatment Success	33.6%	29.1	41.1%	38.4%	35.1%	15.6%
Difference (apo. – plac.) % Treatment Success	15.7%	26.9%	7.1%	26.2%	18.3%	7.7%
p-value (apo. vs. plac.)	< 0.001	< 0.001	0.226	< 0.001	0.001	0.082
# Subjects Dropped from Analysis	9 discont. apo 14 discont. plac. 3 miss. data	20 discont. apo 12 discont. plac. 2 miss. data	8 discont. apo 15 discont. plac. 0 miss. data	15 discont. apo 10 discont. plac. 1 miss. data	4 discont. apo 2 discont. plac.	12 discont. apo 7 discont. plac. 0 miss. data
Design Comments	Cross-over Gart's method for paired data		Cross-over Gart's method		Parallel arm; Exclude data from Inv. Butterworth; Fisher's exact test	Cross-over; Pts. With Controlled Diabetes; Gart's method
Source: Volumes; Figures and/or Tables; SAS Datasets (.sd2)	Vol. 3.108 Fig. 3; Table 11; Stat. Table 14.2.2.1.1 Takehome.sd2		Vol. 1.518, 1.519 Fig. 3; Table 10; Stat. Table 14.2.2.2.1 Takehome.sd2		Vol. 1.556, 1.559 Fig. 3; Stat. Table 14.4.2.2; Takehome.sd2	Vol. 1.615 Fig. 3; Table 10; Stat. Table 14.2.2.2.1; Takehome.sd2

SECTION 6: CLINICAL

TABLE OF CONTENTS

Summary of Clinical Section:
The clinical section of this NDA included six controlled Phase 3 clinical trials, two controlled Phase 2 trials, five long-term, open-label, safety extension studies, and one open-label, at-home, dose-titration study.

Of note, four alcohol interaction studies are reviewed by biopharmaceutics in that section of this briefing package.

There were four Phase 3 trials that provided the bulk of the support for efficacy. These included three randomized, placebo-controlled, crossover trials (M96-470, M97-658 and M98-941), and one, parallel-arm, dose-optimization study (M97-763). In addition to these four studies, the sponsor conducted an additional randomized, placebo-controlled, crossover trial in well-controlled diabetics (M97-804) and an additional randomized, placebo-controlled, parallel-arm trial in patients who had undergone radical retropubic prostatectomy (M97-788).

Following successful completion of any of these safety and efficacy trials, patients were allowed to enroll in an open-label, safety "extension trial". For example, patients in M96-470, M97-658, and M98-941 were allowed to enroll in safety studies M96-471, M97-659, and M98-936, respectively. M97-682 is an ongoing 3-year, safety study, enrolling patients from the previous 6-month safety studies, as well as M97-763. M97-793 is an ongoing 3-year, safety study enrolling those "organic" patients who completed the diabetic and the radical prostatectomy trials.

M97-876 was an open-label safety study designed to determine the potential safety advantages of a dose-titration regiment, without any in-office dose administration.

Finally, M98-930 was a drug interaction study with nitrates and several different antihypertensives.

Brief Summary of Efficacy:

Overall assessment of efficacy:

Overall, the sponsor believes that apomorphine hydrochloride at doses of 2 mg and 4 mg was shown to be effective in the treatment of erectile dysfunction. Several concerns related to the efficacy results have been uncovered during the review. These concerns may be summarized in five major issues:

1. Efficacy was *not* demonstrated in the population of men "with an organic component".

2. It may not be possible to extrapolate the results of these controlled trials to the real-world ED population. The inclusion and exclusion criteria in all of the substantial controlled efficacy and safety trials except M97-804 restricted the enrolled patients to a carefully selected group: men with erectile dysfunction with no major organic component. This trial restricted the enrolled patients to a unique and carefully selected group, men with erectile dysfunction "without a major organic component".

3. The efficacy data, while statistically significant, did not provide evidence of a robust clinical benefit, particularly at 2 mg.

4. There was a potential for difficulty in maintaining the patient blind since the active drug was associated with a relatively common incidence of nausea.

5. The long-term, uncontrolled usage studies did not provide evidence of durable efficacy.

Background:

Uprima is a sublingual formulation of the active drug apomorphine hydrocloride. Apomorphine is a member of the pharmacological class known as dopamine receptor agonists. Apomorphine has been previously used as an oral treatment for symptoms of Parkinson's disease, an emetic in cases of poisoning, a sedative for behavioral disturbances, and as a behavior-altering agent for alcoholics. The sponsor believes that apomorphine demonstrates activity in enhancing penile erection in man. Uprima is intended for use in men with erectile dysfunction, on an as needed basis, immediately prior to anticipated sexual activity.

The controlled clinical trials:

In support of the efficacy of Uprima as treatment for male erectile dysfunction, the sponsor submitted full study reports for six (6) controlled Phase 3 clinical trials, and two controlled Phase 2 trials. The six controlled Phase 3 trials were:

- M96-470
- M97-658
- M97-763
- M98-788
- M98-804
- M98-941

Uprima was administered as a sublingual tablet, taken prior to sexual activity, on an as needed basis. The doses studied in Phase 3 trials were 2 mg, 4 mg, 5mg and 6mg. The first controlled Phase 3 trial, M96-470, employed a slightly different formulation than all the other controlled trials.

Clinical trials M96-470 (n=457), M97-658 (n=420) and M98-941 (n=495) all employed the same study design and all used the same entry criteria to define the study population. Specifically, these were randomized, double-blind, placebo-controlled, two-period, crossover studies, in which each treatment period was 4 weeks in duration separated by a 2 to 3-day washout period. Multiple doses were studied in each of these trials, including 2 mg, 4 mg, 5 mg and 6 mg. The study population was defined as generally healthy men with erectile dysfunction "without a major organic component". Specifically, all patients demonstrated at least a single "normal" erection on baseline nocturnal penile tumescence testing; all patients demonstrated an erection suitable for intercourse within 3 months of the study; and all patients experienced <50% successes upon attempted intercourse within 3 months of the study.

Clinical trial M98-804 (n=218) employed this same design but included only generally healthy diabetic patients. These diabetic patients were defined as having erectile dysfunction, but without the qualifier "without a major organic component".

Clinical trial M97-763 (n=469) was a randomized, double-blind, placebo-controlled study that employed a parallel-arm design. Patients were "titrated" to an optimal dose over 4 weeks and then were maintained on their optimal dose for an additional 4 weeks. Patients were defined as generally healthy men with erectile dysfunction, "without a major organic component", as previously defined.

Finally, clinical trial M97-788 (n=44) was a randomized, double-blind, placebo-controlled, parallel-arm study in men who had undergone a bilateral, nerve-sparing radical retropubic prostatectomy. Although it was adequately controlled, it was not adequately powered to demonstrate superiority of drug over placebo.

Efficacy endpoints and analysis:
The primary efficacy endpoint in all these trials was defined as "the percentage of attempts resulting in an erection firm enough for intercourse" as rated by the patient. The sponsor agreed to include all attempts in the calculation of this proportion. The per-protocol statistical analysis plan specified that this proportion would be compared between drug and placebo group using each individual patient as a separate stratum. Thus, the actual comparison between drug and placebo would be based on the average, per-patient, percentage of attempts resulting in an erection sufficient for intercourse.

Additional secondary endpoints included the percentages of attempts resulting in successful intercourse, the percentage of patients deemed a treatment success (whereby at least 50% of attempts were successful in a treatment period), the International Index of Erectile Function (IIEF) questionnaire (in some trials only), the Fugl-Meyer Life Satisfaction Scale, and the SF-36 Quality-of-Life questionnaire. The sponsor also accumulated data from partners.

Comments regarding efficacy:
Lack of efficacy in the "organic" studies:
Efficacy in "organic" patients was not demonstrated in either Study M97-788 nor M97-804. Table 1 demonstrates the lack of statistically significant treatment effect with 5 mg in radical prostatectomy patients (M97-788). Table 2 and 3 demonstrate the lack of statistically significant treatment effect with 5 mg, and the lack of a clinical meaningful treatment effect with 4 mg in diabetic patients (M98-804).

Table 1. Mean percentage of attempts resulting in an erection firm enough for intercourse in M97-788 (radical prostatectomy patients).

Dose	(n)	Treatment Mean %	APO SL vs. placebo p-value
5 mg	(21)	10.9	0.442
Placebo	(22)	6.1	

Table 2. Percentage of attempts resulting in an erection firm enough for intercourse (based on all attempts) in M97-804 (controlled diabetics).

Dose	(n)	Placebo Success/attempts	%	Apomorphine SL Success/attempts	%	APO SL vs. placebo p-value
5 mg	(86)	190/698	27.2	224/657	34.1	0.179
4 mg	(90)	115/794	14.5	199/808	24.6	0.020
Combined	(176)	305/1493	20.4	423/1465	28.9	0.009

Table 3. Results of the analysis of percentages of patients deemed a treatment "success" (based on all attempts) in M97-804 (controlled diabetics).

Dose	(n)	Placebo #success	%	Apomorphine SL #success	%	APO SL vs. placebo p-value
5 mg	(86)	22	25.6	25	29.1	0.669
4 mg	(90)	14	15.6	21	23.3	0.082
Combined	(176)	36	20.5	46	26.1	0.106

Lack of robust effect in the "non-organic" trials:
While there was a statistically significant effect of both the 2 mg and 4 mg doses, the clinical effect of the 2 mg dose was not robust.

In general, the 2 mg group demonstrated overall success rates of approximately 44% to 46%, while the 2 mg placebo group demonstrated success rates of approximately 32% to 38%. Similarly, the 4 mg group demonstrated success rates of approximately 52% to 58%, compared to the 4 mg placebo group success rates of 31% to 37%.

Tables 4, 5 and 6 present the primary efficacy endpoint results from M96-470, M97-658 and M98-941, respectively.

Table 4. Percentage of attempts resulting in an erection firm enough for intercourse (based on all attempts) in M96-470.

Dose (n)	Placebo Success/attempts	%	Apomorphine SL Success/attempts	%	APO SL vs. placebo p-value
2 mg (136)	389/1207	32.2	558/1219	45.8	<0.001
4 mg (129)	393/1123	35.0	565/1086	52.0	<0.001
6 mg (112)	343/1004	34.2	622/1042	59.7	<0.001

Table 5. Percentage of attempts resulting in an erection firm enough for intercourse (based on all attempts) in M97-658.

Dose (n)	Placebo Success/attempts	%	Apomorphine SL Success/attempts	%	APO SL vs. placebo p-value
2 mg (112)	370/980	37.8	432/982	44.0	0.012
4 mg (99)	310/848	36.6	519/893	58.1	<0.001
5 mg (103)	248/858	28.9	463/877	52.8	<0.001
6 mg (87)	211/719	29.3	470/772	60.9	<0.001

Table 6. Percentage of attempts resulting in an erection firm enough for intercourse (based on all attempts) in M98-941.

Dose (n)	Placebo Success/attempts	%	Apomorphine SL Success/attempts	%	APO SL vs. placebo p-value
2 mg (140)	412/1278	32.2	577/1236	46.7	<0.001
4 mg (134)	358/1167	30.7	663/1231	53.9	<0.001
5 mg (130)	320/1137	28.3	653/1192	54.8	<0.001

Efficacy results when used as labeled:
The results of M97-763 are probably the most indicative of the potential efficacy when the drug is used as labeled. Specifically, this study was designed to allow for optimal titration prior to a 4-week maintenance period. **While statistically significant, the overall "success rate" for the 2 to 4 mg titration arm was 47.5% compared to the placebo arm of 34.7%.** Although these numerical results represent the overall number of successes divided by attempts, as opposed to an average per-patient success rate, the results were similar when the data was re-analyzed.

Several studies provide evidence that the majority of patients do not continue on the 2 mg dose when allowed to self-titrate. For example, in M97-876, an open-label, at-home use trial, the final dose was 2 mg, 4 mg and 5 mg, in 5.5%, 15.8% and 78.8% of patients, respectively. In the first, open-label, 6-month safety extension trial (M96-470), the final dose was 2 mg, 4 mg and 6 mg, in 11%, 27% and 62% of patients, respectively. Finally, in the second, open-label, 6-month safety extension trial (M97-659), the final dose was 2 mg, 4 mg, 5 mg and 6 mg in 6%, 29%, 24% and 41% of patients, respectively.

Brief Summary of Safety:
Summary comments regarding the analysis of safety:
There are substantial safety concerns that impact on the overall risk/benefit analysis for Uprima.

The major areas of concern are outlined below:

1. Syncope, profound hypotension, bradycardia, and life-threatening medically-emergent events were related to the use of Uprima. Adverse event narratives from different studies consistently described several patients in medical extremis. Approximately 41 patients (1.4% of the total dosed population) experienced drug-related syncope and many others experienced "vasovagal"-type symptoms without syncope. The highest incidences of these events were noted at 4 mg, 5 mg and 6 mg.

    - Although many syncopal events were brief, in some patients, hypotension was prolonged (up to 1 hour and 55 minutes). Concomitant weakness, dizziness, pallor and fatigue usually lasted longer (30 minutes to many hours).

    - Although syncope was usually not associated with permanent disability or hospitalization, one patient suffered a skull fracture with brain contusion, one patient suffered a head laceration, and one patient crashed his motor vehicle.

    - Although syncope usually resolved without intervention, some patients were administered IV fluids, oxygen, Narcan, and atropine in an attempt to prevent permanent injury.

    - In a few patients, syncope was accompanied by stoppage of respiration, throat "tightness", and pulselessness.

    - Many patients who experienced nausea and "queeziness" prior to a syncopal event (or a syncopal "prodrome") were also concurrently somnolent. Patients may be too sedated to properly adhere to package insert usage instructions during the prodrome. Sedation appears to be a direct effect of Uprima.

    - When the drug was used in a dose-titration regimen at doses up to 4 mg, some patients still reported syncope, hypotension, and symptoms consistent with clinically meaningful systemic vasodilatation.

    - There were additional patients who experienced hypotension (some with symptoms) but were not discontinued from the study and were not counted as serious adverse events.

    - There is limited information from Phase 2 and 3 studies on the direct effect of apomorphine on blood pressure immediately following dosing. However, one Phase 1 study (M98-838) revealed that dosing with apomorphine SL 6 mg alone was associated with mean decreases in the standing systolic and diastolic blood pressures of 19 mm Hg and 12 mm Hg, respectively. A second Phase 1 study (M98-941) revealed mean decreases of approximately 22 and 12 mm Hg following the same dose.

2. Phase 1 studies demonstrate a definite pharmacodynamic interaction of alcohol and Uprima. There is a worsening of orthostatic drops in the systolic and diastolic BP compared to apomorphine alone. Such an interaction poses a difficult-to-manage, realistic risk. In Phase

3 studies, all patients were instructed to limit their intake of alcohol to "a minimum" for 6 hours prior to dosing. Thus, the real-life potential for concomitant alcohol ingestion was not adequately investigated in controlled clinical trials.

3. The combination of nausea, vomiting, sedation, hypotension and loss of consciousness poses the additional significant risk of pulmonary aspiration.

4. The overall adverse event profile associated with Uprima 4 mg, 5 mg and 6 mg was generally unfavorable, as outlined below.

   - *Nausea and vomiting:*
     Consistent with its use as an emetic, Uprima was associated with a dose-related incidence of nausea, ranging from mild to severe. Nausea generally occurred early in treatment, but could persist through months of therapy. It could be experienced for only minutes after dosing, but often persisted up to several hours. Nausea was often accompanied by "queeziness", "clamminess", diaphoresis and the sensation of imminent fainting. Nausea was frequently accompanied by vomiting, which was often moderate to severe in nature. In some patients (approximately 5%), nausea was so severe as to require pre-medications with anti-nauseants such as Compazine, or post-dosing treatment with Compazine. In some patients, nausea was refractory to Compazine. Nausea was the most common reason for discontinuation due to an adverse event (affecting approximately 5% of patients overall).

     During the Phase 3 trials, the sponsor attempted to control the nausea both pharmacologically (with Compazine) and symptomatically (with eating instructions). The sponsor instructed patients to "wait at least one hour after a full meal, or if nothing was eaten for several hours, to eat some crackers or bread about ½ hour to one hour before taking the study medication."

   - *Sedation and somnolence*
     Consistent with its use as a sedative, Uprima at all doses was associated with clinically meaningful somnolence, sedation, lethargy, fatigue, asthenia and decrease in mental alertness. Phase 1 psychometric testing and Phase 3 clinical trials provided evidence for the sedating effect of Uprima.

   - *Systemic vasodilatation:*
     In addition to the nausea, vomiting, queeziness, clamminess, and sedation, Uprima was associated with systemic vasodilatory adverse reactions including dizziness, pallor, ashen-grey appearance, orthostatic hypotension, flushing, sweating, "vasodilatation" and syncope.

   - *Mouth ulceration and discomfort*
     Approximately 2% of patients in the Uprima trials described oral discomfort, swelling, pain, sour breath, taste perversion or ulcerations of the tongue, lips, mouth, throat or pharynx. In some patients, physical examination revealed shallow ulcerations that took days to heal. One case was associated with lymphadenopathy.

5. The population studied in the Uprima trials was defined as a generally healthy group of men. Most of the men had erectile dysfunction without a major organic component. It is likely that

the safety concerns noted in this population would only be magnified in the more general ED population, as such patients may be at an increased risk for underlying cardiovascular disease.

Materials analyzed in the safety analysis:
Safety data presented in the updated integrated summary of safety (from the 4-month safety update), as well as the following individual clinical trial reports: M96-470, M96-471, M97-658, M97-659, M97-682, M97-763, M97-788, M97-793, M97-804, M97-876, M98-936 and M98-941.

The following four individual Phase 1 study reports that investigated a potential interaction of Uprima with alcohol were also analyzed: M97-745, M97-762, M98-838 and M98-941.

Disposition of patients from the controlled studies:
All patients who completed a Phase 3 controlled trial of Uprima were offered an opportunity to continue taking Uprima in an open-label, safety extension. This "rollover" of patients is delineated below:

- M96-470→316 patients enrolled in M96-471→32 patients enrolled in M97-682.
- M97-658→335 patients enrolled in M97-659→93 patients enrolled in M97-682.
- M97-763→358 patients enrolled in M97-682.
- M98-788→14 patients enrolled in M97-793
- M98-804→101 patients enrolled in M97-793
- M98-941→6 patients enrolled in M98-936

In M98-876, the sponsor studied the safety of apomorphine 2 mg, 4 mg and 5 mg when dosed by optimal titration and without in-office dosing. This open-label trial enrolled 151 patients and of those, 41 patients were "rolled-over" into M98-936.

Uncontrolled study designs:
Safety studies M96-471 and M97-659 were direct, 6-month extensions of their controlled counterparts.

Safety studies M97-682 and M97-793 are ongoing, 3-year extensions of [M96-471 + M97-659 + M97-763], and [M98-788 + M98-804], respectively.

Safety study M98-876 was a 7-week, open-label, at-home, titration study.

Safety study M98-936 is an ongoing, 2-year extension of [M98-941 + M98-876].

Extent of exposure:
Overall, a total of 3172 patients and/or subjects participated in the Uprima Phase 1, Phase 2, or Phase 3 trials. In Phase 2 and Phase 3 trials alone, 2515 patients participated. In Phase 1 studies alone, 657 subjects participated.

Overall, 3035 patients received at least one dose of Uprima. In all Phase 2 and 3 trials combined, 2379 male patients took at least one dose of Uprima. Overall, 461 patients were exposed to Uprima for at least 6 months and 127 patients were exposed for at least 1 year.

In the Phase 2 and Phase 3 studies, the extent of exposure to Uprima by number of days is depicted in Table 7.

Table 7. Number of patients exposed to Uprima for a given number of days.

APO SL dose	1-30	31-60	61-90	91-120	121-150	151-180	181-270	271-365	>365	Total # of patients
2 mg	1179	304	33	12	6	10	9	15	8	1576
4 mg	1079	338	90	47	17	14	21	21	10	1637
5 mg	661	287	107	29	30	11	34	14	6	1179
6 mg	421	224	74	54	54	27	52	36	13	955
8 mg	42	3	0	0	0	0	0	0	0	45
Overall	940	395	169	169	134	89	212	122	127	2379

Patient population:
For all Phase 2 and 3 patients, the mean age was 55 years (range 21 to 76), the mean weight was 200 pounds, and the majority of the group was Caucasian (89%). Overall, 16% were tobacco users (<10 cigarettes per day), 16% were well-controlled diabetics, 31% were hypertensive, 16% had benign prostatic hypertrophy, and according to the sponsor, 16% had a history of coronary artery disease.

Deaths:
There were no deaths reported during any Uprima trial.

Serious adverse events (SAEs):
According to the sponsor's review, overall, 15 serious adverse events were related to Uprima.

The original definition of a serious adverse event (SAE), as noted in M96-470 and M96-471, included those "events that required intervention to prevent impairment/damage." In all future protocols, the sponsor revised the definition to exclude such events as SAEs. Instead, serious adverse events were defined as "any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in perisistent disability/incapacity or is a congenital anomaly/birth defect."

Some additional drug-related adverse events would have been defined as "serious" if the original definition had been maintained. In addition, there were many discontinuations due to adverse events and several cases of syncope that would be considered medically significant, if not "serious", by the revised definition.

In the three "crossover trials" (*M96-470, M97-658 and M98-941*), the sponsor reported a total of five (5) Uprima-related SAEs. These included the following:

- A 33 year old male received his first in-office dose of **4 mg** in M96-470. He was observed for 30 minutes without incident. While driving home, he experienced nausea, fatigue, flushing and diaphoresis. He attempted to stop the vehicle, however, he **lost consciousness and ran into a fence**. He sustained no injuries. The symptoms resolved in 5 hours.

- A 54 year old male received his first in-office dose of **6 mg** in M97-658. Approximately 1 hour after that dose, he experienced nausea, hypotension, diaphoresis, light-headedness and a 30-second loss of consciousness ("**syncope**"). He received 0.4 mg of atropine intravenously. The duration of the event was reported as 1 hour and 10 minutes.

- A 69 year old male experienced a **syncopal event** accompanied by tonic/clonic activity of his left arm, incontinence of urine, diaphoresis, nausea, vomiting, dizziness, pallor, and

hypotension which occurred 20 minutes after taking his first in-office dose of **5 mg** in M98-841. He was unconscious for approximately 10 seconds. Tonic-clonic activity lasted for approximately 15 seconds. His blood pressure was 100/60 and pulse rate was 52 bpm.

- A 44 year old male experienced nausea, **hypotension**, pallor, and diaphoresis 20 minutes after receiving his first dose (in-office) of **5 mg** in M98-941. His blood pressure was 82/58 mm Hg and his heart rate was 58 beats per minute. He was treated with IV fluids, Narcan, Compazine, and oxygen. He was taken to the emergency room.

- A 67 year old male experienced **syncope** and hypotension after his first in-office dose of **5 mg** in M98-941. He was treated with IV fluids and oxygen. The syncope lasted 1 minute and the hypotension resolved after 6 minutes. His specific BP measurement was not reported.

The FDA review revealed an additional four patients in these trials who experienced serious adverse events which may have been related to Uprima. These patients are described below:

- In M96-470, a 68 year old male experienced **chest pain** approximately 12-18 hours after his last dose of **2 mg**. He had a history of angina, coronary artery disease and hypertension. He was admitted for observation and released in stable condition after 2 days. The investigator believed that the event was not related to apomorphine.

- In M97-658, a 59 year old male received his first in-office dose of 2 mg on March 23, 1998. On that day, he was dispensed a box of 19 tablets. Approximately 1 month later, he suffered a **temporary loss of consciousness and was involved in a car accident**. He was hospitalized for a wrist fracture. He used 1 tablet of study drug during this period, but could not remember the exact date of use. He returned the remainder of the unused tablets. The investigator believed that the AE was not related to apomorphine.

- In M98-941, a 49 year old male experienced a **syncopal event** preceded by diaphoresis, dizziness, and nausea 90 minutes after dosing with **5 mg**. He was taken to the hospital and found to have a blood glucose of 15 mg/dL. He was given oral glucose and repeat blood glucose was 121 mg/dL. He did not have a previous history of diabetes. The investigator believed that this event was not related to apomorphine.

- In M98-941, a 51 year old male experienced moderate light-headedness and mild nausea 4 1/2 hours after his ninth dose of **2 mg**. He was seen in the emergency room and was found to have a temperature of 102°F and **ventricular bigeminy**. He had a history of coronary artery disease, myocardial infarction, hypertension, and diabetes. The investigator considered the light-headedness to be not related to apomorphine.

The sponsor reported three SAEs in the parallel-arm Phase 3 study, *M97-763*. These narratives follow:

- A 42 year old man experienced nausea and syncope after his first in-office dose of **5 mg** (eighth dose of apomorphine overall in the "dose-optimizing" arm). One hour after dosing, he felt nauseated. He stood up to "find someone". The nurse on duty heard a loud "thump" and found the patient on the floor, unconscious. Ammonia was initiated and the patient woke up. He had bitten his tongue and he had an abrasion on the back of his head. He was confused. Approximately 15 minutes later, "he felt better". The abrasion was cleaned and bandaged. His mouth was inspected and rinsed. The following day, he complained of a

headache. Two days after the incident, he reported feeling better. Five days after the incident, he complained of a headache again. CT scan of the head revealed a **left occipital skull fracture with a cortical contusion of the frontal lobe of the brain**. MRI of the brain showed a non-depressed left occcipital skull fracture and a contra-coup injury invoving a contusion of the right frontal lobe gyrus. He was discontinued from the study, however, he went on to enroll in the long-term, open-label trial that is currently ongoing.

- A 50 year old man experienced nausea 25 minutes after his first in-office dose of **4 mg** (sixth dose of apomorphine overall). The nurse on duty left the patient to get a dose of Compazine. Upon returning, the office staff found the patient **unconscious** , unresponsive, apneic, diaphoretic and incontinent of urine. "Within a few seconds", without intervention, he began to breath spontaneously and regained consciousness. His vital signs revealed a heart rate of 42 bpm and a blood pressure of 140/80 mm Hg. He was given intravenous saline infusion, oxygen and 10 mg of Compazine. His bradycardia and nausea persisted for over 1 hour. He was observed in the hospital overnight and was discharged in stable condition the next day.

- A 60 year old man experienced a severe **hypotensive event** 8 minutes after his first in-office dose of **6 mg** (eleventh dose of apomorphine overall). He complained of nausea, sweating, yawning and was noted to be pale. His blood pressure was 80/50 mm Hg. He received intravenous saline and 10 mg of Compazine. The duration of the event was 27 minutes.

The sponsor reported two Uprima-related SAEs in the "diabetic" trial (*M97-804*). These included:

- A 57 year old received his first in-office dose of **5 mg**. Twenty-five minutes after drug administration, he became pale and diaphoretic while supine. His **BP was 60 mmHg/palpable** with a pulse of 52 beats per minute. He was treated with IV saline and after one hour and fifty-five minutes he recovered, with a BP of 132/78 mm Hg and a heart rate of 70 bpm.

- A 66 year old received his third dose of **4 mg at home**. Approximately 16 hours later, he experienced **syncope** for about one minute following heavy physical exertion. He was hospitalized where an EKG revealed borderline first degree heart-block and non-specific T-wave flattening. Study medication was continued and he remained in the study without any further syncopal episodes.

In the 6-month, open-label, long-term extension studies, (*M96-471, M97-659 and M98-941*) the sponsor reported one Uprima-related SAE.

- A 63 year old male was noted to have **new atrial flutter** (with moderate ventricular response) on a final visit ECG, after his forty-seventh dose of **6 mg**. He was referred to a cardiologist who prescribed Coumadin. He ultimately underwent radio-frequency ablation therapy and the atrial flutter resolved.

In the extended, long-term study *M97-682*, the sponsor reported one potentially Uprima-related SAE, as follows:

- A 69 year old was noted to have **atrial fibrillation** on an early termination ECG. He was actually being removed from the study due to the exclusion criteria of "pre-existing history of cancer". He had taken 11 doses in this study, five of these were 5 mg. He was admitted to the hospital for treatment of the arrythmia.

In the extended, special population, long-term study, *M97-793*, the sponsor reported no Uprima-related SAE. FDA review revealed one additional case, which may have been related to Uprima:

- A 56 year old male experienced severe **hypotension**, generalized weakness, and diarrhea after his **first in-office dose of 4 mg**. On the morning of the dose, the patient reported abdominal cramping and six watery stools, followed by weakness. He still received an in-office dose. While attempting to stand, the patient lost consciousness for approximately 15 to 20 minutes. Upon awakening, he reported nausea and vomited. He was transported to the emergency room, where he experienced another episode of loss of consciousness. His blood pressure was 60 mm Hg/palpable. He was given intravenous fluids. An ECG revealed non-specific ST-T wave changes. He was admitted to intensive care and IV heparin was started. Laboratory examinations were consistent with dehydration. The presumed diagnosis was gastroenteritis. He was discharged in stable condition, and is continuing in this study. The investigator believed that the event was not related to study drug.

In the alcohol interaction studies (*M97-745, M97-762, M98-838 and M98-891*), the sponsor reported two drug-related SAEs, as follows:

- A 41 year old male experienced diaphoresis and "continuous vomiting" approximately 30 minutes after his first dose of **5 mg**. He became hypotensive (60/43 mm Hg) and experienced a 1 minute **loss of consciousness.** He was administered IV fluids, oxygen (6L/min) and atropine (0.5 mg IV). After 15 minutes, his blood pressure was 101/94 mm Hg and he was alert and oriented. After 1 hour, his blood pressure was 101/94 mm Hg. He was observed in a telemetry unit overnight and was discharged in stable condition the next day.

- A 60 year old male subject experienced "queeziness", nausea, light-headedness, pallor and "**significant hypotension**" (BP 55/38 mm Hg) approximately 30-45 minutes following the Day 3 dosing of apomorphine **5 mg** and 0.6 mg/kg ethanol beverage. The dose of ethanol was equivalent to approximately 4 ounces of
- 80 proof vodka. His blood pressure was 55/38 mm Hg at 45 minutes post-dosing, and 91/58 mm Hg at 90 minutes post-dosing. The investigator reported the total duration of hypotension as 2 hours and 10 minutes. During this event, his ECG revealed new T-wave inversions in leads II, III and aVF. He was treated with 0.9% intravenous saline and 2 liters of oxygen via nasal cannula. He was hospitalized for 2 days.

There were two additional patients who experienced syncope in M98-838, and one additional patient who experienced prolonged hypotension in M97-762. Detailed narratives for these patients may be found in these individual study reviews.

Overall, one additional drug-related SAE (from Study M98-841) was reported, as detailed below:

- A 47 year old man experienced dizziness and **syncope** approximately 35 minutes after **his first 5 mg dose**. He lost consciousness for 3 seconds, while in the seated position. Two minutes after the syncope, his supine BP was 129/74 mm Hg. He was lowered to the floor and then placed supine in bed. He completed the study.

Discontinuations due to adverse events:
Of the 2379 patients who received a dose of Uprima in the Phase 2 and 3 trials, 271 patients (11.4%) discontinued at least in part due to an adverse event. These discontinuations are depicted in Table 7 below:

Table 7. Adverse events which occurred in more than 2 patients and resulted in premature discontinuation from the overall Phase 2-3 trials.

Adverse Event COSTART TERM	Number. of patients n(%)
Nausea	121(5.1%)
Dizziness	60(2.5%)
Sweating	58(2.4%)
Vomiting	45(1.9%)
Somnolence	32(1.3%)
Hypotension	26(1.1%)
Asthenia	21(0.9%)
Pallor	21(0.9%)
Syncope	21(0.9%)
Vasodilatation	15(0.6%)
Headache	15(0.6%)
Glossitis	14(0.6%)
Yawning	14(0.6%)
Pharyngitis	12(0.5%)
Face edema	10(0.4%)
Taste perversion	9(0.4%)
Bradycardia	8(0.3%)
Mouth ulceration	7(0.3%)
Paresthesia	6(0.3%)
Laryngismus	6(0.3%)
Tongue edema	6(0.3%)
Edema	5(0.2%)
Malaise	4(0.2%)
Tongue disorder	4(0.2%)
Dyspnea	4(0.2%)
Accidental injury	3(0.1%)
Confusion	3(0.1%)
Hypertension	3(0.1%)
Pain	3(0.1%)
Palpitation	3(0.1%)
Rash	3(0.1%)

Approximately 5% to 10% of all patients prematurely discontinued in each Phase 2 and 3 trial due at least in part due to adverse reactions. In the three crossover trials combined, Table 8 describes the proportions of such discontinuations:

Table 8. Adverse events resulting in premature termination in the combined crossover trials (*M96-470, M97-658, and M98-941*).

	APO 2 mg n=429 n(%)	Placebo n=436 n(%)	APO 4 mg n=426 n(%)	Placebo n=414 n(%)	APO 5mg n=282 n(%)	Placebo n=263 n(%)	APO 6 mg n=262 n(%)	Placebo n=236 n(%)
Any event	4(0.9)	4(0.9)	20(4.7)	4(1.0)	23(8.2)	0(0.0)	25(9.5)	5(2.1)

Adverse events resulting in premature termination in the single, parallel-arm study (*M97-763*) are presented in Table 9.

Table 9. Adverse events resulting in premature termination in *M97-763*

	APO Dose-optimization n=242 n(%)	APO 6 mg n=89 n(%)	APO 5 mg n=119 n(%)	Placebo n=414 n(%)
Any event	26(10.7)	10(11.2)	8(6.7)	1(0.8)

Adverse events resulting in premature termination in the combined Phase 3, 6-month, safety extension studies are presented in Table 10.

Table 10. Adverse events resulting in premature termination in >2 patients in the combined 6-month extension trials (*M96-471, M97-659, and M98-936*).

Adverse Event COSTART TERM	Number of patients n(%)
Any event	81(11.8%)
Nausea	33(4.8%)
Vomiting	15(2.2%)
Somnolence	11(1.6%)
Sweating	10(1.3%)
Dizziness	9(1.3%)
Hypotension	5(0.7%)
Vasodilatation	4(0.6%)
Headache	3(0.4%)
Pallor	3(0.4%)
Stomatitis	3(0.4%)
Tongue disorder	3(0.4%)
Pharyngitis	3(0.4%)
Taste perversion	3(0.4%)

Adverse events leading to discontinuation in the long-term, open-label trials, M97-682 and M97-793, were similar in incidence and type to those in the 6-month trials.

Some of the adverse events leading to drug discontinuation were medically serious events, including nausea, vomiting, hypotension, syncope, severe fatigue, sedation and mouth ulceration. All of these are described further in the individual study reviews.

Syncope:
The sponsor acknowledges that Apomorphine SL "has the potential to induce hypotension and orthostatic cardiovascular changes secondary to vasovagal events." The sponsor believes that this is secondary to "a peripheral dopaminergic activity that may produce hypotension and/or bradycardia in susceptible individuals in association with orthostatic maneuvers."

Forty-eight (48) syncopal events occurring after apomorphine administration were reported in the Phase 1-3 trials. The investigator believes that apomorphine was related to the event in 41 cases. Eight syncopal events occurred in normal subjects in Phase 1 studies, and 33 occurred in clinical trial patients. Table 11 demonstrates the overall incidence of syncope

Table 11. Overall incidence of syncope in patients treated with apomorphine SL.

Treatment group	Number of patients	Events related to drug n(%)	Events not related to drug n(%)
APO 2 mg	964	2(0.2)	0(0.0)
APO 4 mg	1279	11(0.9)	2(0.1)
APO 5 mg	1416	13(0.9)	3(0.1)
APO 6 mg	1252	15(1.2)	2(0.1)
APO 8 mg	45	0(0.0)	0(0.1)
Total	3035	41(1.4)	7(0.2)

When only the 2 mg and 4 mg data are considered, the overall syncope rate is 0.8%.

There is evidence from the long-term open-label trials that most patients will titrate up to the maximum allowable dose. Therefore, the data support that the 4 mg dose is the most likely dose to be used post-marketing.

Two additional syncopes were probably related to Uprima. These events occurred in M96-471 and in M97-793. Both of these patients were dosed with 4 mg, as described below:

- A 59 year old male consumed ½ bottle of wine two hours prior to taking his **third 4 mg dose** (eighth overall) in Study M96-471. After dosing, he experienced light-headedness, nausea and vomiting for 30 minutes. He then **fell and hit his head on the bathtub**. He experienced loss of consciousness for 30 seconds. As a result of the fall, he had a "bump" and a "cut" on the right side of his head. He took one additional dose and was discontinued due to non-compliance. The investigator believed that the light-headedness was possibly due to drug, but that the loss of consciousness may have been due to the wine, the fall or hitting his head.

- As previously described, a 56 year old male experienced **syncope** after being dosed with **4 mg in the office**. He presented to the office with a baseline gastroenteritis and diarrhea, but nevertheless, received a dose of Uprima anyway. He subsequently was hospitalized for fluid resuscitation and vital sign monitoring.

Adding these 2 patients to the 4 mg dose group would lead to a syncope rate of 1.0%.

The sponsor claims that the timing of syncope after dosing was predictable (approximately 40 minutes, with a range of 20 minutes to 120 minutes post-dosing), and that the mean duration of syncope was brief (approximately 45 seconds, with a range of one second to five minutes). Excluded from this analysis was one patient with syncope occurring 16 hours after dosing, and one patient with syncope lasting "15 minutes".

The sponsor claims that the majority of syncopal events occurred after the first dose of apomorphine or after the first increase to a new dose. FDA finds this to be true in 26 of 41 cases (63%).

The sponsor also points out that there was a suggestion of a "prodrome" of symptoms which preceded syncope. These symptoms included moderate or severe nausea, sweating, dizziness, vomiting, vasodilatation, pallor, hot flashes and/or diaphoresis. The reviewer agrees that many patients experienced such symptoms prior to fainting.

Overall adverse events:
The overall treatment-related adverse events reported by ≥ 5% of apomorphine patients in the combined Phase 2 and 3 trials is demonstrated in Table 12 below. For this summation, the sponsor counted all adverse events experienced by each patient just once, regardless of the study in which they occurred.

Table 12. Treatment-related adverse events reported by ≥ 5% of apomorphine patients in the combined Phase 2 and 3 trials.

COSTART Term	Adverse events n=2379 n(%)
Nausea	756(31.8)
Dizziness	423(17.8)
Sweating	334(14.0)
Somnolence	320(13.5)
Yawning	262(11.0)
Vomiting	195(8.2)
Headache	189(7.9)
Asthenia	149(6.3)
Vasodilatation	140(5.9)

In terms of severity, all adverse events that were classified as "severe" and were reported by at least 0.5% of patients are listed in Table 13.

Table 13. Severe adverse events in the combined Phase 2 and 3 trials.

COSTART Term	All Adverse events n=2379 n(%)	Related adverse events, n=2379 N9%)
Any	143(6.0)	75(3.2)
Nausea	34(1.4)	30(1.3)
Vomiting	19(0.8)	17(0.7)
Syncope	19(0.8)	16(0.6)
Sweating	17(0.7)	15(0.5)
Hypotension	13(0.5)	12(0.5)
Dizziness	12(0.5)	11(0.5)
Pain	12(0.5)	0(0.0)

When these adverse reactions are analyzed only for the 2 mg and 4 mg doses, the incidence of adverse events is reduced. Table 14 presents the overall treatment-related adverse events reported by ≥ 5% of apomorphine patients in the combined Phase 2 and 3 trials for only the 2 mg and 4 mg combined doses.

Table 14. Treatment-related adverse events reported by ≥ 5% of apomorphine patients in the combined Phase 2 and 3 trials, 2 mg + 4 mg doses only.

COSTART Term	Adverse events n=1925 n(%)
Nausea	298(15.5)
Dizziness	180(9.4)
Somnolence	155(8.1)
Yawning	117(6.1)
Sweating	111(5.8)
Headache	102(5.3)

Similarly, when these adverse reactions are analyzed by severity, and only for the 2 mg and 4 mg doses, the incidence of severe adverse events is reduced.

Table 15. Severe adverse events in the combined Phase 2 and 3 trials, 2 mg + 4 mg only.

COSTART Term	Adverse events n=1925 n(%)	Related Adverse events, n=1925 n(%)
Any	143(6.0)	26(1.4)
Syncope	34(1.4)	8(0.4)
Vomiting	19(0.8)	7(0.4)
Nausea	19(0.8)	7(0.4)
Pain	17(0.7)	0(0.0)
Sweating	13(0.5)	4(0.2)
Dizziness	12(0.5)	3(0.2)
Pharyngitis	12(0.5)	1(0.1)
Accidental injury	3(0.2)	0(0.0)
Chest pain	3(0.2)	1(0.1)
Hypotension	3(0.2)	2(0.1)

The sponsor conducted subgroup analyses of the adverse event data. The data was analyzed by age, race, weight, smoking status, alcohol use status, diabetic status, hypertensive status, coronary artery disease status, and BPH status.

An important finding was an effect of age on certain adverse reactions, including nausea and vasodilation. Nausea appeared to decrease in incidence as age increased, but dizziness, sweating, vasodilation, pallor and arrythmia increased along with age.

Table 16. Related adverse events, ≥5% in incidence, combined Phase 2 and 3 studies, all doses, reviewer-selected terms.

COSTART Term	<46 n=353 n(%)	46-55 n=820 n(%)	56-65 n=875 n(%)	>65 n=331 n(%)
Nausea	115(32.6)	260(31.7)	280(32.0)	101(30.5)
Dizziness	54(15.3)	141(17.2)	157(17.9)	71(21.5)
Sweating	37(10.5)	108(13.2)	130(14.9)	59(17.8)
Vomiting	31(8.8)	60(7.3)	70(8.0)	34(10.3)
Vasodilatation	22(6.2)	45(5.5)	46(5.3)	27(8.2)
Pallor	11(3.1)	30(3.7)	26(3.0)	17(5.1)

It is important to note that in the entire Phase 2 and 3 program, of all patients who received at least one dose of Uprima, there were only 331 men over 65 years of age. This represents approximately 14% of the dosed study population.

Interestingly, smoking status had a profound impact on incidence of adverse events. Non-smokers had almost twice the incidence of nausea, dizziness, somnolence, sweating, vomiting and headache, compared with smokers.

Table 17. Related adverse events, ≥5% in incidence, combined Phase 2 and 3 studies, all doses, reviewer-selected terms.

COSTART Term	Smoker n=353 n(%)	Non or Ex-Smoker n=1968 n(%)
Nausea	59(16.3)	669(34.0)
Dizziness	33(9.1)	369(18.8)
Somnolence	27(7.4)	304(15.4)
Sweating	11(3.0)	216(11.0)
Yawning	27(7.4)	178(9.0)
Vomiting	9(2.5)	167(8.5)
Headache	18(5.0)	130(6.6)

Vital sign and electrocardiographic measurement:
In most of the Phase 3 trials, vital sign measurements were performed at routine office visits, but were not performed with any pre-specified temporal relationship to dosing. Nevertheless, post-dosing vital signs were performed in several Phase 1 studies, including the alcohol interaction studies and the drug interaction study with antihypertensives and nitrates.

ECGs were performed at routine office visits, not post-dosing.

Holter monitoring was conducted in 5 different studies: M98-838 and M98-891 (two alcohol interaction studies), the diabetic study M98-804, antihypertensive study M98-930 and a Phase 1 pharmacokinetic study, M98-844.

In terms of routine vital signs, there were several studies (the 6-month extension trials, and the open-label, dosed-escalation trial) in which mean standing systolic BP was noted to decrease by approximately 1-3 mm Hg from baseline. These changes were not considered clinically meaningful.

In the alcohol interaction studies, where blood pressures were monitored rigorously post-dosing, there was a clear increase in orthostatic and change-from-baseline blood pressure reductions when apomorphine was taken with ethanol.

- In the first study (M97-745), which was prematurely terminated due to adverse events, the maximal change from supine to standing blood pressure for apomorphine 6 mg + ethanol [0.6 gm/kg] was -11.4 mm Hg, compared to +1.70 mm Hg for apomorphine 6 mg alone.

- In the second study, using 0.15 mg/kg of ethanol (roughly equivalent to 1 ounce of 80 proof vodka) there were no significant effects on blood pressure or heart rate with apomorphine alone or in combination with alcohol.

- In the third study (M98-838), the maximum drop from baseline in standing systolic BP for apomorphine SL 6 mg + ethanol 0.3 gm/kg (roughly equivalent to two "shots" of 80 proof vodka over 1 hour) was -22 mm Hg, compared to –18 mm Hg for apomorphine alone. For standing diastolic BP, those reductions were –14 mm Hg and –12 mm Hg, respectively.

- In the final study (M98-891), where the maximal dose of ethanol was used (0.6 mg/kg or four "shots" of 80 proof vodka), these differences were again significant. The maximum drop from baseline in standing systolic BP for apomorphine SL 6 mg + ethanol (0.6 gm/kg) was -

27 mm Hg, compared to –21 mm Hg for apomorphine alone. For standing diastolic BP those reductions were –17 mm Hg and –12.5 mm Hg, respectively.

A total of 1702 Holter recordings were obtained from 344 patients (or subjects) participating in one of five studies (M97-804[diabetic], M97-838, M97-891[alcohol], M98-930 [antihypertensive interaction] and M98-844 [pK]). There were abnormalities noted in 17 subjects after dosing with apomorphine and 11 subjects prior to dosing, or while on placebo. The most common abnormalities were "sinus pauses", "junctional rhythm", and atrial fibrillation. These abnormalities were reported with similar frequency in the drug and placebo groups.

Clinical laboratory examinations:
Laboratory values were evaluated in all Phase 2 and 3 studies. The results were analyzed by the use of mean values, "shifts" relative to normal, and "extremes" or markedly abnormal values.

Overall, the changes seen in laboratory values for hematology, chemistry and urinalysis were small and not considered by the sponsor to be clinically meaningful.

Although there were some changes-from-baseline noted in serum liver function tests in some patients throughout the trials, the incidence rates of such changes between drug and placebo were similar.

Summaries of Individual Clinical Trials

Clinical Trial M96-470

Design:

This was the first Phase 3 controlled study of apomorphine SL. It was a double-blind, randomized, placebo-controlled, three-armed study. Each arm consisted of one dose of apomorphine SL (2 mg, 4 mg, or 6 mg) versus placebo in a 2-period crossover design. Each treatment period was 4 weeks in duration. The washout period between treatments was 24-72 hours. In each arm, patients could be enrolled into one of two sequences (drug first, followed by placebo; or placebo first, followed by drug). Prior to Treatment Period 1, all patients underwent a 2 to 4-week, treatment-free, "lead-in" period. The study was conducted at 32 United States centers. The sponsor intended to enroll 450 patients.

During the treatment periods, patients were instructed to take study drug and attempt intercourse a minimum of 2 times per week. Patients were instructed to take the drug no more than once per 8-hour period. Patients were instructed to take study medication by placing a single tablet under the tongue and allowing it to dissolve completely. Once the tablet was completely dissolved, sexual intercourse could be attempted when the couple was ready. Patients were instructed as follows: "You should limit yourself to a minimum amount of alcoholic beverages during the six hours prior to taking study medication." After at least 2 hours had passed after intercourse, patients and partners were instructed to complete a questionnaire regarding that particular sexual experience.

Of note, the formulation of apomorphine SL used in this study was the "F1" formulation. It was a "developmental" formulation. The major differences between "F1" and the "F2" formulation was the removal of an excipient [ ]), a change in the amount of another excipient[ ], and a coloring change.

> **Comment: Despite the change in formulation, the active drug substance was still apomorphine. The dose of active drug did not change. The data from this trial therefore could be somewhat relevant to this drug application.**

Inclusion/exclusion criteria:

Eligible patients were heterosexual males, between 18 and 70 years of age. All men had to have a diagnosis of "erectile dysfunction with no major organic component". Erectile dysfunction was defined as "the ability to attain and maintain an erection firm enough for intercourse with a partner for less than 50% of attempts for a minimum of 3 months prior to Day 1 of treatment Period 1". In addition, all patients had to have demonstrated "an erection of sufficient quality for intercourse on some occasion since the onset of erectile dysfunction as evidenced by nocturnal/morning erections, masturbation, and/or other sexual activity." Finally, all patients underwent nocturnal penile tumescence testing (NPT) using Rigisican at least 60 days prior to Day 1 of Treatment Period 1. All patients had to demonstrate at least 1 successful erection during NPT testing; specifically, a successful erection was defined as one wherein the base of the penis was at least 55% rigid for at least 10 minutes.

All patients had to be involved in a "stable", heterosexual relationship for at least 6 months. All patients and partners had to agree to attempt intercourse at least 2 times weekly. All patients had to be "judged in good general health as evidenced by medical history and physical examination". All pre-study laboratory values had to be within 15% above or below normal range. Fasting blood glucose had to be <250 mg/dL, unless approval was obtained by the medical monitor.

Patients who had up to 75% successful attempts during the lead-in period were eligible for the study. Although patients needed to have a history of <75% success for the 3 months prior to study day 1, some patients who had 75% or more success during the lead-in period were randomized.

> **Comment: The inclusion and exclusion criteria assured a study population that was capable of getting erections and was generally healthy. This population does not represent the larger ED population.**

Patients were excluded for the following reasons:

1. Presence of "neurologic disease" (e.g. Parkinson's disease, multiple sclerosis, or spinal cord injury).
2. Presence of such genitourinary disorders as history of radical prostatectomy, penile prosthesis, or major penile deformity.
3. Presence of hypogonadism (serum T <280 ng/dL), hyperprolactinemia (serum prolactin >20 ng/mL), or diabetes with any episode of ketoacidosis with the last 3 months.
4. Presence of major psychiatric disorder.
5. Presence of "cardiovascular disease" (e.g. systolic BP >180 mm Hg and/or diastolic >100 mm Hg while sitting, hypotension [systolic BP< 90 mm Hg while standing]).
6. Presence of gastrointestinal disease (especially, any disorder resulting in the need for anti-nausea medications in the last 6 months).
7. Any cancer other than basal or squamous cell cancer that has not been in remission for at least 5 years.
8. Any pharmacologic therapy for ED within the preceding 3 months.
9. Greater than 75% successes during the lead-in period.
10. History of drug or alcohol abuse within the past 2 years.
11. Smoking greater than 10 cigarettes per day, or the equivalent use of tobacco in other forms.
12. History of allergic reaction to morphine or any other opiate.
13. Partners with major affective disorder.
14. Partners with a history of female sexual dysfunction.
15. Partners who were pregnant, lactating or planning to become pregnant.

> **Comment: Again, inclusion and exclusion criteria were very strict. The study population is a relatively healthy group and again, is not indicative of the erectile dysfunction population at large.**

Efficacy endpoints and statistical analysis plan:

The primary efficacy endpoint was "the home-use success rate during each treatment period" where an attempt was defined as taking a study drug and completing a questionnaire and success was defined as achieving an erection firm enough for intercourse according to the patient's opinion. Secondary efficacy endpoints included:

1. Achievement of an erection firm enough for intercourse according to the partner's opinion.
2. Number of patients with successful response (defined as erection sufficient for intercourse in 50% or greater number of attempts in a treatment period)
3. Successful intercourse rates according to patients and partners
4. Time to erection
5. Duration of erection
6. Brief Sex Function Inventory questionnaire for the patient and partner
7. Profile of Mood States questionnaire

At ten investigational sites, in-office Rigiscan monitoring was performed. The procedure was initiated 15 minutes prior to dosing. Approximately 10 minute after dosing, a sexually-

stimulating videotape was shown to the patient and Rigiscan monitoring continued during this segment for 20 minutes.

At two investigational sites, Color Duplex ultrasound of the penile arteries was supposed to be performed. However, "due to low enrollment", results for these procedures were not analyzed.

The per-protocol statistical analysis plan for the primary endpoint was that the Cochran-Mantel-Haenszel method. In this methodology, each patient was to be considered as a separate stratum, and the mean score differences would be compared between active and placebo treatments. This analysis would be performed separately for each arm of the study (2 mg, 4 mg, 5 mg and 6 mg). All patients who had at least one attempt in both treatment periods would be included in the analysis.

It is important to note that once the patient was randomized to one of the 6 possible sequences, the first dose in Treatment Period 1 was given in the office. The patient was observed in-office for 2 hours. The same procedure was conducted for the first dose in Treatment Period 2

> **Comments: It is interesting to note that a possible blinding problem. Specifically, the sponsor stated, "Though complete blinding was attempted, the known side effects of apomorphine, specifically nausea and vomiting, did in some patients suggest their randomized treatment sequence. Some patients taking placebo, however, also reported nausea."**

Withdrawals, compliance, and protocol deviations:

Patient disposition:

Five hundred fifty-seven men were randomized into the study. All 457 patients took at least one dose of blinded study drug. Four hundred forty-one (441) patients took at least one dose of apomorphine SL. Three hundred seventy (370) patients completed the study. Of the 87 patients who discontinued the study, 24 discontinued because of adverse events. (Table 1)

Table 1. Reasons for study discontinuation

	APO 2 mg	Placebo	APO 4 mg	Placebo	APO 5 mg	Placebo
Adverse event	1	1	5	1	14	2
Noncompliance	2	4	3	2	1	1
Lack of efficacy	0	0	1	0	2	0
Patient request	2	1	4	3	4	3
Partner request	0	1	1	1	0	1
Lost to follow-up	4	1	3	2	5	3
Death	0	0	0	0	0	0
Other	1	0	2	0	4	0

The adverse events resulting in study discontinuation are discussed in the "safety" analysis.

Treatment compliance: Treatment compliance was assessed through the use of at-home use diaries.

Protocol deviations: Forty-seven patients (47) were included in the study who did not meet the eligibility criteria. Of these, thirty patients (30) had ≥75% successes in the lead-in period. Seven patients had no lead-in questionnaires completed at all. Ten "failed" NPT testing.

Two patients were dosed incorrectly during the trial. Four patients had actually used a pharmacologic treatment for ED within 3 months of this study and 3 of those had actually been enrolled in a trial for a different investigational product for ED.

> **Comment: Of note, thirty patients were enrolled who had excellent success during the lead-in period (75% successes). It is unclear if these patients had any degree of erectile dysfunction.**

Study Population: The treatment groups were well balanced at baseline. The mean age was approximately 54 years and the mean weight was approximately 195 pounds. No additional information was submitted in regard to demographics.

Efficacy analysis:
The primary endpoint was the percentage of attempts in which the patient thought that he had achieved an erection firm enough for intercourse.

The sponsor believes that the results of an analysis of the proportion of *all* attempts resulting in an erection firm enough for intercourse showed statistically significant advantages for each dose level of apomorphine SL over its corresponding placebo dose. These results are summarized in Table 2.

Table 2. Percentage of attempts resulting in an erection firm enough for intercourse (based on all attempts)

Dose	(n)	**Placebo**		Apomorphine SL		Apomorphine SL vs. Placebo P-value
		Success/attempts	**%**	Success/attempts	%	
2 mg	(136)	389/1207	32.2	558/1219	45.8	<0.001
4 mg	(129)	393/1123	35.0	565/1086	52.0	<0.001
6 mg	(112)	343/1004	34.2	622/1042	59.7	<0.001

> **Comments: The data presented are the sum of all successes and all attempts for each group. When re-analyzed as the mean percentage of successful attempts per individual, the results were essentially the same. The data support statistical efficacy of the 2 and 4 mg doses.**

Similar results were observed in the secondary endpoint of percentage of attempts resulting in intercourse (Table 3).

Table 3. Percentage of attempts resulting in intercourse (based on all attempts)

Dose	(n)	**Placebo**		Apomorphine SL		Apomorphine SL vs. Placebo P-value
		Success/attempts	**%**	Success/attempts	%	
2 mg	(135)	318/1183	26.9	452/1182	38.2	<0.001
4 mg	(128)	320/1102	29.0	466/1060	44.0	<0.001
6 mg	(112)	227/963	23.6	518/996	51.0	<0.001

Another secondary endpoint was patients who were deemed a treatment success. Success occurred if at least 50% of all attempts while using the treatment resulted in erections firm enough for intercourse (Table 4).

Table 4. Results of the analysis of percentages of patients deemed a treatment "success" (based on all attempts)

Dose	(n)	Placebo #success	%	Apomorphine SL #success	%	Apomorphine SL versus placebo p-value
2 mg	(136)	47	34.6	62	45.6	0.008
4 mg	(129)	49	38.0	76	58.9	<0.002
6 mg	(112)	39	34.8	71	63.4	<0.001

A subset of patients underwent in-office Rigisican testing. The primary endpoint for these studies was the duration of erections >55% rigid at the penile base. These results are reflected in Table 5.

Table 5. Rigiscan data expressed as erection >55% rigid at penile base.

	Baseline duration (minutes)	Treatment duration (minutes)	Apo SL vs. Placebo P-value
2 mg (n=46) Placebo(n=46)	0 0	2.11 2.85	0.416
4 mg (n=40) Placebo (n=40)	0 0	4.34 3.64	0.628
6 mg (n=47) Placebo (n=47)	0 0	4.76 1.69	0.014

<u>Comment</u>: The 2 mg and 4 mg doses do not have any effect on this pharmacodynamic endpoint.

Safety Analysis :
Extent of exposure : The extent of apomorphine SL exposure is depicted in Table 6.

Table 6. Extent of apomorphine SL exposure

Number of patients exposed to a given number of doses					
Dose	1	2-5	6-12	13-21	Total
2 mg	5	10	104	27	146
4 mg	8	13	107	21	149
6 mg	13	16	89	28	146

<u>Comment</u>: The extent of exposure was limited to 4 weeks in this trial.

Deaths : There were no study deaths.

Serious adverse events:
Eight serious adverse events (SAEs) were reported during this study. In five of these, the patient was taking placebo. Of three patients who experienced an SAE on drug, one of these was clearly not related to drug (new diagnosis of acute lymphocytic leukemia). The other two are described below:

- A 33 year old male received his first in-office dose of apomorphine 4 mg. He was observed for 30 minutes without incident. While driving home, he experienced nausea, fatigue, flushing and diaphoresis. He attempted to stop the vehicle , however, he lost consciousness and ran into a fence. He sustanied no injuries. The symptoms resolved in 5 hours. The investigator believed that the event was probably related to study medication. The investigator believed that this patient's condition was "life-threatening".

  <u>Comment</u>: This case supports concern about patients' ability to drive or perform other potentially dangerous activities immediately following dosing with apomorphine.

- A 68 year old male experienced chest pain approximately 12-18 hours after his last dose of apomorphine 2 mg. He had a history of angina, coronary artery disease and hypertension. He went to the emergency room, where he was diagnosed with unstable angina. The chest pain resolved in 30-45 minutes. He remained in the hospital for 2 days. He continued on treatment upon discharge and successfully completed the study. The investigator believed that the event was not related to study drug.

Premature discontinuations due to adverse event:
Twenty-four patients discontinued the study due at least in part to an adverse event. One of these was discussed above. Two were on placebo. Four patients experienced syncope leading to discontinuation.

- A 46 year old male experienced an onset of nausea and light-headedness approximately 10 minutes after his first in-office dose of apomorphine 6 mg. He became increasingly dizzy and was placed in a supine position. He was then noted to have a brief convulsive movement during which his arms became flexed and were drawn up in the air, his pupils became fixed and he was shaking slightly. This convulsion lasted 30 seconds. He was disoriented for an additional 30 seconds. Afterwards, he was pale, sweaty, weak and had a dull headache. He was taken to the emergency room and released 1 hour later. An EEG performed 6 days later was normal. He took no additional doses and was discontinued. The investigator believed the event was definitely related to apomorphine. The sponsor believed that the patient had a past history of fainting, which may have been related to the event.

  <u>Comment</u>: Of note, this patient experienced loss of consciousness *after* he was placed in a supine position.

- A 68 year old male experienced mild nausea and syncope after taking two doses of apomorphine 2 mg within 4 hours. He experienced loss of consciousness for approximately 4 minutes after the second dose. He took no additional doses and was discontinued. The investigator believed the event was probably related to apomorphine. The sponsor believed that taking 2 tablets (2 mg) may have been related to the event.

- A 65 year old patient experienced dizziness, pallor, lightheadedness, diaphoresis, syncope and tiredness approximately 30 minutes after his first in-office dose of apomorphine 6 mg. Loss of consciousness lasted for approximately 1-2 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 55 year old patient experienced nausea, vomiting and syncope approximately 20 minutes after his first home-use dose of apomorphine 6 mg. Loss of consciousness lasted for approximately 1-2 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

  Comment: This case is of note because the patient tolerated an in-office dose of 6 mg but later experienced syncope at home with 6 mg.

Of the remaining 18 patients, four patients experienced acute hypotensive events following doses of 6 mg or 4 mg. Five patients experienced intolerable nausea. Four patients experienced an acute event comprised of light-headedness, dizziness and diaphoresis. One patient discontinued due to mouth irritation. One patient discontinued due to an abnormal "flash of light" in his right eye after an in-office dose of 4 mg. One patient had 2-3 hour episodes of drowsiness and disorientation after at-home doses of 4 mg.

Two additional patients experienced syncope without discontinuation from the trial. These patients are described in detail below:

- A 36 year old patient experienced pallor, diaphoresis, and syncope approximately 30 minutes after his first in-office dose of apomorphine 4 mg. Loss of consciousness lasted for approximately 3 seconds. Tiredness, weakness, and flushing lasted for approximately 8 hours. Re-challenge the next day with 4 mg was uneventful. The patient went on to take 10 more doses and successfully complete the study. The investigator believed the event was definitely related to apomorphine.

- A 51 year old patient experienced nausea and syncope approximately 25 minutes after his first in-office dose of apomorphine 4 mg. Loss of consciousness lasted for approximately 1 second. The patient went on to take an additional 9 doses and successfully complete the study. The investigator believed the event was probably related to apomorphine.

Overall adverse effects: In the text of the study report, the sponsor summarized the adverse events that were considered by the investigator to be at least possibly related to apomorphine and reported by at least 10% of all patients.

When the overall AEs were tabulated in this manner the results are demonstrated in Table 7.

Table 7. Treatment-emergent adverse events at least possibly related to apomorphine and reported by ≥10% of all patients.

Adverse event	2 mg Group		4 mg Group		6 mg Group	
	P (n=147) %	apo (n=146) %	P (n=144) %	apo (n=149) %	P (n=130) %	apo (n=146) %
Nausea	1.4	2.1	2.8	22.2	1.5	42.5
Dizziness	2.0	2.1	1.4	13.4	0.0	22.6
Somnolence	1.4	0.7	0.7	8.7	0.0	11.6
Sweating	0.0	0.7	0.0	9.4	1.5	19.6
Vomiting	0.0	0.0	0.0	2.7	0.0	13.0

Comment: This table reflects a significantly worse adverse event profile for 4 mg and 6 mg doses compared with 2 mg.

Several of the listed adverse events, including nausea, vomiting, dizziness, somnolence, sweating, yawning, and asthenia suggest possible dose-response (see Table 7). In addition, an analysis of the adverse event terms hypotension, syncope, vasodilatation and dizziness also suggest a possible dose-response. This is depicted in Table 8 below.

Table 8. Additional possibly related adverse events suggesting a dose-response.

Adverse event	2 mg Group P (n=147) n(%) apo (n=146) n(%)	4 mg Group P (n=144) n (%) apo (n=149) n (%)	6 mg Group P (n=130) n (%) apo (n=146) n (%)
Hypotension	0(0.0) 1(0.7)	0(0.0) 6(4.0)	0(0.0) 7(4.8)
Syncope	0(0.0) 1(0.7)	0(0.0) 3(2.0)	0(0.0) 3(2.1)
Vasodilatation	1(0.7) 2(1.4)	0(0.0) 4(2.7)	1(0.8) 14(9.6)
Dizziness	3(2.0) 3(2.1)	2(1.4) 20(13.4)	0(0.0) 33(22.6)

Comment: It is noteworthy that 4.0% of patients reported "hypotension" at the 4 mg dose.

Vital signs and electrocardiographic recordings:
There were no statistically significant differences between 2 mg, 4 mg and 6 mg apomorphine and placebo in mean vital sign measurements.

There were 2 clinically significant ECG changes during the study. Neither was considered by the investigator to be related to drug.

Comment: The measurement of vital signs did not actually follow dosing.

Clinical laboratory examinations: There were no statistically significant difference between apomorphine and placebo in any hematology parameter. There were several mean changes in a few chemistry parameters, however, all of these were very small and none thought to be indicative of a clinically significant trend.

In terms of individual patient changes, three patients experienced abnormally high eosinophil counts (two on apomorphine and one on placebo). Six patients experienced abnormally low hematocrit values (five on apomorphine and one on placebo). Two patients had abnormally high total bilirubin (both on apomorphine) and two had high serum transaminases (both on placebo).

Assessment of efficacy and safety:
The F1 formulation was different than the formulation used in the remainder of Phase 3. However, some information can be derived from this study, nevertheless.

The efficacy data reveals evidence of an overall treatment effect with apomorphine. However, it is unclear whether the mean difference noted between drug and placebo at 2 mg is clinically meaningful (32.2% successful attempts with placebo versus 45.8% successful attempts with drug). In addition, it appears that the percentage of "successful patients" (>50% success) with 2 mg is only modestly improved.

This group of patients was physiologically capable of attaining a rigid erection prior to the study. Over 30 patients had >75% successes in the lead-in period.

In terms of safety, there was an overall incidence of syncope of 1.6%. Syncope was seen at 2 mg, 4 mg and 6 mg. Syncope was seen with first dosing and after numerous doses. One syncopal event was accompanied by a life-threatening motor vehicle injury. The adverse event profile is worse with 4 mg and 6 mg, compared with 2 mg and consists of nausea, vomiting, somnolence, sweating, yawning and vasodilatation/hypotension. Four percent of patients experienced hypotension with 4 mg dosing.

Again, it should be noted that this was a carefully selected group of healthy men. These men do not represent the real-world population of men with erectile dysfunction. It is possible that the risks of apomorphine may be greater in the broader ED population.

Clinical Trial M97-658

Design:

This was a double-blind, randomized, placebo-controlled, four-armed study. Each arm consisted of one dose of apomorphine SL (2 mg, 4 mg, 5 mg or 6 mg) versus placebo in a 2-period crossover design. Each treatment period was 4 weeks in duration. The washout period between treatments was 24-96 hours. In each arm, patients could be enrolled into one of 2 sequences (drug first, followed by placebo; or placebo first, followed by drug). Prior to Treatment Period 1, all patients underwent a 2 to 4-week, treatment-free, "lead-in" period. The study was conducted at 35 United States centers. The sponsor intended to enroll 500 patients.

During the treatment periods, patients were instructed to take study drug and attempt intercourse a minimum of 2 times per week. Patients were instructed to take the drug no more than once per 8-hour period. Patients were instructed to take study medication by placing a single tablet under the tongue and allowing it to dissolve completely. Once the tablet was completely dissolved, sexual intercourse could be attempted when the couple was ready. Patients were instructed as follows: "You should limit yourself to a minimum amount of alcoholic beverages during the six hours prior to taking study medication." After at least 2 hours had passed after intercourse, patients and partners were instructed to complete a questionnaire regarding that particular sexual experience.

> **Comment: The requirement that minimal alcohol be consumed prior to taking a tablet may not be practical to expect in a real-world situation.**

Inclusion/exclusion criteria:

Eligible patients were heterosexual males, between 18 and 70 years of age. All men had to have a diagnosis of "erectile dysfunction with no major organic component". Erectile dysfunction was defined as "the ability to attain and maintain an erection firm enough for intercourse with a partner for less than 50% of attempts for a minimum of 3 months prior to Day 1 of treatment Period 1". In addition, all patients had to have demonstrated "an erection of sufficient quality for intercourse on some occasion since the onset of erectile dysfunction as evidenced by nocturnal/morning erections, masturbation, and/or other sexual activity." Finally, all patients underwent nocturnal penile tumescence testing (NPT) using Rigisican at least 60 days prior to Day 1 of Treatment Period 1. All patients had to demonstrate at least 1 successful erection during NPT testing; specifically, a successful erection was defined as one wherein the base of the penis was 55% rigid for at least 10 minutes.

All patients had to be involved in a "stable", heterosexual relationship for at least 6 months. All patients and partners had to agree to attempt intercourse at least 2 times weekly. All patients had to be "judged in good general health as evidenced by medical history and physical examination". All pre-study laboratory values had to be within 15% above or below normal range. Fasting blood glucose had to be <250 mg/dL, unless approval was obtained by the medical monitor. Patients who had up to 75% successful attempts during the lead-in period were eligible for the study. Although patients needed to have a history of <75% success for the 3 months prior to study day 1, some patients who had 75% or more success during the lead-in period were randomized.

> **Comment: This patient population was physiologically capable of getting erections and was generally healthy. This population does not represent the larger ED population.**

Patients were excluded for the following reasons:

1. Presence of "neurologic disease" (e.g. Parkinson's disease, multiple sclerosis, or spinal cord injury).
2. Presence of such genitourinary disorders as history of radical prostatectomy, penile prosthesis, or major penile deformity.
3. Presence of hypogonadism (serum T <280 ng/dL), hyperprolactinemia (serum prolactin >20 ng/mL), diabetes with an elevated glycosylated hemoglobin at baseline, or diabetes with any episode of ketoacidosis with the last 3 months.
4. Presence of major psychiatric disorder.
5. Presence of "cardiovascular disease" (e.g. systolic BP >180 mm Hg and/or diastolic >100 mm Hg while sitting, hypotension [systolic BP< 90 mm Hg while standing]).
6. Presence of gastrointestinal disease (especially, any disorder resulting in the need for anti-nausea medications in the last 6 months).
7. Any cancer other than basal or squamous cell cancer that has not been in remission for at least 5 years.
8. Any pharmacologic therapy for ED within the preceding 3 months.
9. Greater than 75% successes during the lead-in period.
10. History of drug or alcohol abuse within the past 2 years.
11. Smoking greater than 10 cigarettes per day, or the equivalent use of tobacco in other forms.
12. Presence of AIDS or HIV-positive status.
13. History of allergic reaction to morphine or any other opiate.
14. Partners with major affective disorder.
15. Partners with a history of female sexual dysfunction.

> **Comment: Inclusion and exclusion criteria were fairly restrictive. The study population is a relatively healthy group and again, is not indicative of the erectile dysfunction population at large.**

Efficacy endpoints and statistical analysis plan:

The primary efficacy endpoint was "the home-use success rate during each treatment period" where an attempt was defined as taking a study drug and completing a questionnaire and success was defined as achieving an erection firm enough for intercourse according to the patient's opinion. Secondary efficacy endpoints included:

1. Achievement of an erection firm enough for intercourse according to the partner's opinion.
2. Number of patients with successful response (defined as erection sufficient for intercourse in 50% or greater number of attempts in a treatment period)
3. Time to erection
4. Duration of erection
5. International Index of Erectile Function (IIEF) results at the end of each treatment period
6. Brief Sex Function Inventory questionnaire for the partner
7. Fugl-Meyer Life Satisfaction Scale, and
8. A "Treatment Satisfaction Scale".

The per-protocol statistical analysis plan for the primary endpoint was that the Cochran-Mantel-Haenszel method. In this methodology, each patient was to be considered as a separate stratum, and the mean score would be compared between active and placebo treatments. This analysis would be performed separately for each arm of the study (2 mg, 4 mg, 5 mg and 6 mg). All patients who had at least one attempt in both treatment periods would be included in the analysis.

It is important to note that once the patient was randomized to one of the eight possible sequences, the first dose in Treatment Period 1 was given in the office. The patient was observed

for 2 hours after dosing. The same procedure was conducted for the first dose in Treatment Period 2.

Withdrawals, compliance, and protocol deviations:
Patient disposition:
Five hundred twenty men were randomized into the study. All 520 patients took at least one dose of blinded study drug. Four hundred eighty-eight (488) patients took at least one dose of apomorphine SL. Four hundred four (404) patients completed the study. Of the 116 patients who discontinued the study, 36 discontinued because of adverse events. (Table 1)

Table 1. Reasons for study discontinuation

	APO 2 mg	Placebo	APO 4 mg	Placebo	APO 5 mg	Placebo	APO 6 mg	Placebo
Adverse event	1	0	7	1	11	0	11	2
Noncompliance	2	1	1	2	4	1	5	2
Complete lack of efficacy	0	1	0	0	1	1	0	1
Partial efficacy	2	1	0	0	0	0	0	0
Patient request	2	7	2	3	4	2	3	1
Partner request	0	0	0	0	0	0	2	2
Lost to follow-up	1	4	3	2	2	2	5	2
Death	0	0	0	0	0	0	0	0
Other	0	1	2	2	1	0	1	2

Comment: Adverse events comprised the largest number of reasons for study discontinuation and a dose-related effect is suggested.

The adverse events resulting in study discontinuation are discussed in the safety analysis.

Treatment compliance: Home-use questionnaires were used to assess compliance.

Protocol deviations: Six patients were included in the study who did not meet the eligibility criteria. Two patients "failed" NPT testing. One patient was included who had >50% successful attempts in the 3 months prior to Treatment Period Day 1. One patient was 71 years old (>70 years). One patient smoked >10 cigarettes per day. One patient had a serum T level <280 ng/dL (279 ng/dL). There were no major deviations during the course of the trial.

Efficacy analysis:
The primary endpoint was the percentage of attempts in which the patient thought that he had achieved an erection firm enough for intercourse.

The sponsor believes that the results of an analysis of the proportion of all attempts resulting in an erection firm enough for intercourse showed statistically significant advantages for each dose level of apomorphine SL over its corresponding placebo dose. These results are summarized in Table 2.

Table 2. Percentage of attempts resulting in an erection firm enough for intercourse (based on all attempts)

Dose	(n)	**Placebo** **Success/attempts**	**%**	Apomorphine SL Success/attempts	%	Apomorphine SL vs. Placebo P-value
2 mg	(112)	370/980	37.8	432/982	44.0	0.012
4 mg	(99)	310/848	36.6	519/893	58.1	<0.001
5 mg	(103)	248/858	28.9	463/877	52.8	<0.001
6 mg	(87)	211/719	29.3	470/772	60.9	<0.001

Comments: The data presented are the sum of all successes and all attempts for each group. When the data was re-analyzed as the mean percentage of successful attempts per individual, the results were essentially the same.

Even though the 2 mg data show statistical significance, the clinical significance of an increase in successful attempts from 37.8% (placebo) to 44% (2 mg) is questionable.

Similar results were observed for the secondary endpoint, percentage of attempts resulting in intercourse (Table 3).

Table 3. Percentage of attempts resulting in intercourse (based on all attempts)

Dose	(n)	**Placebo** **Success/attempts**	**%**	Apomorphine SL Success/attempts	%	Apomorphine SL vs. Placebo P-value
2 mg	(112)	348/971	35.8	404/977	41.4	0.031
4 mg	(99)	290/842	34.4	496/886	56.0	<0.001
5 mg	(103)	232/851	27.3	446/867	51.4	<0.001
6 mg	(87)	198/713	27.8	447/769	58.1	<0.001

Comment: At the 2 mg dose, there is again marginal statistical significance and the clinical significance of the treatment effect is questionable.

Another secondary endpoint was patients who were deemed a treatment success. Success occurred if at least 50% of all attempts while using the treatment resulted in erections firm enough for intercourse (Table 4).

Table 4. Results of the analysis of percentages of patients deemed a treatment "success" (based on all attempts)

Dose	(n)	Placebo #success	%	Apomorphine SL #success	%	Apomorphine SL versus placebo p-value
2 mg	(112)	46	41.1	54	48.2	0.226
4 mg	(99)	38	38.4	64	64.6	<0.001
5 mg	(103)	34	33.0	60	58.3	<0.001
6 mg	(87)	25	28.7	57	65.5	<0.001

Comment: The 2 mg dose did not demonstrate statistical significance.

Comments The sponsor submitted numerous tables in which data is presented from secondary endpoints. The reviewer has selected those data to present which are considered most clinically relevant.

Another secondary endpoint was the International Index of Erectile Function domain scores. Table 5 presents the results of the EF domain only. The EF domain consists of 6 questions that refer to the quality of the patient's erection in the last 4 weeks. The lowest possible score is 0 and highest possible score is 30.

Table 5. Results from the IIEF EF domain

Dose	Baseline	Placebo mean	APO Mean	APO SL versus placebo p-value
2 mg	12.4 (n=110)	13.5 (n=112)	15.4 (n=112)	0.002
4 mg	12.7 (n= 99)	13.9 (n=101)	18.7 (n=101)	<0.001
5 mg	12.6 (n=103)	12.3 (n=107)	17.7 (n=107)	<0.001
6 mg	12.5 (n= 87)	12.3 (n= 88)	18.5 (n= 88)	<0.001

Comment: The actual mean difference between apomorphine SL 2 mg and placebo was 1.9 points in the EF domain. The actual mean change-from-baseline in the apomorphine SL 2 mg group was approximately 3.0 points. A mean 3-point change-from-baseline may not be clinically meaningful, and a mean 1.9-point improvement over placebo may not be clinically meaningful.

Safety Analysis :
Extent of exposure : The extent of apomorphine SL exposure is depicted in Table 6.

Table 6. Extent of apomorphine SL exposure

Number of patients exposed to a given number of doses					
Dose	1	2-5	6-12	13-21	Total
2 mg	3	7	96	21	127
4 mg	12	8	73	24	117
5 mg	8	14	87	19	128
6 mg	11	14	67	24	116

Comment: The extent of exposure in this trial was limited to 4 weeks.

Deaths : There were no study deaths.

Serious adverse events:
Three serious adverse events were reported during this study (one report on placebo and two on apomorphine):

- A 55 year old male received his first dose of study drug for Treatment Period 2. Two days later, he experienced chest pain lasting five days. Work-up revealed stenosis of the right coronary artery. When the blind was broken, he was found to be on placebo.

- A 59 year old male received his first dose of study drug in the office for Treatment Period 2 on March 23, 1998 (apomorphine 2 mg). He was dispensed a box of 19 tablets at that time. On April 25, 1998, he suffered a temporary loss of consciousness and was involved in a car accident. He was hospitalized for a wrist fracture. He used one tablet of study drug during

this period. He could not remember the exact date that he took that tablet. He returned the remainder of the unused tablets. The investigator considered the AE as unrelated to study drug.

Comment: Because the patient was unable to remember when he used his last dose of apomorphine, it cannot be concluded that this event was unrelated to study medication

- A 54 year old male experienced nausea, hypotension, diaphoresis, light-headedness and a 30-second loss of consciousness (syncope) approximately 1 hour after his first in-office dose of apomorphine 6 mg. He received 0.4 mg of atropine intravenously. The duration of the event was reported as 1 hour 10 minutes. The investigator believed that the event was definitely related to study medication. The investigator believed that this patient's condition "required intervention to prevent impairment or damage".

Premature discontinuations due to adverse event:
Thirty-six patients discontinued the study due at least in part to an adverse event. Of these, 25 patients reported symptoms which may have been related to an acute drop in the blood pressure following dosing with apomorphine. The sponsor believes that only five patients actually experienced "syncope" during this trial. However, many of the adverse event reports leading to discontinuation described such terms as "hypotension", "vasodilatation", "light-headedness", "pallor", "fatigue", "sleepiness", "clamminess", "queeeziness", etc. These 25 patients are described in detail below.

- The 54 year old patient who expereinced **syncope** , was already discussed in the Serious Adverse Events section.

- A 61 year old male experienced an onset of nausea approximately 2 minutes after taking his fourth dose of apomorphine 6 mg. He became light-headed, went into the bathroom, experienced profuse sweating, **lost consciousness** ("**syncope"**) and woke up on the bathroom floor. It was estimated that he was unconscious for a few seconds. The investigator believed that the event was possibly related to apomorphine. He was discontinued. The sponsor believes that the patients use of Zovirax for intermittent genital herpes 2 days previously may have contributed to the event.

  Comments: This patient is noteworthy because he fainted after his fourth dose of apomorphine, not after his first dose.

- A 66 year old male experienced "**syncope**" 40 minutes after his first in-office dose of apomorphine 4 mg. The syncopal episode was reported to last approximately "10 seconds". He also experienced hypotension (90/58), moderate nausea, light-headedness, pallor and diaphoresis. He was discontinued. The investigator believed the event was probably related to apomorphine.

- A 57 year old patient experienced diaphoresis, **light-headedness**, nausea, pallor and yawning "with" his first in-office dose of apomorphine 5 mg. The duration of this event was reported as 30-60 minutes. He was discontinued. The investigator believed the event was probably related to apomorphine.

- A 53 year old patient experienced **hypotension**, bradycardia (heart rate = 52 bpm), light-headedness, drowsiness, and yawning "with" his first in-office dose of apomorphine 4 mg. The duration of these events was approximately 10 minutes for bradycardia, 14 minutes for hypotension and 61 minutes for drowsiness. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 52 year old patient experienced **hypotension** for 9 minutes, bradycardia for 13 minutes, light-headedness for 17 minutes, nausea for 12 minutes and sleepiness for 55 minutes "with" his first in-office dose of apomorphine 4 mg. Upon re-challenge 3 days later, similar symptoms were observed, including dizziness (7 minutes), light-headedness (7 minutes), sleepiness (74 minutes) and yawning (72 minutes). No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 50 year old patient experienced diaphoresis, **hypotension**, and pallor with the first in-office dose of apomorphine 5 mg. The duration of the hypotension was 14 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 39 year old patient experienced "**queeziness**" fatigue, nausea and vomiting approximately 30 minutes after his first in-office dose of apomorphine 5 mg. The "queeziness" lasted for 1 hour and 18 minutes. Upon re-challenge six days later, similar symptoms were observed. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 51 year old patient experienced **light-headedness**, nausea and yawning 40 minutes after his first in-office dose of apomorphine 5 mg. The duration of the events was 30 minutes. After a second dose, similar symptoms were experienced. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 64 year old patient experienced **hypotension**, bradycardia, diaphoresis and nausea with his first in-office dose of apomorphine 6 mg. The patient was given 0.4 mg of intravenous atropine. The duration of the event (as listed on the CRF) was 1.5 hours. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 64 year old patient experienced **light-headedness**, diaphoresis, nausea and pallor with his first in-office dose of apomorphine 6 mg. Upon re-challenge seven days later, similar symptoms were observed. The duration of the events was 70 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 64 year old patient experienced **light-headedness**, fatigue, nausea, pallor and retching with his first in-office dose of apomorphine 5 mg. The duration of fatigue, nausea and pallor was 70 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 49 year old patient experienced **fatigue** and nausea after his ninth dose of apomorphine 6 mg in the first treatment period. He had experienced similar symptoms following previous

doses. The duration of the event was 22 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 59 year old patient experienced **hypotension**, sweating, yawning and sleepiness after his first in-office dose of apomorphine 4 mg. The duration of the event was 55 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 50 year old patient experienced **hypotension**, diaphoresis, light-headedness, nausea and vomiting after his first in-office dose of apomorphine 4 mg. The duration of the hypotension was 1 hour 20 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 68 year old patient experienced **pallor**, sweating and nausea after his sixth dose of apomorphine 5 mg. Similar symptoms were experienced with the previous dose of apomorphine. The duration of the event was 25 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 56 year old patient experienced **drowsiness**, diaphoresis, nausea and vomiting after his first in-office dose of apomorphine 5 mg. The duration of the diaphoresis and nausea was 1 hour 25 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 62 year old patient experienced **dizziness**, flushing and nausea with his third dose of apomorphine 5 mg. The duration of the dizziness was 30 minutes and the nausea was 1 hour 20 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 69 year old patient experienced **hypotension**, light-headedness, diaphoresis, nausea, sleepiness, vomiting and yawning with his first in-office dosing of apomorphine 6 mg. The duration of the hypotension was 8 minutes, and yawning, 72 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 49 year old patient experienced **hypotension**, weakness, diaphoresis, and nausea with his first in-office dosing of apomorphine 6 mg. The duration of the hypotension was 10 minutes, nausea 65 minutes, and weakness, 75 minutes. Upon re-challenge, similar symptoms were observed. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 60 year old patient experienced **hypotension**, diaphoresis, and nausea with his first in-office dosing of apomorphine 5 mg. The duration of the hypotension was 10 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 52 year old patient experienced **hypotension**, diaphoresis, sleepiness, and nausea with his first in-office dosing of apomorphine 4 mg. The duration of the hypotension was 30 minutes.

The sleepiness lasted for 1 hour 38 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 68 year old patient experienced **lightheadedness** and sleepiness with his first in-office dosing of apomorphine 6 mg. The duration of the events was 60-90 minutes. He again experienced lightheadedness, weakness, diaphoresis and chills after his seventh dose of apomorphine 6 mg. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 69 year old patient experienced **vasodilation** and nausea with his first in-office dosing of apomorphine 6 mg. The duration of the vasodilation was 25 minutes, and nausea 60 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 52 year old patient experienced "**clamminess**", nausea and retching with his first in-office dosing of apomorphine 4 mg. The duration of the retching was 2 minutes and nausea almost 24 hours. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

Of the remaining 11 discontinuations due to AE, seven were clearly not related to study drug. One patient had foot surgery. One patient had chronic intermittent claudication. One patient had new-onset atrial fibrillation on the last day of Treatment Period 1 (on placebo). One hypertensive patient had an increased BP (188/111) on the last day of Treatment Period 1 (on placebo). One patient had increased headaches during Treatment Period 1 (on placebo). One patient was noted to have sinus bradycardia on an EKG during Treatment Period 1 (on placebo). One patient had chest pain two days after his first in-office dose of placebo (see SAEs).

Of the remaining four discontinuations, one patient had epididymal pain while on apomorphine 6 mg. Two reported "sleepiness" while on apomorphine. One patient experienced loss of consciousness and a car accident during one of the treatment periods (while on 2 mg apomorphine). It is unknown if he actually took a tablet prior to that incident.

Overall adverse effects: In the text of the study report, the sponsor summarized the adverse events that were considered by the investigator to be at least possibly related to apomorphine and reported by at least 10% of all patients.

When the overall AEs were tabulated in this manner the results are demonstrated in Table 7.

Table 7. Treatment-emergent adverse events at least possibly related to apomorphine and reported by ≥10% of all patients.

Adverse event	2 mg Group P (n=130) %	2 mg Group apo (n=127) %	4 mg Group P (n=117) %	4 mg Group apo (n=117) %	5 mg Group P (n=118) %	5 mg Group apo (n=128) %	6 mg Group P (n=106) %	6 mg Group apo (n=116) %
Nausea	0.8	1.6	1.7	21.4	2.5	32.8	1.9	35.3
Dizziness	3.1	2.4	1.7	14.5	3.4	20.3	0.9	16.4
Sweating	0.0	1.6	0.0	10.3	0.0	14.8	0.9	20.7
Somnolence	3.9	2.4	1.7	12.8	1.7	11.7	0.9	17.2
Yawning	0.8	2.4	0.9	11.1	1.7	12.5	0.0	15.5
Vomiting	0.0	0.8	0.0	4.3	0.0	10.2	0.0	8.6
Vasodilatation	1.5	0.8	0.9	3.4	1.7	7.8	1.9	10.3
Asthenia	0.0	0.8	0.8	5.1	0.9	4.7	0.0	11.2

<u>Comment</u>: This table reflects a significantly worse adverse event profile for 4 mg, 5 mg and 6 mg compared with 2 mg.

Several of the listed adverse events, including nausea, vomiting, dizziness, somnolence, sweating, yawning, and asthenia suggested possible dose-response (see Table 7). In addition, an analysis of the adverse event terms hypotension, syncope and vasodilatation also suggest a possible dose-response. This is depicted in Table 8 below.

Table 8. Additional possibly related adverse events suggesting a dose-response.

Adverse event	2 mg Group P (n=130) n(%)	2 mg Group apo (n=127) n(%)	4 mg Group P (n=117) n (%)	4 mg Group apo (n=117) n (%)	5 mg Group P (n=118) n (%)	5 mg Group apo (n=128) n (%)	6 mg Group P (n=106) n (%)	6 mg Group apo (n=116) n (%)
Hypotension	0(0.0)	1(0.8)	0(0.0)	7(6.0)	0(0.0)	3(2.3)	0(0.0)	18(15.5)
Syncope	0(0.0)	0(0.0)	0(0.0)	1(0.9)	0(0.0)	0(0.0)	0(0.0)	4(3.5)
Vasodilatation	2(1.5)	1(0.8)	1(0.9)	4(3.4)	2(1.7)	10(7.8)	1(0.9)	12(10.3)

<u>Comment</u>: It is noteworthy that 6.0% of patients reported "hypotension" at the 4 mg dose.

Two additional patients experienced syncope without discontinuation from the trial. These patients are described in detail below:

- A 70 year old patient experienced the onset of vomiting 55 minutes after his first in-office dose with apomorphine 6 mg. As he was walking to the exam room to lie down, he lost consciousness ("**syncope**"). He was unconscious for less than 1 minute. Upon re-challenge, he experienced only sleepiness. He took drug one more time, experienced nausea and discontinued from the study without taking additional drug. The sponsor believed that the event may be related to a "viral syndrome" the patient reported 2 days prior to the visit. The investigator believed the event was possibly related to apomorphine.

- A 69 year old patient experienced **syncope** 45 minutes after his third dose of apomorphine 6 mg. He reported "fainting briefly" (estimated as less than 30 seconds). He was also dizzy

(for 15 minutes) and diaphoretic (for 1 hour 30 minutes). He was re-challenged without incident and went on to take an additional 13 tablets. The investigator believed the event was probably related to apomorphine.

Comments: This patient is noteworthy because he fainted after his third dose of apomorphine, not after his first dose.

Vital signs and electrocardiographic recordings:
There were no statistically significant differences between 2 mg, 4 mg and 5 mg apomorphine and placebo in mean vital sign measurements. There was a statistically significant increase in pulse rate between 6 mg apomorphine and placebo.

Comment: Measurement of vital signs did not actually follow dosing.

One patient experienced clinically significant EKG changes during the study; he only received placebo during the trial.

Comment: ECGs were not obtained following dosing.

Clinical laboratory examinations: A statistically significant difference between apomorphine 5 mg and placebo was observed in percentage of neutrophils and lymphocytes on CBC. A statistically significant difference between apomorphine 5 mg and 2 mg and placebo was observed in serum creatinine. A statistically significant difference between apomorphine 4 mg and placebo was observed in total bilirubin.

Comment: All of these differences were extremely small and clinically insignificant.

Several patients experienced significant laboratory abnormalities while taking apomorphine. None of these were assessed to be clinically significant by the individual investigators. These included: two patient with high monocyte counts (one on drug and one on placebo), three patients with high eosinophil counts (two on drug and one on placebo), four patients with low total RBC count (three on drug and one on placebo), seven patients with high serum glucoses (four on drug and three on placebo), one patient with a high BUN (on drug), three patient with high total bilirubin (one on drug and 2 on placebo), four patients with high SGOT/SGPT (two on drug and two on placebo), and four patients with high serum triglycerides (two on drug and two on placebo).

Sponsor's assessment of efficacy and safety:
The sponsor believes that this study demonstrates that apomorphine SL 4 mg and 5 mg tablets were well-tolerated and effective treatments for erectile dysfunction.

Of particular note, the sponsor believes that the most common side effects were nausea, dizziness, somnolence and sweating, many of which "subsided with subsequent dosing". The sponsor believes that the most serious side effect was syncope, reported in 5 patients (or "1%" of total). The sponsor believes that the syncopal events were "brief" ("reported duration of 1 second to one minute"). The sponsor believes that four syncopal events occurred at the highest dose (6 mg) and only 1 occurred with the 4 mg dose. The sponsor believes that three of the five syncopes occurred with the first dose. The sponsor believes that in two cases, re-challenge was negative.

Assessment of efficacy and safety:
The efficacy data reveal evidence of an overall treatment effect with apomorphine. However, the effect seen with the 2 mg dose is not likely to be meaningful to the individual patient. In the 2 mg group, the percentage of successful responders was not significantly different than placebo. The EF domain scores from the IIEF may not reflect a clinically meaningful treatment effect with the 2 mg dose.

This group of patients all were physiologically capable of attaining a rigid erection prior to this study.

In terms of safety, there is evidence that a significant proportion of patients will not tolerate apomorphine. This conclusion is based on an adverse event profile of nausea, dizziness, hypotension, sweating, vomiting, etc. More important, however, is the pattern of acute hypotension, bradycardia, nausea, vomiting, diaphoresis and possible syncope early in treatment (usually following the first dose). In one patient, the investigator believed that serious impairment or permanent damage could have ensued without immediate medical intervention. In several patients, hypotensive episodes occurred after the first dose. Most medically-emergent cases occurred at the higher doses (5 mg and 6 mg), but some occurred with the 4 mg dose. In addition, 6.0% of patients taking 4 mg reported the adverse event of "hypotension".

Of note, the sponsor did not seek approval for the 5 mg and 6 mg doses based on safety concerns, suggesting a very narrow therapeutic index for this drug.

It should be noted that this was a carefully selected group of healthy men, who were carefully followed in a clinical trial. The real-world population of men with erectile dysfunction may be at increased risk.

Clinical Trial M97-763

Design:

This was a double-blind, randomized, placebo-controlled, parallel-group study. The four parallel groups were as follows:

1. Placebo
2. Fixed dose 6 mg apomorphine
3. Fixed dose 5 mg apomorphine
4. Voluntary dose-optimization regimen consisting of 2 mg, 4 mg, 5 mg and 6 mg apomorphine.

The study design included a 2-4 week lead-in period and an eight-week, double-blind treatment period. Prior to the treatment period all patients were randomized to one of the above groups. After the lead-in period, all patients began their blinded randomized study medication on Day 1. During the first four weeks of the treatment period, patients and physicians could alter the dose on a weekly basis, based on safety and efficacy. However, in all groups except the "voluntary dose-optimization" group, the dose actually was not changed. During the last 4 weeks of the treatment period, all patients remained on their "optimized" dose. Again, it is important to note that only the "voluntary dose-optimization" group actually had their dose altered during the trial. In the other groups, both the patients and the physicians were blinded to the fact that the dose was actually staying the same.

The study was conducted at 59 United States centers. The sponsor intended to enroll 450 patients.

> **Comment: It should be noted that during the conduct of this trial, enrollment into the 6 mg dose group was terminated due to safety concerns. Four hundred and two patients had been enrolled at that point.**

At the first office visit of treatment period 1, a randomized dose of study medication was given to the patient and the patient was required to remain in the office for 2 hours post-dosing.

During the treatment periods, patients were instructed to take study drug and attempt intercourse a minimum of 2 times per week. Patients were instructed to take the drug no more than once per 8-hour period. Patients were instructed to take study medication by placing a single tablet under the tongue and allowing it to dissolve completely. Once the tablet was completely dissolved, sexual intercourse could be attempted when the couple was ready. Patients were instructed as follows: "You should limit yourself to a minimum amount of alcoholic beverages during the six hours prior to taking study medication." After at least 2 hours had passed after intercourse, patients and partners were instructed to complete a questionnaire regarding that particular sexual experience.

> **Comment : The requirement that minimal alcohol be consumed prior to taking a tablet may not be practical to expect in a real-world situation.**

Patients who completed M97-763 were allowed to enroll in a 3-year, open-label extension study (M97-682).

Inclusion/exclusion criteria:

Eligible patients were heterosexual males, between 18 and 70 years of age. All men had to have a diagnosis of "erectile dysfunction with no major organic component". Erectile dysfunction was defined as "the ability to attain and maintain an erection firm enough for intercourse with a

partner for less than 50% of attempts for a minimum of 3 months prior to Day 1 of Treatment Period 1". In addition, all patients had to have demonstrated "history of ability to attain an erection on some occasion since the onset of erectile dysfunction as evidenced by nocturnal/morning erections, and/or sexual activity." Finally, all patients underwent nocturnal penile tumescence testing (NPT) using Rigisican at least 60 days prior to Day 1 of Treatment Period 1. All patients had to demonstrate at least one successful erection during NPT testing; specifically, a successful erection was defined as one wherein the base of the penis was at least 55% rigid for at least 10 minutes.

All patients had to be involved in a "stable", heterosexual relationship for at least 6 months. All patients and partners had to agree to attempt intercourse at least 2 times weekly. All patients had to be "judged in good general health as evidenced by medical history and physical examination". All pre-study laboratory values had to be within 15% above or below normal range. Fasting blood glucose had to be <250 mg/dL, unless approval was obtained by the medical monitor. Patients who had up to 75% successful attempts during the lead-in period were eligible for the study. Although patients needed to have a history of <75% success for the 3 months prior to study day 1, some patients who had 75% or more success during the lead-in period were randomized.

Comment: This patient population was physiologically capable of getting erections and was generally healthy, and does not represent the larger ED population.

Patients were excluded for the following reasons:

1. Presence of "neurologic disease" (e.g. Parkinson's disease, multiple sclerosis, or spinal cord injury).
2. Presence of such genitourinary disorders as history of radical prostatectomy, penile prosthesis, or major penile deformity.
3. Presence of hypogonadism (serum T <280 ng/dL), hyperprolactinemia (serum prolactin >20 ng/mL), diabetes with an elevated glycosylated hemoglobin at baseline, or diabetes with any episode of ketoacidosis with the last 3 months.
4. Presence of major psychiatric disorder.
5. Presence of "cardiovascular disease" (e.g. systolic BP >180 mm Hg and/or diastolic >100 mm Hg while sitting, hypotension [systolic BP< 90 mm Hg while standing]).
6. Presence of gastrointestinal disease (especially, any disorder resulting in the need for anti-nausea medications in the last 6 months).
7. Any cancer other than basal or squamous cell cancer that has not been in remission for at least 5 years.
8. Any pharmacologic therapy for ED within the preceding 3 months.
9. Greater than 75% successes during the lead-in period.
10. History of drug or alcohol abuse within the past 2 years.
11. Smoking greater than 10 cigarettes per day, or the equivalent use of tobacco in other forms.
12. Presence of AIDS or HIV-positive status.
13. History of allergic reaction to morphine or any other opiate.
14. Partners with major affective disorder.
15. Partners with a history of female sexual dysfunction.

Comment: Inclusion and exclusion criteria were fairly restrictive. The study population is a relatively healthy group and again, is not indicative of the erectile dysfunction population at large.

Efficacy endpoints and statistical analysis plan:
The primary efficacy endpoint was "the home-use success rate during each treatment period" where an attempt was defined as taking a study drug and completing a questionnaire and success was defined as achieving an erection firm enough for intercourse according to the patient's opinion. The rate was based on the patients last eight attempts.

Secondary efficacy endpoints included:
1. Achievement of an erection firm enough for intercourse according to the partner's opinion.
2. Number of patients with successful response (defined as erection sufficient for intercourse in 50% or greater number of attempts in a treatment period)
3. Percentage of attempts resulting in intercourse according to patient and partner
4. Time to erection
5. Duration of erection
6. International Index of Erectile Function (IIEF) results
7. Brief Sex Function Inventory questionnaire for the partner
8. Fugl-Meyer Life Satisfaction Scale,
9. SF-36 Quality of Life Questionnaire, and
10. A "Treatment Satisfaction Scale".

The primary analyses of the primary endpoint was a one-way analysis of variance model (ANOVA) with effect for treatment group. A secondary analyses for the primary endpoint was an analysis using the Cochran-Mantel-Haenszel method with investigative site as strata. All patients who had at least one attempt the treatment period would be included in the analysis.

Withdrawals, compliance, and protocol deviations:
Patient disposition:
Five hundred sixty-nine men were randomized into the study. All 569 patients took at least one dose of blinded study drug. Four hundred forty-four (444) patients completed the study. Of the 125 patients who discontinued the study, 46 discontinued because of adverse events. (Table 1)

Table 1. Reasons for study discontinuation

	APO 2-6 mg n=242	APO 5 mg n=89	APO 6 mg n=119	Placebo n=119
Adverse event	25	8	8	1
Noncompliance	8	3	5	3
Complete lack of efficacy	6	3	1	2
Partial efficacy	2	1	2	3
Patient request	6	3	6	1
Partner request	6	0	1	0
Lost to follow-up	6	2	2	3
Other	0	2	4	1

Comment: Based on the results in Table 1, there does not appear to be a safety advantage using the dose-optimization regimen.

The adverse events resulting in study discontinuation are discussed in the safety analysis.

Treatment compliance: The sponsor states that treatment compliance was monitored throughout the treatment period by "tracking home-use questionnaires".

Protocol deviations: All data from one investigative site (n=14) was disqualified because the sponsor determine that the site was not complying with protocol procedures. The site was not keeping adequate source documentation.

Several patients were enrolled in the study who did not satisfy all entry criteria. The most common problem (n=14, or 2.5% of total) was that some men actually had greater than 50% successes at intercourse in the 3 months prior to Day 1 of the Treatment Period but answered the question incorrectly on the baseline questionnaire. Several patients took two doses twice within 8 hours. One patient had a baseline diagnosis of bipolar disorder but was included nevertheless. Two patients smoked more than 10 cigarettes per day. Four patients were over 70 years of age. Several patients were dosed incorrectly on rare occasions during the treatment period.

Efficacy analysis:
The primary endpoint was the percentage of attempts in which the patient thought he had achieved an erection firm enough for intercourse, based on the last eight attempts.

The sponsor believes that the results of an analysis of this endpoint showed a statistically significant advantage for each dose level of apomorphine SL over placebo dose, including the dose-optimization group. When all attempts made on 5 mg and 6 mg were excluded from the analysis in the dose-optimization group, the comparison to placebo was still statistically significant. These results are summarized in Table 2.

Table 2. Mean percentage of attempts resulting in an erection firm enough for intercourse (based on last 8 attempts)

Dose	(n)	**Treatment Mean %**	Apomorphine SL vs. Placebo P-value
2 mg-6mg	(232)	53.9	<0.001
2 mg-4 mg	(232)	47.5	<0.003
6 mg	(84)	53.4	<0.001
5 mg	(112)	54.6	<0.001
Placebo	(114)	34.7	

Comments: It is noteworthy that a mean improvement of 12.8% was noted with apomorphine versus placebo in the dose-optimizing group.

Similar results were observed in the secondary endpoint of percentage of attempts resulting in intercourse (Table 3).

Table 3. Percentage of attempts resulting in intercourse (based on last eight attempts)

Dose	(n)	**Treatment Mean %**	Apomorphine SL vs. Placebo P-value
2 mg-6mg	(232)	52.2	<0.001
2 mg-4 mg	(232)	45.0	0.005
6 mg	(84)	49.6	0.003
5 mg	(112)	52.3	<0.001
Placebo	(114)	33.0	

Another secondary endpoint was patients who were deemed a treatment success. Success occurred if at least 50% of all attempts while using the treatment resulted in erections firm enough for intercourse (Table 4).

Table 4. Results of the analysis of percentages of patients deemed a treatment "success" (based on last eight attempts)

Dose	(n)	#successful patients	%	Apomorphine SL versus placebo p-value
2 mg-6 mg	(232)	140	60.3	<0.001
4 mg-4 mg	(232)	125	53.9	<0.009
6 mg	(84)	46	54.8	<0.030
5 mg	(112)	64	57.1	<0.008
Placebo	(114)	44	38.6	

Another secondary endpoint were the International Index of Erectile Function domain scores. Table 5 presents the results of the EF domain only. The EF domain consists of 6 questions that refer to the quality of the patient's erection in the last 4 weeks. The lowest possible score is 0 and highest possible score is 30.

Table 5. Results from the IIEF EF domain, presented as means

Dose	Baseline	Week 4	Week 8	APO SL versus placebo p-value
2 mg-6mg	12.6 (n=210)	18.5	19.5	<0.001
6 mg	12.0 (n= 73)	17.6	18.8	<0.001
5 mg	12.7 (n= 99)	18.3	19.2	<0.001
Placebo	12.1 (n=104)	13.6	13.9	

Comment: The result for the dose-optimization group may be somewhat inflated because of the inclusion of attempts using doses of 5 mg and 6 mg. It is not possible to derive a IIEF domain score for a month-long treatment period without including those attempts.

Safety Analysis :
Extent of exposure : The extent of apomorphine SL exposure is depicted in Table 6.

Table 6. Extent of apomorphine SL exposure. Number of patients exposed to a given dosage.

Dose	1	2-5	6-10	11-20	21-30	31-40	Total
5 mg	1	9	14	47	43	5	119
6 mg	3	4	8	43	28	3	89
2-6 mg	3	15	18	99	90	17	242

Deaths : There were no study deaths.

Serious adverse events:
Seven serious adverse events were reported during this study. All were taking apomorphine

- A 42 year old man experienced nausea and **syncope** after his first dose of apomorphine 5 mg (eight dose of apomorphine overall). The dose was given in the office. One hour after dosing, he felt nauseated. He stood up to "find someone". The nurse on duty heard a loud "thump" and found the patient on the floor, unconscious. Ammonia was initiated and the patient woke up. He had bitten his tongue and he had an abrasion on the back of his head. He was confused. Approximately 15 minutes later, "he felt better". The abrasion was cleaned and bandaged. His mouth was inspected and rinsed. The following day he complained of a headache. Two days after the incident he reported feeling better. Five days after the incident, he complained of a headache. Results of a CT scan of the head performed on that day revealed a **left occipital skull fracture** with a cortical contusion of the frontal lobe of the brain. MRI of the brain showed a non-depressed left occcipital skull fracture and a contra-coup injury invoving a contusion of the right frontal lobe gyrus. He was discontinued from the study. The investigator believed that the event was definitely related to the study drug. The patient actually enrolled in the long-term, open-label trial and is ongoing in the trial at this time.

  Comment: It is notable that this patient was in the dose-optimizing group

- A 50 year old man experienced nausea 25 minutes after his first dose of 4 mg apomorphine (sixth dose of apomorphine overall). The dose was given in the office. The nurse on duty left the patient to get a dose of Compazine. Upon returning, the office staff found the patient **unconscious** , **unresponsive** , **apneic**, diaphoretic and incontinent of urine. "Within a few seconds", without intervention, he began to breath spontaneously and regained consciousness. His vital signs revealed a heart rate of 42 bpm and a blood pressure of 140/80. He was given intravenous saline infusion and oxygen. He was given 10 mg of Compazine intramuscularly, but this did not relieve his nausea. His bradycardia persisted for at least 1 hour. He was then admitted to the hospital for overnight observation. He was discharged in stable condition, the next day. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

  Comment: It is notable that this patient was in the dose-optimizing group.

- A 60 year old man experienced a **severe hypotensive event** 8 minutes after his first dose of 6 mg apomorphine (eleventh dose of apomorphine overall). The dose was given in the office. The patient began to complain of nausea, sweating, yawning and was noted to be pale. His blood pressure was noted to be 80/50. He received intravenous saline and 10 mg of Compazine. The duration of the event was 27 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

  Comment: It is notable that this patient was in the dose-optimizing group.

In the other 4 serious adverse event cases, there did not appear to be a relationship to study drug. For example, one patient suffered a lower GI bleed immediately after a colonoscopic polypectomy, 6 days after his last dose of apomorphine. Another suffered a myocardial infarction and pneumonia three weeks after his last dose of study medication. Another experienced a right-sided CVA four days after his last dose of study medication. Another patient was diagnosed with prostate cancer during the Treatment Period.

Comment: Serious adverse events occur despite careful dose titration of apomorphine

Premature discontinuations due to adverse event:
Forty-two patients (7.4% of total) discontinued the study primarily due to an adverse event. Of these, six patients discontinued due to a serious AE. These have been described above. Of the remaining thirty-six (36) patients, the majority discontinued after an acute event immediately following dosing with apomorphine. Some patients discontinued due to intolerable nausea and/or vomiting. Several complained of lethargy and fatigue. There were at least eight patients who discontinued due to symptoms consistent with vasodilatation or hypotension. Ten patients discontinued due to symptoms related to mouth, tongue or throat irritation. On most occasions, patients discontinued for more than one of these reasons. Below, the reviewer has selected typical cases from the sponsor's submission to depict the reasons for premature discontinuation due to AEs. It is important to note that this is not a comprehensive list, given time and space limitations in this review.

Nausea and vomiting:

- A 66 year old male experienced nausea and vomiting, headache, facial flushing, "head fullness", bloodshot eyes, tearing and tightness of the throat after his third dose of apomorphine 5 mg (eleventh dose overall). These symptoms lasted 5 seconds to 2 hours. He reported similar events previously. No additional drug was taken and the patient was discontinued. The investigator believed the event was possibly related to apomorphine.

  Comment: It is notable that this patient was in the dose-optimizing group.

- A 47 year old male experienced nausea and vomiting, mouth and tongue pain, and headache after his ninth dose of apomorphine 6 mg. These symptoms lasted approximately 48 hours. He reported similar events previously. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 48 year old male experienced severe nausea, vomiting, generalized weakness and fatigue after his first 6 mg dose in-office. These symptoms lasted approximately 2 hours. He received IM Phenergan and obtained some relief. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 56 year old male experienced nausea, flushing, chills and tingling after his ninth dose of 5 mg apomorphine. These symptoms lasted approximately 2 hours. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

Lethargy, fatigue and "sleepiness":

- A 50 year old male experienced lethargy after his second dose of 4 mg (fifth dose overall). These symptoms lasted approximately 6 hours. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

  Comment: It is notable that this patient was in the dose-optimizing group.

- A 59 year old male experienced "sleepiness" after his ninth dose of 5 mg (ninth dose overall). This symptom lasted approximately 30 minutes. Two additional doses were taken and then the patient was discontinued. The investigator believed the event was probably related to apomorphine.

Mouth ulcers, swollen tongue, swollen lips, etc:

- A 66 year old male experienced mouth irritation, swollen lips after his second dose of 5 mg (twelfth dose overall). These symptoms lasted approximately 3 days. He took an additional 5 mg dose without symptoms. Upon increase to 6 mg, he experienced diaphoresis, yawning, nausea and fatigue. These symptoms lasted from 20 minutes to 1 hour. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 72 year old male experienced swelling of the lips after his first dose of 5 mg (twelfth dose overall). This symptom lasted approximately 2 days. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

<u>Comment</u>: It is notable that both these patients were in the dose-optimizing group.

Dizziness, syncope, diaphoresis, light-headedness, "clamminess", etc:

- A 53 year old male experienced dizziness and syncope approximately 1 hour after taking his fifth dose of 6 mg (sixth overall). The syncope lasted 15 minutes and the dizziness lasted 90 minutes. An ambulance was called to the site. Vital signs and ECG were monitored. The sponsor pointed out that the patient was a diabetic and had not consumed any food prior to dosing, only water. No additional drug was taken and the patient was discontinued. The investigator believed the event was possibly related to apomorphine.

- A 59 year old male experienced dizziness, light-headedness, "clamminess", nausea and sweating after his first dose of 5 mg (first dose overall). These symptoms lasted approximately 50 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 59 year old male experienced severe diaphoresis, generalized weakness, dizziness, and hypotension after his first dose of 6 mg (eleventh dose overall). These symptoms lasted approximately 90 minutes. The patient was transferred to the emergency room where he was treated with IV fluids. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

<u>Comment</u>: It is notable that this patient was in the dose-optimizing group.

- A 68 year old male experienced weakness, dizziness, and faintness after his first dose of 5 mg (ninth dose overall). These symptoms lasted approximately 20 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

<u>Comment</u>: It is notable that this patient was in the dose-optimizing group.

- A 60 year old male experienced light-headedness and severe nausea after his first dose of 5 mg (seventh dose overall). The nausea lasted for 1 hour and 55 minutes and the light-headedness for 2 days. The patient reported similar symptoms after previous doses. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

Comment: It is notable that this patient was in the dose-optimizing group.

- A 45 year old male experienced dizziness, nausea and "listlessness" after his fourth dose of 2 mg (fourth dose overall). The duration of these symptoms was 5 to 8 hours. The patient reported similar symptoms after previous doses. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

Comment: It is notable that this patient was in the dose-optimizing group.

Comments:

1. **Adverse events leading to discontinuation of apomorphine may occur despite careful dose-titration. One cannot conclude that dose-optimization itself leads to fewer discontinuations secondary to AEs.**
2. **The narrative descriptions of these discontinuations are consistent with those presented in Study M97-658.**
3. **Virtually all of the discontinuations occurred when patients were dosed with 4 mg, 5 mg or 6 mg.**
4. **Being able to tolerate a lower dose does not necessarily imply that a higher dose will also be tolerated.**
5. **Many adverse events, including dizziness, light-headedness, and clamminess lasted up to 1 hour or more. Thus, these vasovagal events are not transient in nature.**
6. **Ten patients discontinued due to oral irritation, and lip/tongue swelling. It is unclear if this is a local allergic reaction due to the sublingual tablet or a direct local irritation by some component of the tablet.**

Overall adverse effects: In the text of the study report, the sponsor summarized the adverse events that were considered by the investigator to be at least possibly related to apomorphine and reported by at least 5% of all patients.

When the overall AEs were tabulated in this manner the results are demonstrated in Table 7.

Table 7. Treatment-emergent adverse events at least possibly related to apomorphine and reported by ≥5% of all patients.

Adverse event	2-6 mg Optimized Group (n=242) n(%)	2- 4 mg Optimized Group (n=242) n (%)	5 mg Group (n=89) n (%)	6 mg Group (n=119) n (%)	Placebo (n=119) n(%)
Nausea	72(29.8)	41(16.9)	45(37.8)	44(49.4)	4(3.4)
Dizziness	36(14.9)	20(8.3)	18(15.1)	20(22.5)	0(0.0)
Sweating	35(14.5)	12(5.0)	11(9.2)	16(18.0)	0(0.0)
Headache	32(13.2)	23(9.5)	9(7.6)	10(11.2)	7(5.9)
Yawning	27(11.2)	19(7.9)	18(15.1)	13(14.6)	6(5.0)
Vomiting	22(9.1)	9(3.7)	9(7.6)	14(15.7)	0(0.0)
Somnolence	22(9.1)	14(5.8)	19(16.0)	9(10.1)	2(1.7)
Vasodilatation	15(6.2)	11(4.5)	13(10.9)	7(7.9)	3(2.5)
Asthenia	12(5.0)	5(2.1)	6(5.0)	7(7.9)	1(0.8)
Hypotension	6(2.5)	2(0.8)	6(5.0)	2(2.2)	1(0.8)
Dry mouth	4(1.7)	2(0.8)	1(0.8)	5(5.6)	1(0.8)
Dyspepsia	3(1.2)	1(0.4)	6(5.0)	5(5.6)	1(0.8)
Insomnia	3(1.2)	3(1.2)	6(5.0)	0(0.0)	1(0.8)

Comments:

1. **The results in this table do not suggest that dose-titration of apomorphine limits most AEs; rather, it suggests that restricting the dose to a maximum of 4 mg serves may limit AEs.**
2. **Dose-titration may, however, serve to limit nausea.**

The sponsor believes that patients can develop "tolerance" to the adverse reactions associated with apomorphine. Virtually all apomorphine-related adverse events tend to be reported at lower incidence rates in the maintenance period as compared with the titration period.

> **Comment: The incidence of adverse events appears lower in the maintenance period than in the titration period. This may reflect some degree of "tolerance" to apomorphine-related adverse reactions, or a selection of patients who tolerate drug.**

Four additional patients experienced syncope without discontinuing from the trial. One patient experienced severe hypotension without syncope, and he too remained in the trial. Two of these five patients are described in detail below:

- A 33 year old patient experienced nausea, yawning and "**syncope**" approximately 45 minutes after his first in-office dose with apomorphine 5 mg. As he stood up to go to the bathroom, he experienced nausea and lost consciousness. The duration of the event was 16 minutes. His vital signs at the time of the event were BP 116/76 and heart rate 56. These were stable for 1 hour. He was re-challenged four days later with 5 mg and experienced no adverse events. He went on to complete the study and is currently enrolled in the ongoing trial. The investigator believed the event was definitely related to apomorphine.

> **Comment: It is notable that this patient was in the dose-optimizing group.**

- A 63 year old patient experienced nausea, light-headedness, "clamminess", and "**syncope**" shortly after his first in-office dose with apomorphine 5 mg. He recalls going to the door of the exam room for assistance and falling. Upon examination, he was found to have a cut on the back of the head. It was assumed he hit his head on a nearby table. The syncope lasted "less than 1 minute". The "clamminess" lasted 20 minutes. The nausea lasted 80 minutes. The sponsor pointed out that the patient had fasted 10 hours prior to dosing and took the medication on an empty stomach. The patient wished to continue and did complete the study on a lower dose. He also entered the long-term study.

Comment: It is notable that this patient was in the dose-optimizing group.

Vital signs and electrocardiographic recordings:
There were no statistically significant differences between 2 mg, 4 mg and 5 mg apomorphine and placebo in mean vital sign measurements. There was a statistically significant increase in pulse rate between 6 mg apomorphine and placebo.

Comment: Measurement of vital signs did not actually follow dosing.

One patient experienced clinically significant EKG changes during the study; he only received placebo during the trial.

Comment: ECGs were not obtained following dosing.

Clinical laboratory examinations: Statistically significant differences between apomorphine and placebo were observed in several laboratory parameters. The treatment mean changes were all very small and differences were generally only noted in one apomorphine dose group.

Comment: All of these differences were extremely small and clinically insignificant.

Several patients experienced significant laboratory abnormalities while taking apomorphine. None of these were assessed to be clinically significant by the individual investigators. These included: two patients with high eosinophil counts (one on drug and one on placebo), one patient with a low hemoglobin/hematocrit (on drug), three patients with high SGOT/SGPT (all onj drug), and three patients with high GGT (all on drug).

Assessment of efficacy and safety:
The efficacy data reveal evidence of an overall treatment effect with apomorphine. However, the treatment effect seen with the 2 mg dose may not be meaningful to the individual patient. In the 2 mg group, the percentage of successful responders was not significantly different than placebo. The EF domain scores from the IIEF may not reflect a clinically meaningful treatment effect with the 2 mg dose.

The reader should be aware that this group of patients all were physiologically capable of attaining a rigid erection prior to this study.

In terms of safety, there is evidence that a significant proportion of patients will not tolerate apomorphine. This conclusion is based on an adverse event profile of nausea, dizziness, hypotension, sweating, vomiting, etc. More important, however, is the pattern of acute hypotension, bradycardia, nausea, vomiting, diaphoresis and possible syncope early in treatment (usually following the first dose). In several patients, hypotensive episodes occurred after the

first dose. While most cases occurred at the higher doses (5 mg and 6 mg), some occurred with the 4 mg dose.

Of note, the sponsor did not seek approval for the 5 mg and 6 mg doses based on safety concerns, again, suggesting a very narrow therapeutic index for this drug.

It should be noted that this was a carefully selected group of healthy men being followed in a clinical trial. The real-world population of men with erectile dysfunction may be at increased risk.

Clinical Trial M97-804 (A Phase 3 Safety and Efficacy Study of Two Fixed Doses of Apomorphine SL Tablets Versus Placebo in the Treatment of Male Erectile Dysfunction in Patients with Controlled Diabetes)

Design:
Design summary: This protocol was a multicenter (18 sites), double-blind, randomized, placebo controlled, fixed-dose, two-armed crossover study which compared two doses of apomorphine sublingual tablets (4 mg and 5 mg) with placebo in the treatment of erectile dysfunction in men with controlled diabetes. Patients had either Type I(20%) or Type II(80%) diabetes and were controlled with oral therapy, insulin, or diet. Each of the two treatment arms compared one apomorphine dose (either 4 or 5 mg) to placebo. A 2-period crossover design was utilized which consisted of two 4-week treatment periods separated by a 24 to 96 hour washout period. Two hundred eighteen patients were enrolled. Each patient was randomly assigned to one of the four treatment sequence groups. For each sequence group, patients received placebo in one of the treatment periods and one of the apomorphine SL doses in the other treatment period.

Study population and inclusion/exclusion criteria: Inclusion criteria included "controlled diabetes" which was defined as patients in whom glycosylated hemoglobin was <10% and who had experienced no episodes of ketoacidosis within the past year. Erectile dysfunction was defined by the documentation of <50% successful attempts to attain and maintain an erection firm enough for intercourse with wife/partner as reported by the patient for a minimum of 3 months prior to Day 1 of the first treatment period. Although patients needed to have a history of <50% success for the 3 months prior to study Day 1, some patients who had 50% or more success during the lead-in period were randomized.

> **Comment: The sponsor states that it was unusual for a patient to be enrolled who had >50% success during the lead in period, but the number of such patients is not specified.**

Although Rigiscan data were used as inclusion criteria for previous apomorphine studies, Rigiscan studies were eliminated from this protocol. Exclusion criteria included cardiovascular disease requiring treatment in the year prior to the study with anti-anginals, PTCA, CABG, atherectomy or stents. Use of anticoagulants and antiplatelet drugs (except prophylactic doses of aspirin) in the year prior to the study was prohibited. Other exclusion criteria included uncontrolled hypertension (systolic BP >180 and/or diastolic pressure >100 in the sitting position at rest), hypotension (systolic BP <90 in the standing position), a significantly abnormal EKG, neurologic disease, peripheral neuropathy, nephropathy, retinopathy, and smoking >10 cigarettes/day.

> **Comment: Inclusion and exclusion criteria were fairly restrictive. The study population was a relatively healthy group and is not indicative of the diabetic population at large. None of the patients were taking nitrates.**

Primary and secondary endpoints: The primary endpoint was the home-use success rate based on all attempts to achieve an erection. Success is defined as achieving an erection firm enough for intercourse according to the patient's opinion. Initially, only the first eight attempts were planned to be included in the primary analysis, but, in a meeting held on September 2, 1998, the FDA requested that the primary analysis be an intent-to-treat analysis for all attempts rather than the first eight attempts. Primary analysis data are submitted for both the first 8 and for all attempts. Secondary endpoints include 1) achievement of an erection firm enough for intercourse according to the patient's partner, 2) number of patients with a successful response (erection firm enough

for intercourse in 50% of attempts) according to the patient and the partner, 3) successful sexual intercourse rates according to the patient and the partner, 4) time to erection, 5) duration of erection, 6) IIEF questionnaire for the patient, 7) BSFI questionnaire for the partner, 8) Fugl-Meyer Life Satisfaction Scale, and 9) SF-36 questionnaires.

Withdrawals, compliance, and protocol violations: Two hundred eighteen men were randomized into the study. All 218 patients took at least one dose of blinded study drug. Two hundred five patients took at least one dose of apomorphine SL. One hundred seventy patients completed the study. Of the 48 patients who discontinued the study, 17 discontinued because of adverse events. (Table 1)

Table 1. Reasons for study discontinuation

	APO 4 mg	Placebo	APO 5mg	Placebo
Adverse event	5	2	9	1
Noncompliance	0	1	0	1
Complete lack of efficacy	1	0	2	2
Partial lack of efficacy	0	0	0	0
Patient request	1	2	2	3
Partner request	1	0	0	1
Lost to follow-up	3	1	6	2
Death	0	0	0	0
Other	1	1	0	0

Comment: Adverse events comprised the largest number of reasons for study discontinuation and a dose-related effect is suggested.

The adverse events resulting in study discontinuation are discussed in the safety analysis.

Treatment compliance was monitored through the use of diaries and home-use questionnaires that were completed by the patient each time study drug was taken. Diary entries were compared with the number of study drug tablets returned. Compliance was also monitored by tracking home-use questionnaires mailed to the sponsor by the wife/partner. Two non-compliant patients were discontinued from the study.

Protocol deviations: Numerous patients were entered into the study with elevated laboratory findings that were indicative of their diabetes. In most cases, prior authorization was given in cases where the patient's clinical condition was deemed stable and his diabetes well-controlled. Ten patients with laboratory findings outside the protocol limits were entered into the study without prior approval. One patient entered the study in violation of the smoking criterion and one patient had used pharmacological therapy for erectile dysfunction within two months prior to starting the study. One patient entered the study with a reported allergy to codeine; however, subsequent exposure to morphine was uneventful.

Efficacy analysis:
The primary endpoint was the percentage of attempts in which the patient thought that he had achieved an erection firm enough for intercourse. The sponsor believes that the results of the analysis of the proportion of all attempts resulting in an erection firm enough for intercourse showed numerical advantages for each dose level of apomorphine SL over its corresponding placebo dose as well as for both drug dose levels combined. These differences were statistically

significant for the apomorphine SL 4 mg dose and for the 4 mg and 5 mg doses combined, but not for the 5 mg dose alone. These results are summarized in Table 2.

Table 2. Percentage of attempts resulting in an erection firm enough for intercourse (based on all attempts) – primary endpoint.

Dose	(n)	**Placebo** **Success/attempts**	**%**	Apomorphine SL Success/attempts	%	Apomorphine SL vs. Placebo P-value
5 mg	(86)	190/698	27.2	224/657	34.1	0.179
4 mg	(90)	115/794	14.5	199/808	24.6	0.020
Combined	(176)	305/1493	20.4	423/1465	28.9	0.009

Comments: The data presented are the sum of all successes and all attempts for each group. When re-analyzed for individual patient response, the results were consistent. Interestingly, the 5 mg dose arm demonstrates no statistical significance over placebo. The "combined" analysis is post hoc. No dose response is demonstrated. Even though the 4 mg and combined data show statistical significance, the clinical significance of these data is questionable, due to the relatively modest benefits noted over placebo.

Similar results were observed in the secondary endpoint of percentage of attempts resulting in intercourse (Table 3).

Table 3. Percentage of attempts resulting in intercourse (based on all attempts) - secondary endpoint.

Dose	(n)	Placebo Success/attempts	%	Apomorphine SL Success/attempts	%	P-value
5 mg	(86)	188/699	26.9	212/647	32.8	0.234
4 mg	(90)	114/792	14.4	189/806	23.4	0.049
Combined	(176)	302/1491	20.3	401/1453	27.6	0.025

The sponsor suggests that the 4 mg dosage frequently obtained statistical significance while the 5 mg dosage did not could be attributed to the different patient make-up within the two dosing arms. Patients in the 4 mg dosing arm were on average statistically significantly less likely to have an erection firm enough for intercourse during the lead-in period than patients in the 5 mg dosing arm. In addition, statistically significant differences were identified between the dosing arms in the baseline mean IIEF domains of erectile function (p=0.011) and intercourse satisfaction (p=0.033).

Comment: There may be randomization error in the two treatment arms. The fact that the 4 mg arm had more erectile dysfunction, however, does not necessarily imply that this group would respond better to apomorphine.

Another secondary endpoint was patients who were deemed a treatment success. Success was defined as at least 50% of all attempts resulting in erections firm enough for intercourse (Table 4).

Table 4. Results of the analysis of percentages of patients deemed a treatment "success" (based on all attempts)

Dose	(n)	Placebo #success	%	Apomorphine SL #success	%	Apomorphine SL versus placebo p-value
5 mg	(86)	22	25.6	25	29.1	0.669
4 mg	(90)	14	15.6	21	23.3	0.082
Combined	(176)	36	20.5	46	26.1	0.106

Comment: This secondary endpoint does not reach statistical significance.

Comments: Numerous tables which include data regarding secondary endpoints were presented by the sponsor. Many of these include data which are statistically significant for the 4 mg dose but not for the 5 mg dose. The reviewer has selected those data which are considered most clinically relevant. Such an example is the analysis of mean satisfaction with an attempt based on all attempts (Table 5).

Table 5. Results of the analysis of mean attempt satisfaction

Dose	(n)	Placebo Mean Score	Apo SL Mean Score	p-value
5 mg	(86)	1.94	2.13	0.124
4 mg	(88)	1.71	1.98	0.004
Combined	(174)	1.82	2.06	0.002

Scale:
1=very dissatisfied
2=mostly dissatisfied
3=neutral (about equally satisfied and dissatisfied)
4=mostly satisfied
5=very satisfied

Comment: Although the 4 mg results are highly statistically significant, the responses following placebo and apomorphine are both slightly below the "mostly dissatisfied" rating.

Other secondary endpoints :
The mean duration of erection showed a statistically significant increased mean duration for both the 4 and 5 mg doses compared with placebo. The analysis of mean IIEF indices indicated improvements over placebo in all five domains for both the 4 and 5 mg dose levels. These improvements were statistically significant for the 4 mg dosage for all domains except for the domain of sexual desire. The Brief Sexual Function Inventory for the wife/partner showed statistically significant improvement for the 4 mg, but not the 5 mg, dose. The Fugl-Meyer Life Satisfaction Scale showed no consistent improvement for any index.

Safety Analysis :
Extent of exposure: The extent of apomorphine SL exposure is depicted in Table 6.

Table 6. Extent of apomorphine SL exposure

Number of patients exposed to a given number of doses

Dose	1	2-5	6-12	13-21	Total
4 mg	5	6	72	18	101
5 mg	13	13	73	5	104

(The remaining 13 enrolled patients had discontinued the study prior to receiving any apomorphine SL.)

Deaths : There were no study deaths.

Serious adverse events:
Eight adverse events deemed "serious" were reported (seven apomorphine and one placebo related):

- A 57 year old patient received his first dose of study drug in the office. Twenty-five minutes after drug administration he became pale and diaphoretic while in the supine position. His BP was 60 mm Hg palpable with a pulse of 52 beats per minute. He was treated with IV saline and after one hour fifty-five minutes he recovered with a BP of 132/78 and a heart rate of 70. The patient was discontinued from the study. When the blind was broken, he was found to be on 5 mg apomorphine.

  Comment: The one-hour fifty-five minute duration of hypotension is not consistent with a vaso-vagal episode.

- A 66 year old patient received his third dose of study drug at home. Approximately 16 hours later, he experienced syncope for about one minute following heavy physical exertion. He was hospitalized where an EKG revealed borderline first degree heart-block and non-specific T-wave flattening. Study medication was continued and he remained in the study without any further syncopal episodes. When the blind was broken, he was found to be on 4 mg apomorphine.

- A 51 year old patient experienced headache and was hospitalized 6 days after his last (nineteenth) dose of study drug. He was found to have glaucoma and the investigator assessed the event to not be related to study drug. After the blind was broken, he was found to be on apomorphine 5 mg.

  Comment: The reviewer agrees that this event was not drug related.

- A 55 year old patient experienced hypoglycemia and syncope. He responded to IV glucose and the investigator assessed the event as not being related to the study drug. He was found to be on placebo.

- A 71 year old patient was found to have "bladder polyps." The event was assessed as not being related to the study drug. He was found to be on 4 mg apomorphine.

  Comment: The reviewer agrees that this event was not related to study drug

- A 55 year old patuient experienced cholelithiasis and urinary retention. Neither of these events was thought to be secondary to study drug. He was on apomorphine 5 mg.

- A 53 year old patient experienced severe nausea, diaphoresis and vague shortness of breath while playing golf one day after his fourth dose of study drug. Seventeen hours after taking his fifth dose of study drug he developed a severe episode of nausea, diaphoresis, shortness of breath, and mild chest pain and was seen in an emergency room with sinus tachycardia of 123 beats/minute. He was treated with heparin, a nitroglycerin drip, and oxygen and admitted to the cardiac care unit. Cardiac enzymes were negative for myocardial infarction. He was treated with Pepcid. He continued in the study and the investigator assessed the event as not related to the study medicine. After the blind was broken, he was found to be on 5 mg apomorphine.

  Comment: The reviewer believes that this event is probably not drug related.

- A 72 year old patient experienced right-sided hemiparesis 29 days after his first and only dose of study medication. He was hospitalized for seven days with a diagnosis of lacunar cerebrovascular accident. The investigator assessed the event as not related to the study medication. After the blind was broken, he was found to be on 5 mg apomorphine.

  Comment: The reviewer agrees that this event is not drug related.

Premature discontinuations due to adverse events:
Seventeen patients discontinued the study due at least in part to an adverse event. Three experienced serious adverse events and were discussed above. Four were clearly not related to study drug.

Of the remaining ten patients, two experienced syncope, two experienced nausea and vomiting (both on apomorphine 5 mg), one experienced periorbital edema (on apomorphine 4 mg), one experienced elevated liver function studies (on apomorphine 5 mg), one experienced palpitations, rapid respirations, and esophagitis (on apomorphine 4 mg), and one experienced nausea, diaphoresis, and tingling of the upper extremities (on apomorphine 5 mg).

The remaining two patients experienced hypotension, as described below:

- One patient experienced dizziness, nausea, and vomiting 20 minutes following administration of the first dose of study drug. He was treated with IV fluids and placement in the Trandelenberg position (apomorphine 5 mg).

  Comment: This patient's specific blood pressure was not included in the study report.

- One patient experienced dizziness, nausea, pallor, postural hypotension, and somnolence 26 minutes following his first drug dose (apomorphine 4 mg).

Overall adverse effects: The most common adverse events, occurring in at least 5% of patients, are listed in Table 7.

Table 7. Treatment adverse events reported by >5% of all patients.

Adverse event	4 mg arm Placebo (n=99) n (%)	4 mg arm APO (n= 101) n(%)	5 mg arm Placebo (n=102) n(%)	5 mg arm APO (n=104) n(%)
Nausea	1(1.0)	13(12.9)	1(1.0)	22(21.2)
Somnolence	1(1.0)	11(10.9)	0(0.0)	8(7.7)
Vomiting	0(0.0)	1(1.0)	0(0.0)	7(6.7)
Sweating	0(0.0)	6(5.9)	0(0.0)	6(5.8)
Headache	5(5.1)	4(4.0)	2(2.0)	0(0.0)

Comment: The incidences of nausea and vomiting are significant. Several of these episodes were severe.

During the study, 28 patients (26.9%) receiving 5 mg apomorphine, and 28 patients (27.7%) receiving 4 mg apomorphine reported at least one possibly drug-related adverse event. Overall, 56 patients (27.3%) reported at least one adverse event while taking apomorphine while 15 patients (7.5%) on placebo reported at least one adverse event. Two of the adverse events, nausea and vomiting, suggested possible dose response (see Table 7).

Vital signs and electrocardiographic findings: There were no statistically significant differences between either 4 or 5 mg apomorphine in mean greatest drop from baseline for any vital signs parameter.

Two patients experienced clinically significant EKG changes during the study: One patient developed new T-wave inversion with ST changes in lead III on his final EKG. He had received nine doses of 5 mg apomorphine. He was asymptomatic and the investigator thought this event not related to study medication. The other patient experienced sinus bradycardia with a rate of 43, poor R-wave progression, and T-wave inversion on his final EKG. The patient entered the study without sponsor approval with clinically significant PAC's, T-wave inversion in lead I and AVL, ST changes in V4-V6, and inferior lead Q waves. He received eleven doses of 4 mg apomorphine. He remained asymptomatic.

Twenty patients at four sites had Holter monitor recording at their in-office dosing visits. All readings were within normal limits.

Laboratory abnormalities: A statistically significant difference between apomorphine and placebo was observed in mean chemistry values for sodium, glucose, chloride, and SGPT. These changes were not seen in both dose groups, are extremely small, and clinically insignificant. No statistically significant differences were seen between apomorphine and placebo in any of the mean hematology or urinalysis parameters. A majority of the patients entered into the study had some laboratory values outside the normal ranges and these abnormalities were attributed to their diabetes.

Individual clinically significant abnormalities not attributed to diabetes by the investigator are as follows:

1) Elevated WBC, lymphocytes, monocytes and eosinophils and decreased neutrophils following an in-office adverse event of nausea, hypotension, diaphoresis, and pallor that occurred after administration of study medication.
2) Decreased lymphocytes, hematocrit and hemoglobin with unknown etiology,
3) Decreased hematocrit which was subsequently attributed to ulcerative colitis.
4) Mildly elevated GGT and alkaline phosphatase at baseline that increased to markedly high levels throughout the study. This patient was subsequently found to have a "liver mass" on ultrasound.

Significant safety issues:
Two additional episodes of syncope occurred which were not defined as serious adverse events. One patient was on apomorphine 5 mg and one was on 4 mg. One patient experienced syncope approximately 1 hour after taking 5 mg apomorphine. He fell in the bathroom, was taken to an emergency room, and was discharged to home the same day. The other patient experienced syncope 35 minutes following his first in-office study drug dose. The syncopal episode lasted seconds, and he was described as pale, hot, diaphoretic, and vomiting. He made an uneventful recovery. Therefore, of the four reported syncopal events, three occurred in patients taking apomorphine (two patients on 4 mg and one on 5 mg). Two of these syncopal events were temporally related to apomorphine dosing. The other syncopal episode occurred in a patient taking placebo and the syncopal episode was ascribed to hypoglycemia.

> **Comment: Three syncopal events and three episodes of significant hypotension were reported in patients taking apomorphine.**

Sponsor's assessment of efficacy and safety:
The sponsor believes that this study demonstrates that apomorphine SL 4 mg and 5 mg tablets are well-tolerated and effective treatments in diabetic patients with erectile dysfunction.

Assessment of efficacy and safety:
The efficacy data reported in this study are not convincing. The 5 mg dose arm demonstrated no statistical significance over placebo, based on the primary, pre-specified endpoint. The "combined" analysis was performed post hoc. No dose-response was demonstrated.

Despite statistical significance, the modest effect noted with 4 mg and in the "combined" group may not be clinically significant. The sponsor suggests that randomization error in the two treatment arms may explain the fact that statistical significance was achieved in the 4 mg, but not in the 5 mg dose arm.

In terms of safety, three patients experienced syncope and three others experienced significant hypotension. The incidence of nausea and vomiting is fairly significant and some of these episodes were severe.

Of note, the inclusion and exclusion criteria were fairly restrictive, and the study population was a relatively healthy group, not indicative of the diabetic population with ED.

Clinical Trial M98-941 (A Phase 3 Efficacy and Safety Study of Three Fixed Doses of Apomorphine SL Tablets 2, 4, and 5 mg Versus Placebo in the Treatment of Male Erectile Dysfunction)

Design:
This protocol was a multicenter (54 sites), double-blind, randomized, placebo-controlled, fixed dose, three-armed crossover study which compared three doses of apomorphine sublingual tablets (2, 4, and 5 mg) with placebo for the treatment of male erectile dysfunction. Each of the three treatment arms compared one apomorphine dose to placebo. A 2-period crossover design was utilized which consisted of two 4-week treatment periods separated by a 24 to 96 hour washout period. Four hundred ninety-five patients were enrolled. Each patient was randomly assigned to one of the six treatment sequence groups. For each sequence group, patients received placebo in one of the treatment periods and one of the apomorphine SL doses in the other treatment period (schematic attached). The design for this study was similar to the design for the previous Phase 3 Study M97-658 except for the fact that the 6 mg dose was not included in this study.

Study population and inclusion/exclusion criteria: The study population consisted of men age 18 to 70 with a diagnosis of erectile dysfunction based on the following: 1) the ability to attain and maintain an erection firm enough for intercourse with partner for less than 50% of the attempts for a minimum of 30 days prior to the screening visit and 2) ability to attain and maintain an erection of sufficient quality for intercourse on some occasion since the onset of erectile dysfunction as evidenced by nocturnal/morning erections, masturbation and/or sexual activity and 3) NPT testing by the use of Rigiscan Plus within 60 days prior to Day 1 of Treatment Period 1 indicating that the patient could have a successful erection. A successful erection was defined as a total of 55% or greater base rigidity for a total of at least 10 minutes during sleep on at least one of the two nights of NPT testing. The patient eligibility criteria were designed to obtain a study population comprising men with erectile dysfunction in whom intrinsic penile function was present and who were in general good health. Exclusion criteria included neurologic disease, history of radical prostatectomy, endocrine disorders, psychiatric disorders, uncontrolled hypertension (systolic blood pressure >180 and/or diastolic blood pressure > 100 mm of Hg in the sitting position at rest), symptomatic hypotension (systolic blood pressure <90 mm of Hg in the standing position), clinically significant abnormal EKG, patients who demonstrated the ability to attain and maintain an erection satisfactory for intercourse with wife/partner on >75% of attempts during the lead in period, and patients who smoked more than ½ pack of cigarettes/day.

> **Comment: The study population is a select group of patients with erectile dysfunction. All had the ability to attain and maintain an erection of sufficient quality for intercourse since the onset of erectile dysfunction and all had objective nocturnal erections documented by Rigiscan.**

Primary and secondary endpoints: The primary endpoint was the home-use success rate based on all attempts (an "attempt" was defined as taking the study drug and completion of the home-use questionnaire) during each treatment period. Success was defined as achieving an erection firm enough for intercourse according to the patient's opinion. Secondary endpoints included: 1) achievement of an erection firm enough for intercourse according to the patient's partner 2) number of patients with successful "response" (erection firm enough for intercourse in 50% or greater of the attempts) according to the patient and the partner 3) successful sexual intercourse rates according to the patient and the partner 4) time to erection 5) duration of erection 6)

responses to the IIEF questionnaire for the patient 7) response to the BSFI for the partner and 8) quality of life questionnaires.

Withdrawals, compliance, and protocol violations: Four hundred and ninety-five (495) men were randomized. All 495 patients took at least one dose of blinded study drug. Four hundred and seventy (470) took at least one dose of apomorphine SL. Four hundred and seven (407) patients completed the study. Twenty-seven (27) patients discontinued due to adverse events. (Table 1)

Table 1. Reasons for study discontinuation

	2 mg	Placebo	4 mg	Placebo	5 mg	placebo
Adverse event	2	4	7	1	12	0
Noncompliance	1	2	5	3	3	0
Complete lack of efficacy	0	0	0	0	0	1
Partial efficacy	0	0	0	0	0	1
Patient request	4	4	4	2	4	1
Partner request	0	1	2	0	2	1
Lost to follow-up	2	3	1	4	3	3
Other	0	0	1	2	1	1

Comments: Adverse events comprised the largest number of reasons for study discontinuation and a dose-related effect is suggested. Of the 27 patients who discontinued the study because of adverse events, 21 were taking apomorphine and six were taking placebo.

The adverse events resulting in study discontinuation are discussed in the safety analysis.

Treatment compliance was monitored through the use of diaries and home-use questionnaires that were completed by the patient each time study drug was taken. Diary entries were compared with the number of study drug tablets returned. Compliance was also monitored by tracking home-use questionnaires mailed to the sponsor by the wife/partner. Fourteen non-compliant patients were discontinued from the study.

Protocol deviations: Six patients were randomized into the study even though they did not satisfy the admission criteria for smoking. Four patients were older than 70 years.

Comment: Several other protocol violations (approximately 14) are reported. These protocol violations are minor.

Efficacy analysis:
The primary endpoint was the percentage of attempts in which the patient thought that he had achieved an erection firm enough for intercourse. The sponsor reports that the results of the analysis of the percentage of all attempts resulting in an erection firm enough for intercourse showed statistical advantage for each dose level of apomorphine over placebo. (Table 2)

Table 2. Percentage of attempts resulting in an erection firm enough for intercourse

Dose (n)	Placebo Success/attempts	%	Apomorphine SL Success/attempts	%	Apo vs. placebo p-value
2 mg (140)	412/1278	32.2	577/1236	46.7	<0.001
4 mg (134)	358/1167	30.7	663/1231	53.9	<0.001
5 mg (130)	320/1137	28.3	653/1192	54.8	<0.001

Comments: The data presented are the sum of all successes and all attempts for each group. When re-analyzed by individual patient response, the results were consistent. The clinical significance of the differences between drug and placebo for the 2 mg group is questionable.

Comment: Numerous tables which include data regarding secondary endpoints are presented. The reviewer has selected those data which are considered most clinically relevant.

Patients who were deemed a treatment success was a secondary endpoint. "Success" was defined as at least 50% of all attempts resulted in erections firm enough for intercourse. (Table 3)

Table 3. Results of the analysis of percentages of patients deemed a treatment "success"

Dose (n)	Placebo Number of Successes	%	Apomorphine SL Number of Successes	%	Apomorphine vs. placebo p-value
2 mg (140)	47	33.6	69	49.3	<0.001
4 mg (134)	39	29.1	75	56.0	<0.001
5 mg (130)	38	29.2	75	57.7	<0.001

Another secondary endpoint was percentage of attempts resulting in intercourse. (Table 4)

Table 4. Percentage of attempts resulting in intercourse.

Dose (n)	Placebo Success/attempts	%	Apomorphine SL Success/attempts	%	p-value
2 mg (140)	395/1266	31.2	550/1226	44.9	<0.001
4 mg (134)	347/1159	29.9	640/1223	52.3	<0.001
5 mg (130)	309/1131	27.3	622/1180	52.7	<0.001

Table 5. Results of the analysis of mean attempt satisfaction.

Dose (n)	Placebo mean score	Apomorphine SL mean score	p-value
2 mg (140)	2.0	2.4	<0.001
4 mg (134)	1.9	2.6	<0.001
5 mg (130)	2.0	2.7	<0.001

Scale:
1=very dissatisfied
2=mostly dissatisfied
3=neutral or mixed
4=mostly satisfied
5=very satisfied

Comment: Although the satisfaction scores for apomorphine were significantly greater than for placebo, the mean scores for apomorphine remained in the mostly dissatisfied to neutral level.

The secondary endpoints of duration of erection, average duration of erection, Brief Sexual Function Inventory, IIEF domains, Fugl-Meyer Life Satisfaction Scale, and treatment satisfaction questionnaire all showed statistical superiority over placebo.

Statistical analyses: For most efficacy variables, primary analyses were done using the Cochran-Mantel-Haenszel method with patient as strata or the four factor ANOVA model for cross-over trials.

Safety analysis:
Extent of exposure: The extent of apomorphine SL exposure is depicted in Table 6.

Table 6. Extent of apomorphine SL exposure.

Dose	1 tablet	2-5 tablets	6-12 tablets	13-21 tablets
2 mg	5	8	120	23
4 mg	7	4	116	33
5 mg	15	5	107	27

Deaths: There were no study deaths.

Serious adverse events:
Seven serious adverse events were reported (all seven patients were on apomorphine).

- A 69 year old patient (5 mg apomorphine) experienced a syncopal event in addition to tonic/clonic activity of his left arm, incontinence of urine, diaphoresis, nausea, vomiting, dizziness, pallor, and hypotension which occurred 20 minutes after taking his first office drug dose. He was unconscious for approximately 10 seconds. Tonic-clonic activity lasted for approximately 15 seconds. His blood pressure was 100/60 and pulse rate 52/minute.

  Comment: This episode is probably drug-related. It is not known whether the patient was hospitalized.

- A 51 year old patient (2 mg apomorphine) experienced moderate light-headedness and mild nausea 4.5 hours after his ninth dose of apomorphine. He was seen in the emergency room and was found to have a temperature of 102 and ventricular bigeminy. He had a history of coronary artery disease, myocardial infarction, hypertension, and diabetes. The investigator considered the light-headedness to be not related to the study drug.

  Comment: This episode is possibly related to study drug.

- A 44 year old patient (5 mg apomorphine) experienced nausea, hypotension, pallor, and diaphoresis 20 minutes after receiving his first dose of drug. His blood pressure was 82/58 and pulse 58. He was treated with IV fluids, Narcan, Compazine, and oxygen. He was taken to the emergency room.

  Comment: This episode was probably drug related. No follow-up information is provided.

- A 68 year old patient (5 mg apomorphine) experienced chest pain and shortness of breath 2 days after his last dose of study drug. He was seen in the emergency room, found to be in atrial flutter, and had a pacemaker inserted. He had a history of atrial fibrillation and hypertension.

  Comment: This episode was not related to study drug.

- A 49 year old patient (5 mg apomorphine) experienced a syncopal event preceded by diaphoresis, dizziness, and nausea 90 minutes after dosing. He was taken to the hospital and found to have a blood glucose of 15 mg/dL. He was given oral glucose and repeat blood glucose was found to be 121. He did not have a history of diabetes. The investigator considered this event to not be related to study drug.

  Comment: This event was possibly related to study drug.

- A 61 year old patient (5 mg apomorphine) experienced exacerbation of his left calf pain. He underwent bilateral iliac artery angioplasty and stent placement.

  Comment: This event was not related to study drug.

- A 67 year old patient (5 mg apomorphine) experienced syncope and hypotension after his first office drug dose. He was treated with IV fluids and oxygen. The syncope lasted one minute and the hypotension resolved after 6 minutes. His specific BP measurement is not reported.

  Comment: This episode was probably study drug related.

Premature discontinuations due to adverse events:
Twenty-seven patients discontinued the study due to an adverse event. Two experienced serious adverse events and have been described above. Nine were not related to study drug. Three experienced syncope. In the remaining thirteen patients, the adverse event was at least possibly related to apomorphine.

- A patient (4 mg apomorphine) experienced mild nausea which occurred after his first two doses of study drug.

- A patient (5 mg apomorphine) experienced moderate lightheadedness, sweating, nausea and vomiting after he took his first office dose.

- A patient (5 mg apomorphine) experienced hypotension, dizziness, sweating, nausea, and yawning which lasted for one hour after his first office dose.

- A patient (5 mg apomorphine) experienced partial unconsciousness, dizziness and sweating after his first office drug dose. As the patient was being placed in the supine position, he became unresponsive for approximately three seconds. He was placed in the Trendelenberg position and the dizziness and sweating lasted for 56 minutes.

- A patient (5 mg apomorphine) experienced light-headedness, sweatiness, and grogginess after his first in office drug dose. His symptoms lasted for 70 minutes.

- A patient (4 mg apomorphine) experienced moderate throat tightness, thick tongue and dry mouth after his sixth drug dose. His symptoms resolved eight days after termination from the study.

- A patient (5 mg apomorphine) experienced severe hypotension twenty minutes after his first office dose. His blood pressure was 90/60 mm Hg (baseline 122/72 mm Hg). He was treated with IV fluids, oxygen, and Narcan. Two EKGs revealed bradycardia (rate of 50 bpm). The duration of this event was 85 minutes. He was re-challenged with drug eight days later. Thirty minutes after the second in-office dose, he again became hypotensive (85/50 mm Hg) and was again treated with IV fluids, Narcan, and oxygen.

- A patient (5mg apomorphine) experienced diaphoresis, pallor, dizziness, hypotension and tinnitus 10 minutes after his first office drug dose. His standing blood pressure was 80 mm Hg/palpable. He was treated with IV fluids. The duration of events was 2 1/2hours.

- A patient (4 mg apomorphine) experienced hypotension, dizziness, and nausea 25 minutes after his first office dose. His blood pressure was 72/50 mm Hg. The duration of hypotension was 105 minutes.

- A patient (5 mg apomorphine) experienced diaphoresis and hypotension 30 minutes after his first office drug dose. His blood pressure was 82/54 mm Hg. He was treated with IV fluids and his blood pressure returned to normal in 10 minutes.

- A patient (4 mg apomorphine) experienced moderate nausea and headache after his eighth drug dose. The duration of the adverse event was 4 hours.

- A patient (4 mg apomorphine) experienced throat tightness, chest pressure, diaphoresis, light-headedness and pallor after his first office dose of drug. He was treated with oxygen.

- A patient (4 mg apomorphine) experienced dizziness, hypotension, nausea and vomiting 1 hour after his first office dose. His blood pressure was 88/66 mm Hg. His baseline BP was 98/72 mm Hg. The hypotension lasted 25 minutes.

Comment: Seven of these 13 patients experienced loss of consciousness or significant hypotension.

Overall adverse effects: Overall, 243 (51.6%) of the 470 patients reported at least one adverse event while taking apomorphine SL, while 135 (29.6%) of the 456 patients reported at least one adverse event while on placebo. Those adverse events that were at least possibly related to apomorphine are listed in Table 7.

Table 7. Treatment related adverse events.

AE	Placebo	APO 2 mg	Placebo	APO 4 mg	Placebo	APO 5 mg
Nausea	2(1.3%)	4(2.6%)	2(1.3%)	29(18.1%)	3(2.1%)	45(29.2%)
Dizziness	6(3.8)	7(4.5%)	4(2.6%)	22(13.8%)	3(2.1%)	31(20.1%)
Sweating	0(0%)	4(2.6%)	0(0%)	15(9.4%)	0(0%)	26(16.9%)
Yawning	1(0.6%)	9(5.8%)	1(0.7%)	18(11.3%)	2(1.4%)	21(13.6%)
Vomiting	0(0%)	2(1.3%)	0(0%)	2(1.3%)	0(0%)	11(7.1%)
Somnolence	0(0%)	5(3.2%)	0(0%)	17(10.6%)	0(0%)	18(11.7%)
Hypotension	0(0%)	0(0%)	0(0%)	5(3.1%)	0(0%)	10(6.5%)
Vasodilation	1(0.6%)	1(0.6%)	0(0%)	4(2.5%)	0(0%)	8(5.2%)
Asthenia	0(0%)	0(0%)	0(0%)	4(2.5%)	0(0%)	5(3.3%)
Syncope	0(0%)	1(0.6%)	0(0%)	1(0.6%)	0(0%)	3(1.9%)

Comment: The incidence of nausea, dizziness, sweating, yawning, vomiting, somnolence, and hypotension are significant and suggest a dose relationship. Four percent of patients taking apomorphine 4 mg and 7% of the patients taking apomorphine 5 mg required antiemetics to control their symptoms.

Laboratory abnormalities: A statistically significant difference between apomorphine SL and placebo was found for the 5 mg apomorphine dose with regard to percent neutrophils (treatment mean of 60.8% for apomorphine and treatment mean of 59.6% for placebo (p-value=0.048). A statistically significant difference was found between 4 mg apomorphine and placebo for LDH (treatment mean of 163.7 and 159.6 for apomorphine and placebo, respectively (p-value=0.008).

Comment: Neither of these changes is clinically significant.

Two patients (2 and 5 mg apomorphine) had high percentages of eosinophils (6.6% and 9.5%). Nine patients had some abnormality of liver function studies (four patients on placebo, two on 2 mg apomorphine, one on 4 mg apomorphine, and two on 5 mg apomorphine).

Vital signs: There was a statistically significant difference between apomorphine SL 4 mg and placebo for standing systolic blood pressure (p-value=0.048). No statistically significant difference was seen between the 2 and 5 mg apomorphine SL and placebo in mean vital signs measurement.

EKG: There were no patients who experienced clinically significant EKG changes (other than those described under adverse events) during the treatment period.

Significant safety issues:
Six syncopal events were reported. Three patients were already discussed above under serious adverse advents. The remaining three are:

- A patient (5 mg apomorphine) experienced syncope following sleepiness, light-headedness and diaphoresis which occurred thirty minutes after his first office drug dose. He lost consciousness for about two seconds. His blood pressure was 126/72 mm Hg and his pulse was 52 bpm. He was re-challenged three days later and complained of moderate light-headedness for twenty minutes. His vital signs remained stable. He completed the study without further incident.

- A patient (4 mg apomorphine) experienced syncope and diaphoresis thirty-eight minutes after receiving his first in office drug dose. While diaphoretic, his blood pressure was 117/50 mm Hg and his pulse was 60 bpm. He then fainted and was unresponsive for 2 minutes. He was treated with IV fluids and oxygen. He had a history of coronary bypass surgery and hypothyroidism. He was prematurely discontinued from the study.

  Comment: This patient was not listed by the sponsor under "discontinuation due to adverse events."

- A patient (2 mg apomorphine) experienced a syncopal event accompanied by diaphoresis, nausea, and vomiting thirty minutes after his first office drug dose. The syncopal event lasted three minutes. He was treated with Compazine and oxygen. He was re-challenged with drug six days later without incident. He went on to complete the study.

Of the six syncopal events, one patient was on 2 mg, one was on 4 mg, and four were on 5 mg apomorphine SL. Five of the six episodes occurred with the in-office dose.

Comment: In addition to the above patients, one patient became unresponsive for about three seconds as he was being placed supine following an episode of dizziness after his first 5 mg apomorphine office dose.

Comment: In addition to the syncopal events , the sponsor lists 15 hypotensive events (five at the 4 mg dose and ten at the 5 mg apomorphine dose). Several of these hypotensive events were severe and have been discussed above. No blood pressure measurements were given for many of the patients who complained of light-headedness and dizziness. The number of patients who experienced documented hypotension is, therefore, uncertain.

Sponsor's assessment of efficacy and safety:
The sponsor believes that apomorphine SL 2, 4, and 5 mg tablets are well-tolerated, effective treatments for erectile dysfunction.

Reviewer's assessment of efficacy and safety:
The primary and most of the secondary endpoints demonstrated statistical advantage for apomorphine over placebo. The clinical importance of this advantage in the 2 mg arm is uncertain. Safety issues are concerning. Seven patients experienced loss of consciousness and at least fifteen more patients experienced hypotension. At least seven patients experienced severe hypotension.

Clinical Trial M97-788

Design:

This was a double-blind, randomized, placebo-controlled, parallel-group study conducted at 13 United States centers. The study population consisted of 18 to 65 year old men who had undergone a bilateral nerve-sparing, radical, retropubic prostatectomy within 2 to 12 months prior to the study. Patients were randomized to receive 5 mg apomorphine SL or placebo for 8 weeks. The first dose of randomized medication was given in the office and the patient was observed for 2 hours. The sponsor intended to enroll 50 patients.

Comment: It should be noted that this study was not powered for efficacy.

During the 8-week treatment period, patients were instructed to take study drug and attempt intercourse a minimum of 2 times per week. Patients were instructed to take the drug no more than once per 8-hour period. Patients were instructed to take study medication by placing a single tablet under the tongue and allowing it to dissolve completely. Once the tablet was completely dissolved, sexual intercourse could be attempted when the couple was ready. Patients were instructed as follows: "You should limit yourself to a minimum amount of alcoholic beverages during the six hours prior to taking study medication." After at least 2 hours had passed after intercourse, patients and partners were instructed to complete a questionnaire regarding that particular sexual experience.

Patients who completed this study were eligible to enroll in extension study M97-793.

Inclusion/exclusion criteria:

Eligible patients were heterosexual males, between 18 and 65 years of age. All men had to have a diagnosis of "erectile dysfunction following radical, retropubic prostatectomy using the bilateral nerve-sparing technique." Erectile dysfunction was "evidenced by documentation of inability to attain a penile erection sufficient for intercourse" and by no erections or insufficient erections by the patient's own estimate. Patients were >2 months but ≤12 months post-radical prostatectomy at the time of enrollment. Patients had to have erectile function prior to the prostatectomy, based on the patient's own estimate. The patient's prostate cancer had to have been localized with the specimen confined to the prostate. The serum PSA had to be ≤0.2 mg/mL at the time of enrollment and not rising.

All patients had to be involved in a "stable", heterosexual relationship for at least 6 months. All patients and partners had to agree to attempt intercourse at least 2 times weekly. All patients had to be "judged in good general health as evidenced by medical history and physical examination". All pre-study laboratory values had to be within 15% above or below normal range. Fasting blood glucose had to be <250 mg/dL, unless approval was obtained by the medical monitor.

Patients were excluded for the following reasons:

1. Presence of "neurologic disease" (e.g. Parkinson's disease, multiple sclerosis, or spinal cord injury).
2. Presence of such genitourinary disorders as penile prosthesis, or major penile deformity.
3. Presence of hypogonadism (serum T <150 ng/dL), hyperprolactinemia (serum prolactin >20 ng/mL), diabetes with an elevated glycosylated hemoglobin at baseline, or diabetes with any episode of ketoacidosis with the last 3 months.
4. Presence of major psychiatric disorder.
5. Presence of "cardiovascular disease" (e.g. systolic BP >180 mm Hg and/or diastolic >100 mm Hg while sitting, hypotension [systolic BP< 90 mm Hg while standing]).

6. Presence of gastrointestinal disease (especially, any disorder resulting in the need for anti-nausea medications in the last 6 months).
7. Any cancer other than prostate cancer and basal or squamous cell cancer that has not been in remission for at least 5 years.
8. Any use of radiotherapy or chemotherspy after prostatectomy.
9. Any use of LHRH analogue or antiandrogens prior to or after prostatectomy.
10. Any pharmacologic therapy for ED within the preceding 2 months.
11. History of drug or alcohol abuse within the past 2 years.
12. Smoking greater than 10 cigarettes per day, or the equivalent use of tobacco in other forms.
13. Presence of AIDS or HIV-positive status.
14. History of allergic reaction to morphine or any other opiate.
15. Partners with major affective disorder.
16. Partners with a history of female sexual dysfunction.

Comment: This was a relatively healthy group of patients with localized and surgically treated prostate cancer, and limited co-morbities.

Efficacy endpoints and statistical analysis plan:
The primary efficacy endpoint was "the home-use success rate during each treatment period" where an attempt was defined as taking a study drug and completing a questionnaire and success was defined as achieving an erection firm enough for intercourse according to the patient's opinion. The rate was based on all the patient's attempts.

Secondary efficacy endpoints included:
1. Achievement of an erection firm enough for intercourse according to the partner's opinion.
2. Percentage of attempts resulting in intercourse according to patient and partner
3. Time to erection
4. Duration of erection
5. International Index of Erectile Function (IIEF) results
6. Brief Sex Function Inventory questionnaire for the partner
7. Fugl-Meyer Life Satisfaction Scale,
8. SF-36 Quality of Life Questionnaire, and
9. A "Treatment Satisfaction Scale".

Although the study was not powered for efficacy and there was no pre-defined analysis plan, some endpoints were presented descriptively and some were analyzed as a comparison to placebo, using a one-way analysis of the variance (ANOVA) with effect for treatment group.

Safety variables included physical examination, vital signs and 12-lead ECG, performed at baseline, Week 4 and Week 8.

Withdrawals, compliance, and protocol deviations:
Patient disposition:
Forty-four men were randomized into the study. Forty-four patients took at least one dose of blinded study drug. Twenty-two received apomorphine. Thirty-eight (38) patients completed the study. Of the six patients who discontinued the study, two discontinued at least in part due to adverse events. Both of these were on apomorphine SL (Table 1).

Table 1. Reasons for study discontinuation

	APO 5 mg n=22 n	Placebo n=22 n
Adverse event	2	0
Noncompliance	0	0
Complete lack of efficacy	0	2
Partial efficacy	0	0
Patient request	1	0
Partner request	0	0
Lost to follow-up	1	0
Other	0	1

The adverse events resulting in study discontinuation are discussed in the safety analysis.

Treatment compliance: Treatment compliance was assessed by comparing home-use questionnaires with actual pill count.

Protocol deviations: Twelve patients were enrolled with "previously approved" protocol violations. These included some patients who used Viagra or intracavernosal injections greater than 2 weeks before the study began. Three patients were older than 65 years of age. One patient had his surgery 6 weeks prior to the study initiation. One patient was >12 months since surgery (12 months and 1 week). One patient smoked more than 10 cigarettes per day.

Efficacy analysis:
The primary endpoint was the percentage of attempts in which the patient thought he had achieved an erection firm enough for intercourse, based on all attempts.

The sponsor believes that the results of an analysis of this endpoint showed "numerical advantages" for apomorphine SL 5 mg compared to placebo. These results are summarized in Table 2.

Table 2. Mean percentage of attempts resulting in an erection firm enough for intercourse

Dose (n)	**Treatment Mean %**	Apomorphine SL vs. Placebo P-value
5 mg (21)	10.9	0.442
Placebo (22)	6.1	

Similar results were observed in the secondary endpoint of percentage of last eight attempts resulting in intercourse (Table 3).

Table 3. Percentage of attempts resulting in intercourse (based on last eight attempts)

Dose (n)	**Treatment Mean %**	Apomorphine SL vs. Placebo P-value
5 mg (21)	11.4	0.307
Placebo (22)	4.7	

Another secondary endpoint was the International Index of Erectile Function domain scores. Table 5 presents the results of the EF domain only. The EF domain consists of six questions that refer to the quality of the patient's erection in the last 4 weeks. The lowest possible score is 0 and highest possible score is 30.

Table 5. Results from the IIEF EF domain, presented as means

Dose	Baseline	Week 8	APO SL versus placebo p-value
5 mg	5.7 (n= 21)	8.3	0.095
Placebo	6.3 (n=22)	6.2	

Comment: The results from the Treatment Satisfaction questionnaire showed numerical improvements favoring placebo.

Safety Analysis :
Extent of exposure : The extent of apomorphine SL exposure is depicted in Table 6.

Table 6. Extent of apomorphine SL exposure. Number of patients exposed to a given number of doses.

	1	2-5	6-10	11-20	21-30	31-40	Total
5 mg	1	2	5	9	3	2	22

Comment: The extent of exposure in patients status-post radical prostatectomy is limited. Seventeen of 22 patients exposed received fewer than twenty doses of study drug.

Deaths : There were no study deaths.

Serious adverse events: There were no serious adverse events reported in this study.

Premature discontinuations due to adverse events:
Two patients discontinued the study due at least in some part to an adverse event. One patient experienced headaches after dosing during the first month of treatment. The other patient experienced nausea and drowsiness following each of six doses in the first month of treatment. Both patients were on apomorphine.

Overall adverse effects:
In the text of the study report, the sponsor summarized the adverse events that were considered by the investigator to be at least possibly related to apomorphine and reported by at least 5% of all patients.

When the overall AEs were tabulated in this manner the results are demonstrated in Table 7.

Table 7. Treatment-emergent adverse events at least possibly related to apomorphine

Adverse event	5 mg Group (n=22) n (%)	Placebo (n=22) n(%)
Nausea	6(27.1)	0(0.0)
Dizziness	5(22.7)	2(9.1)
Sweating	4(18.2)	0(0.0)
Somnolence	3(13.6)	0(0.0)
Yawning	2(9.1)	0(0.0)
Headache	1(4.5)	0(0.0)
Hypotension	1(4.5)	0(0.0)

Vital signs, electrocardiographic recordings and physical exam:
There were no clinically meaningful differences in pulse rate or blood pressure between dose groups at Week 4 or Week 8.

There were no individual changes in ECG of clinical significance.

There was no mention of physical examination abnormalities.

Clinical laboratory examinations : A statistically significant difference between apomorphine and placebo was observed in percentage of neutrophils (decreased on drug), eosinophils (increased on drug) and lymphocytes (increased on drug) on complete blood count. A statistically significant difference between apomorphine and placebo was observed in serum BUN and serum uric acid (both increased on drug).

> **Comment: All of these laboratory differences were extremely small and likely to be clinically insignificant.**

In terms of individual patient laboratory abnormalities, two patients had increases in serum LFTs. One patient (on apomorphine) had a moderately elevated GGT at Week 4 that returned to normal levels at Week 8. The other patient (also on apomorphine) had elevated SGPT and serum triglycerides at Weeks 4 and 8. The investigator considered these changes possibly related to study drug.

Sponsor's assessment of efficacy and safety:
The sponsor believes that apomorphine SL was well-tolerated in this patient population. The sponsor believes that numerical trend suggests it may be effective treatment in patients with ED following bilateral nerve-sparing prostatectomy.

Reviewer's assessment of efficacy and safety:
The efficacy data reveal no evidence of a treatment effect with apomorphine in these patients. It is clear that these patients had severe ED following their surgery. In addition, the number of patients studied may have been too small to detect a significant effect of apomorphine.

In terms of safety, there were no serious or severe adverse events reported. The profile for other adverse events was similar to previous studies. One patient reported hypotension.

Safety Study M96-471

Design:

This was an open-label, flexible-dose, 6-month, safety study conducted at 32 United States centers. Patients who completed M96-470 and had a continuing diagnosis of ED were eligible to enroll in this trial. All procedures performed at the end of Treatment Period 2 of M96-470 were considered Visit 1 assessments for this trial. All patients began the study at a dose of 2 mg apomorphine. Dose could be adjusted at monthly in-office visits. Possible doses included 2 mg, 4 mg, and 6 mg.

> **Comment: It is important to note that the investigational product used in this study was the "F1" or "developmental" formulation, and as such, was slightly different in composition compared to product used in Phase 3.**

During the study, patients were instructed to take the drug no more than once per 8-hour period. Patients were instructed to take study medication by placing a single tablet under the tongue and allowing it to dissolve completely. Once the tablet was completely dissolved, sexual intercourse could be attempted when the couple was ready. Patients were instructed as follows: "You should limit yourself to a minimum amount of alcoholic beverages during the six hours prior to taking study medication." After at least 2 hours had passed after intercourse, patients and partners were instructed to complete a questionnaire regarding that particular sexual experience.

Comments:

1. **The requirement that minimal alcohol be consumed prior to taking a tablet may not be practical to expect in a real-world situation.**
2. **Accurate assessment of efficacy in this 6-month, open-label trial cannot be made due to the lack of a control group.**

Inclusion/exclusion criteria:

Eligible patients were patients who had completed both treatment periods of the short-term apomorphine Study M96-470.

Briefly, these patients were heterosexual males, between 18 and 70 years of age. All men had to have a diagnosis of "erectile dysfunction with no major organic component". Erectile dysfunction was defined in M96-470 as "the ability to attain and maintain an erection firm enough for intercourse with a partner for less than 50% of attempts for a minimum of 3 months prior to Day 1 of Treatment Period 1". In addition, all patients had to have demonstrated "an erection of sufficient quality for intercourse on some occasion since the onset of erectile dysfunction as evidenced by nocturnal/morning erections, masturbation, and/or other sexual activity."

In M96-470, all patients underwent nocturnal penile tumescence testing (NPT) using Rigisican at least 60 days prior to Day 1 of Treatment Period 1. All patients had to demonstrate at least 1 successful erection during NPT testing; specifically, a successful erection was defined as one wherein the base of the penis was at least 55% rigid for at least 10 minutes.

All patients had to be involved in a "stable", heterosexual relationship for at least 8 months. All patients and partners had to agree to attempt intercourse at least once weekly. All patients had to be "judged in good general health as evidenced by medical history and the complete physical examination at the end of Study M96-470". All pre-study laboratory values had to be within 15% above or below normal range on the final visit of M96-470. Fasting blood glucose had to be <250 mg/dL, unless approval was obtained by the medical monitor.

Comment: This patient population was physiologically capable of getting erections and was generally healthy. This population does not represent the ED population at large.

Patients were excluded for the same reasons as in M97-658. These included:

1. Presence of "neurologic disease" (e.g. Parkinson's disease, multiple sclerosis, or spinal cord injury).
2. Presence of such genitourinary disorders as history of radical prostatectomy, penile prosthesis, or major penile deformity.
3. Presence of hypogonadism (serum T <240 ng/dL), hyperprolactinemia (serum prolactin >20 ng/mL), diabetes any episode of ketoacidosis with the last 5 months.
4. Presence of major psychiatric disorder.
5. Presence of "cardiovascular disease" (e.g. systolic BP >180 mm Hg and/or diastolic >100 mm Hg while sitting, hypotension [systolic BP< 90 mm Hg while standing]).
6. Presence of gastrointestinal disease (especially, any disorder resulting in the need for anti-nausea medications in the last 8 months).
7. Any cancer other than basal or squamous cell cancer that has not been in remission for at least 5 years.
8. Any pharmacologic therapy for ED within the preceding 5 months.
9. Greater than 75% successes during the lead-in period.
10. History of drug or alcohol abuse within the past 2 years.
11. Smoking greater than 10 cigarettes per day, or the equivalent use of tobacco in other forms.
12. History of allergic reaction to morphine or any other opiate.
13. Partners with major affective disorder.
14. Partners with a history of female sexual dysfunction.
15. Partners who are pregnant, lactating or planning to become pregnant.

Comment: Inclusion and exclusion criteria were fairly restrictive. This study population is a relatively healthy group and again, is not indicative of the erectile dysfunction population at large.

Efficacy endpoints and statistical analysis plan:

The primary efficacy endpoint was the same as in M96-470: "the home-use success rate" for the entire 6-month period. An attempt was defined as taking a study drug and completing a questionnaire and success was defined as achieving an erection firm enough for intercourse according to the patient's opinion. Secondary efficacy endpoints were the same as in M97-658 and included:

1. Achievement of an erection firm enough for intercourse according to the partner's opinion.
2. Number of patients with successful response (defined as erection sufficient for intercourse in 50% or greater number of attempts)
3. Successful intercourse rates according to patient and partner
4. Time to erection
5. Duration of erection
6. Brief Sex Function Inventory questionnaire for the patient and partner
7. The Profile of Moods questionnaire

The statistical analysis plan was a summary or descriptive tabulation of the efficacy endpoints for the entire treatment period, by dose, by month and for the entire treatment period.

Safety endpoints:
Safety endpoints included complete physical examination, including vital signs and body weight, 12-lead EKG, routine laboratory examinations (hematology, chemistry and urinalysis and assessment of adverse events.

Withdrawals, compliance, and protocol deviations:
Patient disposition:
A total of 370 patients completed M96-470. Three hundred sixteen (316) males were enrolled into this study. Three hundred twelve (312) took at least one dose of apomorphine. One hundred eighteen (118) completed the study. Of the 198 patients who discontinued the study, 33 (10.6% of patients who took at least one dose) discontinued at least in part because of adverse events. (Table 1)

Table 1. Reasons for study discontinuation

Reason	Number of patients
Adverse event as "primary reason"	27
Adverse event as at least part of reason	6
Noncompliance	37
Lack of efficacy	67
Patient request	25
Partner request	3
Lost to follow-up	28
Death	0
Other	9

Comment: Discontinuations due to adverse events and discontinuations due to lack of efficacy comprised approximately 11% and 22% of the total dosed population, respectively. It is impressive that in this 6-month study, almost one quarter of patients discontinued due to lack of efficacy, even though doses up to 6 mg were allowed.

The adverse events resulting in study discontinuation are discussed in the safety analysis.

Treatment compliance: Compliance was assessed by collecting home-use diaries and reconciling at-home use documentation with actual pill count.

Protocol deviations: Two patients were included in the study that did not meet the eligibility criteria. Eight patients were dosed incorrectly at some time during the 6-month trial. Most of these were increases in dose without in-office observation.

Efficacy analysis:
The primary endpoint was the percentage of attempts in which the patient thought that he had achieved an erection firm enough for intercourse.

The average percentage of attempts resulting in an erection firm enough for intercourse was 56.8% when all doses were combined, compared to 28.3% at baseline. When calculated separately for the 2 mg, 4 mg, and 6 mg doses, these figures were 45.9%, 53.4%, and 60.7%, respectively. When only the last 16 attempts were analyzed, the total average figure was 58.5%.

When the same endpoint is analyzed on a month by month basis, the results are displayed in Table 2.

Table 2. Percentage of total attempts resulting in an erection firm enough for intercourse.

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Entire study
Percent of successful attempts	51.3%	65.3%	70.2%	74.6%	78.5%	79.2%	66.5%
Total number of patients	302	254	201	158	132	110	305

<u>Comment</u>: Table 3 depicts a month-by-month improvement in the primary endpoint, as fewer and fewer patients remain in the study. Based on a denominator of "all attempts", this table demonstrates improving function in only a subset of patients, while many patients are dropping out of the trial.

Of *all attempts* made during the study, 66.5% resulted in an erection firm enough for intercourse. Of all attempts for 2 mg, 4 mg, and 6 mg, 60.0%, 67.5%, and 68.9% resulted in an erection sufficient for intercourse, respectively.

The sponsor believes that the reason for the differences between these two sets of success rates is that more successful patients made more attempts, compared to less successful patients.

For the secondary endpoint, rates of successful intercourse, the results are similar. For the average percentage of successful intercourse attempts, the rate for combined doses was 49.7%, compared to 23.6% at baseline. For the 2 mg, 4 mg, and 6mg doses separately, those results were 38.3%, 46.0%, and 52.8%, respectively.

For the secondary endpoint, percentages of patients classified as having a successful response (at least 50% successful attempts), the results are as follows: for all doses combined, 63.3%; for 2 mg, 4 mg and 6 mg, individually, the results were 50.8%, 59.5% and 68.4%, respectively.

Safety Analysis :
Extent of exposure : The extent of apomorphine SL exposure is depicted in Table 3.

Table 3. Extent of apomorphine SL exposure by number of doses taken.

	1	2-8	9-19	20-49	50-100	>100	Total
Combined	1	46	86	122	51	8	326
2 mg	4	236	54	16	1	1	324
4 mg	12	165	74	29	4	2	310
6 mg	7	62	64	57	23	1	144

Overall, most of the patients who received study drug escalated to the 6 mg dose. The final dose was 2 mg for 34 patients (10.8%), 4 mg for 84 patients (26.8%), and 6 mg for 196 patients (62.4%).

Comment: It is notable the majority (62.4%) of patients chose to increase the dose to the maximum allowed dose of 6 mg. One explanation for this phenomenon is that patients were dissatisfied with the efficacy of lower doses.

Deaths: There were no study deaths.

Serious adverse events:
Eight patients experienced serious adverse events during this study. According to investigator determination, only one was considered possibly related to drug.

Comment: Two of these serious AEs may have been related to drug.

- A 52 year old male experienced substernal chest pain one day after his fourth dose of 2 mg. The pain lasted 20 minutes. He was brought to an emergency room where a non-Q wave MI was diagnosed. He was transferred to another hospital, where he underwent cardiac catheterization showing multivessel CAD, including a 100% occlusion of a ramus artery. He underwent angioplasty and was discharged in stable condition. No additional drug was taken and the patient was discontinued. The investigator believed the event was not related to apomorphine.

- A 63 year old male was noted to have new atrial flutter (with moderate ventricular response) on a final visit ECG. He was referred to a cardiologist who prescribed Coumadin. He ultimately underwent radi-frequency ablation therapy and the atrial flutter resolved. No additional drug was taken and the patient was discontinued. The investigator believed the event was possibly related to apomorphine.

Premature discontinuations due to adverse event:
Thirty-three patients discontinued due in some part to an adverse reaction. In twenty-seven of these, adverse reaction was the *primary* reason for terminating. Four of these 27 were reported as serious AEs, two were described above and two were not related to drug. Two patients developed upper respiratory infections that provoked discontinuation. One patient had worsening of previous osteoarthritis.

In the remaining twenty patients, one patient had syncope and is described below. The remainder of the patients discontinued for adverse events considered possibly, probably or definitely related to study drug. There was a pattern of adverse events leading to these discontinuations, including intolerable nausea, drowsiness, hypotension, diaphoresis, and oral irritation. In most cases, patients experienced a combination of these symptoms. One patient was discontinued due to increased liver function tests.

Approximately half of all discontinuations occurred at 4 mg and the other half at 6 mg.

The following patients had definite hypotensive episodes following their first doses of 4 mg:

- A 60 year old patient experienced hypotension (70/41 mm Hg), bradycardia (45 bpm), pallor, fatigue and diaphoresis 35 minutes after his first in-office dose of 4 mg (fourth dose overall). He did not lose consciousness. The symptoms persisted for 30-40 minutes and "completely abated" within 2 hours. No additional doses were taken and the patient was discontinued. The investigator considered the event definitely related to apomorphine.

- A 54 year old patient experienced hypotension, dizziness, pallor, diaphoresis, nausea and vomiting sometime after his first in-office dose of 4 mg (third dose overall). The duration of the symptoms was 20 to 65 minutes. No additional doses were taken and the patient was discontinued. The investigator considered the event probably related to apomorphine.

In one patient, nausea was accompanied by dyspnea:

- A 48 year old patient experienced nervousness, nausea and dyspnea after his third dose of 6 mg (fifteenth dose overall). The duration of the symptoms was 45 minutes. No additional doses were taken and the patient was discontinued. The investigator considered the event probably related to apomorphine.

Comments:

1. **Patients experienced acute events after doses of 4 mg, even after tolerating doses of 2 mg. It is notable that hypotension and dizziness lasted for up to 1 hour. Some of these acute events were accompanied by worrisome signs and symptoms, including bradycardia and dyspnea.**
2. **Apomorphine SL was irritating to the mucus membranes of the mouth, tongue and throat in this trial.**

One additional patient experienced syncope without discontinuation from the trial. He is described in below:

- A 52 year old patient consumed 4 ounces of vodka, one beer and one "shot" of rye within a 6 hour timeframe. He then took his sixth dose of 6 mg. Fifty-five minutes later, he became diaphoretic, dizzy and nauseated. He laid down. After laying down, he lost consciousness for 15 seconds. He subsequently vomited. He was taken to the emergency room for tests. He was discharged directly from the ER. He continued in the study and took an additional 59 doses. The investigator believed the event was probably related to apomorphine, although an alternative etiology was the simultaneous use of too much alcohol and study drug.

Comment: This case is concerning. Laying down did not prevent loss of consciousness in this patient. This patient then vomited *after* he lost consciousness. It is possible the event may have been related to the patient using "too much alcohol" and study drug. This case highlights concern that even in a controlled clinical trial which required minimal alcohol intake, this type of significant AE occurred.

Overall adverse effects: In the text of the study report, the sponsor summarized the adverse events that were considered by the investigator to be at least possibly related to apomorphine and reported by at least 5% of all patients.

When the overall AEs were tabulated in this manner the results are demonstrated in Table 4.

Table 4. Treatment-emergent adverse events at least possibly related to apomorphine and reported by ≥5% of all patients.

Adverse event	Overall n(%)	2 mg n (%)	4 mg n (%)	6 mg n(%)
Nausea	87(27.7)	5(1.6)	41(14.3)	63(29.4)
Somnolence	49(15.6)	2(0.6)	25(8.7)	34(15.9)
Dizziness	46(14.6)	3(1.0)	25(8.7)	24(11.2)
Sweating	33(10.5)	1(0.3)	15(5.2)	19(8.9)
Yawning	26(8.3)	0(0.0)	14(4.9)	19(8.9)
Vomiting	22(7.0)	0(0.0)	13(4.5)	12(5.6)
Asthenia	21(6.7)	0(0.0)	9(3.1)	17(7.9)

Two additional adverse events, vasodilatation and pallor also appeared to be dose-related. For vasodilatation, the combined incidence was 4.1%, with 0.6%, 2.1% and 4.2% of patients reporting vasodilatation at 2 mg, 4 mg and 6mg does, respectively. For pallor the combined incidence was 1.9%, with 0.0%, 1.4% and 1.9% of patients reporting pallor at 2 mg, 4 mg and 6mg does, respectively.

> **Comment: These results suggest a significantly worse adverse event profile for 4 mg, 5 mg and 6 mg compared with 2 mg.**

It is noteworthy that overall, approximately 12% of patients used anti-emetic medications to treat or prevent nausea associated with apomorphine.

Vital signs and electrocardiographic recordings:
There were statistically significant decreases-from-baseline in systolic BP at Months 2 through 6. The mean decrease in systolic BP ranged from –1.99 mm Hg (at Month 3) to –3.41 mm Hg (at Month 5). There were also non-statistically significant changes in diastolic BP in all these months.

> **Comment: A mean decrease from baseline in systolic of 2 to 3 mmHg is relatively modest. However, it does suggest that apomorphine has vasodilatory properties.**

Physical examinations: The sponsor does not describe any physical examination findings

Clinical laboratory examinations: There were statistically significant difference from baseline in a few laboratory parameters but these were numerically small and none were considered indicative of a meaningful clinical trend.

In terms of individual patient changes, there were five patients who experienced high eosinophils, two patients with high monocytes and one patient with a low hemoglobin. In terms of chemistry parameters, three patients had high serum glucoses, two had high SGPT and one had a high SGOT. The investigators considered none of these changes to be clinically significant.

> **Comment: It is interesting to note that eosinophilia is reported rarely but consistently in most apomorphine trials. The clinical relevance of this is unknown.**

Sponsor's assessment of efficacy and safety:
The sponsor believes that the results of this long-term study indicate that apomorphine 2 mg, 4 mg, and 6 mg tablets were well-tolerated and effective treatment for up to 6 months in patients with erectile dysfunction with no major organic component.

Reviewer's assessment of efficacy and safety:
There was evidence that most patients escalate to the maximum dose of 6 mg when allowed to titrate ad lib. There was evidence that many patients (22%) did not receive long-term benefit from apomorphine and discontinued prematurely due to this reason. There was evidence that many patients (11%) experienced usage-terminating adverse events. Overall, the drug was not well-tolerated, as evidenced by the adverse event profile of nausea, vomiting, dizziness, somnolence, sweating, etc.

There were two cases of particular concern. In one case, a patient who took apomorphine and ethanol experienced loss of consciousness after laying down, then vomited after losing consciousness. In the other case, a patient experienced nausea, diaphoresis and dyspnea after taking apomorphine.

Apomorphine was irritating to the buccal mucosa, tongue and throat. Apomorphine was associated with several cases of increased eosinophils, of uncertain clinical concern.

Safety Study M97-658

Design:

This was an open-label, flexible-dose, 6-month, safety study conducted at 32 United States centers. Patients who completed M97-658 and had a continuing diagnosis of ED were eligible to enroll in this trial. All procedures performed at the end of treatment period 2 of M97-658 were considered Visit 1 assessments for this trial. All patients began the study at a dose of 2 mg apomorphine. Dose could be adjusted at monthly in-office visits. Possible doses included 2 mg, 4 mg, 5 mg and 6 mg.

During the study, patients were instructed to take the drug no more than once per 8-hour period. Patients were instructed to take study medication by placing a single tablet under the tongue and allowing it to dissolve completely. Once the tablet was completely dissolved, sexual intercourse could be attempted when the couple was ready. Patients were instructed as follows: "You should limit yourself to a minimum amount of alcoholic beverages during the six hours prior to taking study medication." After at least 2 hours had passed after intercourse, patients and partners were instructed to complete a questionnaire regarding that particular sexual experience.

Comments:

1. **The requirement that minimal alcohol be consumed prior to taking a tablet may not be practical to expect in a real-world situation.**
2. **Assessment of efficacy in this 6-month, open-label trial cannot be made due to the lack of a control group.**

Inclusion/exclusion criteria:

Eligible patients were patients who had completed both treatment periods of the short-term apomorphine Study M97-658.

Briefly, these patients were heterosexual males, between 18 and 70 years of age. All men had to have a diagnosis of "erectile dysfunction with no major organic component". Erectile dysfunction was defined in M97-658 as "the ability to attain and maintain an erection firm enough for intercourse with a partner for less than 50% of attempts for a minimum of 3 months prior to Day 1 of Treatment Period 1". In addition, all patients had to have demonstrated "an erection of sufficient quality for intercourse on some occasion since the onset of erectile dysfunction as evidenced by nocturnal/morning erections, masturbation, and/or other sexual activity."

In M97-658, all patients underwent nocturnal penile tumescence testing (NPT) using Rigisican at least 60 days prior to Day 1 of Treatment Period 1. All patients had to demonstrate at least 1 successful erection during NPT testing; specifically, a successful erection was defined as one wherein the base of the penis was at least 55% rigid for at least 10 minutes.

All patients had to be involved in a "stable", heterosexual relationship for at least 8 months. All patients and partners had to agree to attempt intercourse at least once weekly. All patients had to be "judged in good general health as evidenced by medical history and the complete physical examination at the end of Study M97-658". All pre-study laboratory values had to be within 15% above or below normal range on the final visit of M97-658. Fasting blood glucose had to be <250 mg/dL, unless approval was obtained by the medical monitor.

Comment: This patient population was physiologically capable of getting erections and was generally healthy. This population does not represent the larger ED population.

Patients were excluded for the same reasons as in M97-658. These included:

1. Presence of "neurologic disease" (e.g. Parkinson's disease, multiple sclerosis, or spinal cord injury).
2. Presence of such genitourinary disorders as history of radical prostatectomy, penile prosthesis, or major penile deformity.
3. Presence of hypogonadism (serum T <280 ng/dL), hyperprolactinemia (serum prolactin >20 ng/mL), diabetes with an elevated glycosulated hemoglobin at baseline, or diabetes with any episode of ketoacidosis with the last 3 months.
4. Presence of major psychiatric disorder.
5. Presence of "cardiovascular disease" (e.g. systolic BP >180 mm Hg and/or diastolic >100 mm Hg while sitting, hypotension [systolic BP< 90 mm Hg while standing]).
6. Presence of gastrointestinal disease (especially, any disorder resulting in the need for anti-nausea medications in the last 6 months).
7. Any cancer other than basal or squamous cell cancer that has not been in remission for at least 5 years.
8. Any pharmacologic therapy for ED within the preceding 3 months.
9. Greater than 75% successes during the lead-in period.
10. History of drug or alcohol abuse within the past 2 years.
11. Smoking greater than 10 cigarettes per day, or the equivalent use of tobacco in other forms.
12. Presence of AIDS or HIV-positive status.
13. History of allergic reaction to morphine or any other opiate.
14. Partners with major affective disorder.
15. Partners with a history of female sexual dysfunction.

> **Comment: Inclusion and exclusion criteria were fairly restrictive. The study population is a relatively healthy group and again, is not indicative of the erectile dysfunction population at large.**

Efficacy endpoints and statistical analysis plan:

The primary efficacy endpoint was the same as in M97-658: "the home-use success rate" for the entire 6-month period. An attempt was defined as taking a study drug and completing a questionnaire and success was defined as achieving an erection firm enough for intercourse according to the patient's opinion. Secondary efficacy endpoints were the same as in M97-658 and included:

1. Achievement of an erection firm enough for intercourse according to the partner's opinion.
2. Number of patients with successful response (defined as erection sufficient for intercourse in 50% or greater number of attempts)
3. Successful intercourse rates according to patient and partner
4. Time to erection
5. Duration of erection
6. International Index of Erectile Function (IIEF) results at the end of each treatment period
7. Brief Sex Function Inventory questionnaire for the partner, and
8. Fugl-Meyer Life Satisfaction Scale

The statistical analysis plan was a summary or descriptive tabulation of the efficacy endpoints for the entire treatment period, by dose, by month and by last 16 attempts.

Safety endpoints:
Safety endpoints included complete physical examination, including vital signs and body weight, 12-lead EKG, routine laboratory examinations (hematology, chemistry and urinalysis) and assessment of adverse events.

Withdrawals, compliance, and protocol deviations:
Patient disposition:
A total of 404 patients completed M97-658. Three hundred thirty-five (335) males were enrolled into this study. Three hundred twenty-six (326) took at least one dose of apomorphine. One hundred thirty-four (134) completed the study. Of the 192 patients who discontinued the study, 51 (15.6% of patients who took at least one dose) discontinued at least in part because of adverse events. (Table 1)

Table 1. Reasons for study discontinuation

Reason	Number of pts
Adverse event as "primary reason"	40
Adverse event as at least part of reason	11
Noncompliance	12
Complete lack of efficacy	35
Partial efficacy	51
Patient request	21
Partner request	3
Lost to follow-up	21
Death	0
Other	9

Comment: Discontinuations due to adverse events and discontinuations due to lack of efficacy comprised approximately 16% and 22% of the total dosed population, respectively. These results are consistent with trial M96-471, another 6-month, open-label trial. Thus, there is fairly reliable evidence that the long-term patient acceptance of apomorphine is not very impressive.

The adverse events resulting in study discontinuation are discussed in the safety analysis.

Treatment compliance: Compliance was assessed by collecting home-use diaries and comparing those documents to actual pill count.

Protocol deviations: Three patients were included in the study that did not meet the eligibility criteria. Three patients were dosed incorrectly at some time during the 6-month trial. Two patients began the study on 4 mg, rather than the 2 mg dose. One patient's wife became pregnant while the patient was in the trial. The sponsor states that the child "appeared normal at birth".

Efficacy analysis:
The primary endpoint was the percentage of attempts in which the patient thought that he had achieved an erection firm enough for intercourse.

The average percentage of attempts resulting in an erection firm enough for intercourse was 57.1% when all doses were combined, compared to 25.4% at baseline. When calculated separately for the 2 mg, 4 mg, 5 mg and 6 mg doses, these figures were 41.5%, 53.9%, 55.0% and

57.7%, respectively. When only the last 16 attempts were analyzed, the total average figure was 59.8%.

Of *all attempts* made during the study, 67.7% resulted in an erection firm enough for intercourse compared to 25.4% at baseline. Of all attempts for 2 mg, 4 mg, 5 mg and 6 mg, 58.2%, 69.9%, 72.5% and 69.2% resulted in an erection sufficient for intercourse, respectively.

The sponsor believes that the reason for the differences between these two sets of success rates is that more successful patients made more attempts, compared to less successful patients.

For the secondary endpoint, rates of successful intercourse, the results are similar. For the average percentage of successful intercourse attempts, the rate for combined doses was 55.1% versus 25.2% at baseline. For the 2 mg, 4 mg, 5 mg and 6mg doses separately, those results were 39.4%, 51.2%, 54.1% and 56.6%, respectively.

For the International Index of Erectile Function, Table 2 presents the mean EF domain score over time for all patients, all doses combined.

Table 2. Mean EF domain scores over time.

	Baseline Mean(n)	Month 1 Mean(n)	Month 2 Mean(n)	Month 3 Mean(n)	Month 4 Mean(n)	Month 5 Mean(n)	Month 6 Mean(n)	Final Mean(n)
EF domain	12.4(325)	16.8(307)	19.2(259)	21.1(219)	22.8(170)	23.9(148)	25.2(109)	19.0(313)

Comment:

1. **Table 2 reflects the following: Patients who were able to tolerate apomorphine and who received benefit early on in treatment, continued to receive benefit as the study progressed. In fact, in these patients, erectile function appeared to improve over time. Overall, when everyone was included in this analysis, however, the overall improvement in the population was less robust.**
2. **This population is a group of men physiologically capable of demonstrating a rigid erection. In many of these men, it is possible that their erectile dysfunction would have improved spontaneously over time, without any intervention. This study is not designed to appropriately answer that question, as there is no control arm.**

Safety Analysis :
Extent of exposure : The extent of apomorphine SL exposure is depicted in Table 3.

Table 3. Extent of apomorphine SL exposure by number of does taken.

	1	2-8	9-19	20-49	50-100	>100	Total
Combined	1	31	73	168	46	7	326
2 mg	4	249	57	11	3	0	324
4 mg	18	172	88	30	2	0	310
5 mg	5	117	72	24	6	0	224
6 mg	6	55	41	34	8	0	144

Overall, most of the 326 patients who received study drug escalated to the 6 mg dose. The final dose was 2 mg for 21 patients (6.4%), 4 mg for 93 patients (28.5%), 5 mg for 78 patients (23.9%) and 6 mg for 134 patients (41.1%).

Comment: It is notable the majority of the patients chose to increase the to the maximum dose allowed (6 mg). One explanation for this phenomenon is that patients were dissatisfied with efficacy at lower doses.

Deaths : There were no study deaths.

Serious adverse events:
Eleven patients experienced serious adverse events during this study. According to investigator determination, none were related to apomorphine.

Comment: None of these eleven serious adverse events appearred to be drug-related.

Premature discontinuations due to adverse event:
Fifty-one patients discontinued due in some part to an adverse reaction. In forty of these, adverse reaction was the *primary* reason for terminating. Seven off these were described in the serious AE section and were not related to apomorphine. Of the remaining thirty-three (33) patients, there was a pattern of adverse events. Some patients discontinued due to intolerable nausea and/or vomiting. Several complained of lethargy and fatigue. Four patients discontinued due to symptoms consistent with vasodilatation or hypotension. Nine patients discontinued due to symptoms related to mouth, tongue or throat irritation. In some cases, patients discontinued for more than one of these reasons.

It is notable that most of these discontinuations were on 4 mg (n=19). A few occurred on 2 mg (n=3) and on 6 mg (n=3). Some also occurred on 5 mg (n=8).

Below, the reviewer has selected the most representative cases from the sponsor's submission to depict the reasons for premature discontinuation due to AEs. It is important to note that this is not a comprehensive list:

Nausea and vomiting:

- A 62 year old male experienced vomiting 30 minutes after his fifth dose of apomorphine 5 mg (eighteenth dose overall). These symptoms lasted 5 seconds to 2 hours. He reported vomiting after two previous doses of 4 mg and 5 mg. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

Lethargy, fatigue and "sleepiness":

- A 57 year old male experienced lethargy after his fourth dose of 6 mg dose (fifteenth dose overall). These symptoms lasted approximately 4 hours. He had similar symptoms with previous doses. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 57 year old male experienced "sleepiness" within seconds after his fifth dose of 4 mg (ninth dose overall). He had similar symptoms with all previous doses. This symptom lasted approximately 30 minutes. No additional drug was taken and then the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

Mouth ulcers, swollen tongue, swollen lips, etc:

- A 68 year old male experienced a burning, sore tongue with difficulty breathing 19 hours after his eighth dose of 5 mg (twelfth dose overall). These symptoms lasted approximately 5 days. He had similar symptoms with previous doses. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 65 year old male experienced sore mouth, tongue swelling on the inside lower lip and "blisters" after taking his twelfth dose of 5 mg (35 doses overall). No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

Dizziness, syncope, diaphoresis, light-headedness, "clamminess", etc:

- A 50 year old male experienced hypotension, bradycardia, sweating, and warmth approximately 40 minutes after taking his first 2 mg dose in this study. Hypotension lasted 5 minutes, bradycadia lasted 10 minutes and sweating lasted 25 minutes. Apparently, this patient was enrolled in this study despite his never completing M97-658, a protocol violation. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 63 year old male experienced light-headedness, flushing, "clamminess" and hypotension 35 minutes after his first dose of 4 mg (sixth dose overall). No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

Comments:

1. **Adverse events leading to discontinuation occurred at all doses. In this study, many occurred at the 4 mg dose.**
2. **The narrative descriptions of these discontinuations are consistent with those presented previously.**
3. **Again, it was noted that some patients discontinued due to oral irritation and lip/tongue swelling and oral "blisters".**

Two additional patients experienced syncope without discontinuation from the trial. In one of these, syncope occurred 8 days after the last dose of study medication. The other patient is described below:

- A 69 year old patient experienced syncope "after" his first in-office dose of 4 mg. The syncopal episode was accompanied by nausea, dizziness and "mild airway obstruction". The syncope lasted approximately 1 minute, but the remainder of the symptoms lasted for 68 minutes. The patient took 6 more doses without incident. He discontinued due to lack of efficacy. The investigator believed the event was probably related to apomorphine.

Comment: This case is concerning as it involves a patient who experienced syncope after a 4 mg dose, and was accompanied mild airway obstruction.

Overall, eight patients (five patients receiving 4 mg and two receiving 6 mg) experienced hypotension.

Overall adverse effects: In the text of the study report, the sponsor summarized the adverse events that were considered by the investigator to be at least possibly related to apomorphine and reported by at least 5% of all patients.

When the overall AEs were tabulated in this manner the results are demonstrated in Table 4.

Table 4. Treatment-emergent adverse events at least possibly related to apomorphine and reported by ≥5% of all patients.

Adverse event	Overall n(%)	2 mg n (%)	4 mg n (%)	5 mg n (%)	6 mg n(%)
Nausea	88(27.0)	9(2.8)	47(15.2)	30(13.4)	21(14.6)
Dizziness	41(12.6)	4(1.2)	27(8.7)	7(3.1)	9(6.3)
Somnolence	36(11.0)	5(1.5)	20(6.5)	14(6.3)	9(6.3)
Sweating	31(9.5)	3(0.9)	13(4.2)	8(3.6)	11(7.6)
Yawning	23(7.1)	2(0.6)	11(3.6)	7(2.8)	6(3.3)
Vomiting	22(6.7)	2(0.6)	11(3.6)	6(2.7)	4(2.8)

Comment: This table reflects a significantly worse adverse event profile for 4 mg, 5 mg and 6 mg compared with 2 mg.

Vital signs and electrocardiographic recordings:
Although there were a few statistically significant changes in vital signs at some times during the study (e.g. decrease in systolic BP from baseline at Months 1 and 6), none were considered to reflect a clinically meaningful trend.

Physical examinations: There were six patients with physical findings of note. Five of these patients had signs of oral irritation.

Clinical laboratory examinations: There were statistically significant differences from baseline in the following parameters: increase in percent eosinophils and lymphocytes, decrease in hemoglobin and red cells, increase in serum glucose, increase in SGOT/SGPT, and decreases in several serum chemistry parameters. The sponsor considered none of these clinically meaningful.

Several individual patients experienced significant laboratory abnormalities while taking apomorphine. A few had increases in the percentage of eosinophils. One patient had an increase in total bilirubin. One patient had an increase in both total serum bilirubin and SGOT. In this patient, the total bilirubin was 2.0 mg/dL (normal values 0.2-1.2) and SGOT was 146 IU/L (normal values 6-37 IU/L)

Sponsor's assessment of efficacy and safety:
The sponsor believes that the results of this long-term study indicate that apomorphine 2 mg, 4 mg, 5 mg and 6 mg tablets were a well-tolerated and effective treatment for up to 6 months in patients with erectile dysfunction.

Reviewer's assessment of efficacy and safety:
The efficacy data suggest some evidence of a treatment effect with apomorphine, perhaps in a subpopulation of patients. These patients clearly are those who can tolerate the side effects of apomorphine and may experience improvement in their erectile function. Still, it is difficult to determine if this same population of patients might have improved over time if given placebo.

This uncontrolled trial may have exaggerated the benefits of apomorphine. In this group of men with psychogenic impotence, it is likely that many patients would have improved spontaneously over time, especially with the additional placebo effect of taking a tablet immediately prior to intercourse. The study was not designed to exclude these biases.

It is interesting to note that most patients requested dosage titration up to the maximum of 6 mg. This is probably reflective of patient dissatisfaction at lower doses, and confirms the findings of M96-471, also a 6-months, open-label trial.

In terms of safety, there is evidence that a significant proportion of patients will not tolerate apomorphine. This conclusion is based on an adverse event profile of nausea, dizziness, hypotension, sweating, vomiting, etc. More serious is the less frequent occurrence of hypotension, bradycardia, nausea, vomiting, diaphoresis and possible syncope that tends to occur early in treatment (usually following increases in dose). In one patient, mild airway obstruction was reported in conjunction with nausea, drowsiness and syncope. This leads to concern about the potentially life-threatening nature of this type of AE.

Approximately 10% of all discontinuations were noted at the 4 mg dose. Hypotension was reported by four patients at the 4 mg dose.

It should be noted that this was a carefully selected group of healthy men. These men did not represent the real-world population of men with erectile dysfunction. It is possible that the safety consequences may be greater in the broader ED population.

Safety Study M98-876

Design:

This was an open-label, flexible-dose, at-home, safety study conducted at 16 United States centers. There was a 2-4 week screening period. During the first 3 weeks of the subsequent treatment period, patients underwent dose-optimization. Specifically, all patients received 2 mg first, then step-wise dose increases could be made at the investigator's discretion, based on a weekly in-office review. The doses available in the study were 2 mg, 4 mg and 5 mg. Doses were not to be given in the office, unless the patient experienced a "significant drug-related AE". In such cases, the next dose would be given in-office. Patients were dispensed five doses for at-home use per week. At the end of the 3-week optimization period, patients were assigned their "optimized" dose and were dispensed 20 tablets for a 4-week at-home maintenance period.

During the study, patients were instructed to take the drug no more than once per 8-hour period. Patients were instructed to attempt intercourse at least 2 times per week. Patients were instructed to take study medication by placing a single tablet under the tongue and allowing it to dissolve completely. Once the tablet was completely dissolved, sexual intercourse could be attempted when the couple was ready. Patients were instructed as follows: "You should limit yourself to a minimum amount of alcoholic beverages during the six hours prior to taking study medication." After at least 2 hours had passed after intercourse, patients and partners were instructed to complete a questionnaire regarding that particular sexual experience. Patients were told that if nausea, vomiting, dizziness, sweating, hot flashes, light-headedness or pallor ensued after dosing, that they should lie down and raise their legs until the symptoms passed.

Comments:

1. **The requirement that minimal alcohol be consumed prior to taking a tablet may not be practical to expect in a real-world situation.**
2. **Assessment of efficacy in this open-label trial cannot be made due to the lack of a control group.**

Inclusion/exclusion criteria:

Inclusion and exclusion criteria were similar to all previous Phase 3 apomorphine trials. Briefly, these patients were heterosexual males, between 18 and 70 years of age. All men had to have a diagnosis of "erectile dysfunction". The clause "with no major organic component" was deleted. Erectile dysfunction was defined as "the ability to attain and maintain an erection firm enough for intercourse with a partner for less than 50% of attempts for a minimum of 3 months prior to the screening visit."

All patients had to be involved in a "stable", heterosexual relationship for at least 6 months. All patients and partners had to agree to attempt intercourse at least twice weekly. All patients had to be "judged in good general health as evidenced by medical history and the complete physical examination". All pre-study laboratory values had to be within 15% above or below normal range. Fasting blood glucose had to be <250 mg/dL, unless approval was obtained by the medical monitor.

Comment: This patient population that was generally healthy and does not represent the larger ED population.

Patients were excluded for similar reasons as in previous Phase 3 apomorphine trials. These included:

1. Presence of "neurologic disease" (e.g. multiple sclerosis, or spinal cord injury).

2. Presence of such genitourinary disorders as history of radical prostatectomy, penile prosthesis, or major penile deformity.
3. Presence of hypogonadism (serum T <240 ng/dL)
4. Presence of "cardiovascular disease" (e.g. systolic BP >180 mm Hg and/or diastolic >100 mm Hg while sitting, hypotension [systolic BP< 90 mm Hg while standing], or clinically significant abnormal ECG).
5. Any cancer other than basal or squamous cell cancer that has not been in remission for at least 5 years.
6. Any pharmacologic therapy for ED within the preceding 3 months.
7. Greater than 75% successes during the lead-in period.
8. History of drug or alcohol abuse within the past 6 months.
9. Presence of AIDS or HIV-positive status.
10. History of hypersensitivity to morphine.
11. Partners who were pregnant, lactating or planning to become pregnant.

Efficacy endpoints and statistical analysis plan:
The primary efficacy endpoint was the EF domain score from the International Index of Erectile Function questionnaire, as measured at Day 1, Day 3 and Day 7. Secondary efficacy endpoints included:
1. Number of attempts resulting in an erection sufficient for intercourse
2. Number of patients with successful response (defined as erection sufficient for intercourse in 50% or greater number of attempts)
3. Successful intercourse rates according to patient
4. Time to erection
5. Duration of erection
6. Global Efficacy Questionnaire.

All endpoints derived from the IIEF were to be analyzed using a paired t-test for changes from baseline. The analyses would be performed for both Week 3 and Week 7 timepoints. All remaining endpoints would be summarized only.

Safety endpoints:
Safety endpoints included complete physical examination, including vital signs and 12-lead EKG, routine laboratory examinations (hematology, chemistry and urinalysis) and assessment of adverse events.

Withdrawals, compliance, and protocol deviations:
Patient disposition:
A total of 151 males were enrolled into this study. A total of 145 took at least one dose of apomorphine. A total of 112 patients completed the study. Of the 33 patients who discontinued the study, seven (4.8 % of patients who took at least one dose) discontinued at least in part because of adverse events. (Table 1)

Table 1. Reasons for study discontinuation

Reason	Number of patients
Adverse event	7
Noncompliance	0
Complete lack of efficacy	16
Partial efficacy	3
Patient request	5
Partner request	0
Lost to follow-up	2
Death	0
Other	1

The adverse events resulting in study discontinuation are discussed in the safety analysis.

Treatment compliance: Compliance was assessed by collecting home-use diaries and comparing those documents to actual pill count.

Protocol deviations: Four patients were included in the study that did not meet the eligibility criteria. Two patients did not make the required twice weekly attempts at intercourse. One patient received 5 mg tablets on Day 1 rather than 2 mg tablets.

Efficacy analysis:
The primary endpoint was the EF domain score from the IIEF. In this 5-question domain score, 30 points is the best possible score and 0 is the worst.

Table 2 presents the mean EF domain score over time for all patients, all doses combined.

Table 2. Mean EF domain scores over time.

	Baseline Mean(n)	Week 3 Mean(n)	Week 7 Mean(n)	Last visit Mean(n)
EF domain	10.9(146)	15.8(116)	17.3(95)	16.0(142)

In terms of percentage of attempts in which the patient thought that he had achieved an erection firm enough for intercourse, the sponsor analyzed the data for the last eight attempts, for all attempts, and for each dose.

The average percentage of attempts resulting in an erection firm enough for intercourse for the last eight attempts was 39.8% when all doses were combined, compared to 13.7% at baseline. For all attempts, the final figure was 26.9%. When calculated separately for the 2 mg, 4 mg, and 5 mg, these figures were 28.5%, 32.9%, and 32.6%, respectively.

> **Comment: This group of patients had relatively severe ED at baseline. Although there was some improvement during the trial, patients still had moderate ED at study end.**

Of *all attempts* made during the study, 42.3% resulted in an erection firm enough for intercourse compared to 25.4% at baseline. Of all attempts for 2 mg, 4 mg, and 5 mg, 41.4%, 50.1%, and 38.8% resulted in an erection sufficient for intercourse, respectively.

The sponsor believes that the reason for the differences between these two sets of success rates is that more successful patients made more attempts, compared to less successful patients.

For the secondary endpoint, rates of successful intercourse, the results are similar. For the average percentage of successful intercourse attempts, based on the last eight attempts, the rate for combined doses was 40.8% versus 13.4% at baseline. For the 2 mg, 4 mg, and 5 mg doses separately, those results were 29.7%, 33.3%, and 33.6, respectively.

For the secondary endpoint, number of patients with >50% successes, based on all attempts, 41.8% of patients were "successful responders" versus 10.3% at baseline.

Comment: There was evidence of modest improvement in erectile function in this trial.

Safety Analysis :
Extent of exposure : The extent of apomorphine SL exposure is depicted in Table 3.

Table 3. Extent of apomorphine SL exposure by number of doses taken.

	1-2	3-5	6-10	11-20	>20	Total
Combined	1	5	30	77	33	146
2 mg	66	72	1	4	2	145
4 mg	56	66	9	11	0	142
5 mg	15	22	27	49	7	120

Comment: The overall exposure in this trial was limited to 7 weeks.

Deaths : There were no study deaths.

Serious adverse events :
No serious adverse events were reported during this study.

Comment: It is noteworthy that no serious adverse events were reported.

Premature discontinuations due to adverse event:
Seven patients discontinued due in some part to an adverse reaction. One patient experienced hemoptysis that was thought to be unrelated to apomorphine. The remaining six patients are described below:

Syncope:

- A 61 year old patient experienced syncope following his twelfth dose of 5 mg (twenty-first dose overall). Approximately 30 minutes after taking his tablet, he experienced nausea, diaphoresis and heart palpitations. He then proceeded to stand up and experienced a syncopal event. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine. The sponsor states, "it should be noted that the patient did not follow the Patient Warning Instructions."

Comment: This was the patient's twelfth dose of 5 mg and yet he still had a experienced syncope.

Lethargy and dizziness:

- A 60 year old patient experienced lethargy and dizziness after his third 2 mg dose. These symptoms lasted approximately 40 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

Headache, insomnia and nausea:

- A 57 year old patient experienced headache, insomnia, nausea and pruritis after his second 2 mg dose. These symptoms lasted approximately 10 hours. No additional drug was taken and then the patient was discontinued. The investigator believed the event was probably related to apomorphine.

Comment: It is notable that these two discontinuations occurred at doses of 2 mg.

Nausea:

- A 67 year old patient experienced nausea and diaphoresis after his third dose of 5 mg (tenth dose overall). These symptoms lasted approximately 45 minutes. Compazine had been taken prophylactically with the dose and was taken again after the dose. The patient had similar symptoms with previous doses. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 54 year old patient experienced nausea and dizziness after his fourth dose of 5 mg (twelfth dose overall). The symptom lasted 5 hours. He had similar episodes with previous doses. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

Mouth irritation:

- A 60 year old patient experienced moderate taste loss after his third dose of 5 mg (tenth dose overall). These symptoms lasted approximately 32 days. He had similar symptoms with previous doses. He took two additional doses and experienced mouth irritation and dry mouth. He took an additional three doses and experienced tongue edema. No additional drug was taken and the patient was discontinued. The investigator believed these events were probably related to apomorphine.

Overall adverse effects: In the text of the study report, the sponsor summarized the adverse events that were considered by the investigator to be at least possibly related to apomorphine and reported by at least 5% of all patients.

When the overall AEs were tabulated in this manner the results are demonstrated in Table 4.

Table 4. Treatment-emergent adverse events at least possibly related to apomorphine and reported by ≥5% of all patients.

Adverse event	Overall n(%)	2 mg n (%)	4 mg n (%)	5 mg n (%)
Nausea	34(23.3)	6(4.1)	17(12.0)	20(16.5)
Dizziness	19(13.0)	9(6.2)	6(4.2)	7(5.8)
Somnolence	15(10.3)	4(2.8)	6(4.2)	5(4.1)
Headache	15(10.3)			

Other adverse events possibly related to apomorphine and reported by fewer than 5% of patients included vomiting (2.7%), asthenia (2.7%), sweating (2.1%), vasodilation (1.4%), syncope (0.7%) and yawning (0.7%).

> **Comment: In this trial, the incidence rates of serious adverse events and overall adverse events were slightly less than those from other apomorphine Phase 3 trials. This was an open-label trial and perhaps, safety monitoring was less rigorous. In addition, there were fairly explicit patient instructions given that may have affected safety outcomes.**

Vital signs and electrocardiographic recordings:
The mean systolic BP was decreased from baseline at Week 3 (-1.8 mm Hg) and Week 7 (-2.75 mm Hg) compared with baseline. The pulse rates were also minimally decreased. None of these changes in group vital signs were felt to be clinically meaningful.

Physical examinations: The sponsor made no mention of any physical findings.

Clinical laboratory examinations: There were statistically significant differences from baseline in the following parameters: decrease in hemoglobin, hematocrit and red blood cells, increase in serum glucose, increase in SGPT and alkaline phosphatase, and changes in several serum chemistry parameters. The sponsor considered none of these clinically meaningful.

Several individual patients experienced significant laboratory abnormalities while taking apomorphine. One patient had elevation of serum transaminases at Week 3, which resolved by Week 7. One patient had a slightly elevated SGOT, which was repeated and felt "not to be clinically significant." One patient had an elevated SGPT and total bilirubin at the end of Week 3. The labs were repeated and remained elevated at Week 7. The investigator attributed these abnormalities to alcohol use.

> **Comments: This the third patient in the Phase 3 trials who was noted to have serum transaminases and total bilirubin elevated. Attribution to study drug, however, is unclear.**

Sponsor's assessment of efficacy and safety:
The sponsor believes that the results of this study indicate that apomorphine 2 mg, 4 mg, and 5 mg tablets were well-tolerated.

Reviewer's assessment of efficacy and safety:
Apomorphine was better tolerated in this trial than in previous trials. However, there was one reported syncope (0.7%) and several other cases consistent with vasodilatation. Nausea occurred, although at a somewhat reduced rate. Oral discomfort was a problem. There was a single patient with clinically meaningful increases in serum LFTs, but this was confounded by ethanol use.

Again, this trial was designed to enroll men in overall general good health. Such a study population does not reflect the ED population at-large.

Safety Study M97-793

Design:

This is an ongoing, open-label, flexible-dose, 3-year, safety study conducted at 23 United States centers. Any patient who completed M97-804 (controlled diabetics) or M97-788 (radical prostatectomy patients) and had a continuing diagnosis of ED was eligible to enroll in this study. In addition, patients who prematurely discontinued from M97-788 due solely to lack of efficacy were also eligible to enroll. The cut-off date for inclusion in this report was May 31, 1999.

> **Comment: Study M97-788 enrolled only 44 patients and Study M97-804, 166 patients. Study M97-793, therefore, will have a fairly limited population from which to draw safety conclusions about patients with "organic" erectile dysfunction.**

All procedures performed at the end of the previous apomorphine SL trial were considered Visit 1 assessments for this study, provided that no more than 30 days had elapsed. All patients began the study at a dose of 2 mg apomorphine. The initial dose was administered in-office with a 2-hour post-dosing observation period. Dose could be adjusted at monthly in-office visits. Possible doses included 2 mg, 4 mg, 5 mg and 6 mg.

During the study, patients were instructed to attempt intercourse at least once weekly and take the drug no more than once per 8-hour period. Patients were instructed to take study medication by placing a single tablet under the tongue and allowing it to dissolve completely. Once the tablet was completely dissolved, sexual intercourse could be attempted when the couple was ready. Patients were instructed as follows: "You should limit yourself to a minimum amount of alcoholic beverages during the six hours prior to taking study medication." After at least 2 hours had passed after intercourse, patients and partners were instructed to complete a questionnaire regarding that particular sexual experience.

Inclusion/exclusion criteria:

Eligible patients were those who had completed M97-804 (controlled diabetic patients) or M97-788 (radical prostatectomy patients) and had a continuing diagnosis of ED. Patients who prematurely discontinued from M97-788 due solely to lack of efficacy were also eligible to enroll.

All patients had to be "judged in good general health" as evidenced by medical history and the complete physical examination. If the patient was diabetic, the glycosylated hemoglobin had to be <10% and there had to be no episodes of ketoacidosis within the past year.

All patients had to be involved in a "stable" sexual relationship for at least 6 months. All patients and partners had to agree to attempt intercourse at least once weekly. All pre-study laboratory values had to be within 15% above or below normal range on the final visit of the previous study.

Patients were excluded for many of the same reasons as in previous Phase 3 trials and some new reasons. These included:

1. Presence of "neurologic disease" (e.g. Parkinson's disease, multiple sclerosis, or spinal cord injury).
2. Presence of such genitourinary disorders as history of penile prosthesis, or major penile deformity.
3. Presence of major psychiatric disorder.
4. Presence of "cardiovascular disease". This category included:

- Coronary artery disease requiring treatment in the year prior to visit 1 with anti-anginals, percutaneous transluminal angioplasty (PTCA), coronary artery bypass graft (CABG), athrectomy, or stents.
- Use of anticoagulants and antiplatelets (except prophylactic aspirin use) in the year prior to Visit 1 and throughout the study.
- Systolic BP >180 mm Hg and/or diastolic >100 mm Hg while sitting.
- Systolic BP< 90 mm Hg while standing with symtoms.
- Clinically significant abnormal ECG.

5. Presence of gastrointestinal disease (especially, any disorder resulting in the need for anti-nausea medications in the last 6 months).
6. Presence of vascular disease (including any history or suspected cerebrovascular or peripheral vascular disease resulting in ongoing foot ulcers).
7. Presence of peripheral neuropathy resulting in significant peripheral pain or loss of pain sensation in the extremities. Also known or suspected autonomic neuropathy resulting in diminished bowel or bladder control.
8. Presence of nephropathy defined as ≥30 mg/dL.
9. Any cancer other than prostate cancer and basal/squamous cell cancer that has been in remission for at least 5 years.
10. Treatment with radiotherapy or chemotherapy following prostatectomy.
11. Patients who took LHRH analogues or antiandrogens either before or after prostatectomy.
12. Any pharmacologic therapy for ED within the preceding 4 months.
13. Greater than 75% successes during the lead-in period.
14. History of drug or alcohol abuse within the past 2 years.
15. Smoking greater than 10 cigarettes per day, or the equivalent use of tobacco in other forms.
16. Presence of AIDS or HIV-positive status.
17. History of allergic reaction to morphine or any other opiate.
18. Partners with major affective disorder.
19. Partners with a history of female sexual dysfunction.
20. Partners who were pregnant, lactating or planning to become pregnant.

Comment: The study population is a healthy group of diabetics and patients who have undergone radical prostatectomy. This group is not indicative of the erectile dysfunction population at large.

Efficacy endpoints and statistical analysis plan:
The primary efficacy endpoint was the same as in other Phase 3 apomorphine trials: "the home-use success rate" for the entire treatment period. An attempt was defined as taking a study drug and completing a questionnaire and success was defined as achieving an erection firm enough for intercourse according to the patient's opinion. Secondary efficacy endpoints were the same as in other Phase 3 apomorphine trials and included:

1. Number of patients with successful response (defined as erection sufficient for intercourse in 50% or greater number of attempts)
2. Successful intercourse rates according to patient
3. Time to erection
4. Duration of erection
5. International Index of Erectile Function (IIEF) results
6. Fugl-Meyer Life Satisfaction Scale
7. Treatment Satisfaction questionnaire

The statistical analysis plan was a summary or descriptive tabulation of the efficacy endpoints for the entire treatment period, by 6-month periods. Because this was an interim analysis, the plan was modified to present the efficacy data by 3-month periods.

Safety endpoints:
Safety endpoints included complete physical examination, including vital signs and body weight, 12-lead EKG, routine laboratory examinations (hematology, chemistry and urinalysis) and assessment of adverse events.

Withdrawals, compliance, and protocol deviations:
Patient disposition:
As of the interim analysis date, one hundred fifteen (115) males had enrolled into this study. The majority of these came from the diabetic trial (n=101) and the remainder from the radical prostatectomy trial (n=14).

Forty-seven (47) patients were still enrolled as of the interim analysis date. Of the 68 patients who discontinued the study, eight patients discontinued because of adverse events. (Table 1)

> **Comment: It is important to note that 59% of patients who enrolled have already discontinued from this study. This figure is consistent with the percentage of discontinuations from the other long-term, open-label Study M97-682.**

Table 1. Reasons for study discontinuation

Reason	Number of patients
Adverse event	8
Noncompliance	1
Lack of efficacy	49
Patient request	4
Lost to follow-up	5
Other	1

The adverse events resulting in study discontinuation are discussed in the safety analysis.

Treatment compliance: Compliance was assessed by collecting home-use diaries and comparing those documents to actual pill count.

Protocol deviations: The most common protocol deviations were: 1) clinic visits that occurred outside the scheduled monthly visit window, and 2) too few or no monthly intercourse events.

Two patients had dosing errors; they received a higher or lower dose than indicated by the titration scheme. One patient took three 2 mg tablets at one time "because he was dissatisfied with the effect of a single 2 mg tablet." Seventeen patients took doses of apomorphine SL that were less than eight hours apart. None of these patients reported an adverse event associated with such use.

Efficacy analysis:
The primary endpoint was the percentage of attempts in which the patient thought that he had achieved an erection firm enough for intercourse.

The *mean average percentage of attempts* resulting in an erection firm enough for intercourse was 37.0% when all doses were combined, compared to 4.3% at baseline. When calculated separately for the 2 mg and 4 mg combined dose, the mean average percentage of successful attempts was 32.0%.

When calculated separately for the 2 mg, 4 mg, 5 mg and 6 mg doses, these figures were 25.6%, 35.8%, 33.9% and 31.6%, respectively. When only the last 16 attempts were analyzed, the total average figure (all doses combined) was 40.0%.

Of *all attempts* made during the study, 53.5% resulted in an erection firm enough for intercourse. Of all attempts for 2 mg, 4 mg, 5 mg and 6 mg, 37.3%, 59.7%, 55.2% and 59.0% resulted in an erection sufficient for intercourse, respectively.

The sponsor believes that the reason for the differences between these two sets of success rates is that more successful patients made more attempts, compared to less successful patients.

When analyzed by monthly results, these results are depicted in Table 2 below.

Table 2. Percentage of total attempts resulting in an erection firm enough for intercourse. All doses combined, all attempts.

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Entire study
Percent of successful attempts	32.8%	47.2%	54.6%	68.0%	82.6%	84.8%	91.0%	100%	95.5%	53.5%
Total number of patients	114	99	86	53	25	21	14	5	4	114

Comments:

1. **Table 3 depicts a month-by-month improvement in the primary endpoint, as fewer and fewer patients remained in the study. This table demonstrates improving function in a subset of patients.**
2. **Since the sponsor offered no "treatment-free " period during this study and since there was no control, it is not possible to determine if functional improvement noted was spontaneous or drug-related.**

For the secondary endpoint, rates of successful intercourse, the results are similar. For the average percentage of successful intercourse attempts, the rate for combined doses was 37.1% versus 5.3% at baseline. For the 2 mg, 4 mg, 5 mg and 6mg doses separately, those results were 26.0%, 35.0%, 34.0% and 31.2%, respectively.

For the International Index of Erectile Function, Table 3 presents the mean EF domain score over time for all patients, all doses combined.

Table 3. Mean EF domain scores over time.

	Baseline Mean(n)	Month 3 Mean(n)	Month 6 Mean(n)	Month 9 Mean(n)
EF domain score	8.8(114)	14.0(87)	17.0(35)	21.0(8)

Comments:

1. **These efficacy results reflect activity in an enriched population (drug responders at baseline).**
2. **It is not possible to determine if some of this activity could be due to spontaneous improvement.**
3. **Most of the positive results reflect improvement in a subset of the population only, while many patients drop out of the trial.**

Safety Analysis:
Extent of exposure : The extent of apomorphine SL exposure is depicted in Table 4.

Table 4. Extent of apomorphine SL exposure in M97-793 by number of doses taken.

	1	2-8	9-19	20-49	50-100	>100	Total
Combined	1	7	42	54	9	2	115
2 mg	1	92	19	2	1	0	115
4 mg	2	80	16	6	2	0	106
5 mg	4	61	16	4	1	0	86
6 mg	5	31	13	10	0	1	60

Deaths : There were no study deaths.

Serious adverse events:
Four (4) patients experienced serious adverse events during this study. According to investigator determination, none of these was considered related to apomorphine.

Comment: One of these four serious adverse events could have been drug-related.

- A 56 year old patient experienced severe hypotension, generalized weakness, and diarrhea after his first in-office dose of 4 mg. On the morning of the dose, the patient reported abdominal cramping and six watery stools, followed by weakness. He received a 4 mg in-office dose. While attempting to stand, the patient lost consciousness for approximately 15 to 20 minutes. Upon awakening, he reported nausea and vomited. He was transported to the emergency room, where he experienced another episode of loss of consciousness. His blood pressure was 60 mm Hg/palpable. He was given intravenous fluids. An EKG revealed non-specific ST-T wave changes. He was admitted to intensive care and IV heparin was started. Laboratory examinations were consistent with dehydration secondary to gastroenteritis. He was discharged in stable condition, and is continuing in this study. The investigator believed that the event was not related to study drug.

  Comment: This patient may have been dehydrated upon presentation for his in-office dose. However, the 4 mg dose of apomorphine influenced his overall condition. It is very concerning that this patient was unconsciousness for up to 20 minutes. It is possible that patients with baseline low volume status may react to apomorphine with prolonged symptoms.

Premature discontinuations due to adverse event:
Eleven patients discontinued due in some part to an adverse reaction. In three of these, the investigator believed that the event was not related to apomorphine (pulmonary congestion, hematuria and lower extremity edema). In one case, urinary incontinence, the event was not likely to be related to apomorphine.

Of the remaining seven patients, four patients experienced vasodilatory episodes after taking apomorphine, one patient developed mouth ulcerations, one patient experienced fatigue, and one patient experienced intolerable vomiting. Only one of these occurred at a dose of 4 mg (dizziness and nausea). None occurred at 2 mg.

Two of these patient narratives are presented below:

- A 60 year old male experienced nausea, diaphoresis, and hypotension after his tenth dose of 5 mg. The hypotension lasted 5 minutes. The nausea and diaphoresis lasted thirty minutes. No additional doses were taken and the patient was discontinued. The investigator believed that the event was probably related to apomorphine.

- A 62 year old male mouth ulcerations and sore throat after his thirteenth dose of 5 mg. The patient was prescribed an oral antibiotic and Xylocaine mouthwash. The patient reported tongue swelling after previous doses. No additional doses were taken and the patient was discontinued. The investigator believed that the event was definitely related to apomorphine.

Overall adverse effects: In the text of the study report, the sponsor summarized the adverse events that were considered by the investigator to be at least possibly related to apomorphine and reported by at least 5% of all patients.

When the overall AEs were tabulated in this manner the results are demonstrated in Table 5.

Table 5. Treatment-emergent adverse events at least possibly related to apomorphine and reported by ≥5% of all patients.

Adverse event	Overall n(%)	2 mg n (%)	4 mg n (%)	5 mg n (%)	6 mg n(%)
Nausea	22(19.1)	0(0.0)	9(8.5)	8(9.3)	10(16.7)
Pain	11(9.6)	3(2.6)	3(2.8)	2(2.3)	3(5.0)
Rhinitis	9(7.8)	3(2.6)	2(1.9)	0(0.0)	4(6.7)
Dizziness	8(7.0)	0(0.0)	4(3.8)	2(2.3)	3(5.0)
Somnolence	8(7.0)	1(0.9)	3(2.8)	3(3.5)	3(5.0)
Sweating	8(7.0)	1(0.9)	4(3.8)	1(1.2)	3(5.0)
Cough	7(6.1)	4(3.5)	1(0.9)	0(0.0)	2(3.3)
Pharyngitis	7(6.1)	2(1.7)	0(0.0)	2(2.3)	3(5.0)
Vomiting	7(6.1)	0(0.0)	3(2.8)	1(1.2)	3(5.0)
Flu	6(5.2)	1(0.9)	2(1.9)	1(1.2)	2(3.3)
Headache	6(5.2)	1(0.9)	2(1.9)	1(1.2)	2(3.3)

Comment: Nausea and somnolence appear dose-related.

Vital signs and electrocardiographic recordings:
The sponsor believed that there were no clinically meaningful trends in mean vital sign parameters.

Physical examinations: Five patients were noted to have physical examination abnormalities. One of these (burns of the oral mucosa and frenulum) was thought to be related to drug.

Clinical laboratory examinations: There were statistically significant differences from baseline in the following parameters: decrease in hematocrit, red blood cells, and neutrophils, increase in lymphocytes, and platelets. There were changes in several serum chemistry parameters. The sponsor considered none of these clinically meaningful.

Several individual patients experienced significant laboratory abnormalities while taking apomorphine. The sponsor believed that none of these revealed any clinically meaningful trends. One patient was noted to have an elevated alkaline phosphatases, GGT, SGOT and SGPT. He had a history of alcohol use and hepatitis of an "autoimmune type" on liver biopsy eight months prior to enrollment. The serum LFTs remained elevated throughout the course of the study. The investigator believed that the elevated serum LFTs were related to the patient's past history of hepatitis rather than apomorphine.

Sponsor's assessment of efficacy and safety:
The sponsor believes that these interim results indicate that apomorphine 2 mg, 4 mg, 5 mg and 6 mg tablets were a well-tolerated and effective treatment in diabetic patients with erectile dysfunction and patients status-post radical prostatectomy.

Reviewer's assessment of efficacy and safety:
The efficacy data pose several concerns. First, the study population was enriched by having succeeded in previous apomorphine trials. Second, it cannot be determined if these patients would have gotten better without any treatment, due to lack of a control group and lack of a "treatment-free" break. Third, it is not possible to determine how many people needed to titrate to the maximum dose. Finally, it is notable that 59% of patients prematurely discontinued treatment by the cut-off date. Parameters for efficacy improved as more and more patients dropped out, reflecting efficacy in a subset of patients.

In terms of safety, this study was limited in size, in duration, and in design. The study enrolled 116 healthy patients. Most discontinued before 9 months of treatment. The criteria for eligibility were fairly restrictive and serve to prevent extrapolation of the results to the larger ED population

Nevertheless, the side effect profile was similar to that seen in previous trials.

The most concerning adverse event involved a patient who lost consciousness for 15 to 20 minutes after a 5 mg dose. The fact that he was dehydrated at baseline suggests that he may have been predisposed to react more severely. This leads to concern for the larger population, some of whom will have borderline low volume status, or may be taking multiple antihypertensives.

It is again notable that many patients discontinued due to irritation of their mouths, tongues and lips.

Safety Study M97-682

Design:

This is an ongoing, open-label, flexible-dose, 3-year, safety study conducted at 66 United States centers. Any patient who completed a previous Phase 2 or Phase 3 apomorphine trial and had a continuing diagnosis of ED "with no major organic component" was eligible to enroll in this study. Specifically, patients enrolled from the following studies: M96-470, M96-471, M97-658, M97-659 and M97-763. The cut-off date for inclusion in this report was May 7, 1999. By this date, all patients in the study had 3 months to 1 year of exposure to drug,

> **Comment: M96-471 and M97-659 were 6-month, open-label, extensions of previous Phase 3 trials. It is likely that patients who completed these studies and went on to enroll in M97-682 were those who could tolerate apomorphine best and benefited most. This represents an "enrichment" of the study population that is common when patients are "rolled-over" from controlled clinical trials to open-label trials.**

All procedures performed at the end of the previous apomorphine SL trial were considered Visit 1 assessments for this study, provided that no more than 30 days had elapsed. All patients were continue on their optimal dose of apomorphine, as long as one had been determined in the previous trial. If none had been determined, these patients began the study at a dose of 2 mg apomorphine. Dose could be adjusted at monthly in-office visits. Possible doses included 2 mg, 4 mg, 5 mg and 6 mg.

During the study, patients were instructed to take drug no more than once per 8-hour period. Patients were instructed to take study medication by placing a single tablet under the tongue and allowing it to dissolve completely. Once the tablet was completely dissolved, sexual intercourse could be attempted when the couple was ready. Patients were instructed as follows: "You should limit yourself to a minimum amount of alcoholic beverages during the six hours prior to taking study medication." After at least 2 hours had passed after intercourse, patients and partners were instructed to complete a questionnaire regarding that particular sexual experience.

> **Comments:**
>
> 1. **The requirement that minimal alcohol be consumed prior to taking a tablet may not be practical to expect in a real-world situation.**
> 2. **Accurate assessment of efficacy in this 3-year, open-label trial cannot be made due to the lack of a control group and lack of a treatment-free "break" during the study.**

Inclusion/exclusion criteria:

Eligible patients were those who had completed a previous Phase 2 or Phase 3 apomorphine trial and who had a continuing diagnosis of ED with no major organic component.

Briefly, these patients were heterosexual males, between 18 and 70 years of age. All men had to have a diagnosis of "erectile dysfunction with no major organic component". Erectile dysfunction was defined in the previous Phase 3 trials as "the ability to attain and maintain an erection firm enough for intercourse with a partner for less than 50% of attempts for a minimum of 3 months prior to Day 1 of Treatment Period 1". In addition, all patients had to have demonstrated "an erection of sufficient quality for intercourse on some occasion since the onset of erectile dysfunction as evidenced by nocturnal/morning erections, masturbation, and/or other sexual activity."

In M96-470, M97-658, and M97-763, all patients underwent nocturnal penile tumescence testing (NPT) using Rigiscan at least 60 days prior to Day 1 of Treatment Period 1. All patients had to demonstrate at least one successful erection during NPT testing; specifically, a successful erection was defined as one wherein the base of the penis was at least 55% rigid for at least 10 minutes.

All patients had to be involved in a "stable", heterosexual relationship for at least eight months. All patients and partners had to agree to attempt intercourse at least once weekly. All patients had to be "judged in good general health as evidenced by medical history and the complete physical examination" at the end of the previous Phase 3 study. All pre-study laboratory values had to be within 15% above or below normal range on the final visit of the previous Phase 3 study. Fasting blood glucose had to be <250 mg/dL, unless approval was obtained by the medical monitor.

> **Comment: This patient population was physiologically capable of getting erections and was generally healthy. This population does not represent the larger ED population.**

Patients were excluded for the same reasons as in previous Phase 3 trials. These included:

1. Presence of "neurologic disease" (e.g. Parkinson's disease, multiple sclerosis, or spinal cord injury).
2. Presence of such genitourinary disorders as history of radical prostatectomy, penile prosthesis, or major penile deformity.
3. Presence of hypogonadism (serum T <280 ng/dL), hyperprolactinemia (serum prolactin >20 ng/mL), diabetes with an elevated glycosylated hemoglobin at baseline, or diabetes with any episode of ketoacidosis with the last 3 months.
4. Presence of major psychiatric disorder.
5. Presence of "cardiovascular disease" (e.g. systolic BP >180 mm Hg and/or diastolic >100 mm Hg while sitting, hypotension [systolic BP< 90 mm Hg while standing]).
6. Presence of gastrointestinal disease (especially, any disorder resulting in the need for anti-nausea medications in the last 6 months).
7. Any cancer other than basal or squamous cell cancer that has not been in remission for at least 5 years.
8. Any pharmacologic therapy for ED within the preceding 3 months.
9. Greater than 75% successes during the lead-in period.
10. History of drug or alcohol abuse within the past 2 years.
11. Smoking greater than 10 cigarettes per day, or the equivalent use of tobacco in other forms.
12. Presence of AIDS or HIV-positive status.
13. History of allergic reaction to morphine or any other opiate.
14. Partners with major affective disorder.
15. Partners with a history of female sexual dysfunction.

> **Comment: Inclusion and exclusion criteria were fairly restrictive. The study population was a relatively healthy group and again, is not indicative of the erectile dysfunction population at large.**

Efficacy endpoints and statistical analysis plan:
The primary efficacy endpoint was the same as in other Phase 3 apomorphine trials: "the home-use success rate" for the entire treatment period. An attempt was defined as taking a study drug and completing a questionnaire and success was defined as achieving an erection firm enough for

intercourse according to the patient's opinion. Secondary efficacy endpoints were the same as in M97-658 and M97-763 and included:

1. Number of patients with successful response (defined as erection sufficient for intercourse in 50% or greater number of attempts)
2. Successful intercourse rates according to patient
3. Time to erection
4. Duration of erection
5. International Index of Erectile Function (IIEF) results
6. Fugl-Meyer Life Satisfaction Scale
7. Treatment Satisfaction questionnaire

The statistical analysis plan was a summary or descriptive tabulation of the efficacy endpoints for the entire treatment period, by 6-month periods. Because this was an interim analys1s the plan was modified to present the efficacy data by 3-month periods.

Safety endpoints:
Safety endpoints included complete physical examination, including vital signs and body weight, 12-lead EKG, routine laboratory examinations (hematology, chemistry and urinalysis) and assessment of adverse events.

Withdrawals, compliance, and protocol deviations:
Patient disposition:
Four hundred eighty-nine (489) males were enrolled into this study as of the interim analysis date. Four hundred eighty-three (483) took at least one dose of apomorphine. One hundred ninety-four patients (194) were still enrolled as of the interim analysis date. Of the 289 patients who discontinued the study, 38 patients (7.9% of patients who took at least one dose) discontinued because of adverse events. (Table 1)

> **Comment: It is important to again note that 59% of patients who enrolled have already discontinued.**

Table 1. Reasons for study discontinuation

Reason	Number of patients
Adverse event	38
Noncompliance	14
Lack of efficacy	133
Patient request	56
Partner request	3
Lost to follow-up	27
Death	0
Other	18

The majority of the patients came from Study M97-763 (n=358 or 74%). The remainder came from M96-470/M96-471 (n=32 or 7.0%) and M97-658/M97-659 (n=93 or 19%).

The adverse events resulting in study discontinuation are discussed in the safety analysis.

Treatment compliance: Compliance was assessed by collecting home-use diaries and comparing those documents to actual pill count.

Protocol deviations: The most common protocol deviations were: 1) clinic visits that occurred outside the scheduled monthly visit window, and 2) too few or no monthly intercourse events.

Fifteen patients had dosing errors; they received a higher or lower dose than indicated by the titration scheme. In two of these, there were adverse events reported (lightheadedness and nausea/decreased BP). Twenty-five patients took a dose of apomorphine within 8 hours of the last. In three of these, there was an adverse event reported (sleepiness, bitter taste in mouth, and drowsiness with visual disturbance).

Efficacy analysis:
The primary endpoint was the percentage of attempts in which the patient thought that he had achieved an erection firm enough for intercourse.

The *mean average percentage of attempts* resulting in an erection firm enough for intercourse was 64.2% when all doses were combined, compared to 25.8% at baseline. When calculated separately for the 2 mg, 4 mg, 5 mg and 6 mg doses, these figures were 47.2%, 53.3%, 62.3% and 62.0%, respectively. When only the last 16 attempts were analyzed, the total average figure was 64.8%.

Of *all attempts* made during the study, 77.6% resulted in an erection firm enough for intercourse. Of all attempts for 2 mg, 4 mg, 5 mg and 6 mg, 73.4%, 77.3%, 82.8% and 76.4% resulted in an erection sufficient for intercourse, respectively.

The sponsor believes that the reason for the differences between these two sets of success rates is that more successful patients made more attempts, compared to less successful patients.

For the secondary endpoint, rates of successful intercourse, the results are similar. For the average percentage of successful intercourse attempts, the rate for combined doses was 63.1% versus 25.5% at baseline. For the 2 mg, 4 mg, 5 mg and 6mg doses separately, those results were 46.8%, 51.9%, 61.0% and 60.6%, respectively.

For the International Index of Erectile Function, table 2 presents the mean EF domain score over time for all patients, all doses combined.

Table 2. Mean EF domain scores over time.

	Baseline Mean(n)	Last measured Mean(n)
EF domain	12.9(449)	19.2(453)

Comment:

1. **These positive efficacy results reflect activity in an enriched population (drug responders at baseline).**
2. **Some of this activity could be due to spontaneous improvement in these patients with erectile dysfunction with no major organic component.**
3. **Without a control group, it is not possible to accurately assess these results.**

Safety Analysis :
Extent of exposure : The extent of apomorphine SL exposure is depicted in Table 3.

Table 3. Extent of apomorphine SL exposure in M97-682, by number of doses taken.

	1	2-8	9-19	20-49	50-100	>100	Total
Combined	8	31	95	166	139	44	483
2 mg	10	264	65	30	7	9	385
4 mg	14	187	86	53	15	5	361
5 mg	16	131	76	43	25	7	298
6 mg	13	60	44	59	44	10	230

Comment: It is not clear how many patients received apomorphine for 6 months, 9 months and for 1 year in this trial.

Deaths : There were no study deaths.

Serious adverse events :
Twenty-four (24) patients experienced serious adverse events during this study. According to investigator determination, only one of these was considered related to apomorphine.

Comment: None of the twenty-four serious AEs appeared to be drug-related.

Premature discontinuations due to adverse event:
Forty-seven patients discontinued due in some part to an adverse reaction. In thirty-eight (38) of these, adverse reaction was the *primary* reason for terminating. Four of these 38 have been described in the serious AE section and were not related to apomorphine. Three of these were clearly not related to drug (carcinoma of the prostate, increased serum PSA and low back pain).

Of the remaining thirty-one patients, there was a pattern of adverse events. Some patients discontinued due to intolerable nausea and/or vomiting. Several complained of lethargy and fatigue. Eight patients discontinued due to symptoms consistent with vasodilatation or hypotension. Eight patients discontinued due to symptoms related to mouth, tongue or throat irritation. There were three patients in whom serum liver function tests were noted to be elevated. In some cases, patients discontinued for more than one of these reasons.

It is notable that most of these discontinuations were on 5 mg (n=14) and 6 mg (n=20). A few occurred on 2 mg (n=7) and on 4 mg (n=8).

Below, representative cases are presented to depict the reasons for premature discontinuation due to AEs.

Nausea and vomiting:

- A 49 year old patient experienced nausea, generalized weakness and malaise 60 minutes after his eighth dose of apomorphine 5 mg (nineteenth dose overall in this study). These symptoms lasted six hours. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 66 year old patient experienced severe nausea 16 minutes after his first dose of apomorphine 6 mg (tenth dose overall in this study). Twenty-five minutes after the dose, he experienced severe vomiting. Twenty-eight minutes after the dose, he experienced severe

sweating. The nausea lasted seventeen minutes, the vomiting eight minutes and the sweating five minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

Mouth ulcers, swollen tongue, swollen lips, "throat edema", etc:

- A 66 year old patient experienced numerous mouth ulcerations approximately 8 hours after his twenty-third dose of 5 mg (thirty-two doses overall in this study). This symptom lasted eight days. No additional drug was taken and the patient was discontinued. The investigator believed the event was possibly related to apomorphine.

- A 63 year old patient experienced moderate stomatitis 75 minutes after taking his seventh dose of 2 mg (nineteen doses overall in this study). This symptom lasted five days. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

- A 56 year old patient experienced moderate edema in his throat at the time of taking his second dose of 2 mg (fourteenth dose overall in this study). He also complained of nausea and dyspnea. He reported similar symptoms after previous doses. The events lasted ninety minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was possibly related to apomorphine.

Dizziness, syncope, diaphoresis, light-headedness, "clamminess", etc:

- A 71 year old patient experienced severe vasodilatation, vomiting and asthenia approximately 30 minutes after taking his first dose of 5 mg (thirteenth dose overall in this study). The events lasted thirty minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 63 year old patient experienced sweating, dizziness, pallor and somnolence 25 minutes after his sixth dose of 4 mg (tenth dose overall in this study). The events lasted forty-five minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was probably related to apomorphine.

- A 61 year old male experienced nausea 15 minutes after his first dose of 6 mg (fifth dose overall in this study). Thirty-five minutes later he began sweating and experienced moderate hypotension. The nausea lasted for thirty minutes, the sweating for fifty minutes and the hypotension for 1 hour 5 minutes. No additional drug was taken and the patient was discontinued. The investigator believed the event was definitely related to apomorphine.

  <u>Comment</u>: Hypotension lasted for over 1 hour in this case and began *after* nausea had subsided.

Increased liver function tests:

- A 57 year old patient had an "unscheduled" check of his serum GGT five days after his one hundred third dose of 6 mg (119 dose in all studies combined). The serum GGT was 268 IU/L (normal 7-64 IU/L). Follow-up GGT was 241 IU/L. He was known to drink less than one beer daily for 30 years. The sponsor believed that the increased serum LFT might be related to alcohol use. The investigator believed the increased GGT was not related to apomorphine. After five additional doses, the patient was discontinued due to the investigator's concern about the patient's alcohol consumption.

- A 49 year old patient had an “unscheduled” check of his serum GGT eleven days after his second 2 mg dose (27 doses in all studies combined). The serum GGT was 205 IU/L (normal 7-64 IU/L). Follow-up GGT was 178 IU/L. An ultrasound of the liver and gallbladder was negative. He was known to drink less than one to three glasses of beer daily for thirty-three years. The investigator believed the increased GGT was possibly related to apomorphine. After six additional doses, the patient was discontinued due to increased GGT.

- A 54 year old patient had an per-protocol check of his serum LFTs after his seventy-first dose of 6 mg (87 doses in all studies combined). These values were “elevated” (no specifics in the final report). After an additional 6 doses, the serum LFTs were re-checked and found still to be "elevated”. No additional doses were taken and the patient was discontinued due to increase in LFTs. The investigator believed the elevated LFTs were not related to apomorphine. The investigator considered “alcohol abuse” to be the etiology of the findings.

  Comment: It is not clear whether these increases in serum LFTs were related to apomorphine. The potential for alcohol use as a confounder makes a drug-related association difficult to establish.

Three additional patients experienced syncope without discontinuation from the trial. These patients are described below:

- A 55 year old patient experienced severe sweating and hot flashes 30 minutes after his first in-office dose of 4 mg (79 doses overall in this study). Five minutes later he experienced “a syncopal event”. The syncopal episode lasted five seconds. The patient continued the study at 2 mg. The investigator believed the event was definitely related to apomorphine.

- A 69 year old patient experienced moderate nausea and light-headedness 89 minutes after receiving his fourth dose of 4 mg (15 doses overall in this study). Five minutes later he experienced “a syncopal event”. The syncopal episode lasted one minute. The investigator believed that the event may have been due to hypoglycemia in this non-insulin dependent diabetic. The patient continued the study at 2 mg. The investigator believed the event was possibly related to apomorphine.

- A 62 year old patient experienced mild nausea and blurred vision after receiving his twenty-first dose of 5 mg (53 doses overall in this study). Two minutes later he experienced “a syncopal event”. The syncopal episode lasted five minutes. The sponsor believes that the patient’s ingestion of two beers sixty minutes prior to dosing may have been related to the syncopal event. The patient continued in the study but eventually discontinued due to bad taste in his mouth. The investigator believed the syncopal event was probably related to apomorphine.

  Comment: These cases of syncope are notable. Two syncopal events occurred at a dose of 4 mg. All events occurred in patients who had previously tolerated apomorphine for quite some time. One event occurred in a patient who had two beers within one hour of dosing.

Overall adverse effects: In the text of the study report, the sponsor summarized the adverse events that were considered by the investigator to be at least possibly related to apomorphine and reported by at least 5% of all patients.

When the overall AEs were tabulated in this manner the results are demonstrated in Table 4.

Table 4. Treatment-emergent adverse events at least possibly related to apomorphine and reported by ≥5% of all patients.

Adverse event	Overall n(%)	2 mg n (%)	4 mg n (%)	5 mg n (%)	6 mg n(%)
Dizziness	53(11.0)	6(1.6)	16(4.4)	19(6.4)	19(8.3)
Headache	58(12.0)	19(4.9)	29(8.0)	22(7.4)	14(6.1)
Nausea	111(23.0)	12(3.1)	34(9.4)	49(16.4)	45(19.6)
Pain	72(14.9)	24(6.2)	19(5.3)	23(7.7)	17(7.4)
Somnolence	41(8.5)	6(1.6)	16(4.4)	18(6.0)	11(4.8)
Sweating	40(8.3)	1(0.3)	12(3.3)	16(5.4)	17(7.4)
Yawning	28(5.8)	7(1.8)	7(1.9)	14(4.7)	7(3.0)

Comment: Nausea, sweating, and dizziness were dose-related.

Vital signs and electrocardiographic recordings:
Mean systolic BP was significantly decreased from baseline at each 3-month assessment. Of note, the mean change-from-baseline at Month 9 was –8.80 mm Hg. There were also very small changes from baseline in mean diastolic BP at each assessment.

Physical examinations: The sponsor did not comment on any physical findings of note.

Clinical laboratory examinations: There were statistically significant differences from baseline in the following parameters: decrease in hemoglobin and red cells, increase in white blood cells, increase in serum glucose, and changes in several serum chemistry parameters. The sponsor considered none of these clinically meaningful.

Several individual patients experienced significant laboratory abnormalities while taking apomorphine. Ten patients shifted to low hematocrit and ten patients shifted to high white blood cells. Twenty-seven patients shifted to a high serum glucose. Fifteen shifted to a high GGT. Eight shifted to high total bilirubin. Twelve shifted to high SGPT. One patient had slightly elevated serum transaminases and an elevated total serum bilirubin. The sponsor believes that a review of these shifts do not reveal any clinically meaningful trends.

Sponsor's assessment of efficacy and safety:
The sponsor believes that the results of this long-term study indicate that apomorphine 2 mg, 4 mg, 5 mg and 6 mg tablets were a well-tolerated and effective treatment for up to 12 months in patients with erectile dysfunction.

Reviewer's assessment of efficacy and safety:
In terms of efficacy, there are several concerns. Having succeeded in previous apomorphine trials, the study population was an enriched one. It cannot be determined whether patients would have gotten better without any treatment, due to lack of a control group and lack of a "treatment-free" break. It is unclear how many patients titrated to the maximum dose. Finally, it is notable that 59% of patients prematurely discontinued treatment by the cut-off date.

In terms of safety, apomorphine was not well-tolerated. This is particularly impressive in a population of patients who had already succeeded in a previous apomorphine trial. The adverse

event profile of nausea, dizziness, hypotension, sweating, vomiting, etc. was similar to previous trials. The less frequent occurrence of hypotension, bradycardia, nausea, vomiting, diaphoresis and possible syncope was again noted. Some of these more severe adverse events were reported at the 4 mg dose. Some were reported by patients who had previously tolerated many doses without incident.

It is again notable that many patients discontinued due to irritation of their mouths, tongues and lips.

Several patients discontinued due to increase in serum LFTs. Increased serum LFTs have been noted in other apomorphine trials. It is unclear if this effect is related to the drug or to some other cause, such as alcohol use.

Again, the study population was a generally healthy group of men. The safety consequences may be magnified in a population of older men with greater co-morbidity.

Study M98-930 (A Drug Interaction Study to Evaluate the Safety and Pharmacodynamic Effects of Apomorphine Sublingual (5mg) Tablets and Antihypertensives or Nitrates)

Design:
This was a Phase 1 study designed to evaluate the safety and pharmacodynamic effects of 5 mg of apomorphine given to males who were on stable doses (at least 4 weeks) of a variety of antihypertensives or nitrates.

The study was completed in August 1999, and included 11 centers. Male subjects on stable doses of antihypertensives or nitrates were enrolled; all subjects were to be on monotherapy. Twenty-four subjects were to be enrolled in one of the following dosage groups:

- Group I: Ace Inhibitors (n=24)
- Group II: Beta Blockers (n=24)
- Group III: Diuretics (n=24)
- Group IV: Calcium Channel Blockers (n=24)
- Group V: $Alpha_1$ Blockers (n=24)
- Group VI: Short-Acting Nitrates (n=24)
- Group VII: Long-Acting Nitrates (n=24)

Within each medication group, 24 subjects were to be randomized to receive either:

- Apomorphine SL 5 mg in period 1 followed by placebo in period 2 or
- Placebo in period 1 followed by apomorphine SL 5 mg in period 2

Each subject received a single dose of either apomorphine or placebo in a crossover fashion separated by a 24-hour washout period.

Study assessments included:

- Blood pressure and pulse (BP/P) measurements obtained by Dinamap at 30 minutes and 15 minutes prior to dosing (supine and standing; BP/P measurements at 5, 10, 15, 20, 30, 40 and 50 minutes post dosing and 1, 1.5, and 2 hours post dose;
- ECG and Holter monitors were also included.

The study design is reasonable, and it is noteworthy that many different classes of antihypertensives were studied, and relatively large numbers of patients were enrolled. Previously approved drugs for erectile dysfunction have performed only very limited studies of this sort. Due to a prior agreement with FDA, pharmocokinetic levels of apomorphine were not measured. This is somewhat unfortunate since some subjects suffered adverse events (vaso-vagal events or symptomatic hypotension), and PK-PD relationships cannot be assessed in these individuals.

Study Results
Reviewer's Approach to Analysis of Study Results
One hundred and sixty-two (162) subjects were enrolled and completed the study. Results are described within each hypertensive study group. Given the small sample size of subjects per group, the mean changes in blood pressure generally did not change. Review of mean blood pressure data, however, was not felt to give a complete picture of drug safety and tolerability.

Therefore, FDA focused on per subject data, and included a review of individual line listings for blood pressure readings. Readings were considered significant based on the following criteria:

- A fall in standing systolic blood pressure of > 30 mm Hg from the baseline standing systolic blood pressure reading obtained 15 minutes prior to study drug administration **OR**
- Any standing systolic blood pressure reading < 85 mm Hg at any time after study drug administration **OR**
- A fall in standing diastolic blood pressure of > 20 mm Hg from the baseline standing blood pressure reading obtained 15 minutes prior to study drug administration **OR**
- Any standing diastolic blood pressure reading > 45 mm Hg at any time after study drug administration.

In addition, the listings of adverse events reported by patients were assessed. Results of adverse events were considered significant if they included: dizziness, nausea, vomiting, diaphoresis, chest pain, palpitations, light-headedness, or diaphoresis. Adverse events of headache, upper respiratory infection, abdominal pain, or solely flushing were not considered as clinically relevant (and were relatively infrequent overall). Finally, the reviewer read the summary report of this study by the sponsor for additional information of relevance.

Events were then assessed as: **probably unrelated, possibly related, or probably related** to study drug administration based on the temporal association of events to study drug administration, type of event, presence or absence of associated clinical symptoms, and the overall severity and duration of the reaction.

Summary and Conclusions
Table 1 summarizes the results per treatment arm for the antihypertensive agents studied. Brief descriptions for individual patients follow Table 1. Those patients having adverse events considered possibly or probably related to study drug are included in Table 1. Patients with adverse events that were considered "probably unrelated" to study drug are not included in this Table.

Table 1
Number of Subjects Having Adverse Events Possibly or Probably Related to Study Drug

Antihypertensive Group (n=162)	# (%) Subjects With Adverse Reactions Following Placebo	# (%) Subjects With Adverse Reactions Following Apomorphine
ACE Inhibitors (n=25)	1 (4%)	2 (8%)
Beta Blockers (n=26)	1 (4%)	3 (11.5%)
Diuretics (n=21)	0	2 (9.5%)
Calcium Blockers (n=26)	0	1 (3.8%)
$Alpha_1$ Blockers (n=24)	0	3 (12.5%)
Short Acting Nitrates (n=20)	0	6 (30%)
Long Acting Nitrates (n=20)	2 (10%)	5 (25%)
All Enrolled Subjects (n=162)	4 (2.5%)	22 (14%)

ACE Inhibitor Subject Summaries

The placebo event was as follows:

- This subject had a baseline blood pressure of 167/80 mm Hg. Although subsequent blood pressure readings were in an acceptable absolute range, the systolic blood pressure was noted to drop by at least 30 points on multiple readings: 131/51, 136/72, 112/59, 120/56, 128/65, and 133/72 at 15", 40", 50", 1 hr, 1.5 hrs, and 2 hrs post dosing, respectively. The subject's standing pulse during these readings ranged from 68 to 72 bpm. In addition, he suffered diaphoresis, dizziness, and sweating post placebo dosing. All symptoms were mild, and lasted 5 minutes in duration.

The two apomorphine events were as follows:

- The first subject had a baseline blood pressure of 135/76 mm Hg prior to dosing. After receiving apomorphine, readings of 71/48, and 48/40 were noted at 15 minutes and 40 minutes post-dosing. Blood pressure 2 hours post-dosing was 114/101. The baseline pulse was 77 bpm. During the low blood pressure readings, his standing pulse ranged from 50 to 53 bpm. The subject complained of dizziness, nausea, vomiting, and diaphoresis lasting 1 hour and 45 minutes post dosing with apomorphine. These events were considered moderate in severity. He was treated with lowering of the head, elevating the feet and a cool cloth to the head.

- The second subject had a baseline blood pressure of 102/71 mm Hg prior to dosing. After receiving apomorphine, a reading of 64/36 was noted at 40 minutes post-dosing. His standing pulse at the time of the low blood pressure reading was 78 bpm. Other blood pressure readings were unremarkable. The subject complained of light-headedness, pallor, and mild diaphoresis for 20 minutes duration after receiving apomorphine.

Beta Blocker Subject Summaries

The placebo event was as follows:

- This subject experienced nausea and pallor that was considered moderate and was placed in a supine position following placebo dosing. There were no blood pressure changes noted. Pulse ranged from 68 to 75 during the study.

The three apomorphine events were as follows:

- The first subject had a baseline blood pressure of 105/75 mm Hg prior to dosing. After receiving apomorphine, readings of 94/59 and 71/30 were noted at 15 minutes and 20 minutes post-dosing. Standing pulse at these timepoints was 86 and 78 bpm. Blood pressure 1 hour post-dosing was 100/61. The subject complained of dizziness, nausea, and diaphoresis with pallor, tremor and hypotension. These events were considered moderate in severity. He was placed in a supine position and covered with a blanket.

- The second subject had a baseline blood pressure of 101/78 mm Hg prior to dosing. After receiving apomorphine, a reading of 85/52 was noted at 50 minutes post-dosing. Other blood pressure readings were unremarkable. His standing pulse at the time of the abnormal blood pressure reading was 38 bpm. The subject complained of nausea, dizziness, diaphoresis that were considered severe and lasted 15 minutes. He was placed in a supine position. **This subject also experienced syncope of 30 seconds duration associated with an abnormal Holter.** This event was judged severe and the subject required treatment with IV fluids.

- The third subject had an adverse event of nausea for almost 1 hour following apomorphine dosing. There were no associated blood pressure changes, and his pulse ranged from 53 to 58 bpm during the study.

Diuretic Subject Summaries

The two apomorphine events were as follows:

- The first subject had a baseline blood pressure of 123/75 mm Hg that fell to 105/55 30 minutes after apomorphine dosing. There were no other changes in blood pressure. His standing pulse at the time of the low BP reading was 68 bpm, which was noted to be substantially lower than his baseline pulse of 113 bpm. Of note, however, this subject also experienced light-headedness and dizziness for approximately 5 minutes. No treatment was required.

- The second subject had a baseline blood pressure of 85/54 mm Hg prior to dosing. After receiving apomorphine, a reading of 63/40 was noted at 30 minutes post-dosing. No standing blood pressures obtained until 2 hours post-dosing, when a reading of 84/45 mm Hg was noted. This subject's supine pulse ranged from 73 to 76 bpm during the event; no standing pulses were obtained. The subject complained of dizziness, yawning, and nausea diaphoresis that were considered moderate and lasted 5-6 minutes in duration. He was placed supine and his legs were elevated.

Calcium Channel Blocker Subject Summaries

The sole apomorphine event was as follows:

- This subject had a baseline blood pressure of 147/92 mm Hg that fell to 122/64 at 20 minute post-apomorphine and 105/59 at 50 minutes post-apomorphine. His pulse during those low readings ranged from 58 to 66 bpm. At 1 hour post-dose, BP was 107/75, and it remained stable through the end of the study. He complained of diaphoresis, lightheadedness, nausea and pallor that were considered mild by the investigator. No treatment was given.

$Alpha_1$ Blocker Subject Summaries

The three apomorphine events were as follows:

- The first subject had a baseline blood pressure of 94/45 mm Hg. Forty minutes after receiving apomorphine, his blood pressure was 58/38, and at 1.5 hours after dosing it was 76/49. His standing pulse was 85 at 40 minutes post-dosing and was 89 at 1.5 hours after dosing. He complained of lightheadedness and dizziness that was considered moderate. He was treated with deep breathing. He also had mild chest tightness lasting 15 minutes. He was placed with his head lowered and feet raised.

- The second subject had a baseline blood pressure of 126/96 mm Hg that fell to 78/45 forty minutes after receiving apomorphine. His standing pulse at the time of this low reading was 78 bpm. No standing blood pressures were obtained until 1.5 hours after apomorphine. He complained of hypotension, nausea, dizzyness (all considered moderate).

- The third subject had a baseline blood pressure of 137/69 mm Hg that fell at 1 hour post apomorphine dosing (no standing blood pressures were able to be obtained). Pulses throughout the event ranged from 46 to 53 bpm (taken supine or sitting). He complained of dizziness, and a cold sweat for 50 minutes following apmorphine dosing. He was placed in a supine position and his legs were elevated.

Short Acting Nitrate Subject Summaries
The six apomorphine events were as follows:

- The first subject had a baseline blood pressure of 165/82 mm Hg that fell to 135/70, 40 minutes after apomorphine dosing and remained relatively low at 120/68, 50 minutes after dosing. Pulse during these readings ranged from 70 to 82 bpm. Blood pressure was 135/72 and 127/56 at 2 and 3 hours post dosing, respectively. He also complained of light headedness for 17 minutes duration.

- The second subject had a baseline blood pressure of 128/72 mm Hg that fell to 93/53, 40 minutes after apomorphine dosing. Standing pulse was 113 at the time of the low reading. The subject complained of palpitations for 30 minutes post apomorphine dosing.

- The third subject had a baseline blood pressure of 95/75 mm Hg that fell to 69/33 at 40 minutes, 59/35 at 50 minutes, and 94/51 at 1 hour post apomorphine dosing. Pulses during this time ranged from 79 to 102 bpm. He also complained of light-headedness for 7 minutes after dosing and generalized weakness lasting 26 minutes.

- The fourth subject had a baseline blood pressure of 115/76 mm Hg that fell to 93/45, 40 minutes post-dosing and to 88/45, 50 minutes post-dosing. Pulses at the time of the low readings were 67 to 68 bpm. He also complained of nausea for 20 minutes.

- The fifth subject had a baseline blood pressure of 98/64 mm Hg that fell to 72/52, 40 minutes post-dosing. Standing pulse at this time was 64, and fell to 49-50 bpm while the patient lay supine. No standing blood pressures were obtained until 1.5 hours post-dose, when a reading of 95/56 was obtained. This subject complained of light-headedness, nausea, and feeling flushed for up to 30 minutes.

- The sixth subject had a baseline blood pressure of 143/71 that fell to 111/69 15 minutes after apomorphine dosing. No blood pressures were obtained from 30 minutes post-dosing through 1.5 hours post dosing. The subject complained of nausea, sweating, tingly skin, somnolence and yawning after receiving apomorphine. These adverse events were judged mild to moderate, and definitely related to study drug. The subject required treatment with supine positioning and leg elevation. The duration of the events ranged from 20 minutes (sweating) to 48 minutes (for nausea) to over an hour of somnolence. This subject also complained of ½ hour of blurry vision, which the investigator felt was definitely related to study drug.

Long Acting Nitrates Subject Summaries
The two placebo events were:

- The first subject had a baseline blood pressure of 76/54 mm Hg that remained fairly low after dosing. Multiple blood pressures at 30, 40, and 50 minutes, 1 hour, and 1.5 hours post-dosing were low at 68/54, 77/61, 77/52, 75/55, and 73/60. Blood pressure ranged from 58 to 90 during this time. This subject also complained of light-headedness and dizziness for 4 minutes.

- This subject had a baseline blood pressure of 78/53 mm Hg that remained somewhat low after study drug: 72/45, 77/44, 67/47, and 78/50. Pulses ranged from 68 to 70 bpm. He complained of dizziness for 35 minutes as well.

The five apomorphine events included:

- The first subject had a baseline blood pressure of 144/61 mm Hg that fell to 95/57, 40 minutes post apomorphine dosing, to 91/38 at 50 minutes post-dosing. Standing pulse during these measurements ranged from 67 to 69 bpm. No standing blood pressure was performed at 1 hour, and at 1.5 hours post-dosing, blood pressure returned to normal at 155/66. He also complained of dizziness, yawning, and fatigue for 2 hours post dosing.

- The second subject had a baseline blood pressure of 142/69 mm Hg that fell to 72/47, 30 minutes post apomorphine dosing. At 40 minutes, pressure was back up to 105/56. No standing blood pressures were done at 50 minutes post-dosing and a reading obtained at 1 hour post-dosing was 72/48 while at 2 hours it was 75/55. Pulses ranged from 46 to 68 during this timeframe. This subject complained of dizziness, yawning, nausea and fatigue and pallor lasting 2 hours. Multiple extra blood pressure readings were done, and an electrocardiogram was performed.

- The third subject had a low baseline blood pressure of 76/44 mm Hg that remained low after apomorphine dosing on multiple readings: 72/44, 76/41, 55/42, 60/35, 65/53, 72/42, 66/43, 71/34, 71/47, 82/42, 77/43 and 83/37. Pulses at this time ranged from 70 to 81 bpm. The subject also complained of a warm feeling, nausea, mild drowsiness and moderate light-headedness for 1 hour post apomorphine dosing. Although similar low readings were noted after placebo-dosing, he had no associated symptoms with placebo.

- The fourth subject had a low baseline blood pressure of 80/52 mm Hg that dropped to 69/41, 20 minutes after receiving apomorphine and was 78/56 at 30 minutes, 79/59 at 50 minutes, and returned close to baseline (77/58) at 3 hours post-dosing. Pulses ranged from 79 to 89 bpm. The subject noted nausea and mild dizziness lasting 5 minutes after receiving apomorphine.

- The fifth subject had a baseline blood pressure of 93/50 mm Hg that was noted to drop to 71/30, 60 minutes after dosing with apomorphine. Pulse at this time was 70 bpm. All other blood pressures were unremarkable. Of note, however, this subject complained of moderate nausea and pallor and required placement in the supine position for 35-40 minutes after apomorphine dosing.

OVERALL CONCLUSIONS

- There were consistently more subjects who reacted significantly to apomorphine than to placebo within each study group as well as for the overall group of 162 subjects. Reactions included changes in blood pressure usually with associated symptoms, and took into account the temporal association of the reaction to study drug administration, and the degree of the blood pressure change to assess their relevance.

- It is difficult in the non-nitrate antihypertensive study groups to determine if the events noted with apomorphine represent drug-drug interactions or if they represent adverse reactions to apomorphine itself. The incidence and descriptions of these reactions do not differ substantially with those noted in clinical studies. Thus, these events may simply represent adverse reactions to apomorphine (5mg) itself.

- The data from the short- and long- acting nitrate groups show the most concerning results. Adverse reactions occurred in 25 to 30 % of subjects in these groups. With placebo, the comparative rate of adverse reactions in the nitrate groups ranged from 0 to 10 % of subjects. A 5 mg dose of apomorphine was poorly tolerated by approximately one in four subjects taking nitrate therapy versus (at most) one in ten subjects taking placebo.

- The large majority of the events reported in association with apomorphine dosing were vasovagal in nature. Several were notable either due to their severity (i.e. one volunteer, in the beta blocker arm, experienced syncope), or due to their duration. Symptoms lasted up to 1 hour in many patients and required treatment with position changes. Such events, should they occur in an unmonitored setting, could lead to significant risk.

- Of note, this study was performed with a dose of apomorphine of 5 mg, while the sponsor seeks approval for doses ranging from 2 to 4 mg. . The safety profile of apomorphine 5 mg in this small trial of volunteers on antihypertensive therapy, however, suggests that the therapeutic index of this drug may be narrow.

SECTION 7: SPONSOR'S PROPOSED LABELING

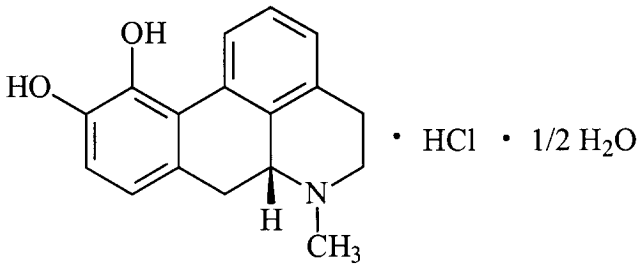
(Nos. 8032, 8034**,** 8035)

UPRIMA™
[u-pree-ma]
(apomorphine HCl tablets) sublingual

DESCRIPTION

UPRIMA™ sublingual tablets contain apomorphine hydrochloride (HCl), USP, which is chemically designated as 4H-dibenzo[de,g]quinoline-10,11-diol, 5,6,6a,7-tetrahydro-6-methyl-, hydrochloride, hemihydrate, (R)- or (6a,R)-5,6,6a,7-Tetrahydro-6-methyl-4H-dibenzo[de,g]quinoline-10,11-diol, hydrochloride, hemihydrate.

Molecular formula : $C_{17}H_{17}NO_2 \cdot HCl \cdot \frac{1}{2}H_2O$. Molecular weight: apomorphine HCl hemihydrate 312.8. Structural formula:



Apomorphine HCl is white to greyish minute glistening crystals or powder and melts with decomposition between 225°C and 236°C. Apomorphine HCl is soluble in alcohol and chloroform and slightly soluble in water (1 gram in 50 mL).

Apomorphine HCl has little structural similarity to opiates and no narcotic pharmacological properties.

UPRIMA is available in three dosage strengths, each administered as a sublingual tablet. Each tablet contains 2, 3, or 4 mg apomorphine HCl, microcrystalline cellulose, hydroxypropylmethylcellulose, citric acid, magnesium stearate, ascorbic acid, edetate

disodium dihydrate, colloidal silicon dioxide, ferric oxide, acesulfame potassium, orange mint flavor, and a sufficient amount of mannitol to attain final tablet weight.

CLINICAL PHARMACOLOGY

Apomorphine is a dopaminergic agonist with affinity for both D_1 and D_2 receptors in sites within the brain known to be involved in the mediation of erection. Studies *in vivo* have shown the erectile function effects of apomorphine are mediated at dopamine receptors in various nuclei in the hypothalamus and midbrain. In particular, the paraventricular nucleus of the hypothalamus has been identified as the site of action. This site may mediate genital and nongenital autonomic aspects of sexual arousal. Oxytocinergic, serotonergic, and possibly nitric oxide signaling may be involved in the cascade of neural events that result from the central action of apomorphine.

Apomorphine acts as a central initiator of erection, and enhances pro-erectile stimuli. The erectogenic effects of apomorphine arise from improved central neural signaling specific to penile vascular response.

Pharmacokinetics

Following sublingual administration, apomorphine is rapidly absorbed, reaching peak plasma concentrations within 40–60 minutes. Apomorphine is rapidly cleared from plasma, having an apparent terminal elimination half-life of 2–3 hours. Mean C_{max} values from the 2 mg and 4 mg UPRIMA tablets were 0.70 ng/mL and 1.25 ng/mL, respectively; mean AUC_{∞} values were 1.23 and 2.37 ng·h/mL. The coefficients of the intersubject variability for apomorphine C_{max} and AUC_{∞} were approximately 40%-70%.

Absorption

Apomorphine is rapidly absorbed from the sublingual cavity and can be detected in plasma within 10 minutes after placing the tablet under the tongue. Peak plasma concentrations are attained within 40–60 minutes. Increasing the dosage strengths of apomorphine sublingual tablets provides dose proportional increases in C_{max} and AUC_{∞}. The bioavailability of apomorphine from the 2- and 4- mg sublingual tablet strengths, relative to subcutaneous administration, is approximately 17%–18%. Due to the sublingual route of administration, the effect of food on the absorption of apomorphine does not require investigation.

Distribution

Apomorphine is approximately 90% bound to plasma proteins, primarily albumin. Protein binding is independent of concentration between 1.0 and 1000 ng/mL, which exceeds the concentration range achieved with the recommended doses. Apomorphine readily penetrates into blood cells, with a blood/plasma ratio of about 1.

Metabolism

Apomorphine is extensively metabolized, primarily through conjugation with glucuronic acid or sulfate. Apomorphine is also metabolized by *N*-demethylation, leading to the formation of norapomorphine, which is converted to glucuronide and sulfate conjugates. The major metabolite in plasma of subjects receiving a single sublingual dose of apomorphine is apomorphine sulfate. The glucuronides of apomorphine and norapomorphine are found in plasma at lower concentrations. These conjugates are not expected to be pharmacologically active. *In vitro* studies suggested that several cytochrome P450 isoforms could *N*-demethylate apomorphine, but the principal isoforms appeared to be CYP1A2, CYP3A and CYP2C19.

Elimination

Following a 2-mg sublingual dose of [^{14}C] apomorphine HCl, radioactivity was eliminated in both urine (93%) and feces (16%). Less than 2% of the apomorphine dose was excreted in urine as free apomorphine. About 59% of the dose was excreted as apomorphine sulfate, 12% as apomorphine glucuronides, and 18% as norapomorphine and its conjugates. Apomorphine, norapomorphine, and their sulfates were found in feces.

Special Populations

Elderly The pharmacokinetics of UPRIMA (5 mg) were investigated in healthy male subjects older than 65 years. The t_{max} was 36% longer and C_{max} was 21% lower in elderly subjects than in young subjects. The AUC was 11% larger in the elderly. Results from this study showed that no dose adjustment is necessary for the elderly. (See **DOSAGE AND ADMINISTRATION** Section.)

Pediatric The pharmacokinetics of UPRIMA has not been studied in subjects/patients younger than 18 years.

Gender The pharmacokinetics of UPRIMA in females has not been investigated.

Renal Insufficiency The pharmacokinetics of UPRIMA (5 mg) were studied in subjects with varying degrees of renal function. AUC_{∞} was increased by 4% in subjects with mild (CL_{cr} = 40-80 mL/min/1.73 m^2), 52% in subjects with moderate (CL_{cr} = 10-40 mL/min/1.73 m^2), and 67% in subjects with severe (CL_{cr} = <10 mL/min/1.73 m^2) renal impairment. C_{max} was affected little by renal impairment. The apparent terminal elimination half-life of apomorphine was predicted to increase by 0.24 hour with each 10 mL/min/1.73 m^2 decrease in creatinine clearance. Plasma protein binding of apomorphine was not affected by renal impairment. The effect of hemodialysis on apomorphine pharmacokinetics has not been studied. Since C_{max} was affected little by renal impairment, it was concluded that patients with impaired renal function may initiate

dosing with UPRIMA at 2 mg. Care should be exercised in any dose increase. (See **DOSAGE AND ADMINISTRATION** Section.)

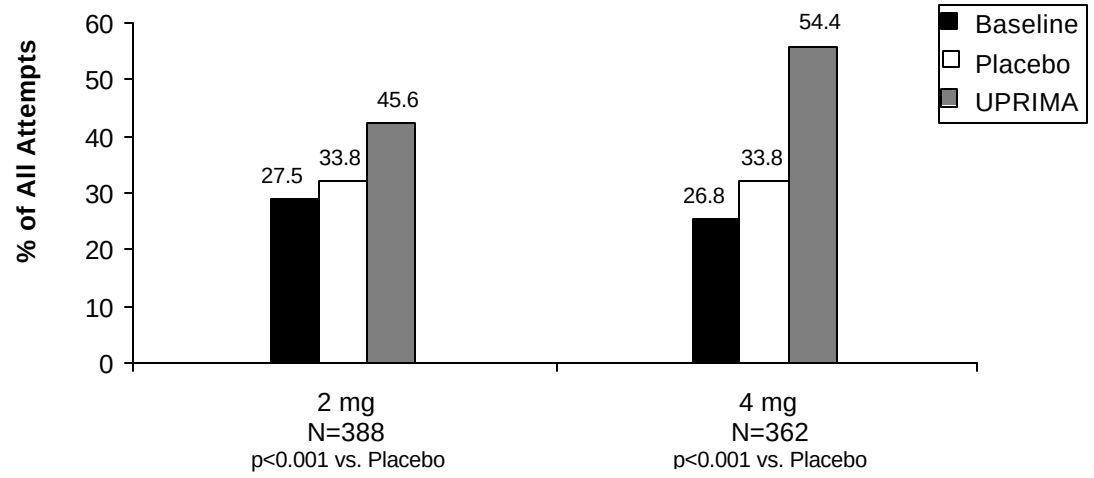
Hepatic Insufficiency The pharmacokinetics of UPRIMA (2 and 4 mg) were studied in subjects with mild, moderate, or severe hepatic impairment based on the Child-Pugh classification. Mean C_{max} was 16-62% higher and mean AUC_{∞} was 35-68% higher in subjects with varying degrees of hepatic impairment than in subjects with normal hepatic function. The apparent terminal elimination half-life of apomorphine (4 mg) was longer (2.9-3.7 hours) in subjects with hepatic impairment than in subjects with normal hepatic function (1.9 hours). Plasma protein binding of apomorphine was not consistently affected by hepatic impairment. Based on the increase in C_{max}, patients with significant hepatic impairment should be administered UPRIMA only when the benefit outweighs the risk. If patients with hepatic impairment receive UPRIMA, dosing should be initiated at 2 mg. Care should be exercised in any dose increase. (See **DOSAGE AND ADMINISTRATION** Section.)

CLINICAL STUDIES

In clinical studies, UPRIMA was administered to 2379 men with erectile dysfunction (ED) of organic, psychogenic, or mixed etiology including hypertensive patients (31%), diabetic patients (16%), patients with benign prostatic hyperplasia (16%), and patients with coronary artery disease (16%) as evidenced by a history of angina, coronary artery bypass surgery, angioplasty, or myocardial infarction. UPRIMA was evaluated for its ability to produce an erection firm enough for intercourse. UPRIMA was evaluated in randomized, double-blind, placebo-controlled studies of various designs (crossover and parallel; fixed dose and escalating dose). UPRIMA demonstrated statistically significant improvement in its primary endpoint, “erection firm enough for intercourse,” for all placebo-controlled studies.

Three multicenter, double-blind, randomized, placebo-controlled, two-period crossover group design studies enrolled 457, 520 and 495 patients, respectively. Following a lead-in baseline period, each patient received placebo in one treatment period and UPRIMA in the other treatment period. In the combined studies, all UPRIMA doses produced a significantly greater percentage of erections firm enough for intercourse than did placebo (P<0.001). See Figure 1.

Figure 1. Percentage of All Attempts Resulting in an Erection Firm Enough For Intercourse (Crossover Studies).

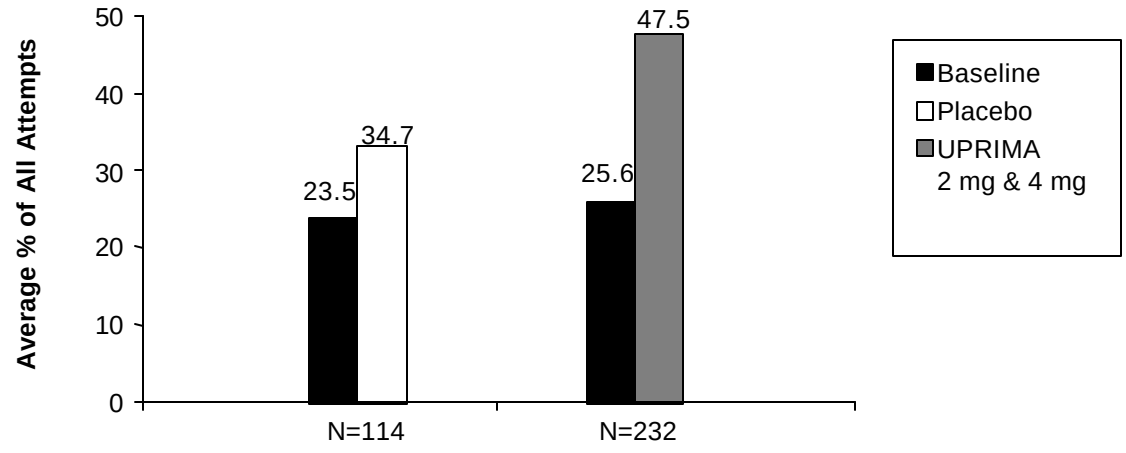


Partner assessments of erection corroborated these findings. The proportion of attempts resulting in an erection firm enough for intercourse based on partner assessment was significantly greater (P< 0.001) for each of the UPRIMA dosages than for placebo.

The percentage of attempts resulting in intercourse was also significantly greater (P< 0.001) for all UPRIMA doses than for placebo.

A separate double-blind, randomized, placebo-controlled parallel group design study (N=569) compared UPRIMA dose-optimization and fixed dosages. This study consisted of a lead-in baseline period, followed by a 4-week period in which patients in the voluntary optimization group were titrated to their optimal dose. A 4-week dose maintenance period followed dose optimization. Analysis of the average percentage of attempts resulting in an erection firm enough for intercourse showed significantly greater improvements (*P*=0.003) for all UPRIMA dosing regimens compared with placebo, based on patient and partner assessments. See Figure 2 for patient data.

Figure 2 Average Percentage of Attempts Resulting in an Erection Firm Enough For Intercourse (Dose Optimization Using UPRIMA™ 2 mg and 4 mg Tablets).



Significantly more attempts resulted in intercourse with either UPRIMA fixed-dose or dose-optimization groups compared with placebo (*P*≤0.002).

Objective measurement of erectile response (hardness and duration of erection) after UPRIMA administration was obtained by RigiScan®. Erectile response showed significant increases at the 4 mg dose.

Analysis of responses to the International Index of Erectile Function Questionnaire revealed statistically significant improvements from baseline for the indices of Erectile Function, Intercourse Satisfaction, and Overall Satisfaction.

Patient satisfaction with UPRIMA was evidenced by the high level of enrollment in long-term studies. Approximately eighty-five percent (85%) of eligible patients continued into several long-term, open-label studies (6 months to 3 years in duration). For patients treated with UPRIMA for one year or more, the average percentage of erections firm enough for intercourse was 84.6%.

Two hundred and eighteen (218) patients with diabetes were enrolled in a double-blind, randomized, placebo-controlled, two-period crossover study. The proportion of attempts resulting in an erection firm enough for intercourse was significantly greater for the 4 mg dose of UPRIMA ($P < 0.05$) compared with placebo based on both patient and partner assessments.

INDICATIONS AND USAGE
UPRIMA is indicated for the treatment of erectile dysfunction.

CONTRAINDICATIONS

UPRIMA is contraindicated for persons with:

1. History of an allergic reaction to morphine (or to any of the other opiates) or

2. Known hypersensitivity to any component of the tablet formulation.

WARNINGS

UPRIMA may produce a vasovagal autonomic syndrome that may manifest as a brief self-limiting decrease in blood pressure and cause fainting/syncope (≤ 1% overall). Virtually all cases have occurred within the first 2 hours of administration. The majority of cases have occurred after the first UPRIMA dose or following an increase in dose. No subsequent fainting episodes were reported in patients who had experienced syncope and continued UPRIMA use. There is no evidence that UPRIMA causes sustained blood pressure changes. Nearly all syncopal episodes were preceded by a prodrome of symptoms that included one or more of the following: moderate to severe nausea, vomiting, pallor, sweating/hot flashes (diaphoresis), and/or dizziness/lightheadedness. (See **ADVERSE REACTIONS** Section.)

Patients should not engage in such activities as driving or performing hazardous tasks for 2 hours after UPRIMA administration because of the possibility of experiencing symptoms of dizziness, lightheadedness and/or fainting. Fainting is most common after the first dose or an increase in dose. If patients experience any of the prodromal symptoms listed above, they should not attempt to stand-up, but should lie down and raise their legs until their symptoms resolve. Each patient should be instructed to then contact their physician prior to taking another dose.

Physicians should consider the cardiovascular status of their patients before initiating any treatment for erectile dysfunction. Patients with preexisting cardiovascular disease potentially have increased cardiac risk during sexual activity. Treatments for erectile dysfunction, including UPRIMA, should not be used in men for whom sexual activity is inadvisable because of underlying cardiovascular status.

PRECAUTIONS

At higher than recommended doses of UPRIMA, a small number of subjects (4/40) with underlying cardiovascular disease who were taking short and/or long-acting nitrates in combination with multiple cardiovascular medications experienced vasovagal symptoms and clinically significant decreases in standing blood pressure. If patients experience any of the prodromal symptoms listed in the **WARNINGS** Section, they should not attempt to stand-up, but should lie down and raise their legs until their symptoms resolve. Each patient should be instructed to then contact their physician prior to taking another dose.

Agents for the treatment of erectile dysfunction should be used with caution in patients with anatomical penile deformity (such as angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions that may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia).

The safety and efficacy of UPRIMA use with other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

UPRIMA provides no protection against transmission of sexually transmitted diseases. Patients who use UPRIMA should undertake adequate and appropriate protective measures to guard against the spread of sexually transmitted agents, including the human immunodeficiency virus (HIV).

Couples using UPRIMA should employ adequate and appropriate contraception if the partner is of childbearing potential or is breastfeeding. There is no information on the effects of apomorphine that may be transferred to the partner.

Information for Patients

Patient information is available from the physician/pharmacist.

Drug Interactions

In vitro studies with human liver microsomes indicated that high concentrations of apomorphine inhibit the activity of CYP1A2, CYP3A4, and CYP2D6. However, C_{max} values (approximately 1 ng/mL) from the 4-mg sublingual dose of apomorphine were at least 1000-fold lower than the K_i values for CYP1A2, CYP3A4, and CYP2D6 activity. These data suggest that apomorphine, at the recommended doses, is not likely to inhibit the metabolism of other drugs by these CYP isoforms. Significant inhibition of CYP2C9 or CYP2C19 activity was not observed in the *in vitro* studies at apomorphine concentrations up to 100 μM.

In vitro studies demonstrated the involvement of several cytochrome P450 isoforms, primarily CYP1A2, CYP3A4 and CYP2C19, in the N-demethylation of apomorphine. Since apomorphine is also metabolized by sulfation and glucuronidation, other compounds that inhibit or induce cytochrome P450 are not expected to affect the pharmacokinetics of apomorphine.

Interactions between UPRIMA and antihypertensives (angiotensin-converting enzyme (ACE) inhibitors, ß-blockers, and calcium channel blockers, and $Alpha_1$ blockers) have been studied. No clinically significant changes in blood pressure, pulse, ECG, or adverse events have been noted.

At higher than recommended doses of UPRIMA, a small number of subjects (4/40) with underlying cardiovascular disease who were taking short and/or long-acting nitrates in combination with multiple cardiovascular medications experienced vasovagal symptoms and clinically significant decreases in standing blood pressure. If patients experience any of the prodromal symptoms listed in the **WARNINGS** Section, they should not attempt to stand-up, but should lie down and raise their legs until their symptoms resolve. Each patient should be instructed to then contact their physician prior to taking another dose.

Interaction studies with Zofran® and Compazine® (ondansetron hydrochloride and prochlorperazine maleate) were performed. There were no pharmacokinetic interactions noted.

In alcohol interaction studies, healthy subjects were administered higher than recommended doses of UPRIMA (6 mg) approximately 30 minutes after ingesting the ethanol beverage. Ingestion of an ethanol (0.3 g/kg) beverage had little, if any, effect on either the bioavailability of apomorphine from UPRIMA (6 mg) or blood pressure. However, ingestion of a larger amount of ethanol (0.6 g/kg) one half-hour before UPRIMA (6 mg) dosing increased apomorphine C_{max} by approximately 23% and the AUC_{∞} by 12% and resulted in significant reductions in mean systolic and diastolic blood pressure (10-16mmHg) at 45 minutes post dosing. In addition, the following adverse events were increased in frequency: dizziness, hypotension, nausea and pallor. Administration of UPRIMA (6 mg) resulted in a slight (8%-12%) but statistically significant decrease in the bioavailability of ethanol from a 0.3-g/kg or 0.6-g/kg dose of alcohol. In a 70 kg (154 lb) man, 0.6g/kg of ethanol equals approximately five 1-ounce shots or 3.3 twelve-ounce beers or 2.5 six-ounce glasses of wine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term carcinogenicity studies in male and female rats were performed. Subcutaneous doses of 0.1, 0.3 and 0.8 mg/kg/day (up to 69-times the clinical plasma level based on AUC_{∞}) were administered to male rats for 97 weeks and resulted in an increase in the incidence of interstitial testicular Leydig cell tumors. These tumors were only statistically significant at the highest dose of 0.8 mg/kg/day and occurred secondary to alteration of hormonal homeostasis. This finding is of no clinical significance since the endocrine mechanisms believed to be involved in the production of Leydig cell adenoma in rats are not relevant to humans. Female rats dosed with 0.1, 0.3, 0.8 and 2.0 mg/kg/day (at more than 140-times the clinical plasma levels following a 4-mg dose, based on the AUC_{∞} value) for 96 weeks did not have any apomorphine-related increase in tumors.

A 6-month study was performed in the p53+/- knockout transgenic mouse model. This model is considered highly sensitive to genotoxic carcinogens. Doses used in male and female mice were up to 20 and 40 mg/kg/day, respectively. These doses produced up to 492 and 787-times the clinical plasma levels (compared to a human dose of 4 mg). There was no drug-related increase in tumor incidence.

The following battery of mutagenicity assays were performed: *in vitro* mouse lymphoma test, *in vitro* cytogenetics in Chinese Hamster Ovary cells (CHO), *in vivo* mouse bone marrow micronucleus test and *in vivo* rat hepatocyte unscheduled DNA synthesis (UDS) assay. Positive responses were observed in the mouse lymphoma and the CHO tests. These positive results were reduced or eliminated by supplementing with the antioxidant glutathione. Absence of glutathione *in vivo* is uncommon except in cases of severe compromise of metabolic enzymes of the liver. In summary, the genotoxic potential demonstrated in the absence of glutathione was negated by consistent negative results using a genotoxic sensitive model *in vivo* for 6 months (*ie,* p53+/- knockout), and in all other *in vivo* tests.

In a male rat reproductive study, a dose of 2 mg/kg/day (83-times the clinical plasma level) did not alter spermatogenesis or fertility, and had no adverse effect on male reproduction.

Pregnancy, Nursing Mothers, and Pediatric Use

UPRIMA is not indicated for use in newborns, children, or women.

Pregnancy Grade C

Studies in pregnant animals have not been conducted with UPRIMA. It is also not known whether UPRIMA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

ADVERSE REACTIONS

More than 2300 men have received UPRIMA during clinical trials in both the United States and Canada. These patients were of varying ages with a diagnosis of organic, psychogenic or mixed erectile dysfunction including hypertensive patients (31%), diabetic patients (16%), patients with benign prostatic hyperplasia (16%), and patients with coronary artery disease (16%) as evidenced by a history of angina, coronary artery bypass surgery, angioplasty, or myocardial infarction.

Adverse events associated with UPRIMA were generally dose-related. Adverse events were considered tolerable at recommended doses.

UPRIMA may produce an autonomic syndrome (vasovagal in origin) that can lead to a brief, self-limiting decrease in blood pressure that can cause fainting/syncope (≤1% overall). (See WARNINGS Section.)

Patients who had a history of hypertension, coronary artery disease, and diabetes who were taking one or more concomitant medications (ie, nitrates, antihypertensives) were included in clinical trials. Adverse events and their frequency in this patient population were similar to that seen in the general population.

In the four multicenter Phase III placebo-controlled studies, the following treatment-emergent adverse events were noted in ≥2% of patients taking the recommended doses.

Table 1. Incidence of Adverse Events Reported by ≥2% of Patients
Where the Incidence With UPRIMA Was Higher Than With Placebo

Body System	**2 mg and 4 mg n=1097**		**Placebo n=969**	
	No.	(%)	No.	(%)
Body as a Whole				
Asthenia	29	(2.6)	6	(0.6)
Headache	92	(8.4)	47	(4.9)
Cardiovascular System				
*Hypotension**	23	(2.1)	1	(0.1)
Vasodilatation (Flushing)	28	(2.6)	8	(0.8)
Digestive System				
Nausea	139	(12.7)	18	(1.9)
Nervous System				
Dizziness	93	(8.5)	24	(2.5)
Somnolence	68	(6.2)	14	(1.4)
Respiratory System				
Pharyngitis	30	(2.7)	18	(1.9)
Yawn	68	(6.2)	10	(1.0)
Skin and Appendages				
Sweating	63	(5.7)	1	(0.1)
Special Senses				
Taste Perversion	43	(3.9)	5	(0.5)

*Predominately associated with vasovagal syndrome.

At doses higher than recommended, adverse events were similar to these, but generally were reported more frequently.

The following additional treatment-emergent events were reported in <2% of patients receiving UPRIMA in these same studies. A causal relationship to UPRIMA is uncertain.

Body as a Whole: Abdominal pain, accidental injury, allergic reaction, back pain, chest pain, chills, cyst, fever, flu syndrome, hernia, hostility, hypothermia, infection, infection fungal, malaise, neck pain, neoplasm, pain, pelvic pain
Cardiovascular System: Bradycardia, cardiovascular disorder, cerebrovascular accident, coronary artery disorder, hypertension, pallor, palpitation, syncope, tachycardia
Digestive System: Constipation, diarrhea, dry mouth, dyspepsia, eructation, gastritis, hepatitis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, sialadenitis, stomatitis, tongue edema, tooth disorder, ulcerative stomatitis, vomiting
Hemic and Lymphatic System: Ecchymosis
Metabolic and Nutritional Disorders: Edema, peripheral edema
Musculoskeletal System: Arthralgia, bursitis, leg cramps, myalgia
Nervous System: Agitation, amnesia, anxiety, ataxia, circumoral paresthesia, confusion, depression, euphoria, hypertonia, insomnia, libido decreased, nervousness, neuropathy, paresthesia, sleep disorder, thinking abnormality, tremor, vertigo
Respiratory System: Apnea, asthma, bronchitis, cough increased, dyspnea, epistaxis, laryngismus, lung disorder, pneumonia, rhinitis, sinusitis,
Skin and Appendages: Acne, dry skin, hair disorder, herpes simplex, lichenoid dermatitis, psoriasis, rash, skin carcinoma, skin disorder, skin hypertrophy, skin ulcer, vesiculobullous rash
Special Senses: Abnormal vision, amblyopia, conjunctivitis, deafness, ear disorder, ear pain, eye disorder, tinnitus
Urogenital System: Abnormal ejaculation, dysuria, epididymitis, penis disorder, prostatic disorder, testis disorder, urinary frequency, urinary incontinence, urinary tract infection

The treatment related adverse events in the long-term studies were similar to those seen in the controlled clinical studies.

One hundred forty-six patients (146) administered their first UPRIMA dose at home. The reported adverse events were generally similar to those observed during both the long- and short-term studies.

Special Populations
Patients with impaired renal or hepatic functions, spinal cord injury, prostatectomy, hypertension and diabetes were included in studies. The treatment-emergent adverse events were similar in type and incidence to those seen in other clinical trials.

Laboratory
No consistent laboratory abnormalities have been noted. The following sporadic laboratory abnormalities were observed in a few patients: abnormal ECG including ventricular extrasystoles, abnormal liver functions tests, albuminuria, hematuria, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperlipemia, hypokalemia, hypoglycemia, increased uric acid level, and leukocytosis.

OVERDOSAGE

Overdosage has not been reported in any of the UPRIMA clinical trials. UPRIMA in high doses may induce vomiting. There is no specific antidote available for UPRIMA. Therefore, treatment should be supportive and symptomatic.

DOSAGE AND ADMINISTRATION

UPRIMA is available as a sublingual tablet in three dosage strengths: 2, 3, and 4 mg.

1. Drink enough water or other nonalcoholic liquid to moisten your mouth just before taking UPRIMA.
2. About 15–25 minutes before you anticipate intercourse, put one UPRIMA tablet under your tongue.
3. The tablet should dissolve under the tongue and should not be swallowed. In some patients, a small amount of the tablet may remain in the mouth. If the tablet does not fully dissolve in 20 minutes, it may be swallowed. UPRIMA is now in your body, so don't take another tablet for at least 8 hours.
4. Proceed with sexual intercourse when you feel ready.

Excessive use of alcohol can affect sexual performance, and may increase certain effects such as nausea. UPRIMA can be taken following moderate alcohol ingestion.

Initial Dose

The recommended starting dose of UPRIMA is 2 mg for all patients.

Subsequent Doses

If necessary, the dose should be increased to a maximal dose of 4 mg. The patient's dose should be adjusted to a dose that is sufficient for sexual intercourse.

One tablet of UPRIMA should be administered to achieve an erection. The onset of the effect of one tablet usually occurs within 15–25 minutes after administration. The actual onset of the erection will vary from patient to patient.

The tablets dissolve best under moist conditions, so the patient should be advised to drink a small amount of water before taking UPRIMA.

The patient should proceed with sexual intercourse when he feels ready.

Patients should allow a minimum of at least 8 hours between doses.

The majority of patients (>96%) in the clinical trials did not require antiemetic medications (prochlorperazine maleate or ondansetron hydrochloride) for the treatment of nausea and/or vomiting. Therefore, patients should administer the first dose of UPRIMA without prior administration of an antiemetic.

No dose adjustment is necessary for the elderly.

The C_{max} was affected little by renal impairment. Therefore, it is recommended that patients with impaired renal function may initiate dosing with UPRIMA at 2 mg. Care should be exercised in any dose increase.

Hepatic insufficiency may increase the apomorphine plasma concentrations and prolong its elimination half-life. Based on the increase in C_{max}, patients with significant hepatic impairment should only be administered UPRIMA when the benefit outweighs the risk. If patients with hepatic impairment receive UPRIMA, dosing should be initiated at 2 mg. Care should be exercised in any dose increase.

HOW SUPPLIED

UPRIMA sublingual tablets are available in the following 3 dosage strengths:

Dosage Strength	Shape	NDC	Product ID
2 mg	Pentagon 	0300-8034-30	30 Tablets debossed with TAP and 2 on opposite sides of tablet.
3 mg	Triangle 	0300-8032-30	30 Tablets debossed with TAP and 3 on opposite sides of tablet.
4 mg	Round 	0300-8035-30	30 Tablets debossed with TAP and 4 on opposite sides of tablet.

The tablets are individually packaged in foil-foil blisters. Each blister strip contains 10 tablets.

Storage and Handling

UPRIMA should be stored at 25° C (77° F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] Protect from light and moisture.

Rx only

Manufactured for
TAP Pharmaceuticals Inc.
2355 Waukegan Rd
Deerfield, Illinois 60015-1595, U.S.A.
by XXXX or XXXX

xx-xxxx-R1-Rev. Month 1999

Draft Patient Package Insert for
UPRIMA™ (apomorphine HCl tablets) sublingual
(u-pree-ma)

This brochure has been created to answer your questions about male erectile dysfunction (ED), the medical term for impotence. It will also help educate you about UPRIMA (apomorphine HCl tablets) sublingual, the drug you and your doctor have chosen to manage ED. This brochure is not intended to be a substitute for information provided to you by your doctor or pharmacist or provided to your physician by TAP Pharmaceuticals Inc.

Be sure to discuss any questions you have about ED or the use of UPRIMA with your doctor or healthcare provider.

What is ED?

Erectile dysfunction, also referred to as ED, is a condition estimated to affect 30 million men in the United States. With this condition, the penis does not harden and expand when a man is sexually excited, and the man cannot have sexual intercourse. Not being able to perform sexually may cause emotional problems for a man and hurt his relationship with his partner.

ED can be caused by mental and physical conditions. Some drugs may interfere with a man's ability to achieve an erection. A man who often has trouble getting or keeping an erection should see his doctor for help.

What is UPRIMA?

UPRIMA is a drug that has been prescribed for you by your doctor. UPRIMA is a small tablet that helps many men achieve and keep an erection. UPRIMA does not increase sexual desire (libido). UPRIMA is placed under the tongue 15-25 minutes before starting sex.

How does UPRIMA work?

UPRIMA works in the brain to produce an erection. It works within 15-25 minutes, although actual time may be different for each patient. UPRIMA is not an aphrodisiac.

What is the most important safety information I should know about UPRIMA?

Some men have had nausea, vomiting, sweating, dizziness, lightheadedness and/or fainting after taking UPRIMA. With any of these symptoms, you may be at risk of fainting. Although fainting is rare (about 1%), you should take steps to reduce risk of injury when you take UPRIMA. Do not perform any hazardous tasks for 2 hours after taking UPRIMA. You should not drive a car, operate machinery, or do anything that might put you at risk of getting hurt.

If you feel lightheaded, dizzy, and/or faint after taking UPRIMA, do not attempt to sit up or stand. Until the symptoms pass, lie flat on your back with your legs elevated on pillows. Then report your symptoms to your doctor. Do not take UPRIMA again until you have spoken with your doctor.

Some men may experience nausea with and without vomiting. Your doctor can prescribe medication to relieve these symptoms if necessary.

Having sex can be dangerous for men with certain heart conditions or high blood pressure. Do not use UPRIMA if your doctor told you that sex may be a hazard to your health. Be sure to tell the doctor who prescribed UPRIMA about any other ailments you may have or drugs you are taking.

How should I take UPRIMA?

Plan to have sexual intercourse with your partner when you will be relaxed and free from distractions.

1. Drink enough water or other nonalcoholic liquid to moisten your mouth just before taking UPRIMA.
2. About 15-25 minutes before you anticipate intercourse, put one UPRIMA tablet under your tongue.
3. The tablet should dissolve under the tongue and should not be swallowed. In some patients, a small amount of the tablet may remain in the mouth. If the tablet does not fully dissolve in 20 minutes, it may be swallowed. UPRIMA is now in your body, so don't take another tablet for at least 8 hours.
4. Proceed with sexual intercourse when you feel ready.

Excessive use of alcohol can affect sexual performance, and may increase certain effects such as nausea. UPRIMA can be taken following moderate alcohol ingestion.

Dosing
Your first dose of UPRIMA will be 2 mg. If this dose does not give you an erection firm enough for intercourse, tell your doctor. Your doctor may increase the dose to 3 or 4 mg to achieve the desired effect.

Overdose
Overdosage has not been reported by any of the UPRIMA patients. However, in case of accidental overdose, a doctor should be called immediately.

Pregnancy and Sexually Transmitted Diseases
UPRIMA does not protect you or your partner from pregnancy or from getting/giving a sexually transmitted disease. Ask your doctor about precautions. The risks to pregnant women or those wanting to become pregnant, nursing mothers, and children are not known.

Who should not take UPRIMA?

Men who have been advised not to have sex should not take UPRIMA.

UPRIMA should not be used by men who have a deformed penis or Peyronie's disease.

UPRIMA should be used only after being prescribed by a doctor.

Contact your doctor before taking this drug if you think that you have ever had an allergic reaction to morphine.

UPRIMA should not be used if your partner is pregnant or breast-feeding.

Do not give this drug to anyone else.

Like any drug, UPRIMA should be kept out of the reach of children.

What are the possible side effects of UPRIMA?

Like any medication, UPRIMA may have certain side effects.

In addition to the symptoms covered in the safety information section, other symptoms observed during clinical studies included weakness, headache, hot flashes, sweating, and yawning. This list does not include all reactions reported, so any symptom should be reported to your doctor.

Medicines are sometimes prescribed for purposes other than those listed in this brochure. If you have any questions about using UPRIMA, you should ask your doctor or pharmacist.

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